2017 International Congress of Parkinson's Disease and Movement Disorders

Fellow, Resident and Student Abstracts







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Two ethnic clusters with Huntington's disease in Israel - The case of Mountain Jews and Karaites

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Objective: To Assess frequencies of Huntington disease among different Israeli sub-populations **Background:** Worldwide prevalence estimates of Huntington's disease (HD) vary widely with no reliable information regarding the Jewish population in Israel.

Methods: This cross sectional study assessed clinical, cognitive and demographic characteristics of 120 HD patients who were treated at the Movement Disorder Unit of the Tel-Aviv Medical Center.

Results: Our cohort was comprised of one-third Ashkenazi Jews, 27% Jews from the Caucasus region, 18% Sephardic Jews and 21% Karaites. No between group differences were detected regarding number of CAG repeats, age of onset, disease duration, years from symptoms onset till diagnosis, gender, years of education, Unified Huntington's Disease Rating Scale or the Montreal Cognitive Assessment scores.

Conclusions: We detected clustering of HD among distinct selective Jewish ethnic groups in Israel, with higher prevalence of the disease among Jews from the Caucasus region and Karaites, compared to the general Israeli population.

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Tremor-dominant clinical phenotype is associated with low risk of levodopa-induced dyskinesia in Parkinson's Disease

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Objective: To evaluate possible associations between epidemiological and clinical data with risk of levodopainduced dyskinesias (LID) onset in Parkinson's disease (PD) patients.

Background: LID are common complications in PD, but there are conflicting data about clinical risk factors associated with their onset.

Methods: A cross-sectional study was conducted with epidemiological and clinical data from Brazilian PD patients to identify clinical risk factors associated with LID onset. PD patients with levodopa therapy were submitted to neurological examination and semi-structured interviews performed by movement disorders specialists. Presence of LID was confirmed if UPDRS Part IV had a score = 1 on item 32. Clinical phenotypes were defined based on the method described by Stebbins et al. (2013) as tremor dominant or postural instability/gait difficulty (PIGD). We performed multivariate logistic regression to identify clinical risk factors associated with LID onset.

Results: 198 Brazilian PD patients were enrolled (males - 59%; mean age 61.8 years). Of these patients, 96 (48.2%) presented LID. At a forward multivariate model with 7 independent variables (p < 0.1 in univariate analysis), tremor dominant phenotype showed a reduced risk of LID onset compared to PIGD patients (OR 0.17, CI95% 0.07-0.39; p < 0.001). Furthermore, longer duration (OR 1.31, CI95% 1.17-1.47; p < 0.001) and higher doses of levodopa therapy (OR 1.00, CI95% 1.000-1.002; p = 0.04), as also as early onset of PD (OR 1.04, CI95% 1.01-1.07; p = 0.009) increased risk of LID.

Conclusions: Together with previous studies, our results showed PD patients with tremor dominant clinical phenotype have a lower risk of LID onset, suggesting this phenotype present a more benign prognosis and a specific physiopathology.

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Increased BMI May Protect against Parkinson's Disease: Evidence From Mendelian Randomisation Study

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Objective: To use two-sample Mendelian randomisation (MR) to study the causal effect of body mass index (BMI) on Parkinson's disease (PD).

Background: Both positive and negative associations between BMI and PD have been reported in observational studies, but it has been difficult to establish causality because of the possibility of residual confounding or reverse causation. To our knowledge, MR, the use of genetic instrumental variables to explore causal effects, has not previously been used to test the effect of BMI on PD.

Methods: Two-sample MR was undertaken using genome-wide association study data. The associations between the genetic instruments and BMI were obtained from the GIANT consortium (1) and consisted of the per-allele

difference in mean BMI for 77 independent variants that reached genome-wide significance. The per-allele difference in log-odds of PD for each of these variants was estimated from a recent meta-analysis (2), which included 13,708 cases of PD and 95,282 controls. The inverse variance weighted method was used to estimate a pooled odds ratio (OR) for the effect of a 5kg/m2 increase in BMI on PD. Evidence of directional pleiotropy averaged across all variants was sought using MR-Egger regression. Frailty simulations were used to assess whether causal associations were affected by mortality selection.

Results: A genetically related 5kg/m2 increase in BMI was associated with a reduced risk of PD (OR 0.82, 95% CI 0.69-0.98). MR-Egger regression gave similar results (OR 0.76, 95% CI 0.51-1.14), providing evidence against directional pleiotropy (intercept 0.002, p-value=0.654). Frailty analysis indicated that the observed negative association between BMI and PD may have been biased by a negative association between BMI and survival, but this did not fully explain the estimated causal effect.

Conclusions: In this large study using two-sample MR, we found evidence to suggest that increased BMI may be protective against risk of PD. The mechanism underlying this protective effect warrants further study.

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Integration of risk factors for PD in two large longitudinal cohorts

I. Kim, E. O'Reilly, K. Hughes, X. Gao, M. Schwarzschild, A. Ascherio (Boston, MA, USA) **Objective:** To derive a risk score for Parkinson's disease (PD) based on lifestyle factors and family history and assess potential multiplicative and additive interaction between predictors of PD.

Background: Numerous lifestyle factors have been related to risk of PD, but little is known on how these factors interact with each other. We sought to determine the overall combined effect of several known predictors of PD using risk scores in two large, prospective cohorts.

Methods: We developed and applied risk scores among 90,638 women in the Nurses' Health Study (NHS) (1984-2012) and 44,815 men in the Health Professionals Follow-up Study (HPFS) (1986-2012). We computed the risk score for each individual based on the following factors previously associated with PD risk: total caffeine intake, smoking, physical activity, and family history of PD for the NHS, and additionally total flavonoid intake and dietary urate index for the HPFS. We assigned one point per increase in quintile for each factor, with the exception of family history, for which we assigned a score of 5 for absence and 0 for presence of family history. The scores were summed to compute the overall score (NHS: 3-20; HPFS: 5-30). We estimated hazard ratios (HRs) using Cox proportional hazards models. Effect modification on the multiplicative scale was assessed by testing significance of the statistical interaction terms in the Cox model and additive interaction was assessed by computing the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (SI). Results: We observed 456 PD cases in NHS and 591 PD cases in HPFS during follow up. The adjusted HRs comparing the highest of the five categories of the risk score to the lowest category of the risk score was 0.28 (95% CI: 0.18, 0.43; ptrend <0.0001) in the NHS and 0.18 (95% CI: 0.10, 0.34; ptrend <0.0001) in the HPFS. Results were similar when applying the risk scores computed by summing the predictors weighted by the log of their individual effect sizes on PD risk in these cohorts. Additive interaction, possibly suggesting a synergic protective effect, was present between no family history of PD and caffeine intake in both the NHS and HPFS and caffeine and physical activity in NHS.

Conclusions: Our results suggest that known protective factors for PD have additive or super-additive effects, so that PD risk is very low in individuals with multiple protective risk factors.

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Experience and outcomes of the first Movement Disorders Clinic in Honduras

J. Ortiz, A. Medina, F. Naranjo (Tegucigalpa, Honduras)

Objective: To describe the frequency and clinical characteristics using standardized scales in patients with movement disorders (MD) recruited by a referral system in Tegucigalpa, Honduras.

Background: Access to public neurologic consultation in Honduras is scarce and no formal Movement Disorders clinic exists. Recently, a public hospital incorporated neurologic consultation with the first neurologist with MD training. Demographic characteristics of MD in Honduras are insufficient and assessment using clinical rating scales is lacking.

Methods: A prospective study was conducted from June to December 2016 in the San Felipe Hospital. A referral system between the two public entities that provide neurologic consultation was established; all patients were referred by general physicians from outpatient clinics and residents from the neurology training program. A total of 123 patients were recruited using the MD referral system, of which 12 were excluded because of lack of follow up

visits. Best medical therapy was initiated with monthly follow up visits. Patients were evaluated using validated scales. A percentage of improvement based on the difference from the initial score and the six months score was calculated.

Results: At all, 63% of patients were female (mean age was 65.8 ± 14.1 years, 54,4%. Parkinsonism was the most common MD, with a frequency of 64.83%, of which 91.4% were idiopathic. Mean disease onset was 64.8 ± 12.5 years. Gap between onset of disease and making the diagnosis was 3.7 ± 3.9 years, 27,14% were drug naive. Mean initial LEDD of $458,88\pm433,15$, increased to 606.7 ± 386.5 after intervention. Mean initial "ON" MDS-UPDRS-III was 36.8 ± 16.0 , reduced to 20.7 ± 12.6 after intervention ($35.45\%\pm21.0\%$ improvement). Tremor were 18,50% of patients, ET was the most frequent (20%) with improvement in the TETRAS part B scale of $31\%\pm8\%$. Other tremors corresponded to enhanced physiological, drug induced, dystonic among others. Dystonias were 11.98%; focal dystonias accounted for 76.9%, hemifacial spasm improvement in the Tolosa-Martin scale was $47\%\pm29\%$ with botulinum toxin injections (BTI). Improvement of cervical dystonia was $33\pm7\%$ with BTI. Choreas were 4.69% all secondary.

Conclusions: After follow up patients had a better outcome and standardized evaluation was implemented. Public awareness with a referral system warrants early diagnosis and treatment to MD in Honduras.

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Research participants are not representative of the population age distribution of PD

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Objective: To describe the distribution of the age at onset in PD incidence studies and to compare this with the age of onset of published studies in PD.

Background: Most sources (e.g. textbooks, review articles, patient information) state that the mean age at onset in Parkinson's disease (PD) is about 60. The only reliable way to identify the true age distribution in a population of PD is through population-based incidence studies, which aim to identify all new cases of PD in a defined population over a specific time period.

Methods: We performed a comprehensive systematic review to identify all incidence studies in PD. From identified studies, we extracted data relating to mean age at onset (or diagnosis) and age-specific incidence rates. We performed Der Simonian and Laird random-effects meta-analysis of mean age at inception (i.e. either onset or diagnosis). We also performed meta-analysis of age-specific incidence rates (in 10-year age bands) in studies published since 2000 and plotted a histogram to illustrate the average distribution of the age of incident PD. We subsequently documented the mean age at onset in all research studies in PD published over six months in Movement Disorders (July to September 2016), and compared this to the pooled mean age at inception from the identified incidence studies

Results: Twelve incidence studies reported data on the mean age at inception in PD. The pooled mean age was 69.3 (95% confidence interval 67.0–71.7) (figure 1) although major heterogeneity was present ($I^2 = 96.8\%$). Some of the heterogeneity may be due to differences between age at onset and age at diagnosis. There was greatest heterogeneity in the oldest age stratum suggesting that some of the heterogeneity may be due to underascertainment in the elderly. The distribution of the age at inception in PD is displayed in figure 2. Of 41 studies published in Movement Disorders during the stated time period, 31 published the mean age at onset. The mean mean age at onset in these studies was 59.1 (median 58.9).



Conclusions: The mean age at onset in PD is nearly 70 which is both about ten years older than usually stated and about 10 years older than the mean age at onset in research participants. Many published studies have therefore used unrepresentative patient groups. This selection bias may have an important impact on the accuracy research findings as well as generalisability and further research should assess its influence.

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Sex Differences in Homebound Advanced Parkinson's Disease Patients

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Objective: To describe sex differences in homebound patients with advanced Parkinson's disease and related disorders in an interdisciplinary home visit program (HVP).

Background: It has been shown that sex is a determinant in the quality of care and disease progression of patients with Parkinson's disease. Women with PD are more likely to be older and have greater disease severity and more comorbidities than men despite similar duration of disease. Women are also less likely to be treated by a neurologist and less likely to receive DBS. Within the PD population, homebound individuals are a particularly vulnerable population facing significant barriers to care. In the context of an HVP, we sought to compare baseline characteristics among homebound men and women with advanced PD and related disorders.

Methods: Retrospective analysis of patients enrolled in the Edmond J. Safra Interdisciplinary Home Visit Program for Advanced PD seen between February 2014 and July 2016. Data collected via in-person interviews and chart review.

Results: We enrolled 85 patients, of whom 52% were women, with a median age of 79.6 years at the initial home visit. PD was the most common diagnosis (79%), followed by DLB and PSP (5% each), MSA (2%), and atypical parkinsonism (9%). Mean total UPDRS at Visit 1 was significantly higher in men than women (85.6 vs 71.2, p <0.01). Men were more likely to bear a PD dementia diagnosis than women (15.5% vs. 0.7%). Women were less likely than men to have any caregiver present (20.5% of women had no caregiver vs. 4.9% of men, Fisher's exact p = 0.05). Women were more likely to be widowed (45% vs 12%) or single (18% vs. 7%); men were more likely to be married (68% vs. 30%) (p <0.01).

Conclusions: Among homebound advanced PD patients, there are sex differences at baseline, including women having a far higher likelihood of living alone. The role of the caregiver in facilitating safe aging-in-place is crucial. While the absence of a spouse or partner caregiver may be explained by variable life expectancies between the sexes, these findings suggest that homebound women with advanced PD may face even greater barriers to accessing care than their male counterparts and may be at higher risk of loss to follow-up without concerted efforts at continuity of care.

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The value of various risk factors in the manifestation of Parkinson's disease in the southern part of Uzbekistan.

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Objective: Using a comprehensive analysis of clinical, medical history and social - hygienic data will examine the factors that determine the development of Parkinson's disease.

Background: The value of risk factors for Parkinson's disease has a lot of importance in the manifestation in the conditions of the southern regions of Uzbekistan, as in these regions is a number of chemical companies which directly affects to the condition of the body workers and the population living near these plants.

Methods: The study included 70 PD patients aged 30 - 85 years (mean - 55.8 + -10.1 years). Of these, 38 patients were born and live in rural areas of Kitab district, 32 - in the city of Karshi, Kashkadarya region of Uzbekistan. The average age of the patients was: rural population - 53.08 + -9.14 years, urban - 58.5 + -10.7. The diagnosis was made based on the criteria of the brain bank UK Parkinson's Disease Society (Hughes et al AJ af., 1992).

Results: There is a tendency to an earlier onset of the disease in rural areas compared with urban residents (+ 48.8 respectively - 9.9 and 53.6 + -9.9 years). Also among the villagers there was noted predominance of men (61.1% of women - 38.9%), whereas among the urban population, on the contrary, a large number of patients were female (61.7%) than men (38.3%), These trends are explained in agriculture men than women most exposed to the harmful effects of pesticides (butifos, magnesium chlorate, DDT - 30), insecticides (BI - 58, trichlorfon) herbicides. When analyzing the data of the average age debut PSU depending on the profession there was a trend to an earlier onset of the disease in the chemical industry workers (47.8 + - 8.4), agricultural workers (50.2 + -7.8) and teachers (51.1 + -9.8). The early development of the disease in the teaching staff, compared with the group as a whole (+ 51.1 respectively -9.8 and 52.4 + -8.8) suggests a possible role in the manifestation of disease stress.

Conclusions: This study showed that Parkinson's disease is more common and more severe in patients living in rural areas compared with urban residents. Established an earlier age of onset of the disease among residents of rural areas (48.8 + -9.9 years) compared with those of the urban population (53.6 + -9.9). Patients living in rural areas, established adverse effects of pesticides (butifos, magnesium chlorate, DDT - 30), insecticides (BI - 58, trichlorfon).

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Dr. Paula Coutinho's seminal contributions to the understanding of Machado-Joseph's disease

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Objective: To recognize the contributions of Dr. Paula Coutinho to Neurology through her studies of Machado-Joseph's disease (SCA3).

Background: One of the unique opportunities in the life of a physician is to closely follow the discovery of a previously unknown disease. Few are those who were involved in the description of the genetics, pathology, clinics, and epidemiology of a new condition. In the past decades one of those individuals, Dr. Paula Coutinho, became acclaimed in Neurology through her study of SCA3.

Methods: The authors present the most relevant contributions of Dr. Coutinho to both Portuguese and International Neurology.

Results: Dr. Coutinho described with details the main characteristics of a new disease that, at the time, was strongly believed to have originated in the Portuguese islands. In her work, published in the Portuguese medical journal "O Médico" in 1977, she was the first person to unite the diagnosis of the families Machado, Thomas and Joseph (described as different neurodegenerative diseases in descendants of Portuguese immigrants in the USA) under the same genetic condition, but with different phenotypical manifestations. After reviewing all cases of the 15 families in the Açores Islands, in 1978 she defined for the first time the clinical characteristics of the disease, further classifying it in subtypes, improving the diagnosis and even establishing the disease's prognosis. In 1980 she rechristened this condition as Machado-Joseph's disease (MJD) and proposed the main diagnostic criteria for MJD, refining them in 1992 in her PhD thesis, in which she detailed its genetics, clinical presentation, pathology and epidemiology.

Conclusions: Dr. Coutinho's work investigation of MJD served as the basis for the genetic tracking of hereditary ataxias and spastic paraparesis in Portugal, as it allowed for the identification of several other families in the country. Similarly, it helped identify many other affected families worldwide.

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Clinical characteristics of Parkinson's disease developed from essential tremor

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Objective: The objective of this study is to compare the clinical characteristics of Parkinson's disease developed from essential tremor (ET-PD) with the clinical characteristics of idiopathic Parkinson's disease (IPD). **Background:** Recent studies genetic and epidemiological studies have observed that there is a link between essential tremor and PD. However, there is lack of data about clinical features of PD developed from essential tremor.

Methods: Twenty-five ET-PD patients and 125 IPD controls were enrolled according to each criterion. Motor and nonmotor features were compared between the two groups.

Results: Rest and action tremors were more severe in ET-PD patients than in IPD patients. In addition, tremor disorder of first-degree relatives occurred more frequently in the ET-PD group than in the IPD group. Among the nonmotor features, frequencies of sleep disorders, especially rapid-eye-movement sleep behavioral disorder, were lower in patients with ET-PD than those with IPD, and smell identification test scores were higher in patients with ET-PD than those with IPD. The prevalence of other nonmotor features between the two groups. **Conclusions:** This is the first comparison of motor and nonmotor features between ET-PD and IPD. ET-PD and IPD have different characteristic motor and nonmotor features. This may suggest that ET can be a risk factor of PD in different way than previously believed.

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Fluvoxamine maleate normalizes striatal neuronal inflammatory cytokine activity in a Parkinsonian rat model associated with depression

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Objective: The objective of this study was to investigate how fluvoxamine maleate treatment regulates depressive-like symptoms, motor impairments and the expressions of IL-1beta, IL-6, IL-10, TGF-beta and TNF-alpha cytokines in the striatum of a stressed Parkinsonian rat model.

Background: Cytokines dysfunction is associated with both depression and Parkinson's disease (PD) pathophysiology. Inflammatory cytokines in neural and behavioral processes are involved in the production and/or maintenance of depression in PD.

Methods: Early maternal separation was used to model stress and depressive-like symptoms in rats. Maternally separated adult rats were treated with fluvoxamine for 30 days prior 6-hydroxydopamine (6-OHDA) lesion. The sucrose preference test (SPT) and the limb-use asymmetry test (cylinder test) were used to evaluate anhedonia and motor impairments respectively. Lipid peroxidation and cytokine expression were measured in striatal tissue using ELISA and real-time PCR techniques respectively.

Results: We found that maternal separation resulted in anhedonia and exacerbated 6-OHDA lesion but fluvoxamine treatment attenuated these effects. Lipid peroxidation, mRNA levels of IL-1beta, IL-6 and TNF-alpha were down-regulated while IL-10 and TGF-beta levels were up-regulated in the lesioned striatum of fluvoxamine-treated rats **Conclusions:** This study shows that early treatment with fluvoxamine may attenuate inflammation on injured striatal neurons by favoring anti-inflammatory cytokine expression while decreasing pro-inflammatory cytokine release in the brain. This suggests a role of fluvoxamine as a potential therapeutic intervention targeting neuronal inflammation associated with PD.

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Interrelation between chronic pain syndrome and cognitive and affective disturbances in patients with Parkinson's disease

K. Stepanchenko (Kharkiv, Ukraine)

Objective: To study interrelation of chronic pain syndrome and cognitive and affective disorders in patients with PD.

Background: Parkinson's disease (PD) is characterized by well-known motor symptoms as well as by non-motor symptoms including pain syndrome which remains poorly understood and often ignored by physicians

Methods: 109 patients (ages 65,8±8,5) with PD were examined. Two groups: 1st (75 pers.) - patients with chronic pain syndrome, 2nd (34 pers.) - patients without pain were formed. Patients with pain and without pain did not differ by age, disease severity (assessed on a scale Hyun-Yar) and duration. Assessment of movement disorders (UPDRS), of pain (VAS, pressalgometry), of cognitive functions (MMSE), of attention (Wechsler Adult Intelligense Scale - WAIS), of visual-spatial functions («drawing hours» test (Manos, 1994)), of memory (visual memory test of SKT scale (H.Lehbeld, H.Erzigkeit, 1980)), of speech (test on the availability and directional association (AR Luria, 1969)), of affective disorders (Beck Depression Inventory, Scale obsessive-compulsive syndrome (Goodman et al, 1984)) were performed.

Results: Assessment of the general state of patients' cognitive functions on MMSE ranged from 27 to 30 points (averaged 28,8 points). The group of patients with pain had lower indicators of neuropsychological functions than patients without pain (p<0,05). Patients with pain had more pronounced disturbances than patients without pain at performance of clock drawing test (7,5±1,1 versus 9,2±0,7), «coding» test (26,8±11,5 versus 34,1±8,2), on speech activity test (10,9±6,7 versus 14,7±3,5), visual memory test (6,9±2,2 versus 9,6±2,5), (p<0,05). However, patients with pain did not differ from patients without pain on the overall level of cognitive function and abstract thinking. Depressive symptoms were observed in 49 (69%) patients with pain syndrome (17,3±7,6 points) and in 11 (28%) patients without pain (12,6±6,8 points). Intensity of pain assessed by the VAS correlated with the severity of depressive symptoms (R=0,51; p<0,001). Intensity of pain in patients from 1st group was higher (53,8±23,2 points) than in patients without pain (43,6±19,1 points), (P=0,03).

Conclusions: The development of chronic pain in patients with PD is associated with depressive, obsessivecompulsive symptoms and neurodynamic and regulatory cognitive impairment

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Gastrointestinal transit time in Parkinson's disease -a novel 3D method

K. Knudsen, T. Fedorova, K. Østergaard, K. Krogh, P. Borghammer (Aarhus, Denmark)

Objective: To study the GI transit time with a novel ambulatory electromagnetic system in PD patients and healthy controls.

Background: The majority of Parkinson's disease (PD) patients experience gastrointestinal (GI) symptoms, such as constipation. Despite GI non-motor symptoms being highly prevalent in PD, data on objective testing of the GI tract is scarce, especially in the small intestine. Thus, we aimed to study the GI transit time (GITT) during 24-hours monitoring with a novel ambulatory electromagnetic system in PD patients and healthy controls (HC). **Methods:** Twenty-two early-to-moderate stage PD patients (H&Y 2 (1-3), 7 female) and 14 HC (4 female) were included. Transit time in the stomach, small intestine, and the coecum-ascending colonic segment were assessed

included. Transit time in the stomach, small intestine, and the coecum-ascending colonic segment were assessed using the novel 3D-transit system, which monitors an ingested electromagnetic capsule via an abdominal worn receiver station (*Motilis Medica SA, Lausanne, Switzerland*). Furthermore, the number of and time to first fast movement (passing <1 colorectal segment in =2 minutes) and first mass movement (passing =1 colorectal segment in =2 minutes) were registered.

Results: The PD group displayed significantly delayed small intestinal (STT) and coecum-ascending transit time (CATT) (p=0.03 and p=0.0063). No significant between-group difference was seen in the stomach (p=0.91). Fast movements were seen in 4 patients and 11 HC (p=0.006) and mass movements were seen in 1 patient and 5 controls (p=0.023).

Conclusions: This is the first study of GITT in PD patients using the 3D-transit system. Significantly prolonged STT and CATT were demonstrated in the PD group compared to matched controls. No difference was seen in gastric transit time. Furthermore, the patients showed significantly fewer colorectal fast movements and mass movements within 24 hours, indicating generalized functional enteric nervous system involvement in PD.

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Pancreatic polypeptide plasma levels in Parkinson's disease – a marker of parasympathetic denervation *K. Knudsen, T. Fedorova, K. Østergaard, P. Borghammer (Aarhus, Denmark)*

Objective: To study plasma PP concentration during sham feeding in PD patients and healthy controls, as a measure of pancreatic vagal innervation.

Background: Most patients with Parkinson's disease (PD) experience signs of decreased parasympathetic function. Lewy pathology is present in the vagus nerve and the dorsal motor nucleus of the vagus very early in the disease course (Braak stage I). The pancreas is densely innervated by the vagus nerve, and the early peak (5-20 min) of the hormone Pancreatic Polypeptide (PP) after food intake or sham-feeding has been validated as a marker of vagal integrity. Thus, we aimed to study plasma PP concentration during sham feeding (chew-and-spit) in PD patients and healthy controls (HC), as a measure of pancreatic vagal innervation.

Methods: Twenty-five early-to-moderate PD patients (H&Y 2 (1-3); 7 female) and 17 HC (5 female) were included. Blood sampling for analysis of PP, glucose, and insulin levels were performed before, during, and 20 minutes after a 5 minute sham feeding session with white bread and chocolate spread. Furthermore, faeces samples from all participants were analysed for pancreatic elastase enzyme levels as a marker of exocrine pancreatic function.

Results: The PD group displayed significantly decreased plasma PP concentrations during the early phase after sham feeding compared to controls (p=0.012). No change in glucose and insulin levels were seen in any of the groups as an indicator of pure sham feeding without food ingestion. Also, no significant group difference was seen in pancreatic elastase levels (p=0.69).

Conclusions: Early-to-moderate stage PD patients showed significantly decreased PP plasma concentrations after sham feeding - an indication of decreased vagal function. Exocrine pancreatic function measured by elastase in faeces was not significantly different in the patient group compared to controls. Glucose and insulin concentrations did not change in either group throughout the test, verifying that sham feeding was performed correctly without unintentional swallowing of food.

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Validation of the Utility of Brief Smell Identification Test Simplified Chinese Version 2 in Chinese Parkinson's disease

M. Cao (Beijing, People's Republic of China)

Objective: To validate the utility and efficiency of Brief Smell Identification Test Simplified Chinese Version 2 (B-SIT CV2) in Chinese Parkinson's disease patients and investigate the familiarity of the odors on questionnaire in Chinese population.

Background: The Brief Smell Identification Test was designed specifically in Chinese population however there were no report for the utility of this olfactory test in the diagnosis of Parkinson's disease in China.

Methods: PD patients recruited from the Movement Disorder Clinic of the Xuanwu Hospital and healthy controls from the Beijing communities from 2014 to 2015. The Brief Smell Identification Test Simplified Chinese Version 2 was applied for olfactory function test and the familiarity of fifty-nine odors questionnaire was performed for the investigation of familiarity of odors.

Results: One hundred and eighteen subjects were participated in the investigation of application of B-SIT, with 45 healthy controls and 73 PD patients. The sensitivity (69.9%), specificity (86.5%), PPV (89.5%) and NPV (63.9%) could reach in the application of B-SIT to identify PD patient. Three thousands and three hundreds fifty-six subjects were enrolled in the odors familiarity investigation, with 1619 subjects in East China group and 1069 subjects in North China group. A quarter odors in the B-SIT were below the 95% of familiarity in the North China group. The odors of Coffee, Smoke, Chocolate and Apple were poor at differentiation of PD from control.

Conclusions: Although some of the odors in the B-SIT Simplified Chinese version 2 might not be familiar with Chinese population, this olfactory function test could be used in Chinese Parkinson's disease.

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Circadian and Homeostatic Modulation of Multi-unit Activity in Dopaminergic and Striatal Structures *K. Fifel (Leiden, Netherlands)*

Objective: The aim of this study is to investigate the circadian and homeostatic modulation of the multi-unit activity of dopamineric and striatal neuronal structures.

Background: Several neurological disorders associated with Basal Ganglia dysfunctioning, like Parkinson's and Huntington's diseases, are characterised by seriously debilitating sleep abnormalities. The involvement of Basal Ganglia in sleep modulation has been recently documented. However, the reciprocal modulation of Basal Ganglia activity by sleep-wake dependent processes is unknown.

Methods: We combined Electroencephalogram (EEG) recordings with electrical multi-unit activity (MUA) in different subdivisions of both Midbrain Dopaminergic structures [Substantia nigra lateral (SNL, n=6), Substantia nigra Medial (SNM, n=5), Ventral Tegmental area (VTA, n=6)] and striatal structures [Striatum Latero-dorsal (STR-LD, n=4), Striatum Medio-dorsal (STR-MD, n=4), Ventral striatum (STR-V, n=4)] under 12:12 light/dark (LD) and constant darkness (DD)conditions. We also investigated the effects of a 6h sleep deprivation on MUA in these areas.

Results: Both under LD and DD conditions, the MUA in the areas examined showed a vigilance state dependency with the highest firing rates during wakefulness and REM sleep compared to NREM sleep (p<0.001, t-test). Interestingly, striatal subdivisions displayed different sensitivities towards changes in homeostatic sleep pressure as evidenced by EEG Slow Wave Activity.

Conclusions: Our results indicate that circadian and homeostatic processes influence the activity of midbrain dopaminergic and striatal structures. These influences may contribute to behavioural changes observed in neurological disorders related to dysfunctioning in the Basal Ganglia.

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Riding the puzzle: deep brain stimulation and the non-motor symptoms in Parkinson's disease

A.C. Campos, E. Talamoni Fonoff, C. Hamani, R. Lima Pagano (São Paulo, Brazil)

Objective: To better understand the benefits of DBS in non-motor symptoms.

Background: Parkinson's disease(PD) is a neurodegenerative disease characterized by the loss of dopaminergic neurons, generating motor and non-motor symptoms, and its treatments are eminently symptomatic. The treatments begin with an effective pharmacological approach that evolves negatively with extreme complications. At this stage, the gold standard of treatment is the deep brain stimulation (DBS) of the subthalamic nucleus (STN), however the evidence of improvement of non-motor symptoms such as depression and pain has been conflicting, which corroborates to the wane of quality of life and it is been often neglected.

Methods: Male Wistar rats were submitted to an intrastriatal injection of $12 \mu g$ of 6-hydroxydopamine (6-OHDA) or saline in the left hemisphere. Then, the animals were implanted or not with stainless steel electrodes in the left STN. All animals were submitted to the paw pressure test (hyperalgesia behavior) before and after 7 days of the surgery. In the 8th day, the animals were divided in four groups: saline or hemiparkinsonian without implant; hemiparkinsonian implanted but not stimulated (control of the implant); and hemiparkinsonian rats implanted and stimulated for 5 days during 2 h (130 Hz, 60μ s). After the last stimulation, animals were submitted to the apomorphine-induced rotation test, and in the other day, they were submitted to the paw pressure test, catalepsy test and forced-swimming test (depression-like behavior).

Results: The model was characterized by the increase in the contralateral rotation in hemiparkinsonian rats without stimulation, and in the immobility of these animals in the catalepsy test. The DBS animals presented less contralateral rotation to the lesion side and catalepsy behavior, showing an improvement of motor deficits. As regards to the non-motor symptoms, our DP model reproduced the finds in humans inducing a decrease in 60% of the nociceptive threshold in both posterior paws and inducing an increase of 45% in immobility in the forced swimming test. However, the DBS was able only to reverse the pain caused by the nigrostriatal lesion, without interfered with the depressive-like behavior.

Conclusions: Our preliminary results showed that STN-DBS improved the motor and painful behaviors related to PD, but more research is necessary to understand the mechanisms and ameliorate the results of the stimulation.

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The impact of Parkinson's disease on faith and spirituality

A. Weldehana (Addis Ababa, Ethiopia)

Objective: The objective of the present study is to assess the impact of Parkinson's disease on faith and spirituality. **Background:** There are some controversies on the effect of Parkinson's disease on faith and spirituality. Active problem-oriented coping, distraction, religious relief and quest for sense were significantly important coping styles for Parkinson's disease (PD) patients. A limited literature suggests that people with PD have reduced religious beliefs, practices and experiences, compared to normal healthy controls. We questioned the rationale behind these suggestions because the results may be confounded by reduced mobility and social isolation associated with Parkinson's disease.

Methods: We recruited age and sex matched 50 Parkinson's patients and 50 controls with rheumatic disease from movement disorder and rheumatology clinics of Black Lion Hospital, respectively. Each subject was examined and assessed on Sheehan Disability Scale (SDS) and spirituality measured by the Brief Multidimensional Measure of Religiousness/Spirituality (BMMRS).

Results: In the present study PD patients maintain their Faith in spite of the disease severity. Compared to controls yet their religiosity scores were undiminished even though their SDS scores were high. Spiritual experiences and involvement in a religious community were maintained despite decreasing mobility.

Conclusions: We questioned the theory which suggests faith is reduced by degeneration of basal ganglia pathways. We recommend a large scale multicentre study.

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Impulse Control Disorders in Early Onset and Familial PD

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Objective: To characterize impulse control problems in early onset and familial PD (EOPD and FPD). **Background:** Impulse control disorders are a set of pathological behaviours that include hypersexuality, compulsive gambling, shopping and eating (1). We have established a clinical cohort study (Parkinson's Families Project) of people with EOPD or FPD.

Methods: Participants were recruited from 20 UK study sites. Demographic and clinical data were collected using validated scales, together with a DNA sample (2). Impulse control disorders (ICD) and behaviours (ICB) were assessed using the Questionnaire for ICD in Parkinson's short form (QUIP-short).

Results: We have studied 122 participants. 43.4% had EOPD (age at onset =45yrs) and 71% had FPD. Median disease duration was 6 years (IQR=7). 40.1% had evidence of ICD or ICB, of whom 29% had >1 ICD/ICB. Compulsive shopping was the most common (15.6%), followed by compulsive eating (13.9%), hypersexuality (13.1%) and pathological gambling (4.9%). Presence of ICD or ICB was 30.2% in those diagnosed =45yrs, 47.8% in those diagnosed >46. However, there was a lower rate of 34.8% among those diagnosed over 65yrs. 41.5% of participants taking dopamine agonists had ICD/ICB compared to 37.7% not taking dopamine agonists.

Conclusions: This cohort is enriched for EOPD and FPD and we will use this cohort to explore: i) single gene (Mendelian) effects on ICD susceptibility; ii) common variant effects on ICD susceptibility and iii) the relationships between family history of PD, family history of neuropsychiatric disease, and ICD. A particular strength of our study is the ability to integrate detailed genetic, clinical and family history data in rarer PD patient groups.

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Motor and non-motor symptoms in old-age onset Parkinson's disease patients

M. Mendonça, T. Lampreia, R. Miguel, A. Caetano, R. Barbosa, P. Bugalho (Lisboa, Portugal) **Objective:** Understand the role of old-age onset in Parkinson's disease (PD) motor and non-motor phenotype. **Background:** Advancing age is a risk factor for PD. With population aging it is expected that the total number of patients with PD onset at old-age increases.

Methods: We recruited 24 patients with PD onset at or over 75 years-old. Each patient was matched with 1 control patient with PD onset between the ages of 40 and 65, matched for disease duration. Groups were assessed with the UPDRS, the Non-motor symptoms scale (NMSS) and other scales to assess non-motor symptoms. Groups were compared with conditional logistic regression analysis

Results: Old-age onset PD were, on average, 80 years old at the time of PD onset while middle age onset were 59. Disease duration was approximately 5 years in both groups. While no difference was observed in the total UPDRS-III scores, old-age onset PD was associated with higher axial symptoms (7.42 vs. 4.63, p=0.011) and a higher frequency of dementia (7/24 vs. 0/24, p=0.009). While no difference in the total number of non-motor symptoms

was observed (6.79 vs. 6.22, p=0.310), old-age onset patients had a higher prevalence of gastrointestinal symptoms (20/24 vs. 12/24, p=0.037).

Conclusions: For the same disease duration, older age onset is associated with worse axial motor dysfunction and dementia in PD patients. Beside gastrointestinal symptoms, non-motor symptoms are not associated with age

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Profiling the Non Motor Symptoms burden in Parkinson's disease patients in Nigeria

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Objective: To determine the frequency of Non- motor symptoms (NMS) burden using the non-motor symptoms questionnaire (NMSQuest).

Background: Over the years, motor manifestations were more associated with Parkinson's disease (PD) with little or no mention of non-motor components. There is emerging evidence that non-motor symptoms (NMS) present earlier and they are associated with quality of life of individuals. The NMS burden poses a greater care challenge to both the health workers and the caregivers.

Methods: This is a cross sectional study of PD patients on NMS longitudinal Natural Histories study. Specifically, the data of 61 consecutive PD patients that completed NMS questionnaire were analyzed using SPSS software. **Results:** Of the 61 subjects most were males 44 (72.1%) while 17 (27.9%) were females. The mean age of respondents were 68.3 (9.6) and ranged from 39-82 years.. The mean NMSQuest score among respondents were 12.8 (5.2). Most of the respondents had NMS burden 2(55.7%) followed by NMS burden 3(31.2%) and NMS burden 4(13.1%). A higher proportion of respondents with HY stage 1 had disease burden NMS 2 (71.4%) compared to those with NMS 3 (28.6%) and none had NMS 4. Those with H and Y stage 2 had a higher proportion with disease burden NMS 2 (78.4%) compared to those with NMS 3 (13.5%), and NMS 4 (8.1). For those with H and Y stage 3, a higher proportion had disease burden with NMS 3 (66.7%) compared to NMS 4 (33.3%), and none had NMS 2. All respondents with HY stage 4 had NMS 3. This difference was statistically significant with Chi square=32.579 and p value <0.001.



Fig 1: Distribution of non-motor burden and motor stage in Parkinson disease

Fig 2: Mean NMSQuest score by HY stage of disease



Conclusions: This shows that NMSQuest could be a useful tool to screen for NMS burden among PD patients especially in resource poor countries and this can be used to tailor specific treatment for individual patient during clinic visits.

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A global survey of the use and linguistic translation of the NMSQuest and NMSScale: implications for nonmotor studies in Parkinson's disease

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Objective: To collect details of linguistic validations and translations of the non-motor symptoms questionnaire (NMSQuest) and non-motor symptoms scale (NMSScale) globally.

Background: The patient completed Parkinson's disease (PD) NMSQuest and the health-professional completed NMSScale were validated since 2006 and recommended by the MDS and other learned societies for holistic assessment of NMS and their burden. The global range of these tools have not been properly evaluated.

Methods: A specific protocol was developed for a global survey involving relevant members of the MDS Non-Motor-Parkinson's disease-Trainee Junior Subgroup. All reviewed literature, conducted interviews with international collaborators and Mapi was contacted (http://mapigroup.com/) to capture available translations of the NMSQuest and NMSScale.

Results: Translations of NMSQuest were available using linguistic validation in Dutch, French, German, Greek, Italian, Japanese, Malay, Chinese (mandarin), Spanish and Swedish. Investigator translated use of NMSQuest was reported from Thailand, India and Brazil. The NMSScale underwent linguistic validation in Danish, French, German, Italian, Norwegian, Spanish and Swedish. Translated use was reported in Malay, Chinese, Arabic and Brazilian (Portuguese). NMSScale has been used as an outcome measure in several industry-sponsored clinical trials (e.g. Abbvie, Britannia, Lundbeck, Pfizer, Cynapsus, UCB among others). Translations for oral administration of both tools are reported from Arab states, Korea, Egypt, India, Turkey, Taiwan, Tanzania, Nigeria and Mali. **Conclusions:** The use of NMSQuest as a flagging tool and NMSScale as a grading holistic measure of NMS in PD indicates the global reach of these instruments which should be regarded as an essential quality standard for assessment of PD in clinic. Furthermore, they should be routinely included in relevant clinical trials and as such it is crucial that these tools are properly validated in different languages.

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Impulse control disorder and associated clinical factors in drug-naïve Parkinson's disease

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Objective: To investigate various clinical factors associated with Impulse Control Disorders (ICD) in Parkinson's disease (PD) patients who have never been exposed to Dopamine Replacement Therapy (DRT).

Background: DRT, particularly dopamine agonist, is a key risk factor in development of ICD in PD¹. Other clinical factors, namely RBD² and cognitive dysfunction³, have also been implicated by different studies but with conflicting results^{4, 5}. Latter may partly be due to the confounding factor of DRT, which impacts both RBD and cognitive function, in addition to being a key risk factor of ICD. There is one small study which has attempted to study ICD in drug-naïve PD patients and reported its association only with depression.⁶ However, there are no other data on this topic.

Methods: Baseline data of 423 PD and 196 healthy control (HC) subjects from the Parkinson's Progression Marker Initiative (PPMI)⁷ was accessed as of December 1, 2016. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP)-Short Form was used to calculate the prevalence of ICD⁸. Statistical testing was done in SPSS 24 software using Chi-square test and student t-test. We used p value of <0.01, rather than 0.05, to test significance for minimizing impact of multiple testing in this cross-sectional analysis.

Results: The prevalence of ICD was equal at 12.4% in both HC and PD groups. RBD questionnaire score and RBD (classified based on RBD questionnaire score > 5) prevalence (table 1) were significantly higher in PD patients with ICD versus without ICD, compared to a non-significant increase in HC. Geriatric Depression Scale (GDS) score (table 1) was significantly higher for ICD subjects in both PD and HC groups. Of note, there were no significant differences in other clinical factors (table 1) and various cognitive function scores (table 2) in subjects with ICD versus without ICD in either HC or PD. MDS-UPDRS part I score was expectedly higher in PD patients with ICD.

Subject Group	HC		PD			
ICD	No (n=169)	Yes (n=24)	p Value	No (n=369)	Yes (n=52)	p Value
Age (years)	61.08 ±11.33	58.75 ± 11.07	0.346	61.78± 9.63	60.31 ± 9.89	0.303
Gender (male /female %)	64.5/35.5	62.5/37.5	0.849	65.3/34.7	67.3/32.7	0.777
Education (years)	16.09 ± 2.96	16.17 ± 2.28	0.902	15.56 ±3.02	15.40 ± 2.87	0.719
Disease Duration (months)	NA	NA	NA	5.80 ± 7.49	6.00 ± 7.71	0.859
GDS Score	1.14 ± 2.01	2.42 ± 2.49	0.005	2.15 ± 2.33	3.63 ± 2.88	0.000
Depression Prevalence (%)	3.6	12.5	0.052	8.4	17.3	0.042
UPSIT Score	33.88 ± 5.02	34.42 ± 3.79	0.617	22.38 ± 8.32	22.12 ± 7.73	0.831
STAI Score	94.22 ± 6.96	91.75 ± 7.15	0.108	93.44 ± 7.81	92.58 ± 9.72	0.472
RBD Questionnaire Score	2.77 ± 2.89	3.29 ± 1.94	0.287	3.96 ± 2.61	5.29 ± 2.91	0.001
RBD Prevalence (%)	19.0	25.0	0.494	34.9	58.8	0.001
ESS Score	5.47 ± 3.34	6.71 ± 3.90	0.099	5.64 ± 2.38	6.96 ± 2.73	0.010
MDS-UPDRS Part I Score	2.76 ± 2.91	4.21 ± 3.23	0.025	5.26 ± 3.90	7.84 ± 4.50	0.000
MDS-UPDRS Part II Score	0.46 ± 1.05	0.42 ± 0.88	0.832	5.72 ± 4.13	7.21 ± 4.46	0.016
MDS-UPDRS Part III Score	1.17 ± 2.22	1.50 ± 2.17	0.500	21.05 ± 8.94	19.82 ± 8.34	0.353

Table 1: Distribution of various clinical variables in HC and PD subjects with and without ICD. Values are shown as mean ± standard deviation.

Subject Group		HC			PD	
ICD	No (n=169)	Yes (n=24)	F Value	No (n=369)	Yes (n=52)	p Value
MOCA Visuospatial / Executive	4.67 ± 0.61	4.67 ± 0.48	0.939	4.50 ± 0.81	4.46 ± 0.73	0.771
MOCA Naming	2.98 ± 0.15	3.00 ± 0.00	0.449	2.94 ± 0.26	2.94 ± 0.24	0.846
MOCA Attention	5.91 ± 0.31	5.88 ± 0.34	0.661	5.75 ± 0.61	5.79 ± 0.45	0.670
MOCA Language	2.75 ± 0.52	2.58 ± 0.65	0.171	2.57 ± 0.66	2.62 ± 0.57	0.629
MOCA Language Verbal Fluency	14.25 ± 4.40	13.91 ± 4.20	0.728	13.09 ± 4.53	12.71 ± 5.49	0.585
MOCA Abstraction	1.98 ± 0.15	1.92 ± 0.41	0.176	1.86 ± 0.40	1.85 ± 0.50	0.765
MOCA Memory / Delayed Recall	3.88 ± 0.99	3.75 ± 0.90	0.521	3.40 ± 1.42	3.13 ± 1.40	0.209
MOCA Orientation	5.99 ± 0.11	6.00 ± 0.00	0.594	5.97 ± 0.21	5.96 ± 0.19	0.845
MOCA Total Score	28.14 ± 1.13	27.80 ± 1.02	0.159	26.98± 2.38	26.75 ± 2.23	0.520
Letter Number Sequencing Score	10.91 ± 2.64	10.75 ± 2.17	0.783	10.61 ± 2.60	10.35 ± 3.07	0.505
Semantic Fluency	51.89 ± 11.13	51.71 ± 11.88	0.940	48.74 ± 11.79	48.15 ± 10.78	0.734
Symbol Digit Modalities	46.96 ± 10.69	45.42 ± 8.40	0.499	41.07 ± 9.50	42.00 ± 11.08	0.520
HVLT-R Immediate / Total Recall	26.05 ± 4.56	26.54 ± 3.75	0.613	24.54 ± 4.98	23.79 ± 4.94	0.312
HVLT Delayed Recall	9.23 ± 2.34	10.00 ± 1.77	0.124	8.41 ± 2.45	8.00 ± 2.73	0.276
HVLT Retention	0.90 ± 0.18	0.95 ± 0.14	0.214	0.86 ± 0.20	0.84 ± 0.24	0.483
HVLT Discrimination Recognition	9.99 ± 2.88	10.50 ± 2.25	0.406	9.71 ± 2.57	9.10 ± 2.98	0.113
Benton Judgement of Line Orientation Score	13.05 ± 1.95	13.67 ± 2.22	0.154	12.79 ± 2.14	12.67 ± 2.03	0.708

Table 2: Distribution of cognitive function scores in HC and PD subjects with and without ICD. Values are shown as mean ± standard deviation.

Conclusions: RBD is associated with ICD in drug-naïve PD patients. Although it needs to be further investigated whether RBD plays an independent role in development of ICD, present finding may guide clinicians in use of dopamine agonist for treating PD patients with pre-existing RBD symptoms or diagnosis. Cognitive function scores of drug-naïve PD patients with ICD are similar to those without ICD. High score on GDS is associated with ICD in both PD and HC.

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Relationship between sleep profiles and clinical features in Parkinson's disease

Y.Y. Lin, R.S. Chen, C.S. Lu, Y.Z. Huang, Y.H. Weng, T.H. Yeh, W.Y. Lin, J. Hung (Taoyuan, Taiwan) **Objective:** To document the prevalence of sleep disturbance and excessive daytime sleepiness (EDS) in Taiwanese Parkinson's disease (PD) patients and to identify the risk factors and correlations among all evaluated parameters. **Background:** Sleep problem is one of the major non-motor symptoms which considerably impair the quality of daily life in PD. However, the correlations between disturbed sleep parameters and clinical characteristics of PD are still unclear, and the sleep efficiency impact on cognition is debatable. **Methods:** This was a cross-section, questionnaire-based interview study in a tertiary medical center in Taiwan. We collected demography, Unified Parkinson's disease rating scale (UPDRS), Hoehn and Yahr (H/Y)stage, Pittsburgh sleep quality index (PSQI), Parkinson's disease sleep scale (PDSS), Epworth sleepiness scale (ESS), 39-Item Parkinson's disease questionnaire (PDQ-39), mini-mental status examination (MMSE), and Montreal cognitive assessment (MoCA) of PD patients.

Results: 225 PD patients were recruited from January 2011 to December 2015. There were 128 males and 97 females. The onset age was 57.53 ± 9.90 , and disease duration 8.18 ± 5.20 years. This study has four major findings: (1) 53.8% of patients were defined as poor sleeper by PSQI > 5. And 26.3% of patients had EDS; (2) The poor sleepers had significant worse scores compared with good sleepers (UPDRS part I and part II p< 0.00; UPDRS part III p= 0.004; MMSE p= 0.039; PDSS p< 0.001; PDQ-39 p<0.001), but there was no differences in MoCA score (p=0.057); (3) EDS had correlation with advanced H&Y stage (p= 0.032) and usage of dopamine agonists (p= 0.02). Nevertheless the levodopa equivalent daily dose (p= 0.67) and hypnotics (p= 0.851) did not play a role in EDS; (4) The most significant predictor of poor sleepers was PDSS questionnaires by using logistic regression analysis (p< 0.001, OR= 0.909). The PDSS score 126 could be a cutoff points to predict if a PD patient a poor sleeper or not (< 126.25, sensitivity 62.8%, specificity 89.4%). Among PDSS, nocturnal PD symptoms and psychosis were the major contributions to poor sleepers.

Conclusions: The prevalence of poor sleepers in Taiwanese PD patients is similar to western countries, but the ratio of EDS is significantly lower than Caucasian PD patients. Sleep disturbance could be an important factor to affect motor symptoms, cognition, and life quality of PD patients even in early stage of the disease.

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Emergence of Non-motor Fluctuations with Reference to Motor Fluctuations in Parkinson's Disease *A. Kim, Y. Kim, A. Kim, C.W. Shin, B. Jeon, H. Kim (Seoul, Korea)*

Objective: To examine the timing of emergence of non-motor fluctuations (NMF) with reference to motor

fluctuations (MF) in Parkinson's disease (PD).

Background: NMF and MF are very frequent in patients with Parkinson's disease (PD) receiving long-term medical treatment. Their incidence and timing have not been examined in a prospective study.

Methods: A total of 334 patients with PD who had neither MF nor NMF were recruited. The "SNUH-Fluctuation Questionnaire" consisting of 29 items (9 on MF and 20 on NMF) was administered every 6 month in the outpatient clinic for 3 years. Age, gender, age at PD onset, disease duration, total levodopa equivalent daily dose, and Hoehn & Yahr stage at baseline were collected. A total of 334 patients with PD who had neither MF nor NMF were recruited. The "SNUH-Fluctuation Questionnaire" consisting of 29 items (9 on MF and 20 on NMF) was administered every 6 month in the outpatient clinic for 3 years. Age, gender, age at PD onset, disease duration, total levodopa equivalent daily dose, and Hoehn & the outpatient clinic for 3 years. Age, gender, age at PD onset, disease duration, total levodopa equivalent daily dose, and Hoehn & Yahr stage at baseline were collected.

Results: 60 patients were excluded from the study (9 with alternative diagnosis during follow-up, 41 with poor Mini Mental Status Examination scores (MMSE<26), 3 with comorbidity such as cancer or epilepsy, and 7 who withdrew consent. 274 out of 334 patients were eligible for Kaplan-Meire survival analysis of symptom fluctuations. MF were more frequent and developed earlier than NMF (cumulative survival of 0.527 for MF and 0.597 for NMF at 36 months follow-up). [Figure 1] 183 patients (90 males and 93 females) were included for subgroup analysis according to the timing of development of fluctuations. MF and NMF developed simultaneously in 47 (25.8%), MF first in 42 (23.1%), and NMF first in only 3 (1.7%). 91 (50%) did not develop either MF or NMF. The age of onset and age at enrollment tended to be younger in the fluctuators. The most frequent MF and NMF manifestation was bradykinesia and fatigue respectively both at the onset of fluctuations and during the entire follow-up period. [Table 1]

		Fluctuation profile					
Variable	Never	Simultaneously	Motor first	Nonmotor first	P value		
N (%)	91 (50.0)	47 (25.8)	42 (23.1)	3 (1.7)			
Male (%)	45 (49.5)	23 (48.9)	20 (47.6)	2 (66.7)	0.938		
Age of onset	59.57±7.73	55.53±9.44	57.24±8.24	61.00±7.00	0.056		
Age (year)	61.74±7.94	57.77±9.63	59.21±8.24	62.67±7.51	0.068		
Disease duration (year)	217±1.42	223±1.37	198±122	1.67±1.15	0,763		
Total LEDD (mg/day)	396.83±286.17	447.82±257.66	475.60±315.09	402.50±206.81	0.449		
H&Y	1.46±0.59	1.17±0.41	138±0.48	N/A	0.453		



Conclusions: NMF usually develop later than MF in PD, but can develop earlier than MF in a small number of patients.

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Female reproductive factors and clinical features of PD

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Objective: The aim of this study is to explore the potential effect of reproductive factors on the clinical features of Parkinson's disease (PD) from a large cohort of Chinese population.

Background: Estrogen not only plays a key role in the risk of developing PD, but also influences the severity of the disease.

Methods: A cross-sectional analysis on 264 female Chinese patients with PD was conducted. The motor symptoms, non-motor symptoms and quality of life of patients with PD were measured with different assessment scales. The reproductive factors including age at menarche, age at final menstrual period and reproductive lifespan were recorded.

Results: Of 264 patients, 68 PD patients (25.75%) reported that the onset of PD were before menopause. Correlative analysis indicated that age at menarche was positively associated with Unified Parkinson's Disease Rating Scale (UPDRS) Part III (r=0.200, p=0.811), Montreal Cognitive Assessment (MoCA) (r=-0.174, p=0.029), Hamilton Depression Rating Scale (HAMD) (r=0.192, p=0.019), Hamilton Anxiety Rating Scale (HAMA) (r=0.199, p=0.282) and Beck Depression Inventory(BDI)(r=0.282, p=0.001) scores, and age at menopause was correlated with PD Questionnaire 39(PDQ-39)scores (r=-0.168, p=0.036). Similarly, reproductive lifespan was positively associated with UPDRS ? (r=-0.198, p=0.013), MoCA (r=0.165, p=0.038), PDQ-39 (r=-0.231, p=0.004), Non-Motor Symptoms Scale (NMSS) (r=-0.232, p=0.004), HAMD (r=-0.173, p=0.035), HAMA (r=-0.215, p=0.009) and BDI (r=-0.274, p=0.001) scores.

Conclusions: Reproductive factors including age at menarche, age at menopause and reproductive lifespan were related to motor symptoms, non-motor symptoms and quality of life in PD, but not related to age at onset.

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Evaluating non-motor fluctuations in Parkinson's disease using a visual analogue scale

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Objective: To further understand non-motor fluctuations (NMF) and their relationship to other symptoms of Parkinson's disease (PD) in a deep brain stimulation (DBS) population.

Background: Non-motor symptoms (NMS) in PD are prevalent, affect a wide range of autonomic, mood, and cognitive symptoms, and are associated with worse quality of life. Similar to individuals with motor fluctuations, some have NMS only during the OFF state. The clinical characteristics of those with NMF remain under-explored and there are few tools designed specifically to examine NMF. Previous work suggested the validity of using a visual analogue scale (VAS), we developed our own VAS to examine NMS during the OFF and ON medication states as an initial step towards understanding NMF in DBS candidates.

Methods: As part of an evaluation for DBS, individuals with PD were given the FLU-VAS, a questionnaire involving 10 common non-motor symptoms rated on a scale from 0 (minimal) -100 (severe). Questions were completed during the OFF state and later during the ON state, and scores for 10 questions were added together to provide the total. Additionally, motor severity in the ON and OFF states was obtained (UPDRS), and all patients underwent neuropsychiatric evaluation.

Results: In this ongoing study, 52 subjects thus far have completed the FLU-VAS in both the OFF and ON state. Subjects were 64.8 years old with 9.6 years of disease duration on average (sd = 9.3 and 4.2, respectively). NMS-OFF were more severe in women than men (p = 0.041), younger vs. older age (p = 0.032), and those with increased motor severity (p = 0.036). NMF did not show a relationship with gender, age, or UPDRS-III. Postural-instability and gait-disorder (PIGD) phenotype was associated with more severe NMS-OFF and greater NMF vs. tremordominant (TD) phenotype (p = 0.011 and 0.033). Global cognition (MoCA) and depression (BDI-II) scores did not correlate with NMS or NMF, though anxiety (BAI) was associated with NMS severity in both ON and OFF state (r2 = 0.18 and 0.16, p = 0.011 and 0.005).

Conclusions: Non-motor response to medication is not well captured from other scales and is important to assess. Motor response does not necessarily predict non-motor response, though NMS tend to be worse in the PIGD subtype and those with anxiety. Understanding NMF in PD is an important initial step towards determining whether NMF can be expected to improve via DBS treatment.

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Genetic susceptibility associated to impulse control disorders and compulsive behaviors in Parkinson's disease from a Spanish population

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Objective: Our aim was to identify if there is any difference in the genetic variants linked to an increased susceptibility to suffer impulse control disorders (ICDs) or compulsive behaviors (CBs) in Parkinson's disease (PD) compared to healthy controls (HC).

Background: ICDs and CBs are non-motor symptoms that frequently appear in PD. The treatment with dopamine agonists are markedly linked to both conditions. Nevertheless, a susceptibility genetic background has been described in PD patients since some variants in dopamine metabolism genes seem to be involved in increasing the risk of develop ICDs and CBs.

Methods: We included 365 PD patients (60% males, 64.8±11.5 years) and 382 HC (50.7% males, 59.5±15.3 years). ICDs and CBs were assessed using QUIP-RS questionnaire. Demographic data were recorded in both groups. Clinical features and dopamine replacement therapy data were collected in PD group. Variants in *DRD2* (rs1800497, rs1800496), *DRD3* (rs6280), *COMT* (rs4680), *GRIN2B* (rs1806201, rs7301328) and *HTR2A* (rs6313) were analyzed in both groups. The genotyping was carried out using the TaqMan technology. Allelic association study was done using PLINK software.

Results: ICDs and CBs were more frequent in PD compared to HC (p<0.001). Adjusted by age and sex this result remained significant. In HC some variants (rs6280, rs1806201, rs4680 and rs6313) had a tendency to influence in isolated ICDs or CBs. In the PD group, the variant rs6313 in *HTR2A* was associated to a higher susceptibility to suffer ICDs (p=0.04). Accounting by specific ICDs and CBs, this variant was significantly associated to gambling, hypersexuality, compulsive shopping and hobbysm.

Conclusions: Some variants may influence in ICDs or CBs in PD and HC. The polymorphism rs6313 in *HTR2A* (serotonin receptor) may act on the serotonin function and have an important impact on ICD and CBs in PD.

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Diagnosis of irritable bowel syndrome increases risk of Parkinson's disease in the Finnish population *T. Mertsalmi, E. Pekkonen, F. Scheperjans (Helsinki, Finland)*

Objective: To assess risk of Parkinson's disease in patients with irritable bowel syndrome in the Finnish population. **Background:** The majority of Parkinson's disease (PD) patients suffer from gastrointestinal symptoms of which constipation is considered the most prominent. Recently, in addition to constipation, irritable bowel syndrome (IBS) was also found to be associated with increased PD risk in Taiwan. IBS is a disorder of gut-brain interaction characterised by abdominal pain and alteration of bowel habits. We wanted to test the hypothesis that a diagnosis of IBS is a risk factor for PD in the Finnish population.

Methods: We conducted a retrospective cohort study with 9563 IBS patients and 33,563 controls using the data from the Finnish Care Register for Health Care (HILMO). The study population was defined as all patients (aged 20 years or older) discharged from inpatient care, day surgeries or specialised outpatient care at least two times with diagnosis of IBS during 1998-2014. For each IBS patient, 4 reference patients of same age (\pm 1 year), sex and born in the same municipality were sought. The controls were matched by index date of diagnosing IBS. All subjects with a diagnosis with inflammable bowel disease, celiac disease, colorectal neoplasms or other movement disorders before or during the follow-up period were excluded from the study. Also patients diagnosed with PD before the index date were excluded. The hazard ratio for PD was assessed by a Cox proportional hazards model.

Results: After exclusions, the ratio of controls to IBS patients was 3.56:1. The demographic data of subjects is presented in Table 1. The PD incidence ratio per 10 000 person years was 4.12 for IBS patients and 2.12 for controls. The unadjusted hazard ratio (HR) for PD was 1.941 (95% CI: 1.225-3.007) for IBS patients compared to controls (p = 0.005). When adjusted for potential confounders age, gender, hypertension, diabetes, depression, peptic ulcer and history of transient ischemic attack or stroke, the HR was 1.942 (95% CI 1.233-3.058) for IBS patients (p = 0.004). [Table 1]

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	IBS	Control	р
Number of subjects	9563	33563	
Female (%)	71.5	72.6	0.033
Age, mean (years ±SD)	49.32 ±17.01	49.41 ±17.05	0.665
Follow-up, mean (years ±SD)	7.36 ±4.44	7.30 ±4.42	0.225

Table 1 – Selected demographic data of subjects

IBS= Irritable Bowel Disease, SD = Standard Deviation

Conclusions: IBS appears to be an independent risk factor for PD in the Finnish population. Constipation is a known premotor symptom of PD. Our results indicate that patients may also have other gastrointestinal premotor symptoms prior the diagnosis of PD.

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Autonomic dysfunction in early Parkinson's disease: cross-sectional study in Hoehn and Yahr stage 1

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Objective: To define frequency, severity and predictors of dysautonomia in patients with Parkinson's disease (PD) at the stage of hemiparkinsonism with disease duration less than 2 years.

Background: Autonomic failure may be present at the time of PD diagnosis. Relatively little data is available on specific profile and clinical correlates of dysautonomia in early PD.

Methods: The study comprised 112 PD patients and 79 healthy controls (HC). Autonomic dysfunction was assessed using SCOPA-AUT. Each subject underwent clinical and cognitive evaluation with MDS-UPDRS and ACE-R and screening for depression, anxiety, and apathy.

Results: PD patients had more cardiovascular, gastrointestinal, urinary, genital and thermoregulatory dysfunction compared to HC. Nocturia (37.5%) and impotence (37.9%) followed by constipation (29.46%) were the most frequent symptoms in PD patients. Twenty-two (27.67%) PD patients had one, 21 (18.75%) had two and 19 (16.96%) had three autonomic systems impaired. Total score of autonomic dysfunction correlated to age, total depression, anxiety, apathy scores and LED. No correlation to the UPDRS-motor score and total ACE-R score was found. The multivariate linear regression model was run to predict total SCOPA-AUT score from age, depression, apathy, anxiety and LED. Only age and HDRS score appeared to be statistically significant predictors of higher total scores of autonomic dysfunction. Older age and depression were predictors for gastrointestinal, urinary and sexual dysfunction. Higher motor scores contributed significantly to the sexual dysfunction domain together with depression and age, while higher doses of dopaminergic medications appeared to be the only significant predictor of cardiovascular dysautonomia in the initial motor stage of PD.

Conclusions: In addition to constipation which is well recognized as an early autonomic feature of PD, other symptoms of dysautonomia are present in a significant number of patients in early disease course. This is a longitudinal study and we believe to report the follow-up analysis data soon.

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What impacts relationship satisfaction in Parkinsonian dementias?

S. Vatter, K. McDonald, S. McCormick, I. Leroi (Manchester, United Kingdom)

Objective: To explore which aspects of well-being impact on marital relationship satisfaction among people with Parkinsonian dementias and their spouses.

Background: Dyadic relationships in Parkinson's disease (PD) are described as mutual and close but, due to the complex nature of the motor and non-motor symptoms, face challenges that can transform a partnership into 'caregiver – care recipient' roles. Depression and apathy significantly predict and contribute to caregiver burden, and this can negatively impact on relationship satisfaction. As such, it is important to investigate the impact of physical, emotional and mental well-being factors on the dyadic relationship satisfaction, which has not been previously explored in Parkinsonian dementias.

Methods: Participants with Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB) and their spouses are being recruited to this cross-sectional study. Measures of physical, emotional and mental well-being, caregiver burden and stress and relationship satisfaction are collected and the associations among these variables, with respect to relationship satisfaction, are explored.

Results: Interim results revealed that people with PDD or DLB who had shorter disease duration, lower disease severity and higher health-related quality of life were more satisfied with their relationship. In contrast, greater relationship satisfaction of spouses was associated with lower levels of anxiety, depression, burden and stress. Interestingly, higher apathy in people with PD was the only neuropsychiatric symptom that significantly contributed to both patients' and spouses' lower relationship satisfaction. Overall, spouses were less satisfied with their marital relationship than their partners.

Conclusions: Relationship satisfaction is associated with physical well-being in people with PDD or DLB and with mental and emotional well-being in spouses. Further analyses among relationship satisfaction and key behavioural variables are being sought.

These unpublished results have been presented at the Parkinson's UK conference on November 7, 2016.

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Investigating the association between anxiety and cognitive impairment in Parkinson's disease: A descriptive study

A. Toft, J. Yang, G. Byrne, J. O'Sullivan, L. Mitchell, D. Copland, N. Dissanayaka (Brisbane, NSW,Australia) **Objective:** This study investigated the relationship between anxiety and cognitive impairment in PD. **Background:** Anxiety and cognitive impairment are prevalent non-motor complications in PD. The average prevalence of anxiety is 31%, while 80% of advanced PD patients develop dementia. Recent evidence suggests higher anxiety rates in newly diagnosed PD with mild cognitive impairment (MCI)¹. This study further evaluates this relationship in PD using standardized measures of anxiety and MCI.

Methods: Thirty (N=30) PD patients were examined for anxiety according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria and for cognitive impairment using a comprehensive neuropsychological test battery based on standard criteria². Deficits in specific cognitive domains were identified when a patient scored =1SD below normative values on =1 test, and MCI was classified when a patient scored =1SD below normative values on =2 tests.

Results: Twelve patients (40%) had an anxiety disorder and 20 patients (66.7%) had MCI. Twenty-eight patients (93.3%) were impaired in =1 cognitive test with impairments in attention and memory being the most common; 22 patients (73.3%) were impaired in =1 test assessing attention, and 16 (53.3%) in =1 test assessing memory. Seven patients (23.3%) had both an anxiety disorder and MCI. Of patients that had an anxiety disorder (n=12), 7 were impaired in =1 test assessing attention, 4 in =1 test of memory, 3 in =1 test of language, 1 in = 1 test of executive function, and none in a test of visuospatial function.

Conclusions: The frequency of comorbid anxiety and MCI found in this study (23.3%) is higher than reports in non-PD populations (10%), highlighting the importance of examining the association in PD. Deficits in attention and memory were the most common in this PD patient sample, and in those with a DSM-5 anxiety disorder. Further research in a larger sample size is required to further understand the association between anxiety and cognitive subtypes in PD. This has the potential to aid identification of PD subtypes for targeted treatment, and development of synergistic treatments, enhancing PD patient's quality of life.

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Non-motor symptoms in patients with Parkinson's disease, essential tremor and both diseases – a group comparison

I. Wurster, A. Abaza, K. Brockmann, M. Rüdiger-Albers, S. Lerche, D. Berg (Tübingen, Germany) **Objective:** To evaluate non-motor symptoms in patients with essential tremor (ET), tremor-dominant Parkinson's disease (PD) and those suffering from both diseases (ET-PD).

Background: ET is the most common movement disorder and PD represents the second most frequent neurodegenerative disorder. In various studies, patients with ET have been observed to have an increased risk of developing PD during their lifetime. Some non-motor symptoms, known to occur in the prodromal phase of PD, have also been identified in individuals with ET. It is tempting to speculate that these particular ET patients may be more likely to develop PD, whereas the majority of ET patients may be more likely to stay PD-free during their life time.

Methods: 44 patients with ET, 19 patients with PD and 18 patients with ET-PD, according to established criteria, were included. All groups were matched for age and the PD groups for duration of PD. Non-motor symptoms were evaluated using the Montreal Cognitive Assessment, Mini Mental Status Examination, the Beck Depression Inventory, REM sleep behavior disorder screening questionnaire, Parkinson Disease Sleep Scale, Sniffin' Sticks, Unified Parkinson's Disease Rating Scale I-II and United Multiple System Atrophy Rating Scale I (UMSARS). Results: According to the non-motor profile, ET-PD patients did not differ from the PD group. Compared to the ET-PD and PD, the ET patients presented less dysfunctions in Sniffin' Sticks in activities of daily living, in sleep scales as well as in the UMSARS.

Conclusions: PD patients with and without preceding ET show similar non-motor profiles. ET patients present with less non-motor symptoms than ET-PD and PD. Longitudinal comparisons to healthy age-matched controls are needed in order evaluate prevalence, severity and progression of non-motor symptoms in order to identify those ET patients who are at a risk of developing PD.

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Excessive daytime sleepiness in Parkinson's disease: Risk factors and clinical associations

O. Babkina, O. Levin, M. Poluektov (Moscow, Russia)

Objective: To examine the frequency and risk factors of excessive daytime sleepiness (EDS) in patients with PD and to determine relationships between EDS and another symptoms of PD.

Background: EDS is a frequent symptom in PD and seems to be multifactorial by nature. The risk factors of EDS and associations with other symptoms are not investigated enough.

Methods: PD patients $[N=32 (18M); 64.7\pm6.3 \text{ years old}; 4.4\pm3.15 (0.3-12) \text{ years motor disease duration, HY range 1-3, and mean MoCA score 25.5±1.9 (22-29)] underwent clinical evaluation including the Epworth Sleepiness Scale (ESS) and the Parkinson's Disease Sleep Scale - 2 (PDSS-2), the Hoehn and Yahr scale and the MDS-Unified Parkinson's disease rating scale (MDS-UPDRS), the Parkinson's disease questionnaire (PDO-39),$

Schwab and England Activities of Daily Living Rating (SE-ADL) and Hospital anxiety and depression scale (HADS). EDS was diagnosed according to the ESS, cutoff score above ten was applied. All patients with EDS underwent one night video polysomnography study and the multiple sleep latency test (MSLT).

Results: 50% of patients had EDS. Baseline characteristics were similar between patients with and without EDS. Patients with EDS had higher PDSS-2 score (p=0.002), more prominent autonomic dysfunction and cognitive impairment (p=0.01), worse quality of life and lower daytime activity (p<0.01). EDS was associated with higher levodopa equivalent dose (LED) (633.8 versus 280.0; p=0,002), longer duration of therapy and Part I, II and total MDS-UPDRS higher score (p=0.01). The mean time of sleep was 6.7 ± 1.1 hours, index of sleep quality was $76.2\pm12.7\%$. Patients had reduced amount of deep wave sleep and a lot of awakenings. 31% had obstructive sleep apnea (OSA), but mean oxygen saturation was 93.8 ± 1.3 . The mean sleep latency (SL) was 7.5 ± 4.3 min. Correlation between the apnea-hypopnea index (AHI) and mean SL was not found.

Conclusions: E EDS occurs in 50% of patients with PD and associated with higher MDS-UPDRS score, more frequent autonomic dysfunction, cognitive impairment, higher LED, lower quality of life and daytime activity. Patients with EDS have fragmented sleep, but sleep duration is sufficient. 31% of patients had AHI>5, that indicates a wide frequency of OSA in PD and a potential role in genesis of EDS. However, SL values in such patients and absence of oxygen desaturation profile of OSA suggest the "abortive" OSA.

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AAV-mediated human alpha synuclein overexpression in the locus coeruleus (LC) leads to a neuronal loss in the nucleus ambiguus of mouse

B. Lee, M. Henrich, W.-H. Chiu, L. Matschke (Marburg, Germany)

Objective: To investigate the impact and temporal aspects of the neuronal loss in the LC neurons induced by alpha-synucleinopathy.

Background: In the Braak staging model of Parkinson's disease (PD), Lewy pathology progresses in a caudorostral pattern from the locus coeruleus (LC) to the substantia nigra (SN). The impact and temporal aspects of the neuronal loss in the LC neurons induced by alpha-synucleinopathy has neither been reported nor used as a prodromal animal model of PD.

Methods: We have performed a unilateral microinjection of recombinant adeno-associated viral vectors (rAAV) carrying human WT-aSYN, A53T-aSYN or luciferase as a control reporter in male C57Bl/6 mice. In total 1.25 μ l volumes of rAAV vectors were delivered in the right hemisphere of the LC at coordinates (from dura) AP -5.4 mm, ML -0.9 mm, DV -3.7 mm. Eight animals in each group were sacrificed 3 weeks post the injection by a transcardial perfusion of PBS followed by ice-cold 4% paraformaldehyde. Immunohistochemistry for tyrosine hydroxylase (TH) for the LC and choline acetyltransferase (ChAT) for the medulla oblongata was performed to quantify neurons using stereological analysis.

Results: 3 weeks post aSYN overexpression we have found an approximate 16% neuronal loss of the LC in the injected hemisphere of rAAV WT-aSYN and A53T-aSYN compared to the non-injected side. The relative numbers of LC neurons in each hemisphere of WT-aSYN or A53T-aSYN group were significantly decreased when compared to that of rAAV-luciferase injected. In addition, we discovered that the number of ChAT positive neurons in the rostral nucleus ambiguus also significantly decreased in both rAAV WT-aSYN and A53T-aSYN injected animals, when compared to that of rAAV-luciferase injected.

Conclusions: rAAV WT-aSYN or A53T-aSYN overexpression in the LC caused a significant neuronal loss in the LC as early as three weeks post injection. Moreover, aSYN seems to play a role in the cell viability of neurons in the nucleus ambiguus. This result may imply a potential direct or indirect role of noradrenergic neurons in modulating motor innervation of the upper gastrointestinal system.

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Histological analysis of a-synuclein pathology in the circadian system in Parkinson's disease

E. De Pablo-Fernandez, J. Holton, T. Warner (London, United Kingdom)

Objective: Assessment of severity of a-synuclein pathology in the circadian system in patients with Parkinson's disease (PD).

Background: Circadian system is responsible for the 24-hour rhythm of physiological function. The central pacemaker is located in the suprachiasmatic nucleus (SCN) of the hypothalamus which regulates the production of melatonin (the main endogenous entraining agent) by the pineal gland. Evidence suggests a disruption of the circadian system in PD with important clinical implications in motor and non-motor symptoms. Although a disruption of melatonin secretion has been shown, the neuroanatomical site of dysfunction of the circadian system in PD remains unclear.

Methods: Formalin-fixed hypothalamic and pineal tissue was obtained from patients with a histological diagnosis of PD and sex- and age-matched healthy controls from the Queen Square Brain Bank archive. Vasointestinal peptide immunohistochemistry was used for identification of the SCN. a-Synuclein immunohistochemistry severity was assessed in the SCN and pineal gland tissue using a semiquantitative score (0-4) as per neuropathological criteria. **Results:** A total of 13 SCNs and 17 pineal glands (from a total of 28 PD patients) were compared with 4 SCNs and 7 pineal glands from 11 controls. a-Synuclein pathology was present in 9 (69.2%) of the SCNs of PD patients but in

none of the controls (p = 0.025). a-Synuclein pathology was only present in the pineal gland of 2 PD cases (11.8%) but in none of the controls, and its severity did not show any significant differences (p = 0.354).

Conclusions: Our study shows that Lewy body pathology is significantly more severe in the SCN but not in the pineal gland in PD patients comparing with healthy controls. These findings suggest that disruption of central regulation within the SCN (rather than melatonin production by the pineal gland) may be responsible of the altered circadian melatonin output in PD.

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Parkinson's disease phenotype across different ethnic groups: comparison of non-motor symptoms in patients living in the United Kingdom and Mexico

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Objective: The aim is to compare and contrast clinical profiles between UK-White Caucasian (UK-WC), UK-Asian, UK-Black African Caribbean (UK-BAC) and Mexican people with Parkinson's disease (PD) (PwP). **Background:** Ethnic differences in PD phenotype (particularly non-motor symptoms (NMS)) are poorly understood.

Methods: Demographics as well as motor, quality of life and non-motor data assessed with validated tools were recorded, as well as nutrition habits.

Results: The mean demographics and results are shown in table 1. Demographics differ between groups with a lower mean age and mean age at onset in the Mexican group and more males in the UK-Asian group. UK-Asian and UK-BAC and Mexican PwP had higher NMSScale (NMSS) total scores compared to UK-WC PwP. The UK-BAC and UK-Asian patients reported worse quality of life compared to the UK-WC and Mexican cohort. The UK-WC PwP consumed more alcohol (mean units per day 5.3 ± 9.4) compared to UK-Asian (2.19 ± 4.5), UK-BAC (0.4 ± 1.1) and Mexican PwP (0.3 ± 0.9).

Ethnicity	UK-WC	UK-BAC	UK-Asian	Mexican
Number	122	38	32	60
Mean age (years)	67.3±12.4	68.2±12.0	64.5±11.1	62.8±11.8
Mean disease duration (years)	6.1±5.2	3.8±3.1	6.2±5.1	6.7±4.2
Mean age at PD onset (years)	61.2±13.2	64.3±13.1	58.3±12.0	56.1±11.6
Male %	63.1	65.8	71.9	63.3
Mean SCOPA- Motor total	16.8±9.2	19.7 <u>±</u> 8.1	19.3±12.1	17.1±7.2
Mean NMSS total	35.5±28.7	46.9±37.8	48.5±52.3	42.9±31.5
Cardiovascular/ falls	1.7±2.8	1.7±2.9	1.9±2.8	1.1±2.3
Sleep/fatigue	7.1±6.8	9.2±8.6	9.7±9.5	9.2±10.0
Mood/cognition	6.1±9.4	8.3±11.7	10.2±12.4	9.1±13.4
Perceptual problems	1.4±3.2	1.4±3.6	2.1±4.4	1.7±5.5
Attention/ memory	4.4±5.7	3.7±4.8	4.8±7.1	3.7±4.6
Gastrointestinal tract	3.3±4.7	3.5±3.8	5.3±7.5	4.6±5.7
Urinary	5.4±7.0	9.9±10.4	6.0±9.4	7.0±9.8
Sexual function	0.9±2.9	2.2±5.0	1.7±4.8	1.5±4.4
Miscellaneous	5.2±6.1	6.9±6.7	6.8±9.2	5.0±6.8
Mean PDSS total	108.8±22.6	105.8±29.7	102.2±32.7	112.2±26.2
Mean PDQ-8 total	7.5±6.0	9.0±7.0	10.6±7.4	7.7±4.6

Table 1 Demographics and clinical profiles

WC = White Caucasians, PD = <u>Parkinson's Disease</u>, NMSS = Non-Motor Symptoms Scale, PDSS = Parkinson's Disease Sleep Scale, PDQ-8 = Parkinson' Disease Questionnaire

Conclusions: These preliminary findings suggest that clinical profiles may possibly differ across different ethnic groups. We are now exploring the detailed presentation as well as underlying mechanisms.

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A new aroma in the new world

H. Fajardo, A. Medina, P. Gomez, R. Medina (Tegucigalpa, Honduras)

Objective: Investigate if olfactory impairment in PD patients are related with other non-motor symptoms **Background:** Non-motor symptoms (NMS) can precede Parkinson's disease (PD) motor phenomenology, like impaired olfaction. Recently, olfactory assessment has been included as one of the supportive tests of the International Parkinson and Movement Disorder Society (MDS) clinical diagnostic criteria for PD. Despite the fact of its certainty in PD diagnosis, an olfactory screening is not included in the MDS-UPDRS-I non-motor aspects of daily living, due that olfaction can not be routinely evaluated by a questionnaire. Different methods for assessing olfaction have been developed. In Honduras, as well as other regions of Central America, olfactory testing has not been assessed neither non-motor symptoms; the relationship between each NMS is inconclusive.

Methods: Olfaction was evaluated in 30 consecutive unselected nondemented patients, fulfilling UKPDSBB criteria for PD using Sniffin' Sticks Test (SST) in San Felipe Hospital Tegucigalpa, Honduras. Olfaction was classified as normosmic or impaired olfaction depending on age and sex cutoffs of SST. Non-motor symptoms were evaluated using MDS-UPDRS-I. Relationships between olfactory groups and non-motor symptoms was evaluated by Fishers exact test and Bivariate correlation between SST and UPDRS-III was performed.

Results: 53.3% were male. Mean age was 67 ± 11 years, and mean MDS-UPDRS-III ON score was 30.1 ± 15.13 . The mean onset of disease was 61 ± 13.3 years. The gap between symptoms onset and initiation of dopaminergic replacement therapy was 5.27 ± 5.26 years and we found a mean LEDD of $2,375\pm1,541$, in addition 36.6% had less

than equal to primary schooling. Overall frequency of impaired olfaction in PD patients was 70%. No correlation was found between olfaction and schooling (p>0.1). The most frequent NMS screened was cognitive impairment, followed by fatigue. Relationship was found between impaired olfaction and cognitive impairment (p < 0.05) but not between other non-motor symptoms. No correlation was found between olfactory impairment and UPDRS-III score. **Conclusions:** Olfactory assessment shows to be reliable and is not affected by schooling. Relationship between impaired olfaction and cognition was found. Ongoing of this study continues using specific scales for each non-motor symptom.

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Gender differences in motor and non-motor features across the Parkinson's disease spectrum

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Objective: To examine how gender differences influence the motor and non-motor features across the Parkinson's disease (PD) spectrum.

Background: There is evidence of male predominance in PD, however less is known about the role of gender in the heterogeneous clinical presentation of PD. The Movement Disorder Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), a recommended scale by the NIH Common Data Elements, provides a uniform way to capture PD features including its motor features and motor and non-motor experiences of daily living across studies.

Methods: We examined MDS-UPDRS Parts I-IV administered in a large cohort (n=1,321) drawn from three studies: the MDS-UPDRS Clinimetric testing program (CTPS), the Rush PD-Cognitive Behavioral Imaging study (PD-CBI), and the Parkinson's Progression Markers Initiative (PPMI). We classified motor phenotypes by tremor dominant/postural instability gait disorder (TD/PIGD) ratios. Using published MDS-UPDRS factor structures (Goetz et al., 2008), we examined gender differences in TD/PIGD phenotype using Chi-square statistic and individual factors from Parts I-IV using a multivariate general linear model controlling (MANCOVA) for age and disease duration.

Results: The cohort was 64.8% male and 35.2% female, with mean (SD) age of 68.71 (10.91) and 68.86 (12.08) years and disease duration 6.44 (6.31) and 6.54 (8.22) years, for men and women respectively. PD onset age and disease duration differed by gender, while TD/PIGD classifications did not. Males scored worse on MDS-UPDRS Part II Factor 1 (fine motor functions) (p < 0.0005), Part III Factors 3 (rigidity) (p = 0.003) and 6 (upper extremity tremor) (p = 0.012), while females scored worse on Part I Factor 2 (depression, anxiety, apathy) (p = 0.011), Part II Factor 3 (dressing, hygiene, walking, balance, freezing) (p = 0.024), Part III Factors 5 (upper extremity bradykinesia) (p = 0.019) and 7 (lower extremity bradykinesia) (p = 0.010).

Conclusions: Based upon the MDS-UPDRS, gender may affect certain aspects of motor and non-motor features and experiences of daily living in PD. Recognition of worse fine motor functions, rigidity, and upper extremity tremor in males and worse mood, dressing ability and bradykinesia in females may influence treatments in PD in the future.

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Pain and Parkinson's disease

H. Wilson, T. Yousaf, G. Pagano, M. Politis (London, United Kingdom)

Objective: We aimed to explore clinical correlates and risk factors in the development of pain, alongside the relationship between pain and striatal dopaminergic dysfunction in early *de novo* Parkinson's disease (PD) patients. **Background:** Pain is a very common and troublesome non-motor symptom in PD. Pathophysiology underlying pain in PD is unclear and whilst studies have evaluated factors influencing PD pain, there is no consensus for clinical measures and biomarkers associated with pain in PD.

Methods: Using the Parkinson's Progression Markers Initiative database, we assessed and compared semiquantified [¹²³I]FP-CIT SPECT as a marker of dopamine transporter (DAT), cerebrospinal fluid (CSF) markers and motor and non-motor features from two groups of early *de novo* PD patients with pain (n=220) and without pain (n=200). We explored clinical and imaging correlates of pain and the predictive significance of these markers in the development of pain in Parkinson's patients without pain.

Results: Parkinson's patients with pain were more depressed (P=0.002), had reduced quality of life (P<0.001), and increased apathy (P=0.001), sleep disturbances (P<0.001) and fatigue (P<0.001) compared to patients without pain. The severity of pain was associated with depression (r=0.206; P<0.001), UPDRS-I Total (r=0.302; P<0.001), apathy (r=0.192; P<0.001), sleep disturbances (r=0.255; P<0.001), fatigue (r=0.299; P<0.001). Cox multivariate analysis, including all clinical and imaging data, revealed that sleep disturbances (P=0.011) and fatigue (P=0.011) are

predictors of the future development of PD pain. In early stages, the presence of pain does not predict motor progression or cognitive decline.

Conclusions: Our findings indicate that pain in early *de novo* PD is associated with higher non-motor burden scores. Sleep disturbances and fatigue are predictors for pain development.

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Long-term levodopa therapy accelerates the circadian rhythm dysfunction in 6-OHDA rat model

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Objective: We aimed to study the effect of L-DOPA on circadian rhythms in 6-OHDA lesioned rats, and to clarify whether the disturbance of the circadian system in PD patients was associated with the disease progression itself, or the long-term L-DOPA replacement therapy.

Background: Parkinson disease (PD) patients with long-term L-DOPA treatment are suffering from circadian rhythm abnormalities, including impaired sleep-wake cycles, disrupted fluctuations of temperature, blood pressure, heart rate, hormonal levels and many other biological processes.

Methods: PD model was constructed by a bilateral stereotaxic injection of 6-OHDA into the striatum. 21days later, the rats received intraperitoneal administration of saline or 25mg/kg of L-DOPA once daily for another 21 consecutive days. Rotarod test, footprint test and open field test were carried out to evaluate the motor function. Next, we collected SCN, striatum, cortex, liver and plasma at ZT4 (Zeitgber Time), ZT10, ZT16, ZT22. Quantitative PCR was used to analyze the mRNA levels of Clock, Bmal1, Per2, Rora; ELISA detected the levels of melatonin and cortisol; HPLC analyzed the expressions of D1R, D2R in striatum and cortex.

Results: Daily injection of L-DOPA alleviated the motor deficits induced by 6-OHDA lesions. And then, we observed the expression of different clock genes in different tissues. After L-DOPA treatment, compared with 6-OHDA group. The rhythm of Clock was abolished and phase of Per2 was reversed from a nocturnal to a diurnal pattern in SCN compared with 6-OHDA group. In striatum, the expression of Bmal1, Rora was lower than that in the 6-OHDA group at ZT10, but the amplitude of Clock was elevated in cortex at four time points in L-DOPA group. In liver, L-DOPA unaltered did not affect the rhythmicity and levels expression of the four clock genes; in addition, secretion of the cortisol secretion was increased and melatonin was further inhibited after L-DOPA treatment at ZT22. Furthermore, the expression of D2R was decreased in the striatum in of 6-OHDA lesions lesioned rats but D1R remained unchanged unaltered in cortex.

Conclusions: Our research indicated that severe performance in circadian system of advanced PD patients owing to not only the progressive degeneration of the disease, but also the continuous L-DPOA treatment.

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Impulsive-compulsive behaviors in patients with Parkinson's disease in Kannur, India

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Objective: The main aim of the project was to determine the frequency of impulsive compulsive behaviors (ICB) in patients with Parkinson's disease (PD) in Kannur, India. The secondary aim was to investigate risk factors relevant for ICB.

Background: PD is a chronic neurodegenerative disorder which effects predominantly dopaminergic neurons located in the basal ganglia, causing the motor manifestations of the disorder. Current treatment aims to strengthen the remaining dopaminergic activity and includes medications such as levodopa and dopamine agonists (DA). Behavioral and psychiatric disorders related to PD and its treatment, for example ICB, can severely interfere with patient's daily function and social life. To prevent the negative consequences of ICB, it is important to detect, monitor and support the effected patients.

Methods: In four different neurology clinics in Kannur, India, PD patients were interviewed in their native language, using validated questionnaires concerning PD and ICB.

Results: 72 patients participated, of which 12 (16.7%) screened positive for ICB. History of gambling and motor complications were significantly related to ICB (p = 0.002 and p = 0.048 respectively). Gender, smoking, alcohol use, previous psychiatric disease, and treatment with levodopa or DA were not significantly related to ICB.

Variables		ICB+	ICB-	p-value	63
N of PD patients		12	60	NA	
Gender (F/M)		5/7	23/37	1.0000	COTHENDING
Age (years)*		61.5 (49-75)	69.5 (36-85)	0.1904	-
Married		11	53	0.814	
Current smoking		0	4	0.630	
Current alcohol use		0	5	0.337%	
History of gambling		4	1	0.002%	
PD duration (years)*		7 (1-36)	4 (0-16)	0.388 ^d	
Hoehn & Yahr stage		2.25 (0-3)	1,5 (0-5)	0.435*	
Motor complications		8	19	0.0486	
Treatment with Dopamine agonists	6	3	13	0.7220	
Treatment with levodopa		12	55	0.582%	
History of psychiatric disease (not I	PD-related)	1	10	0.503 ^b	
Levodopa equivalent dose (mg)		505 (300-1440)	436 (0-1280)	0.2644	
p-value < 0.05 was considered sign	nificant				
= presented as median (range)	⊨ Fisher's ex	act test			
= Pearson Chi-square test	d = Independe	nt Mann-Whitney U-test			

Conclusions: According to our results, ICB is not a rare complication in patients with PD, as 17 % suffered from it. It is important that health care professionals actively inquire about this. Risk factors for ICB are a history of gambling and the existence of motor complications. ICB must be approached with respect and delicacy to allow and encourage patients to report such sensitive and intimate information about their psycho-social condition, and to accept treatment.

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Differential effects of ventral or dorsal predominant dopaminergic denervation of striatum on development of dopamine dysregulation syndrome and punding in a rat model of parkinsonism

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Objective: To model and assess the differential effects of ventral or dorsal predominant dopaminergic denervation of striatum on development of impulsive compulsive behaviors (ICB) in rats.

Background: In Parkinson's disease (PD), dopamine replacement therapy related ICB are associated with reduced quality of life. Molecular mechanism and a detailed anatomical basis of these behavioral alterations are still not known. Few studies demonstrated that punding may stem from a dopamine-dependent sensitization to appetitive stimuli within the dorsolateral striatum and DDS from the ventral striatum.

Methods: Bilateral 6-OHDA injection to ventral tegmental area or substansia nigra were performed for development of dorsal (n=21) or vental (n=17) selective dopaminergic denervation. Controls were sham operated (n=20). Conditioned place preference (CPP) paradigm was used to model DDS. In this model, the rewarding properties of low dose apomorphine (0.1mg/kg) was explored. Chronic intermittent injection of apomorphine (1mg/kg) was performed to induce repetitive behaviors that may both model dyskinesia and punding. Behavioral studies were rated by valid scales. The extent of dopaminergic denervation is mapped with tyrosine hydroxylase immunohistochemistry staining.

Results: All the dopamine denervated rats received chronic apomorphine injection developed dyskinetic behaviors. The severity of dyskinesia increased day by day and they were very strongly and positively correlated with mean lesion volume (r=849, p<0.001). Low dose apomorphine injection induced CPP in rats with parkinsonism but conditioned place avoidance in controls. The conditioning score was strongly and positively correlated with mean ventral lesion volume (r=0.642, p<0.001). Interestingly, stereotypic behaviors were attenuated in rats with dorsal predominat dopaminergic denervation.

Conclusions: In this study we show that development of DDS in PD may be related to the severity of ventral striatal dopaminergic denervation. On the other hand, we found that stereotypies were decreased in rats with dorsal predominant dopaminergic depletion. We think that the insufficiency of classical stereotypy scales in evolution of the rich repetitive behavioral repertoire in subjects with dopamine depleted striatum may account for this finding.

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Non-motor symptoms in Parkinsons's disease patients treated with levodopa-carbidopa intestinal gel infusion- the follow up study

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Objective: To follow up the effect of continuous levodopa-carbidopa intestinal gel infusion (LCIG) on motor and non-motor symptoms in advanced Parkinson's disease (aPD).

Background: Non-motor symptoms have a major effect on the quality of life in PD patients. The long term effect of the LCIG treatment on non-motor symptoms in aPD patients is less known.

Methods: 13 consecutive aPD patients whom LCIG treatment was introduced were recruited in this observational prospective pilot study. Before insertion of percutaneous enteroendoscopic gastrostomy (PEG baseline), patients underwent the following assessments of motor and non-motor symptoms: MMSE, MoCA, PDQ39, BDI, HAS, SCOPA-PC, PDSS2. The same evaluation was performed 6 months, 1 year and 2 years after initiation of LCIG treatment. Student T-test was performed to compare the baseline with the follow-up evaluations.

Results: The average age of aPD patients at baseline was 72.0 +/- 6.5 years, 7 were male. PD duration: 15.0 +/-4.8 years, MMSE score: 26.1 +/-4.0 MoCa: 22.0 +/-4.8, PDQ39: 57.1 +/-23.0, BDI: 20.9 +/-17.6, HAS: 19.9 +/-8.7, SCOPA-PC: 2.2 +/-1.5, PDSS2: 24.0+/-5.5. The follow up evaluations showed stable motor and non-motor signs. No statistically significant changes were observed in the studied motor and non-motor symptoms in the 2 year follow-up study.

Conclusions: LCIG treatment of aPD patients is associated with stable non-motor symptoms status up to two years after the start of the treatment.

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Diabetes mellitus and Parkinson's disease

G. Pagano, S. Polychronis, H. Wilson, F. Niccolini, M. Politis (London, United Kingdom) **Objective:** To investigate the association of type 2 diabetes mellitus (DM) with markers of Parkinson's pathology in patients with early *de novo* Parkinson's disease (PD).

Background: DM is associated with 38% increased risk of developing PD. The mechanisms underlying this association are not fully understood. PD and DM neurodegenerative processes share similar dysregulated pathways. Preclinical data have shown that chronic hyperglycemia is associated with reduced dopaminergic transmission and decreased efficacy by dopamine agonist treatment. DM may promote neurodegenerative mechanisms by increasing tau pathology and has been associated with faster cognitive decline in older adults.

Methods: Using the Parkinson's Progression Markers Initiative database, we performed a case-control study comparing PD patients with DM (PD-DM) to those without DM (PD). The two groups were matched for age, gender, disease duration and years of education. Diagnosis of DM was based on clinical history and confirmed by two consecutive measurement of serum glucose levels >126ml/dl. We investigated for associations and differences in motor and non-motor features, in molecular and structural imaging, and in cerebrospinal fluid (CSF) markers of PD pathology. Subsequently, we performed Cox proportional hazards analysis to investigate whether the presence of DM was predictive for PD progression over a 36-month follow-up period. To assist our conclusions, we also performed in parallel similar comparisons between controls with (C-DM) and without DM (HC).

Results: PD-DM patients had higher motor scores (p<0.01), lower striatal dopamine transporter binding (p<0.05), and higher tau CSF levels (p<0.05) compared to PD patients. C-DM also showed lower striatal dopamine transporter binding (p<0.05), and higher tau (p<0.05) and a-synuclein (p<0.05) CSF levels compared to HCs. DM was a predictor for worse motor progression (Hazard Ratio [HR]=4.521, 95% Confidence Interval [C.I.]=1.468–13.926; p<0.01) and worse cognitive decline (HR=9.314, 95% C.I.=1.164–74.519; p<0.05) in PD patients. **Conclusions:** DM presence predisposes towards a PD-like pathology and when present in patients with PD is linked to a more aggressive phenotype.

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Self-rated burden grading of non-motor symptoms identifies landmarks and subtypes of Parkinson's disease: first report from a Moscow-Madrid-London collaboration

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Objective: To describe clinical and imaging biomarkers of non-motor symptoms burden (NMSB) as defined by NMS questionnaire (NMSQ) scores in a prospective international cohort study of Parkinson's disease (PD). **Background:** NMS are integral to PD and NMSB grading is now validated using NMSQ (1). Relationship of self-declared NMSB with objective biomarkers of PD has not been studied before.

Methods: 179 patients (68.5±11.4 yrs) have been studied (disease duration 7.29±6.85 yrs, 7% drug-naive, median Hoehn Yahr ((HY) 2). Measures of motor state, sleep, depression, anxiety, quality of life (QoL), Datscan and olfaction were collected.

Results: 17% were NMSB mild, 30% moderate, 26% severe, 26% very severe. 12% had very severe and 16% severe NMSB inspite of mild HY. Motor dysfunction was worse in very severe NMSB. Significant deterioration was seen with anxiety (mild 6.1 vs very severe 11) and QoL (mild 5.1 vs very severe 16). PD sleep scale total score worsened significantly with increasing NMSB. Datscan putamen uptake ratios were non-significant between NMSB (Table 1) in contrast to HY (Figure 1). Olfaction was significantly worse in very severe (70%) vs severe (32%), moderate (17%) and mild (13%).

NMS score	NMSB	N	DATscan Uptake ratio (N <u>ormal</u> >2)	
			Right Putamen	Left Putamen
0-5	Mild	31	0.93	0.96
6-9	Moderate	54	1.06	1.14
10-13	Severe	47	0.75	0.70
>13	Very Severe	47	0.92	1.01



Conclusions: Self-declared NMSB grading is capable of identifying subgroups of NMS dominant phenotypes. Very severe NMSB is characterised by olfactory, sleep and anxiety disorders but relatively retained putaminal dopamine transporter uptake.

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Long-term effects of subthalamic nucleus deep brain stimulation on quality of life, non-motor and motor symptoms

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Objective: To study the long-term effects of bilateral subthalamic deep brain stimulation (STN-DBS) on Quality of Life (QoL), motor, non-motor symptoms (NMS) in patients with Parkinson's disease (PD) using validated composite measures.

Background: Class I evidence shows that STN-DBS improves motor symptoms and QoL in patients with PD. However, only few studies have investigated non-motor effects of DBS, in particular its long-term effects. We hypothesized that STN-DBS is associated with a reduction of a range of NMS in patients with PD.

Methods: In this ongoing, multicenter, open, prospective, international study (London, Cologne, Manchester) we investigated non-motor effects of STN-DBS in real-life use in patients with PD. We surveyed PD Quality of Life Questionnaire (PDQ-8), Non-motor Symptoms Scale (NMSS), Non-motor Symptoms Questionnaire (NMSQ), and Scales (ADL, motor examination, and complications) at preoperative baseline, at 6 months follow-up (6MFU) and 24 months FU (24MFU).

Results: Thus far 42 consecutive patients with advanced PD (28 male, mean age: 63.3 ± 7.2 yrs, mean duration of disease: 10.6 ± 4.7 yrs, median Hoehn &Yahr stage: 2.5) have completed 24 MFU. STN-DBS significantly improved all scores (repeated measures ANOVA, all p=0.035). Post-hoc analyses showed a significant improvement from baseline to 6MFU (Wilcoxon signed rank-test, respectively paired t-test when criteria were fulfilled; all p=0.015) followed by a deterioration from 6MFU to 24MFU (motor examination n.s., all other p=0.041). Long-term outcomes comparing baseline to 24 MFU improved significantly for Scopa-motor examination and complications (all p=0.025), but not for PDQ-8, NMSQ and SCOPA-ADL.

Conclusions: This study provides evidence that bilateral STN-DBS has beneficial effects on QoL, non-motor and motor symptoms in patients with PD. The deterioration of all scales from 6MFU to 24MFU may have a variety of causes, e.g. disease progression. This effect was more pronounced on QoL, NMS and ADL which at 24MFU reached levels comparable to preoperative baseline while a significant improvement of motor symptoms was sustained over two years. Long-term effects of DBS on specific NMS domains such as mood, sleep, and autonomic symptoms are now being studied.

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Clinical correlates of severe somnolence in Parkinson's disease: results from an international naturalistic non-motor symptoms cohort

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Objective: To compare patients with mild and severe daytime somnolence using cut-off values from item 15 of the Parkinson's disease (PD) sleep scale (PDSS).

Background: Although risk factors for sudden onset of sleep (SoS) and somnolence in PD have been studied, large scale data is missing.

Methods: We classified 658 patients with PD into 3 subgroups based on PDSS item 15 scores, mild (>7) moderate (5-7) and severe (<5).

Results: Severe sleepiness was present in 38.8% (N=255). Compared to patients with mild sleepiness (N=360), those patients were of older age (mean in years 68.5 ± 10.15 versus 64.8 ± 11.4), had a longer disease duration (mean in years 5.8 ± 5.1 versus 4.9 ± 5), higher Hoehn and Yahr state (median 3 (1-5) versus 2 (0-5)), higher non motor symptoms (NMS) scale total score (63 ± 41.6 versus 39.1 ± 31.3), higher rate of hallucinations on NMS scale (0.8 ± 1.8 versus 0.2 ± 0.9), more autonomic dysfunction on NMS scale (16.8 ± 12.7 versus 10.8 ± 9.9), higher clinical impression of severity index cognition (1 ± 1.1 versus 0.4 ± 0.7), higher hospital anxiety and depression scale (13.4 ± 8 versus 9.8 ± 6.3) and poorer quality of life (mean PDQ-8 total score 10.25 ± 6.5 versus 6.6 ± 5.5). 75.7% of patients with severe sleepiness were treated with levodopa compared to 58.6 % with mild sleepiness (figure 1). Several patients had sudden onset of sleep.



Figure 1: Summary of findings in our 'severe somnolence' PDSS item 15 group.

PDSS: Parkinson's disease sleep scale; NMS: non-motor symptoms scale; CISI: clinical impression of severity index; HADS: hospital anxiety and depression scale; HY: Hoehn and Yahr staging

Conclusions: Severe somnolence likely reflects a specific subtype (Park sleep) of PD (1). There is sensitivity to dopaminergic drugs and a higher NMS burden. These observations have clinical implications regarding personalised medication strategies in this subgroup.

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Motor performance measured with the UPDRS in PD patients with varying degrees of smell loss

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Objective: To establish whether there is a possible link between the motor symptoms, which includes RBD in PD patients in this study, who have mild/moderate microsmia, severe microsmia or anosmia (as measured by the University of Pennsylvania Smell Identification Test (UPSIT)).

Background: Motor symptoms, which also include rapid eye movement behaviour disorder (RBD) in Parkinson's disease (PD) substantially affect patient's and carer's quality of life. There is also good research evidence that the ability to smell is significantly affected by PD compared to the general population.

Methods: This is an open cross-sectional study involving 112 PD patients (of both genders). Motor symptoms were measured using the motor rating subscales in the Unified Parkinson's Disease Rating Scale (UPDRS-III), and rapid eye movement behaviour disorder (RBD) was assessed using the RBD Screening Questionnaire.

Results: Overall, there is a very weak negative correlation r=-0.1192 which is not statistically significant between the motor function score and sense of smell score. However, when examining the individual domains of the UPDRS motor scores against UPSIT scores, correlation is significant in posture (= -.231 p=.014), facial expression (=-.207 p=.029), and rising from a chair (=-.190 p=.045) and is close to being significant in motor domains hand movements (=-.166 p=.080) and speech (=-.166 p=.085). Analysis between UPSIT and RBD scores confirmed this was not statistically significant (= -.021 p=0.823).

Conclusions: The findings of this study conclude that individual motor domains may be linked to the degree of smell loss rather than the motor symptoms as a whole. It also confirms RBD does not correlate with sense of smell loss. Therefore, determining a PD patient sense of smell with a simple bed side test at the outset may help to provide important information as to the range of clinical features that are likely to be encountered in this patient. It may also help to provide very important prognostic information in this person; this can only help in our understanding of PD.

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Subthalamic nucleus local field potential activity during the sleep-wake cycle

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Objective: Characterize changes in subthalamic nucleus local field potential (STN LFP) activity related to stages of the sleep-wake cycle.

Background: Deep brain stimulation (DBS) devices used for the treatment of Parkinson's disease (PD), are designed to emit a constant electrical pulse train with stimulation parameters—including voltage, frequency, and pulse width—determined by clinicians. Efforts to increase the efficacy of stimulation systems have focused on developing feedback control devices that can self-determine optimal stimulation parameters, based on real-time patient-derived physiologic input. Modulating stimulation parameters in response to LFPs recorded from macroelectrode DBS contacts has shown promising preliminary results. Rigorous characterization of LFP is crucial to providing additional spectral markers that developers of feedback control devices can use to gate stimulation to. Here we provide detailed characterization of changes in LFP over the course of nighttime polysomnography in ten PD patients implanted with DBS targeting STN.

Methods: PD patients (n=10) in the "off" medication state underwent STN LFP recording with concurrent polysomnography for a full night (6-9 hours). LFP were recorded through an externalized DBS lead three weeks after implantation. Kruskal-Wallis non-parametric ANOVA with post-hoc Bonferroni correction was applied to determine statistical significance.

Results: We report on the spectral power of STN LFP frequency bands 0-3, 3-7, 7-13, 13-30, 30-90, 90-200, and 200-350 Hz, relative to changes in polysomnograph-determined arousal or sleep state (awake with movement, awake without movement, REM, N1, N2, N3). Novel findings include: (1) significantly (p<0.0001) greater 3-7 Hz median bandpower in REM, N1, N2, and N3 relative to either awake with movement or awake without movement in group analysis, and (2) significant (p<0.0001) median bandpower differences in N1, N2, and N3 compared to REM, awake with movement, and awake without movement were reported for bands (0-3 Hz), (3-7 Hz), (7-13 Hz), (13-30 Hz) and (30-90 Hz).

Conclusions: Our findings suggest that STN LFP may be used to differentiate between awake versus sleep states, which holds significant potential for the creation of closed-loop DBS devices.

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Baseline risk factors of insomnia symptoms after five years of follow-up: a population-based cohort of incident Parkinson's disease

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Objective: To investigate baseline risk factors of insomnia symptoms after five years of follow-up, on average, in a population-based study of Parkinson's disease (PD).

Background: Sleep problems are important and common non-motor symptoms of PD; insomnia is one of those and is also common in the elderly in general. Insomnia is characterized by difficulty in initiating and/or maintaining and poor quality of sleep and is strongly associated with quality of life and mortality in PD. It is significant to the quality of care in PD to study early-disease risk factors for insomnia symptoms in later phases.

Methods: This is a population-based cohort of incident PD cases assessed at three time points from 2001 to 2009 by trained interviewers and neurologists. There are only 8 population-based studies of incident PD and sleep; this is the only in the U.S and the only to have used the Medical Outcomes Sleep Scale (MOS-SS) in PD. We describe the distribution and estimate associations of baseline demographic and clinical features, per insomnia symptoms severity at last assessment, measured by the continuous score (0-100) of the Sleep Disturbance sub-scale. Bi and multivariable linear regression models were used, according to causal models proposed to explain relations of variables, instead of use of pure statistical criteria.

Results: At baseline, 360 patients were included, mean (SD) age and PD duration were: 70.4 (10.2) and 2.1 (1.5), 206 (57.2%) were men and 321 (89.2%) were using levodopa or dopamine agonist. At last follow-up, 186 completed the MOS-SS, mean (SD) disease duration and insomnia score were 7.5 (2.6) and 28.4 (22.4). On bivariable regressions, baseline factors significantly associated with future worse insomnia, with respective mean differences 95% CI were: lifetime average of sleep hours (-1.02,-0.39), depression score (0.14,0.32), UPDRS (0.03,0.10) and PD duration (0.0,0.46). On a multivariable model, worse baseline depression, UPDRS and longer PD duration were all significant predictors of worse insomnia symptoms later in the disease.

Conclusions: Depression and worse motor symptoms early in PD were important predictors of worse sleep after an average of 5.5 years of follow-up and could be target on interventions to improve quality of life in PD. Alternative regression models and loss to follow-up should be considered and explored in future analyses.

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Prevalence of burning mouth syndrome in Parkinson's disease

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Objective: To estimate the prevalence of BMS in PD patients, compared with healthy controls and to identify potential factors associated with the presence or severity of BMS.

Background: Burning mouth syndrome (BMS) is a distressing condition causing painful burning sensation in the oral cavity without clear abnormality. BMS may be idiopathic or secondary, occurring in various diseases such as nutritional disorders, endocrine and autoimmune diseases, and neurological conditions. In population studies, the incidence of BMS ranges 0.7% to 14.8%. One study reported 24% prevalence in Parkinson disease (PD) patients in Northern Ireland, the study was limited in its sample size and selected population. Clinical overlap between BMS and restless leg syndrome (RLS) was observed in a case series of 5 patients. Dopaminergic medications such as levodopa and dopamine agonists have been noted to have variable benefit in BMS. Although pathophysiology of BMS is unclear, dopaminergic dysregulation seems to play a role. There is little literature further evaluating BMS in PD population.

Methods: This is a case control study. Consecutive patients with PD evaluated by movement disorder neurologists at Cleveland Clinic, and their age and gender matched healthy volunteers without PD (eg. spouse of the PD subjects) were recruited. Each subject was asked to complete a survey at their office visit that contained questions regarding demographics, symptoms of burning sensation of the mouth/tongue/lip, presence of dry mouth, change in taste, dental and smoking history, symptoms of RLS. Medical chart review regarding information including medication uses, PHQ-9 score, GAD-7 score, UPDRS I and II were recorded.

Results: So far, 77 patients with PD and 22 healthy controls completed the survey. In PD group, 15 out of 77 PD patients reported abnormal sensation in the mouth. Of those, 8 described the abnormal sensation as burning. In the healthy control group, 2 of 22 healthy controls reported abnormal sensation in the mouth, none described burning. Study will continue to recruit up to 100 subjects in each February 1, 2017, after which data will be available for complete analysis.

Conclusions: Available upon completion of the study.

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Sexual dysfunction in women with Parkinson's disease

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Objective: To assess the prevalence and significance of sexual dysfunction (SD) in women with Parkinson's disease (PD) in comparison to general population, highlight the specific sexual complaints in women with PD using a validated survey, and understand the role of motor and non-motor PD symptoms, medication effect and comorbidities in SD.

Background: PD is a neurodegenerative disease that presents with multiple disabling motor and non-motor symptoms, such as SD. Male SD is more frequently recognized in clinical encounters. This study focuses on SD in women as it is an important factor in patient quality of life and ability to cope with PD symptoms and consequences, such as depression.

Methods: We intend to enroll 100 female PD subjects over 6 -12 months. We have enrolled 16 subjects with ages 46 to 84. Eligibility criteria were applied. Chart review was done. Verbal consent was obtained. 53 questions were given based on the validated Scale for Quality of Sexual Function (QSF). 32 questions were split into four major domains as designed by QSF: Psycho-somatic quality of life, Sexual Activity, SD self-reflection, and SD partner's view. Four main composite scores were calculated based on those domains, and a total composite score (TCS) is the sum of those scores. 21 questions were added to cover demographics, comorbidities, treatments, and other complaints. PD severity was assessed using UPDRS. All scores were compared to QSF normal values. All data collected was anonymous.

Results: The major impact on the TCS was derived primarily from the sexual activity domain as 50% of PD subjects vs 8.2% of general population reported severe SD. SD partner's view had the second major impact on the TCS as 18.75% of PD subjects vs 9.7% of general population reported severe SD. Comorbidities such as anxiety, depression, diabetes, and to a lesser extent medications, such as SSRIs, had the strongest association to a higher TCS. Anxiety around intimacy and dissatisfaction in the absence of partner were also linked to a higher TCS.



Conclusions: Our study shows that SD in women with PD is more common than general population. The presence and perspective of the sexual partner represents a significant aspect. Medical and psychological comorbidities in addition to medications play a major component. Further analysis of specific complaints will be done with PD severity assessment. More subjects need to be enrolled in order to increase the statistical significance of other domains.

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Non-motor symptoms in the first neurology consultation in Cali, Colombia

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Objective: To describe the distribution of NMS of PD in patients assisted by the Outpatient Neurology Service between 2012 and 2016 in a high level hospital in Cali, Colombia.

Background: Parkinson disease (PD) is characterized by motor symptoms, however, non-motor symptoms (NMS) such as REM Sleep Behavior Disorder (RBD), hyposmia, depression, constipation, among others that can appear in the premotor stage of PD, preceding it's diagnosis by years. To date, there is no literature regarding the frequency of NMS in a first consultation in PD patients in Colombia.

Methods: Observational, descriptive cross-sectional study. From 48010 neurological consults, 225 medical records were selected (Fig 1). From the selected patients, clinical and sociodemographic data was collected in the first consultation. Prodromal NMS and motor symptoms to PD diagnosis were assessed by interrogation. A statistical inference was performed using odds ratio of NMS and motor symptoms; the significant level was P<0.05. All statistical analysis was performed using *STATA-13.0*. (Figure 1 insert)

Results: Sociodemographic data is shown in Table 1. There were 23.6% of patients in the premotor group that only presented NMS in the first consult but later in follow up developed motor symptoms and were diagnosed with PD within the next 5 years. From the group that presented motor symptoms during the first consult, 91 (40.4%) had a

previous diagnosis of PD, 64 (28.4%) were diagnosed during the first consultation and 70 (31.0%) were diagnosed in follow ups. Frequency of NMS was RBD 48.8%, hyposmia 29.7%, cognitive symptoms 24.8%, psychiatric and behavioral symptoms 51.1% and autonomic symptoms 28.5%. Odds-ratio analysis between the most frequent non-motor symptoms and the predominant motor feature are presented in Table 2.



Table 2. Associations between the presence of non-motor symptom and the predominant motor characteristic of patients with Parkinson Disease						
Predominant motor symptom	Presence of NMS	No presence of NMS	Crude OR	Adjusted OR**	IC 95%	P-value
REM Sleep Behaviour Disorder						
Bradykinesia	11/(39)	28/(39)	0.3	0.33	0.14-0.75	0.0026*
Gaitinstability	19/(31)	12/(31)	1.86	1.51	0.63-3.5	0.12
Rigidity	16/(23)	7/(23)	2.75	3	1.08-8.34	0.032*
Tremor	29/(60)	31/(60)	0.95	1.07	0.54-2.12	0.89
Hyposmia/Anosmia						
Bradykinesia	15 / (39)	24/(39)	1.35	1.56	0.70-3.50	0.4
Gaitinstability	10/(31)	21/(31)	0.94	0.83	0.33-2.05	0.89
Rigidity	9 / (23)	14/(23)	2.75	1.23	0.46-3.27	0.032*
Tremor	17/(60)	43 / (60)	0.68	0.74	0.35-1.5	0.29

Bold values* p < 0.05

Figure 1.

** Adjusted OR by the other non-motor symptoms analyzed

Conclusions: In the cohort, 23.6% of the patients with NMS were diagnosed within 5 years after the first consultation during follow up. Asking about NMS can be a useful tool to screen early stages of the disease and improve the diagnostic accuracy. In the sample, RBD and Hyposmia were the most frequent NMS with a higher degree of relation with bradykinesia and rigidity and a lower degree of relation with tremor. The relationship between RBD and bradykinesia has been established and it could be considered as a risk factor for PD phenotype characterized for postural instability and gait disorders.

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Phasic activity during non-REM sleep

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Objective: To describe the first reported case of behavioral and phasic neurophysiological activity during slow-wave sleep (SWS) in a patient with symtomatic REM Sleep Behavior Disorder (RBD).

Background: REM sleep is characterized by a constellation of phasic events mediated by pontomesencephalic structures. To our knowledge, phasic activity has not been previously reported during SWS.
Methods: We analyzed the behavioural and polygraphic sleep features evolution of symtomatic RBD in a Parkinson disease patient.

Results: A 64-years-old male with idiopathic Parkinson's disease was initially referred for the presence of motorbehavioral episodes (MBEs) emerging during the second half of night (including vocalizations, punching, yelling, smiling and laughing) consistent with symptomatic RBD. At the age of 68, two consecutive video-PSGs demonstrated the normal cyclic NREM and REM sleep macrostructure features coexisting with dissociated REM sleep (REM sleep without atonia) and dissociated NREM sleep aspects, with intrusion of REM sleep phasic activities into NREM stages (namely, polymorphic isolated or clustered REMs, sometimes associated with muscle twitching, MBEs and breathing pattern irregularities). MBEs were not associated with tachycardia and included jerky/simple movements, unintelligible vocalizations and purposeful movements suggesting RBD-like dreamenacting behaviors. Cognitive status examination was unremarkable, except for a mild apathy and executive dysfunction. On motor status, under 344.5 mg of levodopa equivalent dose, Hoehn-Yahr score was 3 and UPDRS-III score was 31.

Conclusions: The unusual NREM muscle twitching and MBEs mirrored the intrusion of RBD-like phasic activity of REM into NREM sleep, considering the dissociative behaviors phenomenology, clustering pattern and absence of autonomic reactivity to NREM sleep MBEs. This is the first case showing RBD-like MBEs during scorable SWS, which differed from previous cases of *status dissociatus* evolving from an RBD substrate in which continuous nocturnal MBEs were associated with breakdown of state-determining boundaries. This case suggests that in normal individuals, phasic motor activity and behaviors during NREM sleep are actively blocked. Our case may represent an intermediary stage between RBD, parasomnia overlap disorder and *status dissociatus*, during which the disintegration of state-determining markers gradually converges to a simultaneous admixture of all stages.

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Impact of duopa on non-motor symptoms of Parkinson's patients with deep brain stimulation

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Objective: To report the role and impact of duopa on non-motor parkinsonian symptoms in patients with deep brain stimulation within a month from starting therapy.

Background: Duopa (levodopa/carbidopa gel) has shown to improve dyskinesia and off periods in patients with advanced Parkinson's disease and is an alternative to deep brain stimulation (DBS). But there is limited data on its role in patients who already have DBS especially with regards to its impact on non-motor symptoms.

Methods: This is a retrospective chart review of all adult Parkinson's patients who have DBS and have undergone duopa. Clinical, psychosocial history and demographic data pre and post therapy were reviewed. A p value of <0.05 was considered statistically significant.

Results: 4 patients all caucasian males (ages: 56 years, 57 years, 69 years, and 78 years) with STN DBS (average off time: 5 hours daily) underwent duopa therapy. Post-therapy there was significant improvement in pain with pain scales on visual analog scale improving from average 8/10 to 3/10, (0-no pain, 10-worst pain), p<.0.5 within a month of starting therapy. In addition, all patients reported improved interest and motivation in doing activities and tasks. All patients had an average 2 falls within a month of starting therapy (2 orthostatic, 2 mechanical). **Conclusions:** The addition of duopa in patients with DBS has significant improvement in pain, and improved interest and motivation in doing activities while there is an increased risk of fall associated with it.

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Predictors of cognitive impairment in multiple system atrophy

M. Hatakeyama, T. Sato, T. Takahashi, M. Kanazawa, O. Onodera, M. Nishizawa (Niigata, Japan) **Objective:** To determine predictors of cognitive impairment in patients with multiple system atrophy (MSA). **Background:** Although dementia is not a diagnostic criteria for MSA, an increasing number of studies are investigating cognitive impairment in MSA. The clinical and radiological features predicting cognitive impairment in MSA thus remain to be more investigated.

Methods: We prospectively recruited 59 consecutive patients with probable MSA according to the consensus criteria, and analyzed their clinical and MRI findings (Fazekas grade). We analyzed predictive factors related to decline in Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) scores, using simple linear regression analysis for continuous data and ANOVA for discrete data. Then, we drew a regression line relating the MMSE scores to the disease duration and categorized patients that were below the 68% prediction interval as belonging to the severe cognitive impairment (SCI) group. We compared clinical and radiological findings between the SCI group and non-SCI group with simple and multiple logistic regression analysis.

Results: The MMSE scores negatively correlated with disease duration (p = 0.03), unified MSA rating scale (UMSARS) part 1 score (p = 0.02), part 4 score (p = 0.004), and residual urine volume (p = 0.002) and positively with CV_{RR} (p = 0.01). The FAB scores negatively correlated with UMSARS part 2 score (p = 0.03), periventricular hyperintensity grade (p = 0.02), and deep white matter hyperintense signals grade (p = 0.01). Simple logistic regression analysis revealed that predictors for SCI were MSA with predominant Parkinsonian features (MSA-P) (p = 0.03), high UMSARS part 1 score (p = 0.03), high UMSARS part 4 score (p = 0.03), and high residual urine volume (p = 0.006). Stepwise multiple logistic regression analysis including these four factors revealed that a significant predictor for SCI was high residual urine volume (odds ratio, 1.006; 95% confidence interval, 1.0003-1.0112, p = 0.04).

Conclusions: This study demonstrated that high residual urine volume might be a predictor for SCI in patients with MSA. Findings in the present study may facilitate the development of better management protocols for patients with MSA.

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Tyrosine kinase inhibition clears tau and reserves neuropathology and motor symptoms in a novel model of progressive supranuclear palsy

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Objective: Our objective was to examine the effects of tau accumulation in transgenic mice, observing both motor function and behavior.

Background: Tau hyper-phosphorylation is a critical factor in neurodegenerative diseases. To examine the effects of tau accumulation in a novel models of tauopathy we generated a transgenic mouse via modification of an existing strain that expresses the human P301L mutation of tau.

Methods: We bred hemizygous with hemizygous transgenic mice that express P301L tau under the control of a prion promoter (TauP301L).

Results: Accumulation of hyper-phosphorylated tau (p-tau) in hemizygous mice was predominantly detected in the hippocampus, cortex, brainstem and thalamus, reminiscent of tau pathology in human progressive supranuclear palsy (PSP). TauP301L mice show a significant increase in both human and murine p-tau and display motor symptoms that mimic PSP. Homozygous mice are underweight and have severe motor symptoms and may live up to 6 months, while hemizygous mice live longer (up to 1.5 years) and look normal but begin to show anxiety-like behavior and progressive motor abnormalities resulting in paralysis from 6 months old. Daily treatment of these mice with low doses of the tyrosine kinase inhibitors Nilotinib or Bosutinib led to p-tau clearance and improvement in motor symptoms.

Conclusions: Accumulation of p-tau in the brainstem, cortex and thalamus leads to parkinsonian-like symptoms that mimic human PSP and tyrosine kinase inhibition reduces tau pathology and reverses Parkinsonism.

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Which clinical features predict progressive supranuclear palsy pathology? A clinicopathological study on 437 autopsy cases and a literature review

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Objective: To identify clinical features and investigations which predict PSP pathology during lifetime in the largest pathology PSP cohort reported to date compared to autopsy cases with relevant differential diagnoses.

Background: Progressive supranuclear palsy (PSP) is a neuropathologically defined disease entity. Current criteria for the clinical diagnosis of PSP are not sensitive in the early disease stages for manifestations other than Richardson's syndrome. However, early diagnosis is important, particularly for the development of disease-modifying therapies.

Methods: We performed a systematic review of the literature published since 1996 to identify clinical features and investigations that may predict PSP pathology. We then extracted standardized data from clinical charts of patients with pathologically diagnosed PSP, as well as relevant disease controls, and calculated sensitivity, specificity and positive predictive value of key clinical features for PSP in this cohort.

Results: Of N=4166 identified articles identified by an automated database inquiry, N=254 met the predefined standards. The literature review identified clinical features predictive for PSP, including features of the four functional domains "ocular motor dysfunction", "postural instability", "akinesia", and "cognitive dysfunction".

However, no biomarker or genetic findings were confirmed to predict PSP. No biomarker or genetic findings were found reliable to predict definite PSP. High-quality original natural history data was available from patients with pathologically diagnosed PSP (N=206), CBD (N=54), MSA-P (N=51), PD (N=53), and FTLD (N=73). We identified clinical features of differential sensitivity and specificity that predict PSP pathology, including phenotypes other than PSP-RS.

Conclusions: The evidence from this extensive literature review and autopsy cohort presents a valuable basis for the revision of the diagnostic criteria for PSP.

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Cognitive Impairment in MSA Patients from the Catalan Multiple System Atrophy Registry (CMSAR)

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Objective: To assess the cognitive function and its demographic and clinical correlates in MSA patients included in the Catalan Multiple System Atrophy-Registry (CMSAR).

Background: Cognitive impairment has been reported in MSA and related to disease duration. Published figures range from 22% of mild cognitive impairment to up to 14% of patients meeting the dementia definition in the last year prior to death.

Methods: In this cross-sectional assessment of the first 36 MSA patients included in the ongoing longitudinal CMSAR, we analysed their baseline demographic and clinical data relating them to cognition. Specifically, Hoehn & Yahr stages and the Unified MSA rating scale (UMSARS) were applied to assess motor involvement, whereas depressive symptoms were assessed by means of the Beck depression inventory (BDI), neuropsychiatric disturbances with the Neuropsychiatric inventory (NPI) and cognitive performance with frontal assessment battery (FAB), mini mental state examination (MMSE) and Mattis dementia-rating scale (MDRS-2). The study received approval from the respective review boards of all the participating centres, and all subjects provided their written informed consent. The CMSAR project is funded by "Fundació La Marató de TV3".

Results: Over one and half year, we have included 36 MSA patients (17 women), with a mean age at onset of disease of 57.8 years and a mean disease duration of 57.6 months, including 44.4% MSA-P and 55.6% MSA-C, 58.3% of them with a probable diagnosis and 41.7% with possible MSA. Hoehn & Yahr stage was III or IV in 75% of the participants. Mean UMSARS score was of 53.78, with higher scores in MSA-P vs. MSA-C (63.19 vs. 46.25, p=0.002). The MMSE was impaired only in 5.6% showing a significant (but weak) correlation with older age (r=-0.352; p=0.035). The FAB was impaired in 55.6% and significantly associated with higher UMSARS scores without differences in sex, MSA subtype or MDRS-2 scores. However, worse attention/initiation MDRS-2 scores were related to higher UMSARS (r=-0.571; p=0.001). Mean BDI score was 7.53 without differences between groups. **Conclusions:** Dementia is infrequent in our MSA population, with cognitive impairment being mostly dysexecutive and related to older age and severity of motor impairment. The longitudinal monitoring shall enable us to further characterize cognitive impairment in MSA throughout disease evolution.

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Randomize study of occurrence of Parkinson's syndrome in patients with rheumatoid arthritis

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Objective: We aimed to study an occurrence of Parkinson's syndrome (PS), its relationship with duration of disease and age of patients with rheumatoid arthritis.

Background: Rheumatoid arthritis (RA) is a severe systemic disease which leads besides of points and organs to the defeat of central nervous system.

Methods: The clinical research was carried out in the department of rheumatology of the first clinic of Tashkent Medical Academy. We did neurologic exam in 80 patients with RA and did MRI angiography patients with PS. They aged 18-65 years (mean age $47 \pm 1,6$ years), of them 36 women and 14 men, 71.1% and 28.9% respectively. We eliminated patients with inherited Parkinson's disease.

Results: Patients aged 40-60 years were the most common of all patients we studied. The duration of the disease lasts from 1.5 months to 27 years. The average duration of the disease is 10.5 years. In neurologic exam we found muscular rigidity in hands, amimia of face, absence of synkinetic reactions and finger tremor. We detected in 19 (23,75%) patients rigidity form and in 5 (6,25%) patients tremor form of PS. In MRI scan of all patients with PS we found the many rheumatoid vasculitis of subcortical nucleus vessels.

Conclusions: We concluded that PS is occurs in patients with RA to 20-25% more often, than its occurrence in all population. Rigidity form of PS amounts 79%. The severity of PS is higher than the RA is longer and the age of the patients greater.

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Association of nocturnal stridor with clinical features of patients with multiple system atrophy

H.S. Ryu, J.H. Paek, S. You, M.J. Kim, Y.J. Kim, J. Kim, K. Kim, S.A. Lee, S.J. Chung (Seoul, Korea) **Objective:** To investigate the association between findings of night video-polysomnography and clinical feature of patients with multiple system atrophy (MSA).

Background: Nocturnal sleep-related clinical sympotoms are prevalent in MSA patients and critical in some patients. However, little has been known about the objective polysomnographic findings in MSA patients and their clinical implications.

Methods: We retrospectively analyzed clinical data of MSA patients (N = 49) who underwent an overnight vidopolysomnography. Stridor was defined as present when confirmed by an overnight video-polysomnography. The video-polysomnographic findings and clinical features of MSA patients were compared between MSA patients with stridor and those without.

Results: The mean age at onset was 55.7 ± 8.9 years and mean disease duration of MSA was 43.5 ± 24.0 months. Thirty–one (63.3%) of the 49 MSA patients were assessed as having the stridor. MSA patients with stridor showed significantly higher apnea-hypopnea index (31.3 ± 21.8 /hr versus 18.7 ± 18.2 /hr, p = 0.024), respiratory disturbance index (35.6 ± 22.4 /hr versus 23.3 ± 21.1 /hr, p = 0.049), and oxygen desaturation index (31.6 ± 21.3 /hr versus 16.3 ± 18.6 /hr, p = 0.006), compared with those without stridor. The axial motor features of MSA were more severe in MSA patients with stridor than those without (p = 0.017). However, there was no significant difference of sex, age at onset, subtypes of MSA, parkinsonian features, cerebellar ataxia, and autonomic dysfunction between MSA patients with stridor and those without. In logistic regression analysis, longer disease duration (p = 0.04) and more severe axial motor features (P = 0.036) were associated with the presence of nocturnal stridor in MSA patients. **Conclusions:** Our results suggest that MSA patients with nocturnal stridor had more severe axial motor features of MSA.

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[11C]PK11195 PET in Alzheimer's disease and progressive supranuclear palsy: the NIMROD study

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Objective: Here we test whether the intensity and regional distribution of neuro-inflammation differs between Alzheimer's disease (AD), Progressive Supranuclear Palsy (PSP) and controls; and whether neuro-inflammation relates to disease severity.

Background: Neuro-inflammation plays a significant role in the pathogenesis of AD and PSP.

Methods: We used the radiotracer [11C]PK11195 with positron emission tomography and kinetic modeling to compare regional [11C]PK11195 binding in 16 patients with AD pathology (including amyloid-positive mild cognitive impairment), 16 with PSP, and 13 controls. We correlated [11C]PK11195 binding with clinical variables and C-reactive protein.

Results: [11C]PK11195 binding in the medial temporal lobe and occipital-parietal cortex was increased in AD patients, relative to both PSP patients and controls. PSP patients showed elevated [11C]PK11195 binding in the thalamus, putamen, and pallidum relative to controls. [11C]PK11195 binding in the pre-cuneus correlated *negatively* with episodic memory in AD, while [11C]PK11195 binding in the pallidum, midbrain, and pons correlated *positively* with disease severity in PSP.

Conclusions: The magnitude and distribution of neuro-inflammation, indexed by [11C]PK11195, differed between AD and PSP, and mirrored the established neuropathological distribution for each disease. In both AD and PSP, disease severity correlated with neuro-inflammation in the regions most closely associated with principal neuropathological markers including tau aggregates. Immunotherapeutic strategies targeting neuro-inflammation may be a useful strategy in slowing the progression of these neurodegenerative disorders.

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The predictor factors for survival in Chinese Multiple System Atrophy patients

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Objective: Our aim was to explore the predictors of survival in Chinese multiple system atrophy (MSA) patients. Background: MSA is a rare, fatal neurodegenerative disorder with symptoms of autonomic failure plus parkinsonism, cerebellar ataxia, or both. Predictors of survival of MSA remain largely unknown. Methods: A total of 339 probable MSA patients were enrolled. Disease severity was assessed by the Unified Multiple System Atrophy Rating Scale (UMSARS). Kaplan-Meier curves were used to compare survival time. Cox proportional hazards models were used to calculate hazard ratios for shorter survival using age of disease onset, sex, clinical phenotype, neurological and autonomic manifestations as categorical variables. Results: Among the total of patients, 195 patients were MSA-C subtype and 144 were MSA-P subtype. At baseline, there were no significant differences in the disease duration, the frequency of autonomic symptom as initial symptom and autonomic symptoms between the MSA-P and MSA-C patients, however, the MSA-P patients showed higher UMSARS-I, UMSARS-II, and UMSARS-IV scores than the MSA-C patients. Twelve (3.52%) patients were lost during follow-up, 118 patients were deceased, and 209 patients (follow-up period from 12 to 82 months) were alive at the time of the last visit. Median survival from symptom onset to death was 7.3 years (95% CI=6.8–7.8) and median survival from enrollment to death was 4.5 years (3.7-4.6) according to Kaplan-Meier analysis. The older age of onset (>57 years) showed shorter survival time (p=0.027). There were no differences in survival time regarding sub-type or sex. The adjusted Cox proportional hazard model retained the following unfavorable predictors of survival: (i) autonomic onset (hazard ratio=1.736, p=0.029); (ii) UMSARS-IV > 2 (hazard ratio=1.944, p=0.001); (iii) orthostatic hypotension (hazard ratio=1.923, p=0.003); (iv) falls within 3 years (hazard ratio=1.570, p=0.029);

(v) age of onset > 57 (hazard ratio=1.623, p=0.011).

Conclusions: Survival time of Chinese MSA patients was similar with that of Caucasian population. Our study suggests that autonomic onset, orthostatic hypotension, older age onset and falls within 3 years are potential predictors for survival of MSA patients. Additionally, severe global disability measured by UMSARS-IV is the first time suggested to be a poor survival predictor for MSA.

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Depression, anxiety and quality of life in Multiple System Atrophy

L. Zhang, B. Cao, Q. Wei, R. Ou, B. Zhao, J. Yang, Y. Wu, H. Shang (Chengdu, People's Republic of China) **Objective:** To explore the features and determinants of depression and anxiety symptoms in multiple system atrophy (MSA) and the associations between mood dysfunction and quality of life (QOL) in MSA patients in Chinese population.

Background: Features and determinants of depression and anxiety symptoms in MSA and the associations between mood dysfunction and QOL in MSA patients in Chinese population remain unknown.

Methods: A total of 170 MSA patients were enrolled in the study. Neuropsychological assessment was performed using Hamilton Depression Rating Scale-24 items and Hamilton Anxiety Rating Scale. Parkinson's Disease Questionnaire-39 item version was used to evaluate the QOL.

Results: We found that 64.1% and 71.7% patients had at least mild depression and anxiety symptoms, respectively. The severity of depression of MSA patients was associated with sex (P = 0.042), educational years (P = 0.030), disease duration (P = 0.001), disease severity (P = 0.007), orthostatic hypotension (P = 0.009) and global disability (P < 0.0001). While, the severity of anxiety was associated with increased disease duration (P < 0.0001), disease severity (UMSARS-I) (P = 0.020), orthostatic hypotension (P = 0.001) and global disability (P < 0.0001). Spearman's correlation test showed both depression and anxiety symptoms had a close relationship with QOL in MSA patients. Binary logistic regression showed the determinants of depression were female, lower educational years, longer disease duration, orthostatic hypotension and global disability. Meanwhile, disease severity and orthostatic hypotension were the determinants of anxiety.

Conclusions: Depression and anxiety symptoms are common in patients with MSA. Both depression and anxiety symptoms have a close relationship with QOL in MSA patients. Neurologists should pay attention to depression and anxiety in patients with MSA, especially those with orthostatic hypotension and severe disease condition.

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a-Synuclein preformed fibrils induce disruption of myelin basic protein expression in primary oligodendrocyte culture; deciphering glial pathology in Multiple System Atrophy

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Objective: This research focuses on the impact of extracellular a-synuclein preformed fibrils (a-syn PFFs) on oligodendrocytes (OLGs) as a potential contributor exacerbating the pathology of multiple system atrophy (MSA).

Background: The pathological finding in MSA is uniquely observed in OLGs, the myelin-forming cells of the central nervous system. The oligodendroglial a-syn aggregates, widely known as glial cytoplasmic inclusions (GCIs) are reportedly confirmed prior to neuronal loss in MSA brains (1). Another previous investigation detected myelin loss accompanied by preserved numbers of OLGs in MSA brains or transgenic MSA model mice brains, suggesting the existence of dysfunctional OLGs in association with a-syn accumulation (2).

Methods: Primary mixed glial cell culture was obtained from neonatal rats. OLGs culture was prepared through isolation of oligodendrocyte progenitor cells and induction of maturation. Bacterially expressed recombinant human a-syn was purified by ion exchange chromatography, followed by 3-7 days incubation with agitation at 37? for the use of a-syn PFFs. OLGs were incubated for twenty-four hours after a-syn PFFs application and subjected to immunoblot analysis as well as cell viability assays. Immunostaining was performed with confocal microscopy to evaluate the morphological change of OLGs as a result of a-syn PFFs application.

Results: Interestingly immunoblot analysis revealed unnegligible amount of endogenous a-syn in OLGs. While asyn PFFs application did not significantly affect cell viability, the protein expression of myelin basic protein (MBP) was remarkably reduced in a concentration-dependent manner (figure 1 A, B). Immunostaining suggested that OLGs incubated with a-syn PFFs show morphological alteration characterized by fewer processes and decreased MBP expression compared with control OLGs (figure 1 C).



Conclusions: Our study indicated the possible contribution of extracellular a-syn PFFs to the production of MSA pathology in terms of OLGs dysfunction. Given that OLGs support neurons by forming myelin sheath, their dysfunction probably exacerbates neuronal activity, representing a critical pathological aspect of MSA.

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Can CSF and plasma Neurofilament Light Chain predict disease progression in Progressive Supranuclear Palsy?

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Objective: To investigate whether the level of CSF Neurofilament Light Chain (NFL) can predict the speed of disease progression in patients with Progressive Supranuclear Palsy (PSP).

Background: Measuring clinical progression in neurodegenerative conditions is central to defining the effects of therapeutic intervention and disease biology. There is a need for reliable disease progression biomarkers to complement clinical rating scales such as the PSP rating scale (PSPRS). Predicting disease progression with such biomarkers may enable better powered clinical trials, and give insights into the mediators of progression. This study

builds on recent work which has shown that serial measurements of CSF NFL can reliably track disease progression (1), whilst plasma NFL at baseline predicts the severity of subsequent progression (2).

Methods: A prospective cohort of 90 patients and 29 healthy controls were recruited from a single specialist Neurology centre between June 2011 and December 2013. Patients were clinically diagnosed according to current consensus criteria. CSF samples were obtained from patients with clinical diagnoses of PSP (n=29), CBS (n=10), MSA (n=29), PD (n=5) and AD (n=17). Baseline NFL concentration was measured using standard enzyme-linked immunosorbent assay (ELISA). Patients were followed up longitudinally to obtain a total disease duration (date of disease onset to date of death/date of censoring). Survival was analysed using Kaplan-Meier survival and Cox regression analyses.

Results: As previously reported, the mean CSF NFL concentration was higher in the atypical parkinsonian syndrome group (PSP, CBS and MSA) vs PD, AD and healthy controls (2507.2ng/ml vs 1116.0ng/ml, 1429.9ng/ml and 630.6ng/ml). By dividing the PSP subjects into high and low CSF NFL groups based on the median CSF NFL concentration of 2217ng/ml, we found that the high CSF NFL group were over 5 times more likely to die during the monitored time period (hazard ratio 5.75, p = 0.02, 95% CI 1.35-24.43), when corrected for gender, age and disease duration at testing and disease severity at testing according to the baseline PSPRS score.

Conclusions: Our results suggest that baseline CSF NFL levels can predict future disease progression. Our aim is to replicate these findings in both CSF and plasma in a larger cohort using ultrasensitive methods of protein biomarker detection.

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Evaluation of a Radiographic Marker as a Diagnostic Tool for Progressive Supranuclear Palsy

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Objective: To evaluate the sensitivity and specificity of a radiographic marker, midbrain to pons ratio, in brain MRI of Progressive Supranuclear Palsy (PSP) patients as evaluated by different medical specialists.

Background: PSP can be clinically challenging to diagnose early in the disease. Recent investigations show that radiographic markers may aid in the diagnoses; one marker of interest is the midbrain to pons ratio on brain MRI and its sensitivity and specificity in PSP. One study has demonstrated that in a clinically and pathologically confirmed PSP cohort a midbrain to pons ratio of less than 0.52 was 100% specific and 85.7% sensitive for PSP.¹ This ratio is a simple marker that is calculated from midsagittal brain MRI. Application of this tool in clinic may be useful; however variability of measurements amongst different medical specialists may affect the usefulness of this marker.

Methods: A clinically confirmed cohort of age and gender matched PSP and Parkinson's disease (PD) patients who had brain MRI with midsagittal images was selected from the University of Kansas Medical Center's movement Disorder database. Measurements obtained included the midbrain and pons short axis diameter. The midbrain to pons ratio was calculated by dividing the midbrain to pons measurements. The measurements were obtained by a neuroradiologist and a senior neurology resident. Both raters were blinded to clinical information.

Results: Twelve PSP patients with a mean age of 69 years on date of MRI (range 64-77) and 12 PD patients with a mean age of 70 years on date of MRI (range 63-76) were evaluated. Each group was comprised of 83% males. When measured by the neuroradiologist, 12 of 12 PSP patients had a midbrain to pons ratio of less than 0.52, and 2 of 12 PD patients were also measured to be in the PSP range. This resulted in 100% sensitivity and 83% specificity. When measured by the senior neurology resident, 10 of 12 PSP patients had a midbrain to pons ratio of less than 0.52, and 2 of 12 PD patients were also measured to be in the PSP range. This resulted in a midbrain to pons ratio of less than 0.52, and 2 of 12 PD patients were also measured to be in the PSP range. This resulted in a lower sensitivity than the

neuroradiologist at 83% but the same specificity as the neuroradiologist at 83% for PSP. **Conclusions:** The midbrain to pons ratio as a radiological marker may aid in the diagnosis of PSP. It appears that this is a sensitive and specific measure whether calculated by a neuroradiologist or a senior neurology resident.

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Impulse control disorders in Parkinson's disease: description of a New Zealand cohort

A. Garvey, S. Buchanan, N. Cutfield (Dunedin, New Zealand)

Objective: Impulse control disorders (ICDS) are a recognised complication of dopaminergic therapy for Parkinson's disease. We wanted to assess the rates of ICDs in New Zealand where dopamine agonist use has been very low. **Background:** Impulse control and related disorders (ICRD) are a significant complication of dopaminergic therapy for Parkinson's disease. Evidence supports that they may be under-recognised in a clinical setting. ICRD encompasses the individual impulse control disorders of pathological gambling, compulsive sexual behaviour, compulsive spending, and binge eating; and related disorders also associated with dopaminergic medication use

include punding, hobbyism and dopaminergic medication overuse. These disorders have been linked to dopamine agonist use, however, government agency restrictions in New Zealand have meant low rates of use of dopamine agonists in this population.

Methods: A cross sectional sample of non-demented community with PD diagnosed by either a neurologist or geriatrician. Patients self-completed the QUIP-RS, a previously validated screening tool for impulse control disorders Clinical notes were audited. A national ethics board approved this study, and written consent was obtained from each participant.

Results: 50 patients were enrolled. The average age was 68.9 years (range 42-82). 28 were male, with an average disease duration of 6.2 years. 96% of patients were treated with levodopa. No patients were treated with dopamine agonist monotherapy. 9/50 (18%) patients were using a dopamine agonist; eight on ropinerole, one on lisuride. 24% (12/50) of patients screened positive for ICDRD using QUIP- RS. Patients who screened positive were more likely to be male (75%), younger in age and had a shorter disease duration. They had a higher average dose of dopaminergic medication, 761mg / day as opposed to 421mg / day. Of the 12, only 3 had a clinically documented suspicion of ICRD.

Demographics

	Mean	Range
Age (years)	68.9	42 - 82
Male gender	58%	
Disease duration (years)	6.2	1-21
LEDD (mg/day)	542	0 - 1530
Medications		
	Number of patients (%)	
Levodopa	48 (96)	
Dopamine agonist	9 (18)	
COMT Inhibitor	3 (6)	
Amantadine	5 (10)	
MAOI - B	1 (2)	

	ICRD (n=12)	NoICRD (n=38)
Age	67.4	69.4
Male gender	75%	53%
Disease duration	5.3	6.4
LEDD (mg/day)	761	492
Dopamine agonist use	17%	18%

Conclusions: Although this is a small, non systematic cohort, rates of ICDRD seen here appear similar to others recently published, with 22% of patients screening positive. The rate of ICRD seems to be higher in males, and correlate with a higher daily levodopa dose although the sample size was too small to draw statistically significant

conclusions. Only 18% of patients were on a DA. Our findings show that ICDRD should be suspected in patients regardless of DA exposure.

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Brain metabolic patterns in progressive supranuclear palsy phenotypes

M.M. Carmona-Abellan, A. Fontes, E. Prieto, J. Arbizu, R. Luquin, M. Riverol (Pamplona, Spain) **Objective:** To describe changes in cerebral glucose metabolism in patients with different described clinical phenotypes of PSP and to correlate them with the clinical manifestations of the disease.

Background: Clinicopathological studies have led to the recognition of different clinical phenotypes associated with PSP-tau pathology. The most common PSP subtypes are the classic Richardson's syndrome and parkinsonian-PSP. Brain metabolism on fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been identified as a potential biomarker to differentiate PSP from other diseases.

Methods: We performed a retrospective selection of 15 patients diagnosed with PSP who had a brain metabolism study using PET-fluorodeoxyglucose (FDG). Clinically, patients were classified as PSP type Richardson syndrome (RS-PSP, 9 patients) and parkinsonian-PSP (P-PSP, 6 patients).

We proceeded to an image analysis based on voxels using the SPMS program with respect to a control group (n=20). PET-FDG images were normalized by reference to the brainstem. A correction of p <0.0001 with 100 voxels was used.

Results: The brain metabolism pattern of the RS-PSP group with respect to the control group showed a hypometabolism of the caudate, thalamic and midbrain nuclei. The pattern of the P-PSP group with respect to the control group was characterized by hypometabolism of the cingular cortex, caudates and both thalamIc nuclei. Our results indicate that FDG-PET scan might be a useful tool to differentiate PSP subtypes.

Conclusions: In the RS-PSP a thalamic and midbrain involvement is predominant. The P-PSP shows a predominant affectation of the caudate nuclei and the thalamus. The mesencephalic affectation objectified in the RS-PSP group, unlike the PSP-P group, correlates with the paralysis of the characteristic vertical gaze of the first type. These functional neuroimaging findings coincide with the clinical expression of these PSP phenotype subtypes and would help to better identify patients with PSP.

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Gait and Cognition in Progressive Supranuclear Palsy: A Significant Association

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Objective: In this study we explored the association between gait parameters and cognitive function of PSP. **Background:** Gait and cognition are interrelated in patients with progressive neurodegenerative disorders like Parkinson's disease. Perhaps, this association of gait and cognition rooted from similar anatomical control of these functions through basal ganglia and prefrontal cortex. We examined the association of cognitive function and gait in Progressive Supranuclear Palsy (PSP) patients.

Methods: Cognitive functions of 20 PSP patients were initially estimated using MMSE. The cognitive domains were further assessed using Mattis-DRS. Gait velocity, stride length like gait parameters were recorded using gaitrite, a 6.1 metre long electronic walkway. The fall efficacy rating scale was also used to find out the tendency to fall.

Results: The mean age of 20 PSP patients was 63 years where 75% were male. The gait parameters showed no differences across cognitive categories (intact cognition & mild, moderate, severe cognitive impairment) derived from DRS assessment except that patients with severe cognitive impairment had significantly lower cadence (steps/ minute) than mild-moderate cognitive impairment group. Patients with impaired initiation/ perseveration (cognitive domain) had gait velocity of 44 cm/sec compared to 70 cm/sec in patients without impairment (p 0.003). Stride length was significantly lower in the impaired initiation group. Therefore, step count was higher among them. We also observed that patients with impaired attention (cognitive domain) had higher fall efficacy total score of 63 compared to 59 in patients without impairment (p 0.051).

Conclusions: Initiation/ perseveration appeared to be the most robust cognitive domain associated with the gait outcome in PSP patients. Unlike other subdomains patients with impaired attention possibly had a higher fall risk. This study has reinforced a close relationship of gait and cognition in PSP explaining possible thalamo-frontocortical connection.

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Utility of THK-5351 tau-PET for differential diagnosis in patients with hypokinetic-rigid syndromes. *G. Rohrer, S. Schönecker, M. Brendel, J. Havla, G. Höglinger, S. Lindner, C. Zach, F. Vettermann, C. Prix, G. Nübling, P. Bartenstein, K. Furukawa, A. Ishiki, N. Okamura, K. Bötzel, A. Rominger, J. Levin (Munich, Germany)* **Objective:** The objective of our study is to investigate the use of THK-5351 tau- PET-imaging as an additional tool for differential diagnosis in hypokinetic-rigid syndromes suggestive for Parkinson's disease and atypical Parkinsonian syndromes.

Background: The pathophysiology of neurodegenerative typical or atypical parkinsonian syndromes is characterized by deposition of fibrillar aggregates either of tau protein or alpha-synuclein in neuronal and/or glial cells in affected brain areas. Increasing efforts are taken to develop interventions against defined molecular target structures to develop a disease modifying therapy targeting either alpha-synuclein or tau aggregate pathology. As these distinct molecular pathologies can manifest clinically as overlapping syndromes, it is becoming increasingly important to establish biomarkers yielding an *ante mortem* diagnosis of the underlying pathology. The clinical diagnosis of PSP, a primary tauopathy, is based on clinical criteria and MRI findings, which do not take tau pathology into consideration. The presence of tau- deposits is a key finding leading to the neuropathological diagnosis of ,,definite PSP", which is usually established *post mortem*. Therefore, we aim to investigate the utility of THK-5351-PET as a tool to diagnose the presence of tau pathology in hypokinetic-rigid syndromes in vivo.

Methods: Patients with possible or probable PSP or MSA-P according to current criteria received THK-5351 PET scanning. PET scans were co-registered to MRI. A visual as well as a semi-quantitative analysis of tracer binding (standardized uptake value ratio) in predefined brain areas was performed using the cerebellar cortex as reference region. Disease severity measured by the PSP Rating Scale, Unified Multiple System Atrophy Rating Scale, Schwab and England Activities of Daily Living scale and disease duration were assessed.

Results: Increased THK-5351 binding was detectable in striatum, thalamus and brainstem, especially in the midbrain in patients with PSP compared to patients with MSA or healthy controls.

Conclusions: THK-5351 binding patterns correlated well with the known distribution of tau-pathology at autopsy in PSP. Higher THK-5351 retention was evident in patients with PSP compared to patients with MSA and healthy controls. THK-5351 seems to be a useful biomarker of tau deposition and may therefore facilitate differential diagnosis of hypokinetic-rigid syndromes.

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Gut Microbiota in Multiple System Atrophy

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Objective: To investigate the gut microbiome and metabolome in MSA.

Background: Experimental models of prion-like cell-to-cell transfer of alpha-synuclein(AS) and its ability to spread from the enteric nervous system(ENS) to the brain, have reignited Braak's proposal that environmental insults acting on the ENS could trigger the misfolding of AS, subsequently propagating into the central nervous system. This gutbrain-axis in synucleinopathies is further supported by mounting evidence for the role of gut microbiota in regulating diseases via intense bidirectional interplay of neuronal, immunological and hormonal signaling. There is new preclinical evidence that gut microbes promote microglial activation and AS-mediated motor deficits and pathology.¹ Three studies have reported alterations of gut microbiome in PD,² but none has been published in MSA to date.

Methods: We recruited 17 MSA patients and 17 age-matched spouses/siblings(living in the same community, to control for confounding factors such as lifestyle, diet and housing condition). Demographic data and detailed medical history including medications, diet and constipation severity were collected. Stool DNA was extracted and amplicon sequencing targeting the V3-V4 region of the microbial 16SrRNA gene was performed on Illumina Miseq platform. Stool metabolomics were analysed using nuclear magnetic resonance spectroscopy.

Results: There were no significant group differences in age, gender, education level, dietary pattern, smoking and diabetic status. MSA patients had worse constipation severity score(Table 1). Four patients were treatment-naïve and mean MSA duration was 3.7 ± 2.1 years. Fecal microbiota composition was significantly different between patients and controls(Fig 1). MSA patients had a significant 5-fold reduction in the abundance of *paraprevotella* (p=0.02)(Fig 2). There was no correlation between the abundance of *paraprevotella* with constipation severity(r=0.185,p=0.295). We found a clear separation in fecal metabolomics between the two groups(Fig 3), providing further insights into differences in bacterial functions. MSA patients had significantly lower levels of fecal butyrate, propionate, trimethylamine and choline(Fig 4).

Table 1: Demographics and clinical characteristics

	Patient (n=17)	Control (n=17)	P Value
Age Mean ± S.D.	64.8 ± 6.4	65.6 ± 9.9	0.759
Gender		- 9450	1010
% Male	23.5	52.9	0.158
Education Level			
% Tertiary	47.1	70.6	0.518
% Secondary	29.4	23.5	1,2242,522
% Primary	11.8	5.9	
% None	5.9	0.0	
Smoking Status			
% Current Smoker	0.0	5.9	0.463
% Past Smoker	29.4	17.6	0.0000.000000
% Never Smoked	70.6	76.5	
History of Diabetes Mellitus			
% Yes	5.9	18.8	0.335
Dietary Pattern			
Energy intake (kcal/day)	2052.3 ± 868.3	2659.3 ± 1994.1	0.262
Protein intake (g/day)	96.1 ± 65.1	117.0 ± 72.5	0.382
Fat intake (g/day)	74.9 ± 34.0	109.1 ± 85.4	0.135
Carbohydrate intake (g/day)	248.7 ± 93.0	298.8 ± 249.4	0.447
Fiber intake (g/day)	27.4 ± 14.0	33.1 ± 19.3	0.332
Constipation Severity			
Cleveland Constipation	9.9 ± 5.3	3.7 ± 3.2	0.001*
Questionnaire total score		10000	(23)223

*denotes significant between-group differences

Figure 1: Principal component analysis plot of fecal microbiome composition





Figure 2: Between-group differences in the abundance of Paraprevotellaceae





Figure 4: Permuted loading plots of fecal metabolome. Labeled are metabolites that showed significant between-group differences (p<0.03).



Conclusions: Preliminary results suggest an alteration of gut microbiota in MSA patients. The finding of reduced abundance of *paraprevotella* mirrors a previous study in PD.² The potential role of the gut in the etiopathogenesis of synucleinopathies warrants further study.

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Tau Network Genes in a Genome Wide Association Study of Progressive Supranuclear Palsy

T. Chang (Los Angeles, CA, USA)

Objective: To determine how tau network genes overlap with single nucleotide polymorphisms (SNPs) associated with Progressive Supranuclear Palsy (PSP) in a Genome Wide Association Study (GWAS)¹.

Background: PSP is a neurodegenerative tauopathy marked by postural instability resulting in falls, supranuclear ophthalmoparesis, and frontal lobe dysfunction. PSP genetic risk includes microtubule-associated protein tau (*MAPT*) and possibly genes such as Syntaxin 6 identified in a GWAS. As the genetic risks of PSP are not clearly elucidated, investigating gene networks associated with tau dysfunction could uncover specific PSP genetic risk factors.

Methods: Summary statistics from a previous PSP GWAS¹ were obtained. SNPs from the PSP GWAS were associated to genes using Ensembl. Gene networks associated with tau dysfunction were developed using mRNA gene expression in mice with a highly penetrant tau mutation. mRNA was collected from mouse brain tissue. Tau networks were developed via Weighted Gene Co-expression Network Analysis. Mouse tau network genes were represented as human gene homologs. The over-representation of tau network genes among significant SNP associated genes from the GWAS was analyzed with the Fisher exact test.

Results: Twenty percent (2,327) of the genes from the mice with the highly penetrant tau mutation were determined to be involved in a tau network. Sixteen of the most significant SNPs from the GWAS (*p*-value less than 6.2×10^{-4}) were associated with 10 unique genes. Of these 10 genes, 7 were tau network genes (OR 8.8 [2.0-52], *p*-value 0.001). The most significant SNP was associated with *NSF*, a gene involved in Golgi vesicle transport. *NSF* is on the 17q21 chromosome region. *MAPT* is on this region as well. *NSF* was a candidate gene for a GWAS of Parkinson's disease in an Ashkenazi Jewish population. *TNXB* was also a significant SNP associated gene from the tau network. It is an extracellular matrix glycoprotein with anti-adhesive effects. A transcriptomic study² associated *TNXB* with Alzheimer's disease, another tauopathy.

Conclusions: Tau network genes show statistically significant over-representation among SNPs highly correlated with PSP in a GWAS. These genes, including *NSF* and *TNXB*, have been associated with Parkinson's disease and Alzheimer's disease.

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Neuroactive steroids reverse the dopaminergic neurotransmission defectiveness in chronic hepatic (HE) encephalopathy: a possible involvement in HE related parkinsonism

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Objective: In the present study, we describe the changes of the dopaminergic system occurring in the cirrhotic rats and concomitantly we investigated the effect of DHEAS on this system in Sprague-Dawley rats using the expression of tyrosine hydroxylase (TH) as a neuronal marker.

Background: Hepatic encephalopathy (HE) is a neuropsychiatric disorder occurring as a consequence of both acute and chronic liver failure. Advanced HE is generally accompanied with extrapyramidal symptoms including rigidity and tremor, which may reflect alterations of the dopaminergic system. Recently we reported a beneficial effect of the neuroactive steroid dehydroepiandrosterone sulfate (DHEAS) in cirrhotic rats, however the mechanisms of such an effect by DHEAS were not addressed.

Methods: Rats were submitted to bile duct ligation (BDL) surgery and TH immunohistochemistry was assessed in the Substantia nigra pars compacta (SNc), striatum, ventral tegmental area (VTA) and the cortex.

Results: TH immunoreactivity showed a significant diminution in both SNc and VTA concomitantly with the cortical and the striatal outputs in the BDL rats vs. controls. Three daily injections of 5mg/kg of DHEAS to BDL rats significantly normalized TH expression decrease in both SNc and VTA as well as dopaminergic projections to the striatum and the cortex of BDL rats.

Conclusions: The present data support an involvement of the dopaminergic system in mild HE and a possible beneficial effect of the neurosteroid DHEAS as a potential pharmacological treatment of mild HE.

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Acute L-dopa Challenge Test in Early Parkinsonism With Respect To Presence of Red Flag Signs &MRIAbnormalitis

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Objective: In this study we have tried to find any association between acute levodopa challenge responsiveness, red flag signs of parkinsonism and neuroimaging abnormality.

Background: Distinguishing IPD from atypical parkinsonism is challenging because of lack of characteristic signs & symptoms during the early stage.Short-term challenges with dopaminergic agents are used in patients with IPD to predict therapeutic effect of sustained l-dopa treatment.

Methods: In this single centre prospective study we evaluated 36 patients with early parkinsonism (=2yrs) clinically, radiologically along with acute levodopa challenge and followed over a period of 6 months to asses for evolution of bad parkinsonism (evident by presence of red flag signs and neuroimaging abnormality).

Results: Out of 36 patients 2 developed akinetic rigid mutism during antiparkinson drug withdrawl and were excluded, 4 developed intolerance symptoms during acute challenge. Red flag sign was present in 5 (26.3%) patients in responder (19 patients) group compared to 9 (66.6%) patients in non-responders (15 patients) (P=0.031). Neuroradiological abnormality was present in 3 (15.8%) in responder group compared to 11 (73.3%) in non-responder (P=0.012). Except for dysautonomia (P=0.09), other red flag signs like symmetrical `tremor (P=0.003), cerebellar involvement (P=0.001), vertical opthalmoparesis (P=0.001), abnormal limb posturing, bulbar symptoms, blepharospasm & frontal dystonia, cortical sensory loss, pyramidal sign &pseudobulbar affect, dementia & aphasia (P=0.021) were significantly more present in non-responder group. Patients who developed l-dopa intolerance symptoms during challenge developed dysautonomia out of which 1 had also cerebellar involvement. Among radiological abnormality except for periventricular leukoaraiosis (P=0.6), cortical atropy (P=0.01) & hydrocephalous were significantly more present in non-responder group.

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Indivizual Red Flag Signs In The Two Groups



Radiological Abnormality In The Two Groups



Acute Levodoa Resonse In The Different Hoehn And Yahr Stage



Conclusions: Though a small cohort with a short-term follow-up period, a good agreement was found between response to acute l-dopa challenge and absence of red flag signs (except dysautonomia) and neuroimaging abnormality (except leukoaraiosis) which could help us to predict the possibility of bad parkinsonian, but they should be further followed up. Development of intolerance during acute challenge might points towards the possibility of developing dysautonomia. Visible motor improvement after single dose of l-dopa provides good compliance to long term drug therapy.

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Cardiac Autonomic Dysregulation in Probable Multiple System Atrophy

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Objective: The objective was to retrospectively study the nature of cardiac autonomic dysfunction and the effect of phenotype on it in probable Multiple System Atrophy (MSA) patients.

Background: MSA is an adult onset, sporadic, neurodegenerative disorder. It has parkinsonian (MSA-P) and cerebellar (MSA-C) motor subtypes. Limited data exists on the nature of cardiac autonomic dysfunction in Indians affected with MSA. Assessing the differences in the severity of autonomic dysfunction between the subtypes facilitates better understanding as to which has better prognosis.

Methods: It is a retrospective descriptive study. Probable MSA patients who attended our hospital between May 2011 and May 2016, fulfilled diagnostic criteria given by Second Consensus statement and did not have any other co-morbid neurological, psychiatric or systemic illness constituted the study population. There were 45 Probable MSA patients (MSA-P=22; MSA-C=23) and 45 age and gender matched healthy controls. Conventional cardiac autonomic function testing (AFT) and short term heart rate variability (HRV) were the study tools. Differences between MSA-P, MSA-C and control groups were analyzed by parametric and non-parametric tests as appropriate. **Results:** There were 31 males and 14 females in both MSA and control groups. Mean age of MSA patients was 55.68±8.09yrs and controls was 55.64±8.86yrs. Mean age of onset of MSA was 53±8yrs. Median disease duration was 3yrs. Among MSA patients, 55.6% reported postural symptoms and 73.3% reported bladder disturbances. Conventional cardiac AFT showed that in MSA-P group, 18.2% had definitive and 63.6% had severe cardiac

autonomic dysfunction while in MSA-C group, 8.7% had early, 26.1% had definitive and 52.2% had severe cardiac autonomic dysfunction. However, there was no significant difference between subtypes [Graph 1]. HRV analysis showed that overall HRV, sympathetic activity and parasympathetic activity was significantly reduced in both MSA-P and MSA-C patients as compared to controls (p<0.0001). However, there was no significant difference in HRV parameters between subtypes [Table 1].

Parameters		MSA-P (n=22) Median (IQR)	MSA-C (n=23) Median (IQR)	Controls (n=45) Median (IQR)	Chi-Square	p value
Time Domain	SDNN (ms)	14.09 (8.54)	16.59 (13.03)	41.26 (17.36)	55.42	0.0001***
Parameters	RMSSD (ms)	8.7 (9.12)	11.9 (10.07)	30.29(18.12)	44.41	0.0001***
	NN50 (count)	0.001(2)	0.001(1)	26 (60)	46.64	0.0001***
	pNN50 (%)	0.001 (0.58)	0.001 (0.29)	8.53 (15.05)	44.07	0.0001***
Frequency Domain	Total Power (ms ²)	183.78 (250)	255.61 (384.1)	1639.74 (1500)	55.53	0.0001***
Parameters	HF Power (ms ²)	26.03 (38.7)	29.67 (123.93)	352.23 (496.9)	47.89	0.0001***
	LF Power (ms ²)	26.59 (46.77)	48.49 (79.72)	421.28 (390)	54.75	0.0001***
	LF/HF Ratio	1.25 (1.53)	1.76 (2.44)	0.87 (0.88)	4.31	0.116

Table. No. 1. Time and Frequency Don	nain Parameters of Short Term Heart Rate Variabilit
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SDNN: Standard deviation of RR Intervals; RMSSD: Square root of the mean of the sum of squares of differences between adjacent RR intervals; NN50: Count of number of pairs of RR intervals differing by >50ms; pNN50 (%): percentage of count of number of pairs of adjacent RR intervals differing by more than 50 ms; HF power: High frequency Power; LF power: Low frequency power; LF/HF ratio: Sympathovagal balance. Kruskal-Wallis Test: ***p<0.0001

Graph 1: Severity of Autonomic Dysfunction based on Conventional Cardiac AFT



Conclusions: There is autonomic dysfunction in MSA patients as evidenced by symptomatology, conventional cardiac AFT and HRV. Sympathetic as well as parasympathetic nervous system is affected in MSA. There is similarity in the nature of cardiac autonomic dysfunction between the MSA-P and MSA-C phenotypes.

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Diffusion-Weighted MRI discriminates Parkinson's disease from the Parkinsonian Variant of Multiple System Atrophy: a Meta-analysis

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Objective: A systematic review and meta-analysis was performed to evaluate the diagnostic accuracy of DWI in the differential diagnosis of the parkinsonian variant of multiple system atrophy (MSA-P) and Parkinson's disease (PD). **Background:** Numerous studies using diffusion-weighted imaging (DWI) have shown that putaminal diffusivity is increased in patients with MSA-P as compared with PD patients.

Methods: Studies on DWI were identified through a systematic PubMed search. Papers were selected based on stringent inclusion criteria; minimum requirement was the involvement of MSA-P and PD patients and either documented true positive, true negative, false positive and false negative rates or overall sample size and reported sensitivity and specificity. Meta-analysis was performed using the hierarchical summary receiver operating characteristics curve approach.

Results: The PubMed search resulted in 793 results of which 9 studies were deemed relevant. Putaminal diffusivity was assessed in 127 patients with MSA-P, 262 patients with PD and 70 healthy controls (HC). The meta-analysis showed an overall sensitivity of 90% (95% confidence interval: 76.7% - 95.8%) and an overall specificity of 93% (95% confidence interval: 80.0% - 97.7%) to discriminate MSA-P from PD based on putaminal diffusivity. **Conclusions:** Although putaminal diffusivity in general yields good sensitivity and specificity in distinguishing clinically diagnosed cases with MSA-P from PD, the large confidence intervals demand further research as to the reasons of this large variability.

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Differential microRNA expression in a cohort of Parkinson's disease patients

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Objective: To develop a blood test that will use micro RNA (miRNA) to identify patients with PD. **Background:** PD is a progressive neurodegenerative disorder and by the time of clinical symptoms many midbrain structures have already been severely damaged. A need exists to identify PD before clinical symptoms arise to allow future disease modifying therapies to use early and appropriately.

Methods: 11 male patients were selected from a cohort of 51 PD patients based on gender, age and disease duration. They were age and gender matched against controls. All participants had early morning, fasting bloods collected and processed within 2 hours to separate plasma for RNA isolation. miRNA was amplified and purified using the mirVanaTM miRNA isolation kit and quality assessed using the Nanodrop-1000. Pre-amplification was required before creating a cDNA library for analysis. PD samples and their control were analysed together on the same custom made array card from no replacement in drug list after reviewing the miRNA PD literature and including miRNA found from a similar Alzhiemer's study by our group.

Results: We found nine miRNAs to be differentially expressed between the PD and control groups. Five were down regulated and four up regulated. Two had an adjusted P value <0.05, the others of an unadjusted P value <0.05 with one having a 8.36 fold change. Five have been identified in relation to PD before; three in clinical cohorts, one in an autopsy series and one in both a clinical and an autopsy series.

Conclusions: We have found that miRNA expression differs between our PD group and their controls. We are currently increasing the cohort size to further validate our findings with the hope of providing a blood test that will help identify patients with PD.

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Serum mir-30c as a potential biomarker to discriminate MSA from PD patients: a pilot study

A. Vallelunga, M. Sessa, D. Giovanna, M. Picillo, P. Barone, M.T. Pellecchia (Salerno, Italy) **Objective:** In this pilot study we evaluated serum mir-30c levels in MSA and PD patients, to assess if mir-30c can be useful to distinguish these disorders. Moreover, for the first time we assessed mir-30c levels in serum samples stored at -20°C.

Background: Diagnosis of MSA is mainly based on clinical features and due to the overlapping clinical presentation, it can be difficult to distinguish MSA from PD and other parkinsonian disorders. Early differentiation between MSA and PD has clinical, therapeutic and prognostic consequences and may be difficult, if based solely on clinical examination (1.2). No reliable biomarker currently exists for the diagnosis and prognosis of MSA. MiRNAs are small noncoding RNAs with a key role in post-transcriptional gene regulation. Recent studies have revealed that some miRNAs are differentially expressed in human brain and regulate the expression of genes associated with specific neurodegenerative disorders such as PD. However, several miRNAs are differently expressed in plasma and serum samples of MSA patients compared to PD and controls (1.2). Recently, we observed that miR-30c was downregulated only in PD patients compared to healthy controls (2).

Methods: We enrolled 24 patients with PD (60 ± 8 years) and 15 patients with MSA (65 ± 7 years). miRNAs were extracted from 200 µl of serum samples stored at -20°C using total RNA purification kit (Norgen Biotek Corp) and finally eluted in 50 µl volume of elution buffer. Mir-30c was quantified using miRcury LNA assay (Exiqon) and expression fold changes were calculated by the 2-??*CT* method.

Results: Using miRcury LNA assay, we analyzed serum mir-30c in PD and MSA samples. We confirmed that mir-30c was upregulated in PD compared to MSA patients with a fold change of 4.4. Moreover, for the first time we observed that levels of mir-30c of the biobanked sera stored at -20°C were comparable to the profile of <1 year-old sera stored at -80°C.

Conclusions: Our results suggest that serum mir-30c could discriminate PD from MSA patients and be used as specific, non-invasive biomarkers for early diagnosis. Future prospective trials on large cohorts are warranted to

confirm whether this miRNAs can be effectively used for early MSA diagnosis. Finally, our pilot study suggests that circulating miRNAs retain their integrity under long-term sub-optimal storage temperatures opening the way for increased miRNA analyses in MSA and PD.

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Non-motor symptoms and gender differences in multiple system atrophy

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Objective: To determine the frequency and gender differences of non-motor symptoms (NMS) in patients with multiple system atrophy (MSA).

Background: NMS are a core feature in MSA and may precede onset of motor symptoms. Although NMS are gaining awareness as significant cause of morbidity, the frequency of symptoms among MSA subtypes and gender differences remain to be thoroughly characterized.

Methods: The clinical features of patients diagnosed clinically as probable or possible MSA who were treated at the movement disorder unit of Innsbruck, Austria between 2000-2016 were analysed. NMS covering autonomic, neuropsychiatric, sleep and olfactory domains were evaluated based on a review of medical records. Descriptive statistics of nominal and ordinal variables were performed and appropriate parametric or non-parametric tests were applied.

Results: Data from 175 MSA patients (51.4 % men) were included in the analysis. Early autonomic dysfunction as defined by occurrence of at least one symptom within 1 year of motor onset was recorded in 49.1 % of the patients. Overall the most frequent NMS reported by patients at any time throughout the disease course were bladder symptoms (94.8 % of cases), depression (80.7 %) and symptoms of REM sleep behavior disorder (78.8 %) followed by postural dizziness/ syncope (77.8 %) and constipation (75.2 %). Sleep-related breathing disturbance occurred in 66.1 % of patients. Up to 82.9 % of patients experienced at least three symptoms of the non-motor complex. Constipation and sudomotor symptoms were more prevalent in MSA-P (parkinsonian variant) patients compared to MSA-C (cerebellar variant) patients (p < 0.05). The most frequent NMS in men was impotence (96.6 %), and in women urinary urgency (95.8 %). Except for depression which occurred more frequently in women than in men (p = 0.04), the frequency of NMS during the entire disease course was comparable between male and female patients. In contrast early autonomic failure was more prevalent in male patients (58.9 % in male vs. 38.8 % in female, p = 0.008).

Conclusions: Our data show that NMS are prominent in MSA likely affecting quality of life. Gender differences were apparent for depression (women > men) and early autonomic failure (men > women). Further prospective studies are required to confirm our results.

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The environmental and genetic risk factors in multiple system atrophy in a Taiwanese population

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Objective: The etiology of MSA remains uncertain. Cholesterol and its metabolism derangements, a-Synuclein and CoQ2 genetic polymorphism have been disclosed to be associated with the risk of MSA.

Background: No comprehensive study of the environmental and genetic risk factors has been done in the Asian population.

Methods: A case-control study is conducted in a Taiwanese population. The patients fulfilled the criteria of possible and probable diagnosis of MSA were enrolled in the special clinics of Movement disorders in one medical center. The functional scores (UMSARS, MDS-UPDRS) and epidemiological questionnaire for environmental exposure risk factors were obtained. The CoQ2 and spinocerebellar ataxia genetic mutation of type 1,2,3,6, and 17 were examined. Serum total cholesterol (T-CHO), triglyceride (TG), anti-TPO and anti-GAD were checked. A group of age- and gender-matched healthy controls (HC) were included in the clinic of family doctor.

Results: The demographic data of 104 MSA patients included are 54 men, 50 women; 21 MSA-C, 62 MSA-P, and 21 mixed MSA; 34 probable MSA, 70 possible MSA; mean age of onset, 63.60 years; median of disease duration, 3.93 years. No mutation of SCA is noted but 4 patients with COQ2 V393A variant; 24 anti-TPO Ab and 8 anti-GAD Ab positive with no association of the score of UMSARS. Of note, the T-CHO and TG levels are significantly lower in 100 MSA patients compared with 88 HC (T-CHO: 117 ± 40.6 vs. 200.42 ± 38.52 , TG: 100 vs. 117, p < 0.001). The T-CHO is significantly higher in MSA-C compared with MSA-P and mixed MSA arms separately (p = 0.006). Furthermore, the T-CHO level is negatively correlated with the score of UMSARS among total or subgroups of

MSA patients (p < 0.001). The exposure to smoking and alcohol drinking is significantly lower in 70 MSA patients compared with 70 matched HC (p < 0.001) or 472 non-matched HC, but not in the exposure of well water or pesticides.

Conclusions: The exposure of smoking and alcohol drinking are lower in MSA group versus healthy control, which is consistent with previous studies in the western population. Of importance, patients with MSA had a lower T-CHO serum level compared with controls. The severity of MSA is negatively correlated with the serum level of T-CHO. Whether systemic lipid metabolism is connected with MSA warrants further study. Regarding the SCA genetic testing in MSA, it is not recommended as a routine examination.

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Differential diagnosis and progress monitoring in Progressive Supranuclear Palsy – a potential role of pulmonary function tests

G. Nuebling, C. Abright, M. Schuberth, S. Schoenecker, K. Boetzel, J. Levin, S. Lorenzl (Munich, Germany) **Objective:** To determine the utility of pulmonary function tests in the differential diagnosis and monitoring of disease progression of Progressive Supranuclear Palsy.

Background: Pulmonary complications such as aspiration pneumonia are a leading cause for hospitalisation and death in patients with Parkinson's disease (PD) and Progressive Supranuclear Palsy (PSP). While respiration has been extensively studied in PD, little is known about respiratory dysfunction in PSP. The aim of this study was to determine whether pulmonary function tests (PFT) reflect pulmonary dysfunction in PSP and may serve as additional tools for differential diagnosis and monitoring of disease progression.

Methods: Patients with PSP and PD were evaluated concerning differences in multiple readout parameters of PFT including VC, FEV1, PEF and MVV in a retrospective (PSP: n=29; PD: n=28) and a prospective (PSP: n=44; PD: n=22) cohort. PSP patients further underwent a follow-up investigation after one year. PFT were correlated with symptom burden as measured by Hoehn&Yahr (retrospective analyses) as well as Schwab & England Activities of Daily Living scale (SEADL), Frontal Assessment Battery (FAB), Mini mental state examination (MMSE) and PSP rating scale (PSPRS).

Results: In PSP, respiration is affected earlier and more severely than in PD at comparable levels of disability. Maximum Ventilatory Volume (MVV) was the most sensitive PFT parameter to differentiate PSP and PD and correlated well with disease severity in PSP (as measured by PSP-RS), but not in PD. Furthermore, our analyses demonstrate that MVV changes over one year may prove to be a valid additional parameter of disease progression in PSP.

Conclusions: PFT may be a useful additional tool in the differential diagnosis between PD and PSP. Since pulmonary dysfunction showed a stronger correlation with motor symptoms than with cognitive dysfunction, it can be speculated to be more likely due to axial rigidity than due to breathing apraxia. Furthermore, PFT should be evaluated further as an objective marker of disease progression and prognostication, and may be useful for future clinical trials.

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Dynamic Instability and Stride Width in Parkinsonism

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Objective: To compare differences in local dynamic stability (LDS) and its association with stride width in individuals with idiopathic Parkinson's disease (iPD), individuals with frontal gait disorders (FGD), and healthy elderly.

Background: LDS is often described as an indicator of the ability of the neuromuscular control system to attenuate local perturbations, and it is a sensitive predictor of fall risk in elderly adults. Despite the high rate of falls and gait disorders in individuals with iPD or FGD, the complex dynamics of gait such as LDS have not been well explored. In particular, it is unknown whether wider strides adopted by subjects with FGD, considered cautious and more statically stable than narrower strides, benefit LDS.

Methods: Thirty-eight subjects with iPD (69 ± 12 yrs, MDS-UPDRS Part 3: 34 ± 12), 17 subjects with FGD (73 ± 7 yrs), and 24 healthy control subjects (71 ± 8 yrs) participated. No subject with iPD reported freezing of gait on the NFOG-Q. Subjects with iPD or FGD were tested >12 hours after withholding anti-PD medication. Subjects walked overground at their comfortable pace for two minutes. Inertial sensors (APDM) on the sternum collected tri-axial accelerations and angular velocities at 128 Hz. Multiple bouts of 5 steady state strides were extracted and time-normalized. A 9D state space was constructed using the 3D accelerations and twice-time-delayed copies. LDS was estimated from the maximum finite-time Lyapunov exponent by taking the slope of the mean log divergence curve

from 0-0.5 strides. Separately, participants walked across an 8 m GAITRite mat three times and the average stride width was extracted. ANOVA and Tukey post-hoc tests compared LDS and stride width across groups, and Pearson correlation coefficients compared LDS to stride width.

Results: Subjects with FGD had wider strides and worse LDS compared to subjects with iPD and controls (p < 0.01). LDS did not differ between controls and subjects with iPD. Across all subjects, stride width was inversely correlated with LDS (r = 0.39, p < 0.01) (Fig 1). [figure1].



Conclusions: Neurological dysfunction associated with FGD produces less stable dynamic control of the upper body during gait. The association between wider strides and less LDS suggests wider steps may adversely affect LDS, potentially caused by larger mediolateral velocity of the center-of-mass. Future studies should examine the relationship between preferred step width, LDS, and falls throughout disease progression.

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Parkinsonism through astrocytic GABA induce motor symptoms

M.J. Lee, Y. Jang, J. Han, S.J. Kim, J. Kim, I. Ryu, X. Ju, M.J. Ryu, S.-Y. Choi, G.R. Kweon (Daejeon, Korea) **Objective:** Although reactive gliosis is a prominent feature of PD, its role in pathogenesis has remained elusive. Here we show that aberrantly synthesized GABA from reactive astrocytes tonically inhibits neighboring dopaminergic neuronal firing in SNpc, reducing dopamine production and release, leading to parkinsonian motor symptoms.

Background: Parkinsonism is a clinical syndrome of movement abnormalities seen in Parkinson's disease (PD), which has been attributed to cell-autonomous mechanism of doparminergic neuronal death in the substantia nigra pars compacta (SNpc).

Methods: To identify the GABA from reactive astrocyte in PD, we used toxin induced model (MPP+, 6-OHDA rat model, MPTP mouse model) and overexpressed alpha synuclein mouse model. Moreover, we also assessed it in postmortem PD patients' brain.

Results: The released GABA from astrocyte tonically inhibits pacemaker action potential firing of neighboring DA neurons, resulting in reduced tyrosine hydroxylase expression and Parkinson-like motor symptoms. Impairments are fully restored by treatment with the MAO-B inhibitor, selegiline. The effects of glial GABA and selegiline were mimicked by optogenetic silencing and activation of DA firing, respectively. Brain samples of PD patients revealed a plethora of GABA-positive reactive astrocytes with a significantly increased MAO-B mRNA expression. **Conclusions:** Our study proposes that glial GABA is inextricably linked to parkinsonism, which can arise even before substantial dopaminergic neuronal death.

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Neurogenic bladder in progressive supranuclear palsy: A comparison with Parkinson's disease and multiple system atrophy

K.J. Kim, J.M. Kim (Seongnam-Si, Korea)

Objective: To compare the features of urinary dysfunction in Progressive supranuclear palsy (PSP) with those of idiopathic Parkinson's disease (IPD) and multiple system atrophy (MSA).

Background: PSP can manifest urinary symptoms, like IPD and MSA do. However, urinary symptoms and its corresponding bladder dysfunctions in PSP have not been well studied to date.

Methods: We conducted a retrospective analysis of urodynamic data in patients diagnosed of parkinsonian disorders (PSP, IPD, and MSA) and presented urinary symptoms. Clinical information including demographic factors, onset age, duration, severity, treatment of parkinsonism and urinary symptoms in each patients were collected.

Results: A total of 131 patients (10 with PSP, 79 with IPD, and 42 with MSA) were included. The mean age and the age of disease onset of PSP patients were similar to those of IPD patients, and older than those of MSA patients. The duration of disease until the onset of urinary symptoms in PSP patients was similar to that of MSA patients, and shorter than that of IPD patients. In the urodynamic study, storage phase dysfunctions in patients with PSP were similar to those in patients with IPD or MSA. However, PSP patients showed the higher rates of voiding failure than IPD patients during a pressure-flow study and indicated the lower maximum flow rate, higher post-void residual volume, and higher proportions of impaired detrusor contraction than IPD patients, but rather similar to MSA patients.

Conclusions: Patients with PSP have variable urinary dysfunctions as much as those with MSA do and have more severe voiding phase dysfunctions than those with IPD. This may reflect the extensive degenerative process of neural structure in patients with PSP.

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Rolipram, a PDE-IV inhibitor protects against experimental Parkinsonism in mice

N. Kumar, R. Khanna (Jaipur, India)

Objective: Rolipram, a specific inhibitor of the phosphodiesterase IV (PDE IV), has recently been shown to exert neuroprotective effects in an Alzheimer transgenic mouse model and in hypoxic-ischemic damage in the rat brain. It activates the cAMP-dependent protein kinase (PKA)/cAMP regulatory element-binding protein (CREB) signaling pathway and it inhibits inflammation. The cAMP mediated signaling is regulated by the activity of cyclic nucleotide phosphodiesterases (PDE) that cleave the second messenger. In the present study, we tested neuroprotective effects, if any, of rolipram drug, a specific inhibitor of the phosphodiesterase IV in 1-methyl- 4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in mice.

Background: Parkinson's disease (PD) is a neurodegenerative disease and a movement disorder characterized by loss of dopaminergic neurons in the substantia nigra causing dopamine depletion in the striatum.

Methods: Experimental animal is muscular weighing 25–30 g of 4–5-month-old. The drug was given four times at 12 h intervals by gavation (25–100 mg/kg) in animals made parkinsonian following two doses of MPTP (30 mg/kg, i.p.). Control mice were injected with the same volume of pure DMSO. MPTP-induced striatal dopamine depletion was significantly attenuated by higher dose of rolipram. MPTP-induced catalepsy and akinesia, as well as loss in swim ability, were blocked dose-dependently by rolipram. Brain was used for biochemical and histopathological study.

Results: Present study further shows that rolipram can dose-dependently attenuate both in vitro hydroxyl radical production in a Fenton-like reaction, and also ex vivo 1-methyl-4-phenylpyridinium (MPP+)-induced hydroxyl radical generation in isolated mitochondria. These results indicate that the observed neuroprotective effects of rolipram stem from its significant antioxidant action.

Conclusions: The preliminary results suggest that rolipram is a neuroprotector, and mechanism other than lipid lowering action could be the basis of this effect. Present data show a neuroprotective effect of the PDE IV specific inhibitor rolipram against dopaminergic neuron degeneration, suggesting that PDE IV inhibitors might be a potential treatment for Parkinson's disease.

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Neuropsychiatric and Cognitive Predictors of Early Diagnosis of Progressive Supranuclear Palsy

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Objective: To define differences of neuropsychiatric and neuropsychological profile among Progressive Supranuclear Palsy (PSP) -Richardson syndrome (PSP-RS), PSP-parkinsonism (PSP-P), and Parkinson's disease (PD), in order to identify non-motor predictors of precocious PSP diagnosis.

Background: The two main variants of PSP, PSP-RS and PSP-P, display motor and non-motor features similar to PD, particularly in the early stage.

Methods: 180 subjects suffering from degenerative parkinsonism since less than 24 months were enrolled in the period 2006-2012. They were diagnosed retrospectively according to international diagnostic criteria as suffering from PD (n=155), PSP-P (n=11) and PSP-RS (n=14). At enrollment, all patients were submitted to neuropsychiatric diagnostic evaluation and a comprehensive neuropsychiatric and neuropsychological evaluation. Multivariate logistic regressions including neuropsychiatric and neuropsychological features that differed significantly among groups was applied to identify predictors of PSP diagnosis.

Results: There were no significant differences at any demographic or neurological feature among groups. Prevalence of apathy and depression was significantly higher in the 2 PSP groups with respect to PD. As to neuropsychiatric scales, the three groups differed significantly only in Apathy Rating Scale score. PSP-P and PSP-RS patients displayed significantly worse performances at several neuropsychological examined with respect to PD. Phonological verbal fluency deficit significantly predicted PSP-RS diagnosis whereas a formal diagnosis of apathy significantly predicted PSP-P diagnosis.

Conclusions: Our results demonstrate that PSP-P and PSP-RS patients are characterized by peculiar patterns of neuropsychiatric and cognitive symptoms, detectable early along disease course. Thus, within the first 24 months after onset of symptoms, poor performances in tests investigating apathy and phonologic verbal fluency may support diagnosis of PSP rather than PD. In particular, impairment of phonological verbal fluency predicts diagnosis of PSP-RS, whereas the presence of apathy supports PSP-P diagnosis. These findings suggest that comprehensive cognitive and neuropsychiatric evaluations might represent useful and cost-effective contributors to the diagnostic work-up of patients with progressive parkinsonism early along disease course.

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Secondary Vascular Parkinsonism in Uzbekistan: hormonal pathogenetic effects and vascular-immunological basics

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Objective: We aimed to analyze the PD related hormonal factors and VP hormonal endothelial factors. **Background:** As we know the Vascular Parkinsonism (VP) and Symptomatic Parkinson's Disease (PD) is very similar, but both the etiology and pathogenesis of the disease is different. VP and PD had to be separated from each other with different techniques and special diagnostic scales, however, now VP and PD are being diagnosed difficultly.

Methods: We chose the cortisol to study the hormonal mechanisms, and Alpha-fetoprotein concentration to analyze the endothelial factors; we conducted this research from 02.09.2015 till 01.01.2017 in the 1st Clinic of Tashkent Medical Academy. A total of 87 patients were participated in our investigation, 44 patients of them are suffering from VP, whereas 43 patients are with PD. All patients were tested anamnestic, neurological and

neuropsychological examination. We used the MMSE and Khachinskiy scale methods; moreover we studied cortisol levels and the concentration of Alpha-fetoprotein in blood serum in the morning using immunofluorescence methods.

Results: According to the results of the investigation the concentration of cortisol was doubled in 20 patients with VP (45%), 7 patients (15.9%) showed the increase by 1,5 times, and the concentration of cortisol was not changed in 17 patients (38.6%). The patients with PD group, 5 patients (11.6%) showed the increase by 1,5 times in cortisol concentration, the cortisol level doubled in 3 patients (9.3%) and was not changed in 35 patients (79.5%). According to the results of neuropsychological tests and scales the higher levels of cortisol concentration, the higher cognitive impairment was observed in those patients. The Alpha-fetoprotein levels were higher in 23 (52.27%) patients with VP, but in 21 patients (47.72%) it was not determined. Finally, the Alpha-fetoprotein levels were higher in 13 (29.51%) patients with PD.

Conclusions: To sum up the mechanisms of VP and PD are different from each other's, which seem to be the result of hormonal changes. The higher concentration of cortisol in blood serum, the higher cognitive impairments in patients with VP. Cortisol levels always play an important role in the pathogenesis of Cognitive impairments in patients with VP and PD. The concentration of Alpha-fetoprotein is higher in blood serum in patients with PD.

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Cognitive profiling in patients with Parkinson's disease, multiple system atrophy and progressive supranuclear palsy: a 15-month longitudinal study

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Objective: To characterize the progression of cognitive decline and compare the neuropsychological 15-month profile across PSP, MSA and PD.

Background: Cognitive impairments are frequently reported in these parkinsonian disorders. However rate of cognitive decline is still unclear.

Methods: Longitudinal study consisting of 40 patients (10 MSA, 10 PSP and 20 age, education and disease duration matched-PD) who underwent an extensive neuropsychological and clinical assessment. It was investigated daily functioning (ADL/IADL), global cognitive status (MMSE and MoCA) and performance in five cognitive domains (executive, memory, attention, visuospatial and language abilities). Each patient was re-tested at a mean of 15-month follow-up. Non-parametric tests were used.

Results: Table 1 shows a summary of demographic and clinical variables at baseline. [table 1] At 15-month followup both MSA and PSP patients showed increased motor severity (MDS-UPDRS, z=-2.380; p=0.017 for both) and reduced ADL (z=-2.032, p=0.042; and z=-2.207, p=0.027 respectively) and IADL scores (z=-2.530; p=0.011; and z=-2.043; p=0.041 respectively). From a cognitive perspective, PSP patients had a decline in the TMT-A (z=-2.073; p=0.038) and delayed story recall (z=-2.207; p=0.027); MSA group's performance worsens at the MMSE (z=-2.271; p=0.023), TMT-B (z=-2.197; p=0.028), semantic fluencies (z=-2.041; p=0.041) and incomplete letter recognition tasks (z=-2.203; p=0.028). Finally, PD patients showed reduced ADL (z=-2.264, p=0.024), and a poorer performance in the copy of a complex figure (z=-2.087; p=0.037) and TMT-A (z=-2.254; p=0.024).

Table 1 Demographic and clinical characteristics of MSA, PSP, and PD at baseline

	MSA (n=10)	PSP (n=10)	PD (n=20)
Age (years)	64.7 (5.3)	69.4 (7.2)	63.8 (11.3)
Education (years)	8.1 (4.0)	9.2 (3.0)	7.9 (2.6)
Disease Duration (years)	4.2 (2.0)	3.9 (2.1)	6.0 (2.4)
Age of onset symptoms (years)	60.3 (4.9)	65.6 (7.9)	57.8 (11.7)
MDS-UPDRS (total)	69.3 (28.2)	54.2 (21.1)	43.9 (21.1)
LDED	639.0 (292.6)	450.0 (333.1)	641.1 (442.3)
DAED	111.8 (101.2)	46.3 (73.69)	78.9 (94.0)
MMSE	28.8 (1.14)	25.0 (4.7)	27.8 (2.0)
MoCA	23.6 (3.0)	21.1 (4.9)	22.95 (3.1)

Note. Values are mean (SD). MDS-UPDRS Movement Disorder Society Unified Parkinson's Disease Rating Scale, LDED levodopa equivalent daily dose, DAED dopamine agonist equivalent dose.

Conclusions: PSP and MSA patients showed consistent motor and functioning decline at 15-month follow-up. Overall we observed specific patterns of cognitive decline across groups. Namely, PSP showed attentive and memory deficits and MSA and PD patients cognitively declined in attention/executive and visuospatial tasks. Noteworthy, at baseline MoCA total score was significantly lower than MMSE for each group. Moreover, in the MSA group, MMSE score decreased significantly at the follow-up compared to MoCA. These findings confirm MoCA as better cognitive screening scale vs. MMSE (Fiorenzato et al., 2016) and may support the concept of MMSE as a more sensitive scale to identify rate of cognitive decline (Biundo et al., 2016).

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Causes, Complications and Outcomes of hospitalization in patients with Dementia with Lewy Bodies

C. Spears, A. Besharat, D. Martinez-Ramirez, L. Almeida, M. Armstrong (Gainesville, FL, USA) **Objective:** To identify causes, complications and outcomes of hospitalization in patients with dementia with Lewy bodies (DLB).

Background: Hospitalization is a known contributor to morbidity and mortality in neurodegenerative conditions such as Parkinson's and Alzheimer's disease, but, there is scarce published data in patients with DLB.

Understanding the causes, complications and outcomes of hospitalization in DLB may allow for development of strategies to prevent, decrease, or better manage hospitalization.

Methods: We conducted a cross-sectional chart review and analyzed data for patients with a diagnosis of DLB who were hospitalized at UFHealth from 2014-2015. Variables collected included age, living situation prior to hospitalization, home medications, reason for hospitalization, inpatient medications, hospital complications, duration of stay and discharge disposition. Results are presented descriptively.

Results: We reviewed 179 hospital presentations representing 121 distinct patients, where 58% were male; mean age 79 \pm 8. The most common reasons for presentation included worsened confusion-hallucinations (40%), falls (24%) and infection (23%). Prior to hospitalization, 64% of patients were living at home; 31% were taking an antipsychotic [quetiapine 56%, clozapine 8% and other 36%]. While hospitalized, 50% developed new or worsening confusion and 38% were prescribed antipsychotics [quetiapine 56%, clozapine 5% and other 39%]. The average length of stay was 7 \pm 8days. At discharge, only 52% returned to their living situation prior to admission; all others required a higher level of care.

Conclusions: Patients with DLB are at a high risk of hospitalization due to worsening confusion-hallucinations, falls, and infections which may ultimately lead to clinical deterioration and change in level of care. These disease complications suggest a need for both improved preventative strategies to reduce hospitalization as well as improved in-hospital management.

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Clinical phenotype in patients with multiple system atrophy in the Mexican population

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Objective: To describe the clinical phenotype of patients with MSA in a center in Mexico City **Background:** Multiple System Atrophy (MSA) is an adult-onset; progressive, neurodegenerative disease characterized by autonomic failure, Parkinsonism and cerebellar ataxia. It can be divided into parkinsonian (MSA-P) and cerebellar (MSA-C). Onset is in the 6th decade of life; mean survival from the onset of symptoms is 6-10 years.OSA affects 40% of patients. On MRI we observe atrophy of putamen, middle cerebellar peduncle, pons or cerebellum or "hot-cross-bun sign"in T2-weighted sequences. On FDG-PET the most common pattern is hypometabolism in posterior putamen and cerebellum.

Methods: We reviewed the database of patients seen at the Movement Disorders Clinic during the last 3 years. Patients diagnosed with probable MSA were included. The following variables were collected: demography, clinical features, subtype and diagnostic tests.

Results: Fourteen patients were included (8 women). Mean age was 65.1 years (48-83). Mean age of onset of symptoms was 59.9 (42-74). Current disease duration was 5.4 years (2-9). The most frequent variant was MSA-P. Five patients had urinary alterations at the time of diagnosis. Cognitive impairment was found on working memory and dysexecutive functioning. Thirteen patients had different combinations of sleep disorders. In all patients, MRI showed decreased cortical volume in the frontal and parietal. Most patients showed signs of cerebellar atrophy, 2 bulbar/pontine degeneration, 1 pars compact atrophy, and 9 microangiopathy. Thirteen patients had SSEPs with proprioceptive alterations, 9 showed generalized cerebellar hypometabolism on FDG-PET and 9 dysautonomic alterations. Only 6 patients with AMS-P showed a mild response to Levodopa.

Conclusions: Medical Literature describes a male predominance, we found a female predominance. Other populations showed the average onset of disease to be 50 years, in our population it was 65.07. Our most frequent clinical variant was MSA-P. The mean age of survival is 5-9.5 years; n our population the average was 6 years. Most of our patients had OSA and all of our patients with SSEPs presented alterations. These clinical differences as well as the age of onset could be explained by ancestry and it would be worthwhile to carry out additional studies in our population.

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Progressive Supranuclear Palsy : About one case at the Neurology Department - Dakar

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Objective: We report an observation of a case received at the consultation in the Neurology Department of National Teaching Hospital Fann.

Background: Progressive supranuclear palsy (PSP) is a neurodegenerative disease (see the image below) whose characteristics include supranuclear, initially vertical, gaze dysfunction accompanied by extrapyramidal symptoms

and cognitive dysfunction. The disease usually develops after the sixth decade of life. and the diagnosis is purely clinical.

Methods: Patient of 67 years , without specific medical history , which has since 6 months: falls, difficulty maintaining the sitting position , execution of daily activities (eating, bathing ...) , urination, and alteration of mood behavior with loss of interest in pleasurable activities. The patient was in fairly good condition, and has an extrapyramidal syndrome without tremors, lateral gaze palsy, and a frontal syndrome. His MMSE' score was 14/30. The MRI shows a bi-frontal atrophy with shrinkage of the midbrain.

Results: The treatment with L-dopa was inefficient with no improvement.

Conclusions: The diagnosis of progressive supra nuclear palsy is purely clinical. Key features typically develop over time. Physical therapy and rehabilitation medicine involvement may help maximize ambulation safety and facilitate instruction in the use of a walker, wheelchair, or other aids.

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Movement disorders caused by benign brain tumor

A.M. Magnerou, P.E. Sounga Bandzouzi, H.F. Ngoungoure, M.M. Ndiaye (Dakar, Senegal) **Objective:** Describe unusual etiology of movement disorders (MD).

Background: Benign brain tumor can be manifested by MD. The clinical description and role of brain imaging in the diagnosis of a patient with MD symptoms is discussed.

Methods: We collected patients during the external consultation of neurology which presented MD with or no other neurological symptoms; having an imaging suggestive of a brain tumor.

Results: Five patients (3 men, 2 women) with a mean age of 38.2 ± 4.2 years consulted with MD, among them 2 had partial seizures. The rest of neurological examination including cognitive functioning was unremarkable. The patient's family history was negative for any neurological conditions, including Huntington's disease, chorea and other MD. Imaging by computed tomography or magnetic resonance imaging was mandatory asked in the diagnosis of neurological disorders. All of these tumors were extrinsic with reference to basal ganglia and thalamus: there were four meningioma with parkinsonism and one neurofibromatosis with focal dystonia. We observed a relief of MD after the surgery in all of patients.

Conclusions: Movement disorders in general are uncommon presenting features of brain tumors. The mechanical pressure caused by the enlargement could lead to various movement disorders, which may even coexist as presented in our case. Early recognition of such lesions by imaging is important to arrest further deficit.

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Alien Limb Syndrome induced by a dopamine agonist in a patient with parkinsonism and agenesis of the corpus callosum

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Objective: To examine the case of a patient with parkinsonism and agenesis of the corpus callosum whose alien limb phenomenology ceased after withdrawal from ropinirole.

Background: Alien limb phenomenon (ALP) is one of the oddities in neuroscience. The hallmark of ALP is involuntary yet purposeful limb actions devoid of conscious control. These can manifest as levitation, inter-manual conflict, mirror movements, enabling synkinesis, groping apraxia, and compulsive manipulation of tools. Sufferers deny ownership of the movements. Though the phenomenon is seen with corticobasal syndrome and various cerebrovascular lesions affecting the corpus collosum, there has been no previously reported connection with dopamine agonists.

Methods: Case Report

Results: A patient with advanced parkinsonism initially presented to us with left hand resting tremor, mild anomia, paraphasia and constructional apraxia. He had mild leg wearing-off dyskinesias and gait freezing requiring a walker. The tremor responded to carbidopa/levodopa, but ropinirole was added once motor fluctuations developed. Soon afterwards, his left hand exhibited involuntary grasping and inter-manual conflict, consistent with ALP. MRI imaging revealed complete corpus callosum agenesis and colpocephaly. Ropinirole was eventually discontinued due to his experiencing hallucinations and confusion. His levodopa was not changed. The ropinirole discontinuation was followed by immediate resolution of the hallucinations and the ALP.

Conclusions: This case 1) provides evidence that dopaminergic pathways may be involved in the pathophysiology of ALP, and 2) that more than one lesion may be required to manifest ALP, a second lesion hypothesis. Use of a dopamine agonist in the setting of callosum agenesis was enough to induce ALP in our patient. Dopamine plays a very important role on modulating motor programs, thus dopamine agonists potentially influence motor behaviors in

the right setting. There are known diffuse dopaminergic projections within the striatum, the limbic system and the cortex. The dopamine pathways in the mesocortical and mesolimbic systems have been implicated in behavior, perception, memory and cognition. Affectation of the mesocortical system could have caused ALP in our patient with callosum agenesis, but submit the role of dopamine in this phenomenology requires further research.

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Gait impairment and cognitive changes in a case of thalamic dementia and motor neuron disease

S. O'Shea, O. Levy, J.P. Vonsattel, E. Cortes, K. Marder, H. Mitsumoto, R. Alcalay (New York, NY, USA) **Objective:** To describe a case of a 54-year-old woman diagnosed with atypical corticobasal syndrome (CBS). Neuropathological studies revealed that she had thalamic dementia with motor neuron disease (MND). **Background:** Thalamic dementia with MND is a rare pathologic entity that has been previously described once in a patient with cognitive decline, aphasia, progressive rigidity, and quadriparesis (1). Earlier studies reported thalamic involvement in cases of familial MND, but were not associated with dementia (2). This pathology has not been previously associated with CBS.

Methods: We report the clinical evaluation, diagnostic studies and neuropathological findings of a person with thalamic dementia and MND.

Results: Our patient, a 54 year-old right-handed woman, developed right leg weakness, followed by behavioral disturbances, dysarthria, cognitive decline, and gait difficulty. There was a maternal family history of cognitive decline and gait disorder. Her exam was notable for asymmetric bradykinesia, rigidity, and gait apraxia, which were not responsive to levodopa. She was diagnosed with atypical CBS. She clinically deteriorated over the course of eight years, and developed asymmetric spastic quadriparesis, myoclonus, and seizures, which localized to the frontal lobe. Brain MRI revealed diffuse atrophy. Cervical spine MRI was normal. There was mildly decreased glucose metabolism in the region of the frontal lobes on FDG-PET. CSF studies revealed elevated protein. EMG was normal. Transcranial magnetic stimulation demonstrated left more than right central pathology. Sequential neuropsychological testing revealed deficits in memory, executive, and visuospatial function. Neuropathologic examination demonstrated paracentral, frontal, and parietal atrophy, and neuronal loss and gliosis within the dorsomedian nucleus of the thalamus, sparing the sensory and motor nuclei. Demyelination of the lateral corticospinal tract was noted, indicative of MND. No pathologic inclusions were detected.

Conclusions: Thalamic dementia with MND is a rare neuropathological diagnosis, which may be considered in cases of atypical CBS. Parkinsonism was a minor feature of her presentation and spasticity and behavioral changes were significant features, emphasizing that our case is not typical of CBS.

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Primary progressive apraxia: an unusual ideomotor syndrome

Y. Fernandez, S. Frucht (New York, NY, USA)

Objective: We describe and demonstrate by video 2 cases of primary ideomotor progressive apraxia with progressive difficulty with hand dexterity and manipulation and mild parkinsonism in the absence of significant radiologic findings.

Background: Neurodegenerative disorders usually present with cognitive and physical findings, with localizing imaging findings. Our patients have physical exams showing hand apraxia with no imaging correlates. **Methods:** Case report

Results: Patient 1, 72-year-old man. The patient could not show 2 fingers on the left hand, tap fingers or mimic hand postures. There was preserved knowledge of how to use tools. He was unable to pantomime movements, write letters on a page or copy figures. There was vertical gaze apraxia and inability to smile on command. Spontaneous smile was intact. MRI of the brain showed moderate cerebral atrophy, chronic right frontal cortical infarcts and white matter ischemic changes. FGD PET showed nonfocal decreased metabolism in the frontal lobes, basal ganglia and brainstem. Patient 2, 72-year-old woman. Her speech, language, prosody, and comprehension were intact. Voice was slightly hypophonic. There was minimal left wrist rigidity. Her hands were severely impaired. She was unable to pantomime, had body utilization, was unable to show an "OK" or a salute. She was unable to do rapid alternating movements with hands. MRI and FDG PET scan were normal for age.

Conclusions: We report two unusual presentations of what are most likely neurodegenerative disorders, possibly tauopathies. In both cases, there is preserved cognition, language skills, muscle power and tone, and gait in the setting of profound progressive hand apraxia. Imaging is remarkable in our two cases for a lack of any discernable pattern, specifically a lack of parietal lobe involvement. Both cases demonstrated a lack of response to Sinemet.

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Phenotypic heterogeneity in psp variants – A case series

S. Bhadran, S. Abraham, B. Natarajan, A. Mekkattukunnel, J. Krishnan, R. Isaac, P.K. Pal (Thrissur, India) **Objective:** To present the phenotypic heterogeneity we observed in 5 PSP variants.

Background: Progressive supranuclear palsy (PSP) is a primary tauopathy characterised by progressive gait disturbances, postural instability, supranuclear gaze palsy and fronto-limbic cognitive deficits, classical

Richardson's Syndrome. This is the commonest Parkinson plus syndrome constituting 5-6%.¹There is considerable phenotypic heterogeneity in the presentation of PSP. Until date 5 variants are well described and newer variants are still evolving. We are presenting our experience of 5 patients with PSP variants.

Methods: Between 2015 and 2016, we encountered 5 patients with PSP, all of which were atypical. All of them met the probable PSP criteria of NINDS-PSPS. However, they varied in their clinical manifestations and had discernible features differing from classic RS-PSP. The clinical characteristics are summarized in table 1.

Results: The PSP-CBS and PSP-P variants we encountered had polysomnographic proven evidence of RBD. This finding is less prevalent in PSP. This would probably be explained from the degeneration of PPTg nuclei in the brain stem, which appears to be vital for the generation of REM sleep.²The median interval between onset and diagnosis is 3 years (range, 0.5-9years). The PSP-PNFA variant presented as early as 4 months. Another peculiarities observed in this patient were rapidly progressing dementia, vertical gaze palsy at symptom onset and substantial reduction in spontaneous speech. The PSP-P variant seems to be the oldest case of PSP reported hitherto, came to the medical limelight when he developed aspiration pneumonia.

	PSP-CBS variant	PSP-PNFA variant	PSP-PAGF variant	PSP-P variant	PSP-PAGF variant
Age of onset	61	67	68	88	52
Duration	5 years	4 months	2 years	2 years	1 year
Rigidity: Axial > Asymmetric limb	Yes	Yes	Yes	Symmetric	Yes
Bradykinesia	Moderate	Moderate	Severe	Mild	Mild
Tremor	No	No	No	Yes	No
Early falls	Yes	Yes	Yes	Yes	Yes
Early postural instability	No	No	Yes	Yes	Yes
Early cognitive decline	Mild	Severe	Moderate	Mild	No
Early ocular abnormalities	Yes	Yes	Yes	Yes	Yes
Sleep abnormalities	RBD	Yes	Yes	RBD	Yes
Response to levodopa	Minimal	No	Mild	Mild	Mild
MRI Brain MB/P Ratio	<52%, diffuse cortical atrophy	< 52%	< 52%	< 52%	<52%

Conclusions: The recognition of PSP variants suggests that other than classic Richardson's syndrome there are other related, but distinct clinical syndromes, which could be easily misdiagnosed in the early stages. A proper understanding of the variants is crucial in the management considering the rapid progression of this disorder and refractoriness to levodopa therapy.

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Parkinsonism revealing cerebral hematoma with moya moya disease

Z. Brahem, I. Bedoui, A. Riahi, M. Mansour, J. Zaouali, R. Mrissa (Tunis, Tunisia)

Objective: The aim of this study is to describe a rare cause of parkinsonism.

Background: Moyamoya disease (MMD), a rare chronic, progressive cerebrovascular disease leads to occlusion of intracranial internal carotid arteries and its proximal branches. Movement disorders, as for parkinsonism, are rarely revealing this pathology.

Methods: We report a case of a 51-year-old female, who presented a tremor localized in her left arm.

Results: Clinical examination showed unilateral extrapyramidal syndrome. In the CT scan, we found a thalamic hematoma and intraventricular hemorrhage. She was diagnosed MMD based on the angiography demonstrating

bilateral intracranial internal carotid artery stenosis with puff of smoke appearance. She did not consent for revascularization procedure and she had only medical treatment.

Conclusions: MMD is commonly associated with cerebral hemorrhages in adults. Intracerebral hematoma is the most frequently in the basal ganglia region. Thalamic bleed is relatively uncommon and found in about 21.4% patients. Clinical manifestations are usually hemiparesis. Movement disorders and especially parkinsonism as revealing symptom are very rare. To our knowledge only 8 patients had movement disorder in this context due to anatomical or functional lesions in basal ganglia. Movement disorders are rarely associated with hemorrhagic stroke as well as with MMD. In front parkinsonism, angio-MRI is mandatory to not misdiagnose this disease.

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Progressive supranuclear palsy presenting with corticobasal syndrome: a case report

M. Sousa, R. Varela, C. Januário, A. Morgadinho (Coimbra, Portugal)

Objective: Clinical description and interpretation of complementary diagnostic exams of a patient with probable PSP with corticobasal syndrome phenotype (PSP-CBS).

Background: Underlying pathologies of CBS are heterogeneous, but 70% of cases have a tauopathy. CBS, however, is a rare presentation of PSP and PSP-CBS comprises of only 4% of PSP cases.

Methods: A 78 years-old, female patient with a previous history of anxiety disorder developed at age of 77 yearsold gait difficulties, loss of balance with frequent falls (mainly backwards) and cognitive complains. In the neuropsychological assessment, she scored 25 in MMSE and 14 in MoCA (12 years of education), affecting mainly executive functions. At neurological examination, she presented asymmetric blepharospasm, slow vertical saccades with vertical superior limitation, bilateral asymmetric limb apraxia much more marked in left side, dystonic posturing of left upper limb with motor overflow, progressive clumsiness of left upper limb with functional disability, bradykinesia, axial rigidity without appendicular rigidity and severe loss of postural reflexes. Treatment with levodopa/carbidopa was started until doses of 750 mg/day, with no clinical benefit.

Results: The brain MRI presented a prominent midbrain atrophy with preserved pons dimensions (Hummingbird sign) and right side upper parietal lobe atrophy [Figure 1]. The beta-CIT PET revealed asymmetric bilateral dopaminergic deficit more evident in right side [Figure 2]. CSF biomarkers showed slight elevated levels of Tau and phosphorylated Tau protein with normal beta-amyloid levels.





Conclusions: This case depicts the importance of confronting clinical and complementary diagnostic exams to reach the more accurate diagnosis possible, *in vivo*, and identify the different PSP variants. A better understanding of the factors that influence the selective pathological vulnerability in different PSP variants will provide further insights into neurodegenerative process underlying tauopathies.

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A case of Dementia with Lewy Bodies co-occuring with Multiple Sclerosis

A. Hannoun, E. DeGrush, K. Smith, T. Kao, A. Deb (Worcester, MA, USA)

Objective: To describe a unique case of Dementia with Lewy bodies (DLB) co-occurrence with Multiple Sclerosis (MS).

Background: Various movement disorders have been described in patients with MS, usually secondary to demyelinating lesions in the basal ganglia or related circuits. Reports of co-occurring Parkinson's disease (PD) and MS are rare, and to our knowledge, we are describing the first case of co-occurring DLB and MS. This may be relevant given recent evidence supporting immune system involvement in PD and related conditions **Methods:** Case Report

Results: A 64-year old woman with relapsing-remitting MS diagnosed in her thirties, treated with high dose steroids but never on immune modulating therapy was initially seen in the clinic at age 61. She had hand tremor for two months. Additionally, the family reported mild but progressive cognitive impairment and short term memory loss causing daily dysfunction. Memory was impaired on exam at that time. She was lost to follow up until 3 years later when she presented with formed visual hallucinations and worsening memory and cognition. She had experienced an episode of increased leg stiffness and immobility after receiving quetiapine. On exam, she had rigidity in all extremities, and mild bilateral bradykinesia. There was also concurrent spasticity. MoCA was 21/30. Due to both extrapyramidal and pyramidal features, parkinsonism was considered. MRI brain with and without contrast shows chronic supratentorial and infratentorial white matter lesions consistent with MS, but no lesions within the basal ganglia. DAT scan shows bilateral symmetric decrease in putamen uptake. She reported a robust response to carbidopa/levodopa with clear on and off time Given onset of parkinsonism and cognitive impairment within one year, with abnormal DaTscan, she was diagnosed with DLB

Conclusions: This is the first description of DLB occurring in a patient with MS. There may be shared clinical characteristics, such as tremor and increased tone, and the phenomenology of these features may be difficult to differentiate between pyramidal and extrapyramidal etiologies. Moreover, progression of motor and non-motor symptoms will be influenced by both diseases. Whether these two neurodegenerative conditions share causality, for instance immune mediated mechanisms, or are merely co-incident remains unclear. Studying a potential overlap in pathophysiology might help in future management considerations

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Pre-synaptic dopaminergic deficit in a patient with familial FTD

M. Sousa, R. Varela, C. Januário, A. Morgadinho (Coimbra, Portugal)

Objective: Clinical description of a patient with familial FTD with a rapidly progressive parkinsonism. **Background:** FTD typically presents with behavioral and cognitive deficits, but extrapyramidal symptoms are also common. The pathophysiologic basis of these symptoms is unclear and generally had a poor response to dopaminergic replacement therapies. The results of dopaminergic imaging in patients with FTD in literature are controversial, and even less information is available in the cases of familial FTD. **Methods:** A 81 years-old male patient, developed at age of 75, cognitive deficits characterized initially by obsessive behaviors, irritability and aggressive behaviors. His symptoms progressively worsened and at age of 80, he has lost functional autonomy and was institutionalized. At age 81, he displayed for the first time an asymmetrical akinetic-rigid syndrome, and treatment with levodopa/carbidopa was started, with poor clinical benefit. He presented in neuropsychological assessment a MoCA of 16 and FAB of 14(7 years of education). In neurological examination, he presented symmetric apraxia, asymmetrical akinetic-rigid syndrome (more prominent in the left side), moderate loss of postural reflexes, freezing of gait and parkinsonian gait (MDS-UPDRS-III:72;H&Y:4). 8 months after the beginning of extrapyramidal symptoms he loss gait autonomy and was bedridden. The patient's mother and sister presented a similar clinical picture with behavioral symptoms beginning at age of 70's, and with a rapid progressive asymmetric parkinsonism.

Results: Brain MRI demonstrated generalized brain atrophy, slightly asymmetrical (more prominent in left hemisphere), and more obvious in fronto-temporal regions. DATSCAN revealed markedly asymmetric bilateral dopaminergic deficit, more prominent in right side [Figure 1]. FDG-PET showed frontal, temporal and parietal hypometabolism (slight left hemisphere predominance) [Figure 2]. CSF biomarkers showed marked increase in Tau and p-Tau with normal beta-amyloid levels. Results of genetic test will be presented.



Conclusions: This case describes a case of familial FTD with autosomal dominant pattern of transmission with evidence of dopaminergic deficit markedly asymmetrical in DATSCAN. Furthermore it, highlights the importance of dopaminergic imaging in this case to guide not only diagnosis but also management, due the implications that dopaminergic therapies can have on behavioral symptoms.

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Corticobasal degeneration and frontotemporal dementia - an overlapping continuum

R. Varela, C. Duque, J. Carvalho, A. Moreira, A. Morgadinho, C. Januário (Coimbra, Portugal) **Objective:** This clinical case intends to highlight the continuum between frontotemporal dementia and corticobasal syndrome.

Background: A substantive overlap between corticobasal degeneration and frontotemporal dementia has been demonstrated, although perfectly mimicking cases are sparsely described in literature.

Methods: We obtained retrospective data from clinical history, neurological examination, resonance imaging, nuclear medicine, and genetic testing.

Results: We report a case of a 66-year old male presenting to the emergency department with suicidal ideation for the past two months. The patient was referred to the Psychiatry outpatient clinic and started on antidepressants. A few weeks later he is observed in the ER for loss of consciousness and neurology observation was then requested. Examination showed signs of frontal dysfunction, ideomotor apraxia on the left side, visual and tactile extinction, alien hand, supranuclear vertical gaze palsy, axial and left bradykinesia (mUPDRSIII 42) as well as absence of postural reflexes. Neuropsychological examination disclosed significant frontal function impairment and severe construction deficit (MMSE 20, MoCA 9). Brain MRI showed mild right frontotemporal atrophy, PET(11C)beta-CIT was normal; in the 18F-FDG a right-left perfusion asymmetry was clear with a normal 11C-PIB-PET. Genetic studies (c9orf72, progranulin, MAPT) were negative. Final diagnosis: Frontotemporal dementia. **Conclusions:** The presented case highlights a continuum between two clinical entities whose boundaries are further diluted as we realize that, like in the presented case, they can be clinically indistinguishable. Overlapping cases settle the clinical ground for unifying definition in need.

Quality Of Life/Caregiver Burden in Movement Disorders

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Understanding the illness experience of people living with Parkinson's disease: A mixed methods study JJ.Y.-Y. Kwok, M.M. AuYeung, H.Y.-L. Chan (Hong Kong, People's Republic of China)

Objective: This study aimed to (i) examine the relationship of psychological distress and HRQoL and (ii) explore the illness experience among people with PD.

Background: Neuropsychiatric symptoms like anxiety and depression are the most prevalent non-motor symptoms among PD patients. Since non-motor symptoms have a great effect on HRQoL, few studies have investigated the relationship between psychological distress, HRQoL and illness experience in PD population.

Methods: This is a mixed method study. People with idiopathic PD, aged = 45 years old and communicable were recruited. A set of rating scales were administered, including UPDRS-III, Hospital Anxiety and Depression Scale, PDQ-8, ADL-Staircase and a demographic sheet. Hierarchical linear regression was used to assess the effect of psychological distress on HRQoL. Then, semi-structured interviews were done with purposive sampling of informants with diverse socio-demographic background and survey results. Thematic analysis was used to identify themes about their unmet care needs. Ethics approval was granted (CUHK-CREC 2015.715).

Results: A convenience sample of 123 PD patients completed the questionnaire. Sample characteristics and outcome variables were summarized in Table 1. Psychological distress was prevalent and highly correlated with HRQoL (Table 2). In hierarchical linear regression (Table 3), ADL performance and psychological distress significantly predicted HRQoL. After adjusting for demographic and clinical results, psychological distress further accounted for 20.1% of variance of HRQoL. From the semi-structured interviews (n=14), two major themes emerged from participants' narratives: 'confronting changes brought by PD' and 'readjusting towards changes'. Informants appeared to go through a complex illness trajectory facing turmoil and demoralization resulting from losing functions and mastery, role change and unaddressed psychosocial needs. Emotion-focus coping strategies like acceptance were identified to help them reaching a state of calmness in facing changes brought by PD.

Table 1. Descriptive statistics of socio-demographics characteristics, HADS, PDQ-8, ADLstaircase and UPDRS III (n=123)

Variabl	les	n (%)	Mean (S.D.)
Age, y	ears	123 (100)	70.4 (9.2)
-	Male	63 (48.8)	70.1 (8.0)
8.70	Female	60 (51.2)	70.8 (10.5)
Marita	l status		
-	Single	7 (5.7)	
	Married	89 (72.4)	
_	Divorce/ Separation	11 (8.9)	
-	Widowed	16 (13.0)	
Numbe	er of children		2.5 (1.5)
Educat	ion level		
-	Illiterate/Primary	47 (38.2)	
	Secondary	54 (43.9)	
-	Tertiary	22 (17.9)	
Living	status		
-	Alone	9 (7.3)	
-	Living with spouse	41 (33.3)	
-	Living with families/friends	64 (52.0)	
-	Old age home	9 (7.3)	
On soc	ial security allowance	54 (43.9)	
AED a	ttendance within the past year	49 (40.0)	
	Number of times of AED attendance		0.6 (1.0)
Hospit	al admission within the past year	42 (34.1)	
-	Length of stay		1.6 (4.3)
The Ho	behn and Yahr scale		
	1-1.5	4 (3.3)	
-	2-2.5	57 (46.3)	
-	3	25 (20.3)	
	4	19 (15.4)	
	5	18 (14.6)	
HADS	1		16.2 (7.8)
-	Anxiety		7.4 (4.3)
	Depression		8.8 (4.4)
HADS	≥15	67 (54.5)	
PDQ-8	summary index ²		34.4 (20.1)
ADL-s	taircase ³		
-	Personal-ADL performance		3.6 (2.9)
-	Instrumental-ADL performance		4.7 (3.2)
UPDR	S III ⁴		24.0 (13.5)

AED, Accident & Emergency Department. ¹HADS: Hospital Anxiety and Depression Scale, a higher score indicates higher level of anxiety and depression, a cut-off value of 15 for the full scale is used to indicate the presence of psychological distress; ²PDQ-8: Parkinson's Disease Questionnaire-8, scored 0-4 per item, higher scores indicate worse HRQoL; ³ADL-staircase: scored 0-3 per item, higher scores indicate worse daily activity of the score of the scale score of the score scale scale and the full Motor Examination living; "UPDRS III: The Unified Parkinson's Disease Rating Scale – Part III Motor Examination, higher scores indicate more motor disabilities.

	P-ADL	I-ADL	UPDRS-III	HADS	PDQ-8
Age ¹	γ=0.228**	γ=0.297***	NS	NS	NS
No. of children ¹	NS	NS	NS	NS	NS
H&Y staging ²	γ=0.514***	γ=0.536***	γ=0.639***	γ=0.338***	γ=0.411***
P-ADL ¹		γ = 0.724***	γ = 0.645***	γ =0 .517***	γ=0.650***
I-ADL ¹	γ = 0.724***		γ=0.619***	γ=0.448***	γ=0.586***
UPDRS-III ¹	γ=0.645***	γ=0.619***		γ=0.293***	γ=0.402***
HADS ¹	γ=0.517***	γ=0.448***	γ=0.293***		γ=0.774***

Table 2 Summary of correlation between socio-demographic characteristic, disease staging, ADL performance, severity of motor symptoms and level of psychological distress (n=123)

NS, Non-statistically significant

PDQ-81

¹Pearson's correlation coefficient, ²Spearman correlation coefficient

γ=0.650***

Table 3. Hierarchical regression analysis of predictors of health-related quality of life (n= 123)

γ=0.402***

γ=0.774***

γ=0.586***

Model	Variables	Unstandardized	Standardized	р-	Model st	atistics
		β	β	value	p-value	\mathbb{R}^2
1	Age	-0.267	-0.129	0.076	< 0.001	0.513
	Gender	0.150	0.000	0.994	_	
	No. of children	1.159	0.090	0.164	_	
	Allowance	0.659	0.013	0.831	_	
	Marital category	4.569	0.101	0.094		
	Education: primary				-	
	as reference				_	
	Education:	-0.352	-0.009	0.894		
	secondary				_	
	Education: tertiary	-0.692	-0.014	0.829	_	
	P-ADL	1.702	0.252	0.006		
	I-ADL	1.185	0.194	0.027		
	UPDRS-III	-0.095	-0.066	0.461		
	H&Y staging	1.106	0.065	0.420		
2	HADS	1.421	0.548	0.000	< 0.001	0.714

p-value and estimates of independent variables in the table were from the final model (Model 2).

Conclusions: Both psychological distress and ADL performance are significant and modifiable predictors of poor HRQoL in PD population. Since emotion-focus coping could aid the coping process towards PD, mind-body interventions like yoga, that teach mindfulness along with physical training (1) could maximize the potential benefit on HRQoL of PD patients.

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PD Check-In: Supporting people with Parkinson's disease in self-managed maintenance of communication following intensive speech treatment

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Objective: To investigate a supported self-management model of care, PD Check-In, for long term maintenance of speech, communication and quality of life in Parkinson's Disease (PD) over two years following intensive treatment.

Background: Ninety percent of people with PD will develop the speech disorder hypokinetic dysarthria as the disease progresses. The changes in speech and communicative function result in social isolation and a diminished quality of life for people with PD and their families. Speech-language pathology provides intensive, evidence-based treatment for the speech disorder in PD through the Lee Silverman Voice Treatment (LSVT LOUD). On completion of treatment, home practice is recommended on a daily basis. However, currently there is no evidence-based management plan for the long- term maintenance of speech following intensive treatment.

Methods: A total of 20 participants with PD and family members will be recruited to the study. Participants undergo LSVT LOUD followed by the PD Check-In program in which they will be reviewed by a SLP at 6 and 12 weeks, and at 6,12, and 24 months post LSVT LOUD. The PD Check-In intervention leads reflection and discussion of self-management themes and allows for treatment revision and development of strategies and goal setting for ongoing speech maintenance and quality of life. A repeated measures longitudinal study design will examine clinical outcome, quality of life and participant satisfaction measures pre and post LSVT LOUD and at each of the PD Check-In time points over two years.

Results: The preliminary results for 6 participants from this study will be presented.

Conclusions: PD Check-In is a model for supported self-managed maintenance of speech and communication following LSVT LOUD. Preliminary results suggest that PD Check-In facilitates the improvement of speech characteristics and develops increased awareness of communication in everyday life.

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Aspects of quality of life in MSA and PSP

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Objective: The aim of this study was exploring the correlation between disease severity and QoL in PSP and MSA. **Background:** MSA and PSP are atypical Parkinsonian disorders that progress more rapidly than PD, have a poor response to symptomatic treatments and have a marked impact on QoL. As the emphasis of clinical care has shifted to promote QoL in movement disorders, it is important to clarify how disease impacts upon different aspects of QoL to improve clinical care.

Methods: 47 participants were recruited; 24 had a diagnosis of PSP and 23 had MSA. They were assessed using a comprehensive battery of disease severity and quality of life measures, both objective, subjective, disease-specific and generic. Analysis was carried out using IBM SPSS 21. Spearman's Rho testing was used to assess correlation between measures. Mann-Whitney U tests were used to compare QoL, Palliative Outcome Score (POS-PD) and demographics between patient groups.

Results: When MSA and PSP patients were considered overall using generic surrogates of severity (ADL score) and health status (RAND36) a negative correlation was found between functional ability (Bristol Activities of Daily Living scale) and Mental Composite RAND score (mental health status) r=-0.345 p=0.018. A positive correlation was found between disease-specific quality of life (PSP-QoL) and disease-specific severity (PSPRS) in PSP, r=0.768, p=0.00 but no significant correlation was found between in MSA r=0.399, p=0.059. When subjective rather than disease-specific QoL was considered using SEIQOL-DW, QoL did not correlate significantly with severity using BADLS or UMSARS/PSPRS scores. Negative correlation was found between subjective QoL and palliative care need (POS-PD) as well as depression (DASS) and also between disease-specific QoL and POS/Depression.

Conclusions: Disease specific severity correlates with disease-specific QoL measures, which would be expected as these scores look specifically at problems related to disease. Subjective QoL scores do not have this relationship but do have a correlation with depression and palliative care requirement which may impact more upon the person's whole sense of well-being and ability to adjust to disease. There is crossover with disease-specific severity measures and depression/palliative care need which suggests that addressing low mood and using a palliative approach to symptoms may be effective in improving global QoL in these atypical Parkinsonian disorders.

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Psychosocial impact of X-linked Dystonia Parkinsonism (XDP) of Panay

J.N. Ong, C. Go, G. Solinap, P. Acuna (Manila, Philippines)

Objective: The study will determine the patient's quality of life and their subjective psychological well-being by using the Parkinson Disease Questionnaire (PDQ) - 39 and the World Health Organization (WHO) - 5 Index of Well Being Scale.

Background: X-linked Dystonia of Parkinsonism (XDP) or DYT3 Dystonia is a movement disorder unique to adult Filipino men which usually starts a focal dystonia which eventually generalizes and later would develop

parkinsonian features (Lee, LV. et al., 2004). Gastrointestinal dysfunction leading to malnutrition and aspiration pneumonia is the usual cause of the demise (Rosales, RL, 2010); however, the growing number of suicides where important personal and social factors such depression, anxiety, stigmatization and interpersonal relationship should be considered.

Methods: Fifty clinically confirmed XDP patients from the Movement Disorder Registry of Jose R. Reyes Memorial Medical Center and the XDP Registry in Health Centrum Dystonia Clinic in Roxas City, Capiz who consulted from October to November 2016 were included. The PDQ 39 scale and WHO-5 Index of Well Being questionnaires were administered and the quality of life profile and emotional wellbeing of the patients were determined. The PDQ 39 Score, as well as its domains, were correlated with the WHO-5 Index of Well Being score to determine if there is a relationship between the quality of life of the patients and their psychological well-being. **Results:** Six out of the eight domains of the PDQ 39 showed median scores while both the social support and cognition domains showed below the median scores $(3.7 \pm 3.4 \text{ and } 4.9 \pm 3.7 \text{ respectively})$ [Table1]. The eight domains of the PDQ 39 and WHO-5 Index of Well Being Scale scores were subsequently analyzed using the Pearson's Product Moment Correlation but showed negligible correlation which is also statistically not significant [Table2].

Parkinson's Dis	ease Questionnaire - 39 (F	PDQ-39) Scale
Domain	No. of Items	Mean ± SD
Aobility	10	22.9 ± 11.0
Activities of Daily Living (ADL)	6	12.1 ± 7.4
motional Well-being	6	13.8 ± 5.7
Soma	4	8.4 ± 5.1
locial Support	3	3.7 ± 3.4
Cognition	4	4.9 ± 3.7
Communication	3	7.3 ± 3.3
odily Discomfort	3	6.3 ± 3.6

PDQ-39 Domain	Pearson's R	P-Value
Mobility	0.03	0.837
Activities of Daily Living (ADL)	-0.07	0.629
Emotional Well-being	-0.07	0.605
Stigma	-0.03	0.858
Social Support	-0.14	0.324
Cognition	0.09	0.526
Communication	0.16	0.260
Bodily Discomfort	0.26	0.069
PDQ 39 Total Score	0.03	0.864

Conclusions: The impairment of quality of life was observed in the physical, social and emotional aspects of the disease. This study suggests that the severity of impairment of the quality of life does not equate to a poor emotional well-being of the individual. There may be other factors of the disease which may significantly affect the emotional well-being of the patient. We are recommending further studies on identifying other factors which may have an impact on the emotional well-being of XDP patients.

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A pilot study of mindfulness yoga on psychological distress in people with Parkinson's disease (PD) JJ.Y.-Y. Kwok, J.C.-y. Kwan, H.Y.-L. Chan (Hong Kong, People's Republic of China)

Objective: This study aimed to examine the feasibility of a mindfulness yoga programme among people with PD. **Background:** Psychological distress like anxiety and depression is prevalent among PD population, which further aggravates one's physical symptoms and HRQoL. Mind-body interventions, such as yoga, that teach mindfulness along with physical activity may be well suited for reducing psychological distress in people with PD (1). **Methods:** A pilot study was conducted from Sept to Nov, 2016. People with mild to moderate idiopathic PD were recruited (Table 1: eligibility criteria). Assessments were done before and after completion of this 8-weekly yoga programme. Outcome measures included: psychological disease (Hospital Anxiety and Depression Scale), chronic stress (heart rate variability), motor symptoms (MDS-UPDRS III), mobility, balance and fall risk (Timed Up and Go test), spiritual wellbeing (Holistic Wellbeing Scale), and HRQoL (PDQ-8). The 60 minutes yoga classes
included controlled breathing, mindfulness meditation and yoga poses designed specifically for PD. Process evaluation was done. Ethics approval was granted (CUHK-CREC 2016.323-T).

Results: A convenience sample of 10 PD participants completed the study. The enrolment rate was 58.8% and class adherence rate was 97.5%. There was no adverse event. Results of process evaluation were summarized in Table 2. All participants were satisfied with this programme. Perceived benefits included improving flexibility, gait and balance and constipation, lessen back and shoulder pain, relaxing body and mind, easier to fall into sleep, less anxious, calmer and better mood. Significant improvements were found for psychological distress (p=0.006) with a moderate effect size of 0.4 and spiritual wellbeing. Future protocol was suggested to increase the duration of each class from 60-minute to 90-minute, so as to ensure adequate time for teaching and learning in a stepwise approach among participants with PD symptoms. Bi-weekly self-practice gatherings were self-initiated by participants after completion of the programme, indicating their interest and motivation in continuing yoga practice.

Table 1. Eligibility criteria

Inclusion criteria						
(i)	diagnosed of idiopathic PD,					
(ii)	with a disease severity rating of stage I to III on the Hoehn and Yahr scale,					
(iii)	aged above 45 years,					
(iv)	stable medication usage within recent three months,					
(v)	able to stand unaided and walk with or without an assistive device, and					
(vi)	participants who could give written consent					
Exclu	sion criteria					
(i)	currently receiving treatment for mental disorders or with uncontrolled					
	mood disorders,					
(ii)	currently participating in any other behavioural or pharmacological trial or					
	instructor-led exercise programme,					
(iii)	with cognitive impairment indicated by the Abbreviated Mental Test lower					
	than 6, and					
(iv)	other debilitating conditions except PD, e.g., vision or hearing impairment					
	that would impede full participation in the study.					

Table 2. Summary of process evaluation

	Strongly agree	Agree	No comment	Disagree	Strongly disagree
1. The content of exercise programme is appropriate.	6	3	1		
 The total number of classes and duration of each class was appropriate. too short for each class (n=1) 	3	6		1	
3. The venue was appropriate.	3	7			
 I think that the difficulty level of exercise being taught in classes is appropriate for me. 	4	5	1		
5. I think that the breathing exercises is useful for me.	4	6			
6. I think the mindfulness meditation is useful for me.	3	6	1		
7. I think that the yoga poses are useful for me.	5	5			
 The information being provided related to this exercise programme is appropriate. 	4	5	1		
 I am satisfied with the teaching methods delivered by the instructor. 	8	2			
10.I can remember the exercises learned from class.	3	5	1	1	
 In daily living, I have time to practice the exercises learned from class. 	3	6	1		
12. After the completion of exercise programme, I am confident that I could continue the exercise practice in daily living	3	4	2	1	
13. Overall speaking, I am satisfied with this exercise programme.	5	5			

Conclusions: The mindfulness yoga intervention and study procedures were feasible for people with mild to moderate PD. Improvements in psychological distress, symptoms perceptions and wellbeing merit more powered and controlled future studies of mindfulness yoga in PD population.

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A national Swedish self-management program for people with Parkinson's disease - patients and relatives view

C. Hellqvist, C. Berterö, M. Levander, N. Dizdar, P. Hagell (Linköping, Sweden)

Objective: To identify and describe experiences that people with PD and their relatives after participation in the self-management intervention NPS (National Parkinson School) find valuable for managing daily life. **Background:** A self-management program called NPS was developed as a collaboration of healthcare providers, researchers and patient organizations. NPS is aiming to provide tools and strategies for people with PD and their relatives to increase ability to manage symptoms and consequences of disease and thereby improving conditions for a good life. Self-monitoring and self-management are central concepts. NPS focuses on life with PD, which via 7 sessions consisting of education/lectures and group discussions are mediated. Home assignments make participants practice the new skills in their own life.

Methods: The last session, evaluation of the NPS, was audio recorded in its whole and transcribed verbatim. Data was collected from five separate clinics and analysed both inductively and deductively using Thematic Analysis and by applying the Self-and Family management theory.

Results: Through inductive analysis three themes; *Exchanging experiences and feeling support, Adjustment and acceptance of PD for managing daily life* and *Promoting life satisfaction*, were identified and described. The themes are capturing the meaning, value and experience of being a participant of NPS. Deductive analysis indicated that

the Self-and Family management theory was useful and valid for this group of patients and generated a modified framework applicable for patients with PD and their families [figure1].



Conclusions: Living with PD affects patients as well as relatives. Meeting others in the same situation gives support and strengthen their self- image. Having the opportunity sharing experiences and practical advices showed that there was a hopeful future to come. Techniques to accept and manage life with PD included seeking information about disease and treatments, self-monitoring in order to adjust to new situations and improve symptoms of disease and having a positive mind-set. Living an active life, participating in enjoyable social, cultural, and physical activities were important to feel happy and satisfied with life. Participation in NPS covered many areas of importance for the ability of self-management in PD. The framework for self-management in chronic disease was found relevant also for the PD population

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Impact and communication of OFF periods in Parkinson disease

T. Rastgardani, M. Armstrong, A. Gagliardi, C. Marras (Toronto, ON, Canada)

Objective: To review existing literature on the impact and communication of OFF periods for patients with Parkinson disease (PwP) and carepartners.

Background: Studies show associations between OFF periods and health-related quality of life (HR-QoL), but there is little published on the specifics of how these negatively impact PwP and carepartners. Poor understanding of the personal impact of OFF periods, compounded by their complex symptomology, makes communication about OFF periods between PwP and physicians challenging.

Methods: A scoping review was performed. MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, and PsycINFO were searched from 2006 to current. Quantitative and qualitative studies examining impact of OFF periods on PwP or care partners, or communication about OFF periods between health care providers and PwP or carepartners were eligible. Data extraction was standardized between and performed by three investigators.

Results: 2021 abstracts were identified, 51 full texts screened, and 14 papers met eligibility criteria. Of the 14 included studies, 7 showed an association between OFF periods and poorer HR-QoL (as measured by PDQ-39 SI, PDQ-39 VAS, or EQ-5D IS scores), but without further exploration of the nature of the impact of OFF periods on PwP or carepartners. 2 qualitative studies were identified, which highlighted the significant burden of OFF periods and unpredictability of functioning and reliance on others for timely medication administration as specific negative impacts. Communication was indirectly addressed by 1 study, where detection rates of OFF states between a neurologist's evaluation and a self-administered "wearing off" questionnaire (WOQ) were compared. Clinical

interview detected OFF phenomena less frequently (57% of 617 PwP) compared to WOQ (67%). There were no studies addressing strategies, barriers, or facilitators of communication about OFF periods between PwP or carepartners and physicians (Table 1).

Study	Research design	Types of participants	Setting	Methods of data collection	Study outcome relevant to OFF periods
van Rumund et al (2014)	Qualitative interviews and focus groups (single cohort prospective)	PwP, 'informal caregivers', health care workers	Nursing homes (from 12 Dutch nursing home organizations)	Interviews (patients and caregivers) and focus groups (one for for nurses and another for all other health care professionals)	Residents and caregivers expressed their need for more emotional support and empathy, particularly in negard to OFF timing and symptoms: Residents and caregivers perceived the lack of empathy as a result of limited knowledge, mainly among nurses, about PD in general and futuations in motor functioning in particular. The main comparisor were than turses did not uncertaine (1) the resident's addit futuations in PD symptoms, and (2) the importance of timely saministration of levodops and avoiding (protein-icin) main to the simple characterization of timely saministration of levodops and avoiding (protein-icin)
Haahr et al (2010)	Qualitative interviews (single cohort prospective)	PwP	Recruited in an academic movement disorders clinic, interviews at patient homes	Interviews	Means a last line for outpose induct A major theme identifies as starting PWP with advanced PD related to unpredictability due to OFF periods. OFF phenomenon were a significant problem, as not knowing how the body would act and react hampered planning and preparation.
Tanji et al (2008)	Comparative cohort prospective survey	PwP and spouses	Academic outpatient setting	Paired PwP-spouse questionnaires	Motor fluctuations were one of several factors (including gait, balance, uninary incontinence) identified as particular stressors on mutuality between spouses, and the marital relationship.
Santos-Garcia et al (2015)	Cross-sectional prospective survey	PwP and caregivers	Academic neurology clinic	Questionnaires (administered to caregivers)	UPDRS IV, assessing motor complications, was not associated with levels of caregiver burden or strain, as measured by ZCBI or CSI scores in multivariable analysis.
Politis et al (2010)	Single cohort prospective survey	PwP	Single academic neurology clinic	Single question survey: PwP asked to name 3 most troublesome symptoms in the last 6 months	Among patients with advanced PD (x-5 years duration of symptoms), ineffective medication response (DFF periods) was the topmost prevalent complaint.
Leentjens et al (2012)	Cross-sectional prospective survey	PwP	movement disorders, neurology, and psychiatry clinics from 6 centres in Europe, US and Australia	Questionnaires	Patients with motor fluctuations had more than twice as high a prevalence of generalized anxiety disorder (23% vs 9% , p=0.001). They also scored higher on Hamilton and Beck anxiety rating scales.
Stocchi et al (2014)	Single cohort prospective survey	PwP and physicians	Movement disorders clinic	Questionnaires and dinical interviews	Motor fluctuations were under-recognized by clinical interview (37%) compared with WCQ (67%). The difference was most marked in patients with short disease duration and short duration of treatment.
Hechtner et al (2014)	Cross-sectional prospective survey	PwP	Multi-site outpatient speciality clinics (neurology and geriatrics)	Questionnaires	The presence of on-off fluctuations was significantly associated both with poorer QoL measures, as measured by EQ-3D index score (beta = -7.1, px0.001) and PDQ-39 SI (beta = 3.6, p = 0.01).
Luo et al (2009)	Cross-sectional prospective survey	PwP	Single academic specialist clinic (with the catchment area of a small country's population)	Questionnaires	The presence of "wearing off" periods was significantly associated with poorer QoL as measured by EQ- 3D index score (0.62 with "wearing off" vs 0.83 without, pv0.0001).
Souza et al (2007)	Single cohort prospective survey	PwP	Academic outpatient setting	Questionnaires	Presence of motor fluctuations were associated with poorer QpL as measured by PDQ-39 SL
Winter et al (2011)	Cross-sectional prospective survey	PwP	Single outpatient academic neurology clinic	Questionnaires	Significant correlations with presence of motor fluctuations (distinct from 'dyskinesias') and quality of life as measured by EQ+VAS (jp = 0.003) and EQ>30 (px0.003) were found. On multivariate regression analysis to evaluate factors which are independent predictors for EQ>30 index and EQ+VAS. The coursence of motor industations was a HPQL-reducing factor for both scales.
Gomez-Esteban et al (2011)	Cross-sectional prospective survey	PWP	Single academic outpatient clinic with catchment from multiple clinics from Vizceye region in Spein	Questionneires	Duration, unpredicability and soulty of DFF periods were among several factors identified as impacting QoL as measured by POQ-30. Other factors succisted with poorer QoL included depression, agitation, apathy, anivety, hallucinations, delusions, uninary incontinence, morning painful posturing, restlessness in bed, and morning fatigue.
Kerr et al (2016)	Cross-sectional prospective survey	PwP	Community neurology clinics, identified by 'specialist recruitment agency'	Questionnaires	"Off" time significantly impacted QoL as measured by ED-3D and PDQ-3B. 10 basic daily activities were rated as most affected by OFF time and bothersome to patients. A stated preference discrete choice experiment (SPDCE) survey showed increased predictability of OFF periods as highly valued by PwP.
Rascol et al (2015)	Cross-sectional prospective survey	PWP	Community neurology clinics across France	Questionnaires and clinical interview	Failing cozurted more frequently in 'off' states (24% vs 22%), in particular failing related to freezing of gail, showing the impact of OFF on ambulation.

Conclusions: This scoping review shows paucity of knowledge regarding the lived experiences of OFF periods for PwP and carepartners, and communication about these between PwP or care partners and treating physicians. Further research is required to explore the impact and communication of OFF periods among PwP, carepartners, and physicians, to ultimately improve their treatment.

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Table 1 Study characteristics and outcomes

Internet-based cognitive behavioral therapy for general function in patients with Parkinson's disease: A randomized controlled trial

M. Kraepelien, R. Schibbye, P. Svenningsson, N. Lindefors, V. Kaldo (Stockholm, Sweden)

Objective: This study investigates the effect of therapist-guided internet-based cognitive behavioral therapy (ICBT) for general function in Parkinson's disease (PD) compared to a waitlist.

Background: In an uncontrolled pilot study, ICBT alleviated depression and anxiety in PD patients [1]. **Methods:** 77 patients with PD and self-reported problems with general function (WSAS>15) were randomized to 10

weeks of ICBT specially adapted for PD or to a waitlist. Change in general function, quality of life, depression, anxiety and insomnia symptoms were explored.

Results: Participants receiving ICBT reported lower symptoms of anxiety, depression and sleep problems compared to the waitlist. However effects on functioning and quality of life were inconclusive.

Conclusions: The results suggests that ICBT could be a way to alleviate depression, anxiety and sleep problems for some people with PD.

Study of an early wellness program in Parkinson's disease: impact on quality of life and early intervention guidance

B. Page, H. Shill (Phoenix, AZ, USA)

Objective: This study examined whether intervening early in PD with a comprehensive Wellness Program is feasible and promotes lasting habits that will continue to provide sustained benefit. It was hypothesized that intervening early in PD with an intensive program involving structured exercise, socialization and PD specific education would serve to maintain or improve quality of life while decreasing healthcare utilization.

Background: Previous studies have shown that PD patients are at an increased risk for a variety of complications impacting health related quality of life (HRQoL). Additionally, these various complications often lead to increased healthcare utilization. Wellness intervention in PD has shown to be effective in improving HRQoL and objective measures of disease burden such as motor functioning.

Methods: Twenty-one consenting ambulatory adult subjects diagnosed with PD within the last five years completed various screenings at baseline and following a required 6-month Wellness Program intervention. Subjects were assessed at 12 and 18 months if they continued to participate. Patient demographics, HRQoL, objective mobility, healthcare utilization and falls were assessed. Data were collected at Banner Sun Health Research Institute which is located in Sun City, Arizona. All p-values were 2-tailed and P<0.05 was considered statistically significant. **Results:** Twenty of twenty-one subjects completed the required 6-month intervention. Continued participation was 70% at 12 months and 60% at 18 months. Overall HRQoL was stable at 18 months. Significant improvement was seen in patient reported mobility and emotion sub-areas at 12 months. Communication specific HRQoL was significantly worsened at 12 months. Subjects demonstrated a stable level of physical activity while fatigue was significantly decreased. All objective measures were significantly improved from baseline. Healthcare utilization was decreased by 18 months. A total of 5 falls were reported by 3 subjects during the 6-month interventional period. **Conclusions:** Comprehensive wellness intervention in early PD is feasible, effective, safe and valuable in establishing long-term beneficial habits while potentially reducing healthcare utilization. The results also highlight the importance of addressing communication specific symptoms early. Ultimately, this study will aid the design and implementation of future PD wellness interventions.

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Quality of life and its influencing factors in a local population of advanced geriatric Parkinson's disease patients

M. Klietz, A. Tulke, C. Schrader, L. Diekstall, L. Müschen, D. Dressler, F. Wegner (Hannover, Germany) **Objective:** Parkinson's disease (PD) is the second most common neurodegenerative disease. The movement disorder is characterized by the clinical hallmarks tremor, akinesia, rigidity and postural instability. Progress in PD is accompanied with motor fluctuations and additional non-motor symptoms such as obstipation, sleep disorders, depression, dementia and psychiatric symptoms.

Background: This course of disease progression leads to severe burden of patients and caregivers as well. By accumulation of these symptoms patients lose their autonomy and are more and more care dependent. Unfortunately there is a huge lack of knowledge regarding quality of life and the care situation of severely diseased PD patients. **Methods:** In an ongoing study of our group we characterize quality of life, care situation and influencing factors in a local cohort of advanced PD patients. Additionally, the need for palliative care should be quantified in structured interviews.

Results: 76 geriatric patients suffering from advanced PD have been characterized. The average Hoehn and Yahr Stage was 4.01 (3 - 5), the mean age was 75.5 (65 - 89). The mean Barthel Index was 62 (0 - 100). Interestingly, a huge number of these patients showed cognitive deficits in the MoCA test of cognition. Quality of life measured by the PDQ-39 correlated highly significant with motor deficits (MDS-UPDRS part III), Barthel Index, MoCA-Score and activities of daily living (UPDRS II). The equivalence dosage of levodopa calculated for each patient did not correlate with quality of life at all.

Conclusions: Here, we show that quality of life is dramatically reduced in these patients. Factors found to be negatively correlating with quality of life are motor impairments, cognitive deficits and the ability to perform activities of daily living. These data help to plan interventions for advanced geriatric PD patients in order to stabilize quality of life during disease progression.

Palliative care in Parkinson disease

A. Patterson, L. Almeida, M. Okun, I. Malaty (Gainesville, FL, USA)

Objective: The objective of this study was to derive a baseline understanding of palliative care among the Parkinson disease (PD) patient population at a single movement disorders center.

Background: Advanced PD patients suffer similarly to metastatic cancer patients when measured on palliative care scales, with symptoms including constipation, anxiety, dysphagia, and pain. Palliative care in PD is a potentially useful but underutilized resource. The reason for this is likely multifactorial, but deficits in patient understanding of palliative care likely contribute.

Methods: We offered a questionnaire to PD and parkinsonism patients, of any disease stage, seen at our center over an 8-week period. The questionnaire included 15 basic items assessing knowledge of palliative care and one item assessing whether patients had advance directives. Response options on the 15-item quiz included "true", "false" and "unsure".

Results: Advance directive information was available in 204 patients. Our study population was 61% male, 92% Caucasian, 78% married, 67% religious or spiritual, 90% havingv children, and 58% having completed college or beyond. 18% were < age 60, 39% were in their 60's, and 42% were 70 or older. Groups were relatively equally divided between symptom duration 5 years or less, 6-10 years, and >10 years. 80% of patients reported having an advance directive (71% had a living will, 55% had a healthcare power of attorney, and 55% had an advance directive itself). Age was the strongest predictor of having an advance directive. Other positive predictors were higher level of education, married relationship status, presence of children, and Caucasian race. Gender was not predictive and, surprisingly, duration of disease was not predictive. Responses on palliative care questions among the 228 questionnaire respondents ranged from 29-59% correct, 1-13% incorrect, and 39-62% unsure. Those with less formal education were more likely to select "unsure" but even the college educated patients answered 'unsure" 28-61% of the time. Patients with college education or beyond were more likely to respond correctly.

Conclusions: A surprising majority of patients at our tertiary movement disorders center had an advance directive, implying that patients are anticipating and planning for the future. Despite this finding, there was a considerable gap in knowledge about palliative care which supported the hypothesis that underutilization may at least partially be due to lack of understanding.

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Changing patterns of intimate relationships as dementia emerges in Parkinson's disease

S. Vatter, K. McDonald, S. McCormick, I. Leroi (Manchester, United Kingdom)

Objective: To explore relationship satisfaction and aspects of intimacy in female partners of people with cognitive impairment associated with Parkinson's disease (PD) using qualitative methods.

Background: The diagnosis of a movement disorder such as PD in an individual may have repercussions on their life partner and the couple's relationship may alter. As dementia emerges, the burden of clinical symptoms and functional impairment increases, which may also impact on the relationship and have implications for outcomes of the condition. To date, relationship satisfaction of partners of people with Parkinson's-related cognitive impairment (mild cognitive impairment, PD-MCI; Parkinson's disease dementia, PDD, or Dementia with Lewy Bodies, DLB) has yet to be fully explored.

Methods: Individual, in-depth, exploratory semi-structured interviews with life partners of people with PD-MCI, PDD or DLB were undertaken at participants' homes. Reflective diary and field notes were written after each interview. Data were analysed using thematic analysis.

Results: Initial analyses of female life partners, who were the primary care providers for individuals with PD-MCI, PDD or DLB, were conducted. These revealed that the emergence of cognitive impairment (regardless of disease severity and duration) and neuropsychiatric disturbances were significantly more difficult to accept, manage and cope with than the motor symptoms of PD. The presence of Parkinson's resulted in a practical need for couples to spend more time together to enable the spouse to support their partner in managing activities of daily living. In contrast, at an emotional level, the spouse felt more distanced from their partner. All participants expressed that their relationship satisfaction was significantly different compared with the early stage of the disease, and multiple types of intimacies, including social, emotional, intellectual and physical, had changed as a result of their partners' illness. **Conclusions:** The experiences of life partners can provide valuable insights about how intimate relationships transform as dementia develops in PD. Recognising and understanding these perspectives is essential in order to foster positive outcomes in the condition.

Assessing the extent of carer strain in Parkinson's disease

R. Varadarassou, V. Queen, E. Pearson, F. Murphy, M. Turner, C. Carroll (Plymouth, United Kingdom) **Objective:** To evaluate the extent of carer strain in newly diagnosed Parkinson's disease (PD) compared with that in long-standing PD, to inform development of carer-support services within our patient pathways.

Background: There is little provision for the carers of people with PD (PwP), leaving carers feeling anxious, isolated and unassisted. Resultant carer strain increases risk for PwP and potential for hospitalisation and institutional care. We are keen to evaluate the level of carer strain and impact on quality of life in order to inform the need for and development of a carer-support service within both our newly-diagnosed patient and complex disease pathways.

Methods: 20 Carers of PwP diagnosed within the last 12-18 months and 20 carers of PwP diagnosed for more than 5 years will be invited to participate in telephone interviews. The interviews will consist of open-ended questions to evaluate the scope of care provided as well as two measures: the Parkinson's Disease Questionnaire – Carer (PDQ-C) and the Parkinson's Disease Caregiver Burden Questionnaire (PDCB-Q) to evaluate carer quality of life and caregiving burden respectively.

Results: This project is currently at the data collection stage. The results will demonstrate the extent of carer burden in both long-standing and newly diagnosed PD, and evaluate the impact of this on carer quality of life.

Conclusions: The findings will enable us to provide a rationale for developing carer support services within both our new-diagnosis and complex disease pathways. We plan to incorporate elements of the evaluation into routine service to identify those carers potentially at risk of strain and resultant reduction in quality of life.

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Physical activity and quality of life in people with Parkinson's disease – a long-term follow-up study *I-F. Shih, K. Paul, J. Bronstein, B. Ritz (Los Angeles, CA, USA)*

Objective: This study aims to examine associations between changes in physical activity (PA) and health-related quality of life (HRQOL) among Parkinson disease (PD) patients.

Background: Physical activity is beneficial for patients with Parkinson's disease in general and for disease-specific outcomes, but it is not yet understood whether changes in PA over time impact HRQOL, and long-term prospective data in PD patients are not available.

Methods: We examined PA in a longitudinal cohort of 242 incident PD patients diagnosed between 2001 and 2007 in a population-based study in Central California and followed on average 7.5 years after diagnosis. We obtained adult PA information at baseline and collected daily PA and HRQOL via the 36-Item Short Form Health Survey (SF-36), EuroQol (EQ-5D) and Functional Activity Questionnaire (FAQ) at follow-up. In multiple regression analyses, we controlled for age, sex, education, race, disease duration and severity, and cognitive function. **Results:** PD patients who were younger, male, of non-European ancestry, and more highly educated were more likely to consistently engaged in high level of PA throughout follow-up. Consistently high level of PA was associated with increased physical functioning, vitality, social functioning, general health and SF-36 total scores and less mobility problem (EQ-5D) at follow-up (p<0.05). Compared with participants who reported a decrease in PA level, those who reported the same or an increase displayed greater physical functioning and less pain. There were no association between changes of PA and instrumental functions.

Conclusions: This study provides preliminary evidence to suggest that maintaining or even increasing levels of PA leads to better overall HRQOL in terms of physical functioning, vitality, social functioning, general health and mobility controlling for demographic factors and disease severity and duration.

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Implanted brain-computer interface for communication in people with motor impairment

E. Pels, E. Aarnoutse, M. Vansteensel, S. Leinders, Z. Freudenburg, M. Branco, M. Vanden Boom, T. Denison, N. Ramsey (Utrecht, Netherlands)

Objective: In people with movement disorder communication can be challenging and depends heavily on their caregiver. Here we describe an ALS-patient utilizing the first fully implanted Brain-computer Interface (BCI) for communication independently at home.

Background: A particular burdensome movement disorder is locked-in syndrome (LIS). Characterized by the loss of all voluntary movement LIS results in quadriplegia and the loss of speech, while cognition is intact. LIS has various causes, including brainstem stroke, trauma and ALS. Communication is a key aspect in the lives of these patients and the ability to do so is correlated with a high quality of life.

Methods: We developed a method for communication in LIS-patients based on a fully-implanted BCI. This system consists of subdural ECoG electrodes placed on top of the motor cortex and an amplifier/transmitter (Activa PC+S, Medtronic) placed subcutaneously in the left thorax. The signal is received wirelessly through the skin by an antenna and streamed to a tablet running signal processing software translating it to a control signal for spelling software (figure 1). A late-stage ALS patient (ALS-FRS-r: 3) was implanted with this system and has been using the BCI since late 2015¹.



Results: The participant was able to use attempted hand movement as a control signal from the start. Independent control of a spelling computer was realized only 28 weeks after implantation. The participant is now using the system for >15 months and the signal and user-control remain stable and reliable as confirmed by 3 tasks: 1) Screening task (alternations of attempted hand-movement and rest): high correlation of control signal (65-95 Hz band power) with task conditions of 0.88, 2) High performance on a 1-dimensional cursor-control task (attempted movement for up, rest for down): $91\pm6\%$ correct, 3) Baseline power of high frequency band stable from week 8 onwards $0.44\pm0.04a.u$. The participant now uses the system independently at home, only requiring antenna placement by a caregiver, and reported high satisfaction.

Conclusions: Results indicate that (1) the motor cortex of people with movement disorder can be used to generate a reliable signal for BCI control, (2) the implanted electrodes are durable and information transfer is preserved over the course of 14 months, showing that an implanted BCI meets the needs of a user for an assistive communication device.

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Predictors of patient satisfaction with rechargeable deep brain stimulator implantable pulse generators *K. Mitchell, M. Volz, S. Wang, A. Lee, J. Ostrem (San Francisco, CA, USA)*

Objective: To assess predictors of patient satisfaction with rechargeable implantable pulse generators (IPGs) **Background:** Deep brain stimulation (DBS) is an effective therapy for Parkinson Disease (PD), tremor, and dystonia. Traditional IPGs require surgical replacement every few years. Rechargeable IPGs can prevent these frequent surgeries and the inherent risks of complications but typically require daily recharging by the patient. A better understanding of patient experience regarding these rechargeable devices will help guide patient selection, training, and counseling.

Methods: All patients previously implanted with rechargeable IPGs at our center are being contacted in an ongoing study. 24 patients have completed comprehensive surveys evaluating experience with the devices. Surveys are modified versions of previously validated scales from Timmermann et al (2013) as well as open ended qualitative questions. Outcomes of patient satisfaction with fit/comfort, recharging, display, training, programmer, and overall

satisfaction were analyzed with respect to age, diagnosis, new DBS versus conversion from non-rechargeable IPG, and body mass index (BMI).

Results: The combined study group had high overall satisfaction (82.2). Patients with dystonia had significantly higher satisfaction than patients with PD in fit/comfort (92.6 vs 70.1, p<0.01), recharging (85.5 vs 57.5, p<0.02), and programmer (90.7 vs 70.3, p<0.05) and a trend towards higher overall satisfaction (88.4 vs 63.7, p=0.06). There was no correlation of advancing age with patient satisfaction in a regression model. There was no difference in patient satisfaction when comparing patients with first time DBS to those with conversion from standard IPGs or between patients with normal and overweight BMIs. Common open-ended positive responses were "fewer surgeries," "small" size, and "easy to recharge." Common negative responses were difficulty "finding the right position to recharge," and need to "recharge every day."

Conclusions: Patient experience with rechargeable IPGs was largely positive. Dystonia patients had the highest satisfaction across multiple categories. Younger age did not correlate with higher satisfaction in any category our patient population. Pre-operative counseling about potential frustrations with coupling of the recharging system and recharging needs is necessary to allow informed decisions for patients.

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SweetSpot of antidystonic effect in pallidal neurostimulation: a European multicentre imaging study *M. Reich, L. Lange, J. Roothans, A. Horn, F. Wodarg, J. Runge, M. Aström, F. Steigerwald, K. Witt, R. Nickl, P. Plettig, M. Wittstock, V. Coenen, P. Mahlknecht, W. Poewe, W. Eisner, C. Matthies, A. Kühn, J. Krauss, G. Deuschl, J. Volkmann (Würzburg, Germany)*

Objective: We investigated Volumes of Tissue activated (VTA) in dystonia subjects under DBS. We aimed to disentangle the SweetSpot for dystonia suppression within the pallidal region.

Background: GPi-DBS is an established therapy for generalized and cervical dystonia. Average improvement of dystonia severity amounts to 50-60%, but outcomes are often variable and studies report up to 25% non-responders. Variability in electrode placement may account for a large proportion of outcome variability. So far no study has been able to identify an "optimal efficacy volume" within the GPi.

Methods: 85 subjects with dystonia (41 cervical mean TWSTRS 20.3 ± 3.6 points/44 generalized dystonia, mean BFMDRS 45.8 ± 20.5 points) under chronic bilateral GPi-DBS from 8 European DBS centres were stratified for chronic motor improvement (median reduction of $46.7(\pm27.7)$ % after 12.0 months in cervical / median reduction of $52.3(\pm35.9)$ % after 34.8 months in generalised dystonia). We simulated VTAs for each lead in subject's related MRI space based on chronic stimulation parameters obtained from a chart review and associated with

BFMDRS/TWSTRS improvement. All patient images were registered to a common average MRI. Only VTAs with a motor improvement >50% were taken for the visualisation of three different areas, defined by allegorizing only voxels that were overlapped by >15(*green*); >30(*orange*) VTAs and the "SweetSpot", overlap volume of >50(*red*) VTAs.

Results: Wide variability of lead location, stimulation parameters and chronic motor improvement was observed in this cohort of 85 subjects. VTA size did not exhibit a significant correlation with improvement in motor symptoms. Model-based analysis of 108 responding VTAs showed a core mean volume (="sweetspot") located within and below the ventroposterior GPi. Stereotactic coordinates of the center of gravity were *lateral:20.0, anterior:2.3 and inferior:2.6* (based on AC-PC in mm).



Figure 1: Overlap volume of 108 VTAs corresponding to a motor improvement >50% in BFMDRS or TWSTRS scores. <u>GPe</u> in blue, <u>GPi</u> in light blue, <u>ansa lenticularis</u> in light brown, optical tract in brown, Voxels overlapped by >15 (green); >30 (orange) VTAs by >50 VTAs (<u>sweetspot</u> in red).

Conclusions: In this study, we showed that the magnitude of current injection is not decisive for the therapeutic DBS effect. *In fact*, the outcome is highly correlated with the precise location of neuromodulation within the region of interest. The most beneficial (sweet-)spot hints to a relevant contribution of subpallidal white matter, which could indicate a possible modulation of the ansa lenticularis for the anti-dystonic effect of DBS in addition to stimulation of the presumed sensorimotor region of the GPi

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Focused neuromodulation by short pulse width improves gait ataxia in thalamic DBS

M. Reich, N. Pozzi, G. Brandt, A. Leporini, C. Palmisano, R. Lehrke, J. Volkmann, I. Isaias (Würzburg, Germany) **Objective:** To investigate the efficacy of selective neuromodulation to overcome stimulation-induced gait ataxia in patients with essential tremor (ET) and thalamic deep brain stimulation (DBS).

Background: Thalamic DBS is a mainstay treatment for severe and drug-refractory ET, but postoperative management may be complicated in some patients by a delayed-onset progressive cerebellar syndrome. Typically, this syndrome manifests with severe gait ataxia months after an initially effective DBS therapy and it reflects an excessive current spread in the cerebellar-thalamic pathway.

Methods: We clinically evaluated seven subjects with ET and progressive gait ataxia under stable bilateral (sub)thalamic-region stimulation (2 males; median age: 73 years, range: 65-86 years). Patients were consecutively recruited and evaluated with the Fahn-Tolosa-Marin tremor rating scale (TRS) and the SARA1-3 scale for ataxia before (baseline), at 30 min and 14 days after reducing the stimulation pulse-width to 30µs. Such a short pulse width (30µs) was chosen to possibly target exclusively to the fast conducting dentate-thalamic myelinated fibers. **Results:** Short pulse-width (30µs) dramatically improved gait ataxia (baseline SARA1-3 score: 6.8 ± 2.8) in all patients already at 30 min (SARA1-3 score: 2.6 ± 2.8 ; student t test, p<0.01) and at two weeks follow-up (SARA1-3 score: 3.0 ± 2.0 ; student t test, p<0.01). Tremor was always well controlled by DBS (TRS score at baseline: 10.2 ± 9.5 ; TRS score at 30 min 6.5 ± 10.3 ; TRS score at 14 days: 4.8 ± 4.2 ; student t test, p=n.s. all).

Conclusions: DBS-induced chronic progressive gait ataxia in ET patients can be effectively managed by focusing the stimulation to fast conducting dentate-thalamic myelinated fibers, which is the proper target for tremor control. This can be achieved, by reducing the stimulation pulse-width to $30\mu s$, without losing the positive effect of DBS on tremor. Focused stimulation may prevent current spread and antidromic activation of the uncinate tract, which might be responsible for the delayed-onset of cerebellar side effects.

Differences in the oscillatory activity of the globus pallidus in dystonia, Parkinson's disease and gilles de la tourette syndrome

M.M. Carmona-Abellan, M. Valencia, J. Guridi, R. Luquin, J. Artieda, M. Alegre (Pamplona, Spain) **Objective:** To compare local field potentials features in Parkinson's disease (PD), dystonia and Gilles de la Tourette syndrome (GTS) recorded from the Globus Pallidus internus (GPi).

Background: Local field potentials in the subthalamic nucleus have been recognized as potential biomarkers of PD and other non-parkinsonian movement disorders but the oscillatory activity features in PD compared to other movement disorders such as dystonia, chorea or tics in the GPi has not been ascertained.

Methods: We recorded local field potentials from the GPi in surgically treated patients with deep brain stimulation, in PD (n=2), dystonia (n=7) and GTS (n=2). Spectral power and phase-amplitude coupling characteristics were analyzed.

Results: There are differences in the beta band activity recorded from the GPi in patients with PD, dystonia and GTS. High and low beta band was recorded in the GPi in PD patients, whereas dystonia patients showed only high beta band. Beta band was not present in theGPi in GTS patients. High frecuencies oscillations (HFO) are present in all PD, 28.5 % of dystonia patients and in all patients with GTS.

Conclusions: High frequency oscillations are present in different movement disorders such as PD and GTS but only in some patients with dystonia. Beta band activity and HFO recorded from the GPi of different diseases suggest that oscillatory activity might have a role as specific biomarker of movement disorders.

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Evolution of globus pallidus internus (GPi) deep brain stimulation targeting over 15 years

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Objective: To evaluate the evolution of GPi DBS targeting over time in a large single center cohort. **Background:** Deep brain stimulation (DBS) targeting the globus pallidus internus (GPi) is an effective therapy for treatment of motor symptoms in Parkinson's disease and dystonia. Accurate targeting is the primary determinant of outcome for these patients and the evolution of improved direct targeting techniques over the last two decades has enabled more effective stimulation with fewer side effects.

Methods: A retrospective single-center study identified 451 GPi DBS leads in 299 patients. Lead locations in AC-PC space (Cartesian coordinates using a mid-commissural point origin) were evaluated by year from 2002 to 2016. Data analysis employed robust regression and linear slope statistical models. A-P, Lateral, and axial coordinates were measured for each lead, comparing the post-op lead location to the intra-operatively chosen final target. Weighted annual mean errors were calculated and compared to annual mean errors predicted by regression models. Scatter plots of the original observed errors and estimated trend lines with 95% confidence intervals were generated. **Results:** Each x, y, z coordinate set was analyzed and the progression of the mean value was revealed in scatter plots separated by year. The lateral location (x) of the lead demonstrated a significant increase (p<0.0001) in its value over the years [figure 1]. The axial location (z) exhibited a significant increase (p=0.024) in the negative value, meaning that the lead position was more ventral (deeper) [Figure 2]. The A-P location (y) did not change significantly. The 3-D, lateral, A-P and axial error analyses revealed a significant decrease in predicted error which evolved over time.



Conclusions: The addition of direct targeting techniques based on high resolution magnetic resonance imaging coupled with a deformable atlas might explain our progression to a more lateral and slightly deeper GPi target. The evolution to a more lateral target may be the result of clinical feedback: lateral placement decreases the likelihood of inadvertent internal capsule stimulation and widens the therapeutic window for DBS programming. The trend toward more ventral placement may have reflected a bias to avoid loss of efficacy in the event of dorsal lead migration. A multi-center dataset could potentially answer many unresolved questions.

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Treatment outcomes for deep brain stimulation in sex-linked dystonia parkinsonism (XDP, DYT3) up to 60 months follow-up – a case series

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Objective: This case series presented the treatment outcomes of the eight (8) XDP patients who underwent DBS in a tertiary hospital and compared it to previous cases reported in literature. It described the percent improvement of their Burke-Fahn Marsden Dystonia Rating Scale and UPDRS-III scores from baseline over time with a longest follow-up of 60 months.

Background: X-linked dystonia-parkinsonism (XDP; DYT3; Lubag Disease) is a progressive hereditary neurodegenerative disease primarily affecting Filipino adult men. It has shown that surgical management in the form of bilateral globus pallidus interna (GPi) deep brain stimulation improves dystonia and has less adverse effects in single case reports.

Methods: This is a case series wherein eight (8) cases of diagnosed X-linked Dystonia Parkinsonism patients that underwent Deep-Brain Stimulation Surgery since 2009 to 2016 in a tertiary hospital were reviewed. The data from patients and similar cases reported in the literature were then tabulated to summarize it. A graph of the percent

improvement of their BFMDRS and UPDRS-III motor scores for the patients over time was done, with its longest follow-up of 60 months.

Results: There were eight (8) cases of diagnosed X-linked dystonia parkinsonism (XDP) patients that underwent deep brain stimulation (DBS) surgery in a tertiary hospital from 2009 to 2016. The median duration of the disease prior to surgery was 4.5 years (range 1-9 years). There was an immediate response to treatment in 7 cases with the highest percentage improvement of the BFMDRS score of 85.71% and UPDRS-III score of 66.67% compared from baseline. After 12 months, it has shown that the response over time were variable in terms of controlling dystonia while there was a trend towards worsening of parkinsonism. The peri-operative adverse events were reported but it had no significant post-operative morbidity.





Conclusions: Bilateral GPi deep brain stimulation may be considered as a treatment option for X-linked dystonia parkinsonism. It had shown to be effective in the first 12 months in controlling dystonia with variable resoponse in controlling parkinsonism. Its long-term benefit was not clearly seen in this series probably due to the progessive degenerative nature of the disease and other confounding factors.

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First report of clinical outcomes resulting from use of directional deep brain stimulation in Parkinson's disease and essential tremor

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Objective: To evaluate clinical motor outcomes, the patient's subjectively perceived benefit and the frequency of the use of directional lead stimulation in subjects with Essential tremor (ET) and Parkinson's disease (PD) after implantation of segmented-lead electrodes in the ventrolateral thalamus (VIM), subthalamic nucleus (STN) or globus pallidum (GPI).

Background: Directional Deep Brain Stimulation (DBS) provides the capability to customize the stimulation field in order to maximize the therapeutic efficacy while minimizing side-effects. To date, there is a lack of evidence on the clinical outcomes resulting from use of directional DBS.

Methods: PD and ET patients were bilaterally implanted in the STN or the GPI and the VIM, respectively. After initial monopolar review, patients initially received conventional, ring-mode, omnidirectional stimulation. During subsequent patient evaluations, unidirectional or bidirectional stimulation was utilized to compensate for stimulation-related side effects. Clinical Global Impression (CGI-C_{sub}; 7 point-scale: 1=very much improved, 7=very much worsened) scale was used to quantify and track patient progress and treatment response over time. Additionally, motor symptom relief was also assessed through use of appropriate standardized clinical scales.

All evaluations were performed 3-6 months post-permanent implant.

Results: A total of 11 patients [5 PD patients (age= 67.0 \pm 4.3 years, 2 males); 6 ET patients (age= 71.7 \pm 4.3 years, 5 males)] were included in this analysis. At 3-6 months post-stimulation, PD patients with STN-DBS reported that their treatment response was "much improved" (CGI-C_{sub} =2 \pm 1). One PD patient receiving GPI-DBS claimed no subjective change (CGI-C_{sub} =4). In ET patients with VIM-DBS, the outcome "improved" (CGI-C_{sub} =2.6 \pm 2.1); there was excellent response in 3 patients, but postoperative stimulation-induced worsening of ataxia in 1 patient. **Conclusions:** Preliminary clinical data resulting from use of directional DBS in movement disorders patients suggests an improvement in some patients in the motor outcomes while minimizing stimulation-induced side effects.

Our clinical experience with directional DBS indicates that it is safe and effective in providing optimal therapeutic benefit in patients with movement disorders.

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A case of idiopathic adult-onset truncal extension dystonia treated with bilateral pallidal deep brain stimulation

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Objective: To describe the outcome of deep brain stimulation (DBS) to the globus pallidus interna (GPi) in an adult patient with idiopathic truncal dystonia with a rare extensor phenotype.

Background: Focal dystonia is the most common type of adult-onset dystonia, however, it infrequently affects truncal musculature. Most patients with primary truncal dystonia exhibit flexion while truncal extension is rare and often attributed to secondary etiologies such as tardive syndromes and neurodegenerative disease. However, adult-onset idiopathic truncal dystonia with primary extensor phenotype has been reported. The majority of these patients are refractory to oral medications and botulinum toxin injections. Although the efficacy of DBS for primary dystonia, especially generalized DYT-1 positive dystonia, is well established; it has been shown to be efficacious for idiopathic truncal dystonia, specifically camptocormia, with no known reports of its application for an idiopathic focal extensor phenotype.

Methods: We present a case of a 49 year-old woman with no known family history of dystonia who complained of backward pulling of her trunk. At age 35, she developed abnormal arching of her back, which progressed to stereotyped extension and rightward tilting of her back that emerged when standing or walking. The dystonia abated in the seated or supine position. This caused severe difficulties walking and she employed sensory tricks such as running or leaning against a wall. She was not exposed to neuroleptics or antiemetics and had no structural lesions on her brain MRI. Trials of trihexyphenidyl, baclofen, carbidopa/levodopa, leviteracetam, hydroxyzine and botulinum toxin injections were not beneficial.

Results: Staged bilateral GPi DBS was implanted without complications. Improvement in the pre-operative Burke-Fahn-Marsden Dystonia Rating Scale motor score went from 12 to 4 at four months after initial programming and her disability score improved from 5 to 3.

Conclusions: GPi DBS can be particularly beneficial in patients with the rare phenotype of truncal extension in idiopathic truncal dystonia refractory to medications and botulinum toxin injections.

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Gait analysis in orthostatic tremor treated with thalamic deep brain stimulation

T.K. Tareen, A. Duker, G. Mandybur, J. Tuazon, M. Rosso, A. Espay, A. Fasano, A. Merola (Cincinnati, OH, USA) **Objective:** To evaluate the effects of Thalamic Deep Brain Stimulation (DBS) on Gait in Orthostatic tremor (OT) **Background:** OT is a rare hyperkinetic disorder of weight-bearing limbs, characterized by postural unsteadiness when standing and a high-frequency tremor of 13-18 Hz (1-2). The effects of ventral intermediate nucleus deep brain stimulation (Vim-DBS) on gait in OT patients remain unclear.

Methods: A 74-year-old woman underwent bilateral Vim-DBS for medication-resistant OT. She received good benefit from the procedure, but the effects lessened over time. Eight years after Vim-DBS placement, a thorough gait analysis-assisted assessment of DBS settings was performed. The patient was evaluated in the following conditions: 1) DBS-OFF; 2) DBS-ON baseline (Left: contact 2-/case+, 3.9Volts, 90µsec, 185Hz; Right: contact 9-/case+, 3.9Volts, 90µsec, 185Hz; Right: contact 9-/case+, 3.9Volts, 90µsec, 185Hz); 3) DBS-ON, while evaluating different stimulation settings. Spatio-temporal gait parameters, dynamic stability index (ratio between single and double support times), and coefficient of variation of step length and swing phase were recorded and analyzed in the different conditions.

Results: After examining several parameters, a reduction of stimulation intensity (decreasing voltage by 0.3Volts and pulse width by 30µsec bilaterally) was found to be associated with objective and subjective gait improvements. The following improvements were seen in different conditions (DBS Optimized vs. DBS at Baseline vs DBS Off) respectively; *Gait Velocity* in cm/sec (34.93 vs 34.59 vs 33.39), *Step Length* in cm (49.15 vs 47.42 vs 44.87), *Cadence* in steps/min (85.51 vs 87.31 vs 89.52). Both DBS ON conditions also reduced the spatial and temporal variability of gait when compared to DBS-OFF. However, supra-therapeutic stimulation worsened dynamic balance in the medio-lateral and antero-posterior axes.

Conclusions: These data suggest that Vim-DBS may exert a complex and multifaceted modulation of gait in OT, most likely related to the delicate balance of two main factors: 1) an improvement of OT symptoms, which may result in increased velocity and step length; and 2) a potential induction of gait ataxia, which may result in increased

stride width and time spent on double support time. This case, however, highlights the clinical utility of an integrated clinical/gait analysis approach in balancing these two opposing stimulation-related outcomes.

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Transient loss of psychic self-activation following bilateral thalamic ventral intermediate nucleus stimulation for essential tremor

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Objective: To report a case.

Background: Loss of psychic self-activation or even akinetic mutism has rarely been described in patients who suffered bilateral thalamic insults. Its pathophysiology is not completely understood but it is thought to be related to the disturbance of the striatal-ventral pallidal-thalamic-frontomesial limbic loop.

Methods: Case report

Results: 61-year-old female diagnosed with late-onset essential tremor at the age of 55. The postural and action tremor first affected both hands, with a slight left predominance, and then the head and legs. No known family history. The different therapeutic strategies failed due to side effects. The tremor became increasingly disturbing for daily activities. The patient was thoroughly studied due to the detection of a right mesencephalic lesion on MRI that was concluded to be an ischemic scar. Her neuropsychological profile was judged fit, and the patient underwent awake bilateral deep brain stimulation of the thalamic ventral intermediate nuclei without intra-operative complications. Post-operatively, the patient showed significant psycho-motor slowness, progressing to a state of apathy and akinesia mimicking a language disturbance. Although awake and capable of walking, the patient showed scarce eye contact and did not respond to questions or commands. Her head CT and blood workup were unremarkable. The electrodes were correctly positioned and there was no sign of surgical complications. This state did not differ according to the stimulation parameters. The patient was managed by the team psychiatrist and progressively medicated with sertraline 100mg daily. The neuropsychiatric symptoms gradually and completely subsided during the following 10 days at which point the patient performed an MRI. A small area of cytotoxic edema was found on the left corona radiata, posterior to the electrode. The patient was discharged home with an excellent motor benefit from the stimulation.

Conclusions: To our knowledge this is the first description of transient loss of self-activation following deep brain stimulation. We hypothesize it might be due to a transient disturbance of the deep circuitry involved in purposeful behavior, temporally and anatomically related to the electrode implantation in the thalamus. It is important to keep this diagnosis in mind when managing post-operative complications of these procedures.

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Safety and tolerability of deep brain stimulation in early stage Parkinson's disease: five-year follow-up of medication use and adverse events

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Objective: To evaluate the long-term safety and tolerability of subthalamic nucleus deep brain stimulation (DBS) for early stage Parkinson's disease (PD).

Background: Twenty-nine subjects with early stage PD were randomized to receive Optimal Drug Therapy (ODT) or DBS and ODT (DBS+ODT) and completed a two-year pilot trial (NCT#00282152). Subjects were followed for three additional years to gather longitudinal outcomes. PD medications were managed by the referring neurologist (not the principal investigator). During follow-up, four subjects randomized to the ODT group elected to receive standard-of-care DBS.

Methods: We analyzed levodopa-equivalent daily dose (LEDD) of PD medication [1] and adverse events (AEs). Within-subjects change in LEDD from baseline to five years was analyzed using Wilcoxon signed rank tests in an intention-to-treat (ITT) analysis and a censored analysis excluding data collected from subjects in the ODT group after they received DBS. AEs were collected prospectively; AEs that occurred between years two and five were included in this analysis.

Results: In the ITT analysis, LEDD did not change from baseline to 5 years in the DBS group (409±316mg to 774±590mg, p=0.10) but increased significantly in the ODT group (491±216mg to 1158±678mg, p=0.003). The censored analysis confirmed these findings in the ODT group (466±240mg to 1151±515mg, p=0.007). A total of 134 AEs were identified: 66 in the DBS+ODT group, 50 in the ODT group, and 18 in the ODT group after DBS surgery. Five of the 134 AEs were related to the surgery or device: three in ODT subjects who received DBS during

follow-up (cognitive disorder, confusional state, pneumocephalus) and two in the DBS group (post-procedural hematoma, medical device site scar). Of 13 study-related AEs, the most common was nausea (n=2 in DBS+ODT, n=1 in ODT). Of 116 unrelated AEs, the most common was depression (n=3 in DBS+ODT, n=3 in ODT). **Conclusions:** Medication requirements remained stable five years after DBS but increased significantly in the ODT group. Furthermore, this analysis suggests that DBS in early PD has a favorable long-term safety profile. The FDA has approved (IDE#G050016) a prospective, double-blind, placebo-controlled pivotal trial testing DBS in early stage PD in 280 subjects at 18 centers.

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Correspondence between MRI borders of the subthalamic nucleus and its electrophysiological borders: a comparison study using intraoperative CT

S. Bus, P. Van den Munckhof, M. Bot, G. Pal, B. Ouyang, S. Sani, L. Verhagen-Metman (Chicago, IL, USA) **Objective:** To compare dorsal and ventral subthalamic nucleus (STN) borders as seen on 3-Tesla (3T) T2-weighted (T2) and Susceptibility Weighted Images (SWI) with borders obtained during microelectrode recording (MER) in patients undergoing deep brain stimulation (DBS) for Parkinson's disease (PD).

Background: Clear representation of the STN and delineation of its dorsal and ventral borders is key in determining the location for lead placement in DBS for PD. Magnetic resonance imaging (MRI) can visualize the STN. Which sequence most accurately corresponds with the electrophysiological STN (MER-STN) remains a matter of debate. CT/MRI fusion allows for comparison between the MER-STN and the STN visualized on preoperative MRI (MRI-STN).

Methods: Intraoperative CT (iCT) was performed after each MER track before removing the microelectrode. iCT images were merged with preoperative images using planning software, allowing for projection of MER tracks on T2 and SWI sequences. Dorsal and ventral borders of each track were determined and compared to MRI-STN borders. Distances between T2 MRI-STN, SWI MRI-STN, and MER-STN borders were calculated.

Results: A total of 125 tracks were evaluated in 45 patients. Dorsal MRI-STN borders showed MER-STN activity in 67% (T2) and 57% (SWI) of tracks. For Ventral MRI-STN borders this was 27% (T2) and 23% (SWI).

Comparing MRI-STN to MER-STN, distances of 1.9 ± 1.4 mm (T2) and 2.5 ± 1.8 mm (SWI) were found between dorsal borders. Distances of 1.9 ± 1.6 mm (T2) and 2.1 ± 1.8 mm (SWI) were found between ventral borders. MER-STN started and ended more dorsally than respective dorsal and ventral MRI-STN borders on both sequences. **Conclusions:** Border discrepancies between MRI-STN and MER-STN were found, most notably when comparing the ventral border, with T2 performing better than SWI. We suggest that a cautious approach should be taken when relying solely on MR imaging for delineation of the STN, particularly its important ventral border.

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Deep brain stimulation (DBS) for Parkinson disease in the Philippines: outcomes and practice of the first DBS center

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Objective: The study aims to determine the outcomes of all PD patients who underwent DBS in the Philippine Movement Disorder Surgery Center (PMDSC), in terms of objective motor improvement and reduction in PD medication dosage. The current practices of the PMDSC, one of only two institutions doing DBS in the country, is also documented.

Background: Deep brain stimulation (DBS) is an established treatment modality for Parkinson Disease (PD). Currently, there is no local data on the practices and outcomes of DBS for PD.

Methods: This is a mixed methods research utilizing interviews and review of records. A retrospective, longitudinal and observational study of all patients (n=17) who underwent DBS for PD in the PMDSC was done. The primary outcome of change in the motor component score of the Unified Parkinson Disease Rating Scale (UPDRS) was determined through review of patient records spanning the pre-DBS period until their most recent follow-up. The practices of the DBS center was documented by doing a questionnaire guided interview of the center's staff and sifting through official records.

Results: There was a statistically significant reduction in the UPDRS score of patients 3 months (51.8%; p=0.003), 6 months (29.5%; p=0.003) and 3 years (66.7%; p=0.067) after the surgery in the off-medication state. A statistically significant decrease in the dosage of PD medications was also seen until the second year of follow-up (52.3%; p<0.001). Adverse effects included attempted suicide in one patient and a device related infection in the other. Established in 2005, the PMDSC, housed in a private tertiary center, has done 17 DBS surgeries for PD. The great majority of the procedures were purely out-of-pocket expenses.

Conclusions: This is the first study that tackles the local experience of DBS for PD. DBS for PD improves the UPDRS motor score and reduces PD medication dosage. The practice and outcomes of Institution A are at par with international centers featured in earlier studies for DBS in PD.

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An objective tool to guide target selection for deep brain stimulation (DBS) in Parkinson's disease (PD) (GPi vs STN)

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Objective: To create a simple tool to aid in selection of the proper target for Deep Brain Stimulation (DBS) in Parkinson's disease (PD).

Background: Two targets exist for DBS in PD, the subthalamic nucleus (STN) and globus pallidus interna (GPi). Although there are advantages and disadvantages to implanting in either target, current evidence does not guide selection of the appropriate target in the individual patient. We believe that in select cases, certain factors can help to determine the ideal target for patients. We also believe that the decision to implant into one site or another is a major factor in DBS outcomes.

Methods: We performed a Pubmed search of all available DBS studies comparing STN to GPI between 1998 and 2016, identifying 14 such studies. We then identified the following 13 factors that we believe could help guide our decision: tremor, dyskinesia, gait, bradykinesia, rigidity, medication reduction, depression, cognition, dysphagia, dystonia, quality of life, battery life, and ease of programming. Based on the results of each study and statistical significance of the data, we assigned a value of 0.25, 0.5 or 1.0 to either GPi or STN for each of the 13 factors. A 0.5 was assigned if there was a small difference between GPi and STN or if only one study showed statistically significant change. A 1.0 was assigned if there was a moderate difference noted between the two targets and there were at least 2 studies that showed a statistically significant change. A 0.25 was assigned to 3 non-ratable subgroups. **Results:** Our literature review revealed factors favoring each of the targets. Advantages of STN include: reduction of tremor, bradykinesia and rigidity, desire for medication reduction, and better battery life. Advantages of GPi include: ease of programming, improvement in dyskinesia, dystonia and quality of life, less gait dysfunction, depression, cognitive dysfunction and dysphagia. In addition to the history and physical, a Unified Parkinson's Disease Rating Scale (UPDRS), Montreal Cognitive Assessment Score (MOCA), and Global Dystonia Scale Score (GDS) would be performed to complete the assessment.

Conclusions: We have created a preliminary tool that we plan to use in our Multidisciplinary DBS Center that we hope will aid in the decision on where to implant. We hope that the use of such a tool will improve the eventual outcome for patients undergoing DBS.

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Safe Functional MR Imaging in STN-DBS implanted Parkinson's disease

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Objective: Evaluation of clinically optimized settings in bilateral STN-DBS Parkinson's disease, allows anatomical correlations with benefits and side effects.

Background: MRI acquisition can cause permanent damage to implantable pulse generator (IPG) or heating of DBS leads limiting clinician's needs to review the effects of STN-DBS on functioning of basal ganglia. A preliminary study using a phantom with Medtronic DBS leads (3389) and IPG (Activa PC 37601) conducted at University Hospitals, Cleveland, (OH), USA, determined DBS safety within MR environment. Our study is novel in two ways: (1) Use of actual IPG and electrodes in a PD patient. (2) evaluation of fMRI activation recorded in response to therapeutic and sub-therapeutic settings of IPG. We ensured (a) temperatures = 1° C at the active electrode lead contacts (b) intact lead contacts (DBS impedance studies), (c) regular IPG cycles within the scanner for low SAR sequences used, and using (d) custom built Tx/Rx Head coils (e) chest implanted newer IPG with built in safety shunt circuitry (without magnetic reed switch).

Methods: Two bilateral STN-DBS right-handed implanted PD (P1 & P2), were observed at their individual therapeutic and sub-therapeutic DBS settings. Imaging was performed (on-med) on a 3T Verio (Siemens). Sagittal T1 and EPI Images for both left and right electrode (therapeutic and sub-therapeutic DBS settings) were acquired separately with IPG cycling (30s on/off). Data was processed using FSL. A boxcar design with six cycles of alternate DBS 'on' & 'off' was used to determine fMRI activation due to the stimulation [figure1]

Results: Therapeutically, both patients evoked BOLD activation in bilateral occipital cortex, left thalamus, and contralateral cerebellum, for the left, both patients presented a clear significant BOLD activation in the pallidum,

(P1-right; P2-Left) for electrode stimulation; while sub-therapeutically, P1 presented similar activation as
therapeutic for the right side, but no thalamic or pallidum activation in P2 for either sides. [figure2]

Sequence	IPG State	Head SAR	Time Minutes	Avg. Temp Rise (° C)	Std Error	Max Temp Diff (° C)
Scout	No Stimulation	0.4W/Kg	0.13	0.02	0.02	0.22
beout	Stimulation On	0.4W/Kg	0.13	0.01	0.02	0.24
	Stimulation Cycling	0.4W/Kg	0.13	0.05	0.01	0.22
GRE Field Man	No Stimulation	0.4W/Kg	0.52	0.01	0.01	0.21
one menumap	Stimulation On	0.4W/Kg	0.52	0.01	0.01	0.28
	Stimulation Cycling	0.4W/Kg	0.52	0.01	0.02	0.22
Anatomic	No Stimulation	0.4W/Kg	6.06	0.07	0.04	0.25
Anatonne	Stimulation On	0.4W/Kg	6.06	0.09	0.03	0.30
	Stimulation Cycling	0.4W/Kg	6.06	0.14	0.03	0.28
CE EDI	No Stimulation	0.4W/Kg	12.06	0.02	0.03	0.30
OL-LFI	Stimulation On	0.4W/Kg	12.06	0.04	0.02	0.42
	Stimulation Cycling	0.4W/Kg	12.06	0.07	0.02	0.34



Conclusions: This study clearly indicates a safe fMRI acquisition in STN-DBS implanted patients. It opens a new direction for evaluation of patient specific therapeutic voltage threshold, apart from establishing erroneous activation responsible for side effects in STN-DBS implanted patients.

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Quantitative measures of brain MRI as a predictive factor of cognitive outcomes after subthalamic nucleus deep brain stimulation for Parkinson's disease

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Objective: To explore whether pre-surgical white matter lesion volume, measured quantitatively on brain MR images, is predictive of cognitive outcomes following subthalamic nucleus deep brain stimulation (STN-DBS) in idiopathic Parkinson's disease (iPD) patients.

Background: Studies evaluating cognitive outcomes following STN-DBS report significant declines in domains such as executive function, verbal fluency, and attention. However, few studies have assessed predictors of cognitive decline in iPD patients treated with STN-DBS. Thus, identification of pre-surgical MRI predictors might provide an important clinical tool for better risk-to-benefit assessment.

Methods: This retrospective study included data from 43 iPD patients with STN-DBS. For cognitive assessments, pre-surgical and =6 month post-surgical neuropsychological (NP) evaluation scores were collected. To quantify lesion volume, white matter hyperintensities were segmented from pre-surgical T2-FLAIR MRI. Mean pre/post NP test scores for measures of executive function, attention, verbal fluency, memory, and visuospatial function were analyzed. The correlation between log (lesion volume) and changes in performance on pre/post cognitive tests was investigated, covarying for age, education, and vascular risk factors.

Results: There were significant declines on cognitive measures of verbal fluency, executive function, attention, and visuospatial function. Pre/post change on tests of memory function were insignificant. Log(lesion volume) were weakly and not significantly correlated with cognitive outcomes for most cognitive measures, with and without adjusting for covariates. A significant negative correlation was observed between larger lesion volume and impaired performance on a visuospatial task, even when adjusting for covariates. Increased age and vascular risk factors were strongly correlated with larger lesion volume and impaired performance on NP tests.

Conclusions: Results of this study demonstrate that post-STN-DBS cognitive impairments are largely independent of pre-surgical lesion volume, suggesting that lesions, beyond any clinical vascular predictors, do not put DBS candidates at a significantly increased risk for cognitive impairments. Other quantitative measures of brain MRI, such as brain volume, may be correlated with STN-DBS cognitive impairments and warrant further investigation.

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Evaluating use of the DBS patient programmer

D. Whitney, J. Karl, G. Pal, D. Ocegueda-Ramirez, B. Ouyang, L. Verhagen Metman (Chicago, IL, USA) **Objective:** To characterize use of the Medtronic® DBS patient programmer among patients with DBS for movement disorders.

Background: Patients who undergo deep brain stimulation receive a handheld device that can be used at home to check settings or adjust therapy, but this is an underutilized resource. There have not been any published studies evaluating patients' impressions of this device, commonly or uncommonly used features, or barriers to more frequent or effective use.

Methods: A 21-item questionnaire was developed, focusing on patient demographics, patterns of device use including frequency and common features, comfort level with the device and technology in general, and education on use of the device. Questionnaires were distributed to interested DBS patients before or during routine clinic visits and collected by office staff.

Results: To date, 17 (85% of those approached) of a planned 50 patients have completed the questionnaire; continued data collection is ongoing. In this preliminary group, patients tended to be male (64.7%), younger than 60 years old (58.8%), and have DBS for Parkinson's disease (76.5%). Patients most frequently use their patient programmer once per month or less (76.5%), while 17.7% never do. There was no difference in frequency of use among younger versus older patients. Patients most frequently use the device to check DBS battery life (58.8%), or change therapy settings using groups (41.2%) or individual stimulation parameters (41.2%). Patients generally felt 'somewhat' or 'very' comfortable with using the device (70.6% for the basic features and 75% for the more advanced features). Some thought they would benefit from refreshers on common features (35.3%) or a quick reference guide (23.5%), but many (35.3%) did not want or need further education. Patients were split on whether they would use a smart phone or tablet application more than the standalone device, with 47.1% 'somewhat' or 'much' more likely to use an application while 41.2% were neither more or less likely; there was no correlation with patients' overall comfort level with these technologies.

Conclusions: In our preliminary data group, patients generally reported not using their DBS patient programmer much despite relative comfort with the device. With a larger sample size we hope to identify trends that could lead to better patient education and ultimately more frequent and effective use of this device.

Comparison of pallidal and subthalamic deep brain stimulation in Parkinson's disease: Therapeutic and adverse effects

H.S. Ryu, M.S.K. Kim, S. You, M.J.K. Kim, Y.J. Kim, J. Kim, K. Kim, S.J. Chung (Seoul, Korea) **Objective:** To compare the therapeutic and adverse effects of the globus pallidus interna (GPi) and subthalamic nucleus (STN) deep brain stimulation (DBS) for the treatment of advanced Parkinson's disease (PD).

Background: DBS of both the GPi and STN has been shown to be effective in the treatment of the cardinal motor signs of PD. However, it is still unclear whether there are definite advantages or disadvantages in selecting optimal target for DBS in PD patients.

Methods: We retrospectively analyzed the clinical data of PD patients (n = 14) underwent GPi DBS surgery and those (n = 28) underwent STN DBS surgery between April 2002 and May 2014. Subjects were matched for age at DBS surgery and disease duration. The Unified Parkinson's Disease Rating Scale (UPDRS) scores and levdopoa equivalent dose (LED) at baseline and 12 months after DBS surgery were used to assess therapeutic effects of DBS. The adverse effects after DBS surgery were compared between two groups.

Results: At 12 months, the mean changes of scores for UPDRS total and each part I-IV did not differ significantly between two goups. However, subscores for gait disturbance and postural instability, and subscores for dyskinesia were significantly more improved after GPi DBS, compared with STN DBS (p = 0.024, and p = 0.016, respectively). LED was significantly more reduced in patients with STN DBS than those with GPi DBS (p = 0.004). Serious adverse effects did not differ between two groups (p = 0.697).

Conclusions: PD patients had greater improvement in gait disturbance and postural instability, and dyskinesia after GPi DBS, compared with STN DBS, although PD patients had a greater reduction in LED after STN DBS. These results may provide useful information for optimal target selection of DBS for PD patients.

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Deep brain stimulation for Parkinson's disease: Short-term outcomes, referral patterns and health disparities D. Di Luca, V. Aldahondo, W. Jermakowicks, L. Segala, H. Moore, C. Singer, B. Levin, J. Jagid, C. Luca (Miami, FL, USA)

Objective: To describe the practice patterns at University of Miami (UM), short term outcomes and health disparities among ethnic groups.

Background: Deep brain stimulation (DBS) has been shown to improve quality of life in Parkinson's disease (PD) patients. However, few studies have examined referral patterns for deep brain stimulation (DBS) patients from multi-ethnic communities.

Methods: Retrospective chart review from the University of Miami DBS referred patients.

Results: 195 patients have been referred for DBS surgery for PD at the UM from January 2014 to January 2016. After multidisciplinary team evaluation, 54 patients (28%) underwent BL STN DBS (n=49) or GPI DBS (n=5). The mean age at the time of referral was 66 years (+/-15). 61,2% patients were white, 35,1 % Hispanic and 3.7% African American. The mean MDS-UPDRS score pre-DBS off medications was 48 (+/-16). At 12 months after the surgery the motor score improved 62.5% (DBS ON, MEDS ON= 18+/-7) With DBS ON, meds OFF mean MDS UPDRS was 23 +/- 8 (52% improvement). Patients also reported an overall decrease in levodopa equivalent daily dose (LEDD) from 999 (+/-461) to 633 (+/-331, 37% reduction). Surgical complications included 1 infection and 1 lead edema.

Conclusions: Despite the majority Hispanic and African American population in Miami, the referral pattern in this city includes mostly the white population illustrating the health care disparities among these ethnic groups. The disparity may be explained by poor access to movement disorders specialists in Hispanic and African American communities. All patients demonstrated significant improvement in motor UPDRS and a significant decrease in medication after DBS regardless of ethnic group. Efforts should be made ??to increase the access to DBS procedure among the Hispanic and African American population.

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Cognitive safety of eight-hours adaptive deep brain stimulation (aDBS) in Parkinson's disease

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Objective: The purpose of this study is to assess the effects of eight-hours aDBS on neuropsychological functions in patients with Parkinson's disease (PD).

Background: Adaptive Deep Brain Stimulation (aDBS) promises better clinical motor outcomes than conventional DBS in PD patients. An important issue before aDBS comes into practice is to prove its feasibility and safety. **Methods:** 7 patients with PD [(mean±SD) age 61±6.4; UPDRS 32.14±13.22; 1 Female] and implanted with electrodes in the bilateral STN underwent cognitive evaluation to asses, language (Semantic and Phonemic Verbal Fluency, Naming, Repetition), memory (Word Recognition Task) and attention (Simple Reaction Times, RTs) at baseline T0 (aDBS off, Drug treatment off) and after eight-hours T1 (aDBS on, Drug treatment off). The assessment was conducted 6 days after surgery and patients were stimulated with an external aDBS device. **Results:** There was no significant cognitive change after aDBS [(mean±SD; T0 vs T1) Semantic Verbal Fluency 12.3 ± 3.3 vs 15 ± 3.4; p=0.12; Phonemic Verbal Fluency 10.4 ± 3.7 vs 9.7 ± 1.8; p=0.56; Naming 19.7 ± 0.7 vs 10.6 ± 0.8; p=0.36; Word Recognition Task 19.7 ± 1.6 vs 19.1 ± 1.6; p=0.28; RTs 447.6 ± 78 vs 426.1 ± 50; p=0.36]. No errors occurred during words and sentences repetition task. Also, no significant change of UPDRS total provide the during words and sentences repetition task. Also, no significant change of UPDRS total provide the during words and sentences repetition task. Also, no significant change of UPDRS total provide the during words and sentences repetition task. Also, no significant change of UPDRS total provide the during words and sentences repetition task. Also, no significant change of UPDRS total provide the during words and sentences repetition task. Also, no significant change of UPDRS total provide the during words and sentences repetition task. Also, no significant change of UPDRS total provide the during words and sentences repetition task. Also, no significant change of UPDRS total provide the during words and sentences repetition task. Also, no significant change of UPDRS total provide tables and table table tables to tables to tables to ta

score was observed after eight-hours aDBS. UPDRS total score improved by about 50% after eight-hours aDBS. **Conclusions:** Our data show that eight-hours a DBS in PD patients failed to influence their cognitive performances. These findings can help the discussion about the safety of aDBS.

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Effect of deep brain stimulation of the subthalamic nucleus on cranial tremor in Parkinson's disease *L. Cameron, C. Kilbane, A. Shaikh (Cleveland, OH, USA)*

Objective: To analyze the effect of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on cranial tremor in Parkinson's disease (PD).

Background: STN DBS has been shown to improve appendicular tremors significantly. While bilateral thalamic (VIM) DBS has shown some benefit in essential tremor, little is known of improvement in cranial tremor with bilateral STN DBS. A study of 13 patients with essential tremor found that bilateral thalamic DBS was more effective than unilateral DBS at controlling appendicular and midline tremors.

Methods: We utilized a secure electronic DBS database to search all PD patients who have undergone DBS of bilateral STN at University Hospitals Cleveland Medical Center and analyzed changes in cranial tremor from the UPDRS pre and post DBS. We compared the numerical value of cranial tremor documented on the UPDRS immediately before surgery as well as 3 and 6 months after surgery. We excluded patients with unilateral STN DBS, or those patients who have had undergone DBS lead replacement surgery.

Results: We analyzed 71 PD patients who underwent bilateral STN DBS. 20/71 (28.2%) patients were found to have had cranial tremor prior to DBS. 20/71 patients (85%) showed an improvement in cranial tremor 3 and 6 months after DBS. Two (10%) patients were noted to have had the same intensity cranial tremor pre and post DBS. One (5%) patient's cranial tremor was noted to be worse at 3 and 6 months after DBS. Three (4.2%) patients developed a cranial tremor at 6 months post DBS. Sub analysis data is being collected for positioning of DBS lead contacts to better understand the anatomical location at which cranial tremor improved after DBS. The likely explanation for tremor development after DBS is disease progression. Further knowledge on cranial tremor improvement from STN DBS can assist physicians in counseling patients regarding likely benefit from DBS. Our next step is to compare lead placement with those patients that had cranial tremor improvement versus no cranial

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tremor improvement.

Directional distribution of subthalamic nucleus beta activity in patients with Parkinson's disease

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Objective: To investigate the spatial distribution of subthalamic nucleus (STN) beta activity in Parkinson's disease (PD) recorded from directional deep brain stimulation (DBS) electrodes.

Background: New DBS electrodes able to steer the stimulation field in different directions, entered the marked recently. Previous studies demonstrated that directional DBS has the potential to increase the therapeutic window for improved symptom control in patients with PD. However, this advantage is limited by a substantially increased time needed for clinical contact testing. For the conventional 4-ring electrode lead it has been shown that local field potential (LFP)- beta activity (13-35 Hz) can inform about the contact with high clinical efficacy. Here we explore the LFP spectral beta characteristic from directional DBS electrodes.

Methods: We recorded STN local field potentials in PD patients during DBS surgery using the directional DBS lead (Vercise PC; Boston Scientific, Valencia, CA) after placement in the final position within the DBS target structure.

During the recording patients were in a wake and resting state. The beta spectral power density for each stimulation contact was calculated and compared across stimulation contacts.

Results: We found that several subjects with detectable resting beta activity showed differences in its spatial distribution. These differences were evident along the lead axis, but also differentially weighted in the axial direction to specific segmented contacts. The degree of the directional beta localization was variable between subjects.

Conclusions: LFP recording from directional DBS leads seems to indicate direction specific distribution of LFP beta activity and to help localize the main anatomical beta source. Individual differences of beta distribution are partially related to differences in the spatial relationship between contacts and DBS target structure. These spectral differences could inform the clinician about a preferred direction to steer the stimulation field and, thus, to facilitate multicontact lead DBS programming. Further investigations and clinical comparisons are required for the future.

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Longitudinal changes in speech and voice functions after subthalamic stimulation in Parkinson's disease patients

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Objective: To elucidate longitudinal changes of speech and voice functions in Parkinson's disease (PD) patients treated with subthalamic nucleus deep brain stimulation (STN-DBS).

Background: Previously, we reported that PD patients treated with STN-DBS had five distinct phenotypes of speech and voice disorders: relatively good speech and voice function type, stuttering type, breathy voice type, strained voice type, and spastic dysarthria type and that some PD patients also had hypokinetic dysarthria (J Neurol Neurosurg Psychiatry 2015; J Neural Transm 2015). However, changes of these phenotypes over time are still unknown.

Methods: Thirty-two consecutive PD patients were assessed before and up to 1 year after surgery (PD-DBS). Eleven PD patients treated with medication were also assessed longitudinally (PD-Med). Speech and voice functions (Assessment of Motor Speech for Dysarthria and GRBAS scale), motor function (Uni?ed Parkinson's Disease Rating Scale III (UPDRS-III) and UPDRS-IV), cognitive function (Mini-Mental State Examination, Montreal Cognitive Assessment, and verbal ?uency), activity of daily living (Schwab & England Scale), and levodopa equivalent daily dosage (LEDD) were evaluated.

Results: At baseline, speech and voice functions of the two groups were not significantly different. At 1 year after surgery, slight but significant deterioration in speech intelligibility (p = 0.001) and grade of dysphonia (p = 0.001) were observed only in PD-DBS group. Although the incidence of hypokinetic dysarthria (63% of PD-DBS vs 82% of PD-Med), stuttering (50% vs 45%), breathy voice (66% vs 73%), and strained voice (3% vs 9%) was similar at baseline, significant score deterioration associated with strained voice (28%) and spastic dysarthria (44%) were observed in only PD-DBS patients during 1 year follow-up. After stopping stimulation, most PD-DBS patients who had strained voice and spastic dysarthria showed significant improvement in these phenotypes.

Conclusions: The increasing incidence of strained voice and spastic dysarthria after DBS in this longitudinal study was consistent with the results from our previous reports. An improved understanding of the above-mentioned phenotypes may help clinicians detect DBS-induced speech and voice disorders during early phase.

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Automated deep brain stimulation contact selection using coherence in Parkinson's disease

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Objective: To investigate whether subthalamic nucleus (STN)-EMG coherence can be used to predict the most effective deep brain stimulation (DBS) contact.

Background: Although DBS is an established therapy for Parkinson's disease (PD), there are still limitations in terms of efficacy, tolerability and efficiency. For instance, the optimal titration of stimulation parameters is still performed manually and requires lengthy clinical programming sessions. In order to proceed to automated DBS programming, a symptom-specific *biomarker* is necessary. In the current study we evaluated STN-EMG *beta* (15-30 Hz) coherence as a potential biomarker for automated DBS contact selection and aimed to reproduce the finding of Marsden et al. (Brain, 2001) in a larger cohort.

Methods: Fifteen PD patients (59±7 yo, 9 male, disease duration: 10±2 yr) indicated for bilateral STN-DBS surgery were included. Direct after DBS lead placement, STN local field potentials (LFP) and contralateral wrist extensor

muscle EMG were recorded during a 2 minute gripping isometric force task (10% of maximum contraction). Segments with continuous muscle activity were selected for calculating three bipolar STN-EMG coherence profiles (respectively DBS contacts "0-1", "1-2", and "2-3"). The DBS contact that was used for stimulation 6 months post-surgery was identified as the clinical most effective contact. The cathode stimulation contact was correlated (two-sided Spearman's rank) to the bipolar contacts with the highest median beta STN-EMG coherence.

Results: In total 29 STNs were recorded. One hemisphere was excluded since the DBS lead was repositioned after initial surgery. In 17 of 29 (59%) hemispheres, the bipolar LFP with the highest median beta coherence included the (cathode) DBS contact that gave the best clinical response. In line with this, a significant correlation between best coherence contact pair and DBS stimulation site was present (R=0.46, p=0.01) (Fig. 1).

Correlation DBS contact – STN-LFP coherence



Conclusions: Our data suggest that STN-EMG coherence profiles might assist in selecting the most effective DBS contact in PD and potentially could be used in future automated DBS programming algorithms. However, our correlation was less strong compared to the study of Marsden et al. (Brain, 2001). This might be due to the fact that some patients had not yet achieved the optimal stimulation parameters after 6 months and that we only assessed isometric and not dynamic contraction.

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Spinal cord stimulation reduces freezing of gait and improves gait in advanced Parkinson's disease

O. Samotus, N. Kumar, S. Memar, M. Jog (London, ON, Canada)

Objective: The primary objective was to investigate the therapeutic effect of spinal cord stimulation (SCS) on gait dysfunction including freezing of gait (FOG) in advanced Parkinson's disease (PD) patients. The secondary objectives were to determine the effects of pulse width and frequency SCS parameters on FOG and spatiotemporal gait parameters.

Background: Dopaminergic therapy and deep brain stimulation (DBS) alleviate motor features in PD however their effects on axial features such as gait dysfunction reduces with disease progression. Epidural SCS may be a new therapeutic approach for levodopa-resistant motor symptoms in PD.

Methods: A total of five advanced PD male patients (mean age of 71 ± 10 years with 14 ± 4 years with PD) not eligible for DBS, with significant gait disturbances, FOG and postural instability underwent mid-thoracic SCS. A range of SCS settings at 200-500 microseconds and 30-130 Hz at suprathreshold intensity were tested in eight study visits over a six-month period. A 20-foot Protokinetics Zeno Walkway measured dynamic gait characteristics, such as step length, stride width, stride velocity, step, and stance and swing times. Timed sit-to-stand and automated FOG detection using foot pressures were also analyzed. FOG questionnaire, Unified Parkinson's Disease Rating Scale (UPDRS) motor items, Activities-specific balance confidence scale (ABC), and Parkinson's disease questionnaire (PDQ-8) were completed at each study visit.

Results: Three patients found SCS setting combination of 300 microseconds and 60 Hz provided the best improvement in timed sit-to-stand, stride velocity and step length with a mean improvement of 63.8%, 76.2% and

91.1%, respectively. Two patients found a combination of 130 Hz with 200 or 300 microseconds more beneficial with a mean improvement by 58.4% for timed sit-to-stand, 36.6% for stride velocity and 56.7% for step length. Sixmonths post-implantation, there was a mean improvement by 39.4% in the UPDRS motor score, by 26.8% in the FOG questionnaire, and by 116.9% in the ABC score. The mean number of FOG episodes reduced significantly from 16 pre-surgery to 0 at six-month period while patients were "ON" levodopa and OFF stimulation. **Conclusions:** This pilot study demonstrated the safety and therapeutic efficacy of SCS in advanced PD. A larger clinical study will be utilized to investigate the neurophysiological changes occurring at different SCS parameters.

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Patient characteristics vary by DBS indication in Parkinson's disease patients

A. Pusso, S. Sperling, M. Harrison, F. Wooten, J. Elias, B. Shah, M. Barrett (Charlottesville, VA, USA) **Objective:** To determine whether there are clinical differences in Parkinson's disease (PD) patients based on their indication for deep brain stimulation (DBS) surgery.

Background: Deep brain stimulation (DBS) is an effective treatment for advanced PD motor symptoms that cannot be managed adequately with oral medications. Little is known about whether patient characteristics differ by indication for surgery.

Methods: We retrospectively analyzed clinical characteristics of 127 PD patients who received clinical evaluations prior to deep brain stimulation between January 2010 and July 2016 at our center. Patients completed the Unified Parkinson Disease Rating Scale (UPDRS), the Parkinson's Disease Questionnaire-39 (PDQ-39), Beck Depression Inventory-II (BDI-II), the Montreal Cognitive Assessment, Controlled Oral Word Association, semantic fluency (animals), Stroop Color Word Test, Symbol Digit Modalities Test, Wisconsin Card Sorting Test, Digit Span, Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test - Revised, and Trail Making Test A & B. Motor subtype was calculated using the UPDRS.¹

Results: PD subjects were 29.9% women, had a mean age of 62.0 years (SD=9.1), and had a mean duration of disease of 10.1 years (SD=4.6). Indications for deep brain stimulation surgery were motor fluctuations (n=90), medication-refractory tremor (n=22), motor fluctuations and tremor (n=8), medication intolerance (n=5), and dystonia (n=2). As expected, those receiving DBS for medication-refractory tremor were more likely to be classified as tremor-dominant disease (70.0% vs 23.3%, p<0.001). Compared to those undergoing DBS for motor fluctuations, men were more like to pursue DBS for medication-refractory tremor with or without fluctuations (n=30) (90.0% vs. 63.3%, p=0.006). Those with indication of motor fluctuations had higher UPDRS Part 2 score compared to those with medication-refractory tremor (17.4 vs 13.1 points, p=0.0006). There was no association between surgical indication and age, duration of PD, UPDRS Part 1 or Part 3 scores, any of the cognitive measures, PDQ-39 score, or BDI-II score.

Conclusions: Patients undergoing DBS for tremor were more likely to be men. While patients with indication of motor fluctuations reported greater impairment in activities of daily living on UDPRS Part 2, this scale may not fully capture the disability associated with medication-refractory tremor as there was no difference in PDQ-39 score.

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Weight changes in STN and GPi Deep Brain Stimulation: Long term follow up

S. Shah, L. Almeida, A. Patterson, J. Hilliard, A. Wagle Shukla, K. Foote, M. Okun, D. Martinez-Ramirez, P. Zeilman (Gainesville, FL, USA)

Objective: To determine the impact of Deep Brain Stimulation (DBS) during long term follow-up of post-operative weight changes in Parkinson's disease (PD).

Background: PD patients have been observed to experience weight gain following DBS, however specific phenotypes of predisposed patients, specific target associations, and long-term follow-up has not been widely reported.

Methods: A retrospective chart review of PD DBS patients implanted at the University of Florida targeting subthalamic (STN) or globus pallidus interna (GPi) was conducted from January 2005 to December 2014. Clinical, demographic, and weight was recorded at baseline (pre-surgery) and at 6,12, 24, and 36 months postoperatively. A repeated measure analysis of variance (ANOVA) was performed to evaluate changes in mean weight at each of the targets across different time points, assuming a p=0.05 for statistical significance.

Results: Preliminary results revealed that 174 patients had unilateral DBS (96GPi and 78 STN) and 73.6% were male with mean age of 63.8±8.8 years. Seventy-eight patients (43 GPi and 35 STN) completed 3-years of follow-up. Both GPi and STN groups gained weight during the first 6 months post-surgery (2.3% increase for both GPi and STN, respectively). However, subsequent follow-up visits revealed opposite weight changes among targets, where a

gradual average weight gain for the STN group (additional 1.3% weight gain) was observed contrasting with a subsequent gradual weight loss in the GPi group (3.4% weight loss) (p=0.035) at 3-year follow-up.



Conclusions: Our data suggest that DBS though initially leading to weight gain in both targets, may be associated with weight loss in GPi target at long-term follow-up. Possible contributing factors including patient's characteristics, comorbidities, or disease phenotypes were not studied. Additionally, binge eating in STN DBS could have been a factor. Future prospective studies are needed to further clarify possible mechanisms.

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UPDRS benefit from dual frequency DBS fields sculpted by intentionally overlapped interleaving

Y. Fernandez, D. Caputo, D. Schneider, R. Dipaola, S. Danish, E. Hargreaves (New York, NY, USA) **Objective:** We show that UPDRS-III scores after interleaving compared to those prior to interleaving reflect a gain in benefit by lowered scores.

Background: Previously, we have shown that interleaving using adjacent or near adjacent contacts to create two alternating fields that are intentionally overlapped at half the standard frequency, works effectively to conserve neurostimulator batteries. The generated two-tiered frequency fields anecdotally appear to engage multiple symptom clusters, while releasing DBS induced side-effects, notably dysarthria and gait issues.

Methods: We reviewed the charts of the 18 accepted into the original battery study and examined the charts of 32 more, for a total of 50. From these, 25 were included into the study. Those accepted into the study had been implanted bilaterally in the subthalamic nucleus (STN) for Parkinson's disease. UPDRS-III scores were aggregated up to 120 days prior and subsequent to interleave implementation. As before, 5 had the frequency remain the same, while the remaining 20 had the frequency substantially reduced or halved. The main reasons for exclusion were being implanted in the GPi (n=2), no interleave (n=5), or interleave implemented too soon after contact screen for adequate accumulation of UPDRS-III measures (n=15). Remaining rejection reasons were being staged across months, or being followed outside of our center.

Results: The average score preceding interleave implementation was compared to post interleave aggregate UPDRS-III scores. For those with the halved frequency, results indicated a mean UPDRS-III of 19.31 sem=2.65 prior to interleave compared to a mean of 16.17 sem=2.27 subsequent to the interleave implementation, with a mean difference of 3.13 sem=1.28. Differences were tested with a paired t-test, using a two-tailed distribution, and revealed a statistical difference favoring the aggregate scores after the interleave implementation with lowered values (p=0.024). Although too few to analyze, those interleaves at standard frequencies exhibited increased UPDRS-III scores.

Conclusions: Results from our interleaving technique show that overlapped fields where the frequency is halved can be beneficial, as reflected in reduced UPDRS-III scores. However, this benefit is not universal, as 5 of the 20 individuals did not show decreased UPDRS-III scores subsequent to interleaving.

Efficacy and tolerability of low-frequency Deep Brain Stimulation during daytime only in Parkinson's disease: a pilot study

F. Dematteis, M. Zibetti, E. Montanaro, L. Rizzi, M. Lanotte, L. Lopiano, M. Rizzone (Torino, Italy) **Objective:** To compare the efficacy and tolerability of low-frequency stimulation (LFS) during daytime only to LFS applied 24 hours a day, in PD patients bilaterally implanted for subthalamic nucleus deep brain stimulation (STN-DBS) who develop drug- and stimulation-resistant freezing of gait (FOG).

Background: High-frequency electrical stimulation (HFS) of the STN, typically in the range of 130 - 185 Hz, is an effective procedure to treat parkinsonian symptoms such as tremor, bradykinesia and rigidity. Nevertheless, in the long term a number of patients develop gait disturbances, especially FOG that is poorly responsive to HFS and/or dopaminergic treatment. Several studies reported that LFS (typically 60 - 80 Hz) could be useful to improve gait disturbances and FOG. However, not all patients tolerate LFS well due to worsening of motor symptoms, and need to return to conventional HFS.

Methods: Prospective, randomized, cross-over, double-blind study of PD patients treated with STN-DBS at conventional HFS for at least 12 months, who developed disabling FOG (FOG-questionnaire item 3 > 3). Patients will be randomized in two groups: one group will receive continuous LFS (60 Hz) 24 hours a day while the second group will receive LFS only during daytime and switched back to 130 Hz during the night. After one month, the two groups will be crossed over. Neurological evaluations will be performed at the time of study entry, and repeated after one and two months. Patients and neurologists involved in the clinical evaluation will be unaware of the stimulation settings.

Results: The study will evaluate the efficacy of LFS on disabling FOG and establish whether LFS applied only during the daytime reduces the number of patients who need to return to HFS due to worsening of motor symptoms. **Conclusions:** This study explores the possible role of neuroplasticity mechanisms in conditioning changes in clinical response to continuous DBS. Furthermore, it could help to better understand the relation between variations of stimulation frequency and improvement of freezing of gait during STN-DBS.

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Cognitive effects of GPi versus STN Deep Brain Stimulation in Parkinson's disease: experience with patients with moderate cognitive impairment

C. Marques-Matos, C. Sousa, J. Lima, P. Monteiro, P. Linhares, R. Vaz, M.J. Rosas (Porto, Portugal) **Objective:** To compare the cognitive effects of GPi versus STN deep brain stimulation for PD in patients with moderate cognitive impairment.

Background: Patients with moderate cognitive impairment are considered borderline candidates for DBS surgery. Most RCT comparing the cognitive effects of GPi versus STN DBS in PD (1, 2) included only patients with no cognitive impairment. Although both targets are generally considered cognitively benign and similar in terms of motor benefit, STN DBS has been associated with a selective decline in frontal subcortical cognitive functions. **Methods:** Retrospective case-control study, including all the patients who went through GPi DBS surgery for PD in a reference center and 1:1 controls, matched for age at surgery and pre-op DRS (Dementia Rating Scale)-2 score percentile. DRS-2, MMSE (Mini Mental State Examination), FAB (Frontal Assessment Battery) and verbal fluency were assessed at 6, 18 and 60 months.

Results: A total of 20 patients were included. The mean years of school was 6.15 and the mean age at surgery 63. The mean disease duration was 13 years and the mean UPDRS part III score OFF medication was 43. The median follow-up time was 18 months. There were no differences between the groups regarding this baseline variables. The mean DRS-2 baseline score was 123.20 for the GPi group and 128.00 for the STN group (p=0.294). For the total of patients, there was a decline in semantic verbal fluency at 18 months (13.08 vs. 10.75, p=0,019). Both in the STN and the GPi groups separately, verbal fluency was the only neuropsychological measure that showed a significant variation at the different time points. Besides that, the semantic fluency score at 18 months was worse for the STN group (8.20 vs. 12.57, p=0.032). There was no difference between groups regarding motor outcome (70.14% vs. 78.16%, p=0.103) but the STN group showed a greater reduction in dopaminergic therapy (36.81% vs. 62.97%, p=0.029).

Conclusions: In our experience, there is no cognitive advantage in choosing GPi over STN as a DBS target in patients with moderate cognitive impairment except for the verbal fluency, which seems to be more adversely affected in the STN group. What is more important, our findings encourage the eligibility of this patients for surgery, since they have the expected motor benefit without significant accrual of their cognitive impairment.

Dynamics of subthalamic nucleus beta bursts in Parkinson's disease during ON and OFF dopaminergic state *G. Tinkhauser, A. Pogosyan, H. Tan, A. Kühn, P. Brown (Oxford, United Kingdom)*

Objective: To investigate the dynamics of beta bursts in subthalamic nucleus (STN) local field potentials (LFP) in patients with Parkinson's disease (PD) before and after administration of levodopa.

Background: Elevated basal ganglia beta activity can be suppressed by dopaminergic medication in patients with PD and the degree of suppression is correlated with the relative improvement in motor symptoms. Basal ganglia beta activity is not constantly elevated but fluctuates and appears in beta bursts, which have a state dependent dynamic, as recently shown for the resting and movement state in non-human primates. Here we investigate how levodopa interferes with beta bursts in comparison to the OFF levodopa state.

Methods: Local field potentials were recorded in the STN of PD patients during temporary lead externalisation. The recordings took place at rest following overnight withdrawal of levodopa and after administration of levodopa. Beta bursts were defined by applying an amplitude threshold and burst properties were compared between the two conditions.

Results: Our results show that beta bursts come in different durations and amplitudes. Burst duration and amplitude have a strong positive relationship during both OFF and ON levodopa state, in line with a progressive increase in beta synchronisation over time. Strikingly, there was a reduction of long duration high amplitude bursts and an increase in short duration low amplitude beta bursts after levodopa administration. The overall burst duration and amplitude were therefore decreased ON levodopa. Beta bursts also overlapped in time in the left and right STN more than expected by chance, and such overlap was reduced ON levodopa. Importantly, short duration beta bursts were negatively correlated with motor impairment, while the opposite was true for long beta bursts. Findings were preserved across different percentile amplitude thresholds.

Conclusions: We demonstrate that dopaminergic activity regulates pathological beta synchronisation by reducing long duration - high amplitude beta bursts and thereby limiting the uncontrolled beta synchronisation related to motoric impairment in PD. The tendency for beta bursts to synchronise between hemispheres is also dopamine dependent. These results highlight the importance of the temporal dynamics and properties of beta bursts in PD and have important implications for the optimal design of closed loop DBS algorithms.

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Effects of Deep Brain Stimulation in genetic parkinsonism

L. Oliveira, R. Cury, E. Barbosa (Sao Paulo, Brazil)

Objective: The aim of this systematic review is to explore studies on the effects of DBS in genetic parkinsonism. **Background:** Therapeutic strategies for Parkinson's disease (PD) should be individualized to patients' needs¹. Although it is clearly recognized that factors such as age, stage of the disease, and associated symptoms should influence therapy, it is unclear whether genetic background should guide specific therapy. Few studies have described the outcome of Deep Brain Stimulation (DBS) in different genetic forms of PD. Whether genetic PD benefits from surgical therapy in the same amount as sporadic PD is unclear.

Methods: A selective literature search for articles published from 2000 to 2016 using MEDLINE was performed. Articles were selected regarding the effects of DBS on: i) autosomal dominant or recessive forms of PD; ii) PD patients presenting with mutations associated with an increased PD susceptibility. Twenty-one articles were included. Data on motor outcome (UPDRS III), LEDD and motor complications (UPDRS IV) were retrieved. **Results:** Age at onset ranged from 10 to 57 years-old and duration of disease at DBS implant from 4 to 45 years. The set of articles (n=22) reported the outcome for 44 patients with mutation in parkin gene, 37 patients with LRRK2 mutations, 3 patients with Pink1 mutations, 19 patients with mutation in GBA gene, 2 patients with SNCA mutations, 2 patients with mutation in the VPS35 gene and 1 patient with C9ORF72 mutation. Subthalamic nucleus was the DBS target in most of the studies (n=19). Follow-up ranged from 1 month to 10 years. The improvement in UPDRS III ranged from 18% to 85.41%. Considering the short-term follow-up (up to 2 years), two studies reported less than 35% improvement, 35-70% improvement was noted in 12 studies and more than 75% improvement was observed in 2 studies (range: 18 to 85.41%). The motor improvement on long-term follow-up ranged from 15.79 to 88.89%. The rate of improvement in LEDD (at maximum 1 year follow-up) ranged from 44% to 93%. Dyskinesias improvement ranged from 20% to 100%.

Conclusions: Although the DBS response in the genetic PD patients was quite variable, most of the studies reported satisfactory outcomes (>35% improvement)². Limitations included uncontrolled and small sample studies. Additionally, due to heterogeneity of the studies, only qualitative analysis was performed. Larger, controlled studies are required to better investigate the response to DBS in genetic PD patients.

Disparities in Access to DBS Surgery Based on Demographics of Patients with PD Admitted for DBS Surgery in the United States from 2003 to 2013

F.S. Benesh, S. Gupta, V. Sung (Birmingham, AL, USA)

Objective: To better understand current demographics of DBS use and identify non-medical barriers to its utilization.

Background: Parkinson's Disease (PD) has seen increasingly more sophisticated methods of management with direct neuromodulation with Deep Brain Stimulation (DBS) being an increasingly common consideration. Given its proven efficacy and widening availability, understanding current trends in patients undergoing DBS implantation will help identify barriers to its utilization.

Methods: Analysis of National Inpatient Sample data from 2003 to 2013 showed a total of 509,951 patients (53.8% male, mean age 77.18 \pm 9.8, 81.9% Caucasian, 6.4% African American) with a diagnosis of PD (ICD-9 332.0) and, of those patients, 4,632 were admitted for implantation of intracranial neurostimulator leads or DBS (ICD-9 Procedure Code 02.93). These patients were characterized by age, gender, race, insurance source and income quartile. A Pearson's *chi*-squared analysis was used for scaled variables and independent scaled *t*-test for nominal variables. Subjects with incomplete data for one of these variables were excluded.

Results: PD patients admitted for DBS surgery were more often younger (64 versus 77, p<0.001), male (1.1% versus 0.6%, p<0.001), privately insured (3.5% of total, p<0.001) and in the top income quartile of their zip code (1.1%, p<0.001). In regards to racial identity, African Americans were a significantly lower proportion of DBS admission than other reported racial groups (0.2%, p<0.001) [table1].

	Neurostimulation	No Neurostimulation	P Value
Age (mean, in years)	64.26	77.37	<0.001
Race			<0.001
Caucasian	0.9%	99.1%	-(25222)
African American	0.2%	99.8%	
Hispanic	0.9%	99.1%	
Asian	1.0%	99.0%	
Native Americans	1.1%	98.1%	
Other	1.6%	98.4%	
Gender			<0.001
Female	0.6%	99.4%	
Male	1.1%	98.9%	
Insurance Source			<0.001
Medicare	0.7%	99.3%	
Medicaid	0.7%	99.3%	
Private Insurance	3.5%	96.5%	
Self Pay	0.6%	99.4%	
No Charge	0.8%	99.2%	
Other	1.8%	98.2%	
Income Quartile			<0.001
1"	0.7%	99.3%	
2 ^{ne}	0.9%	99.1%	
3"	1.0%	99.0%	
4 ^m	1.1%	98.9%	

Table 1. Characteristics of PD patients based on neuromodulation admissions.

Conclusions: These results demonstrate that while there is widening use of DBS in PD treatment, there are concerning gaps in its utilization within certain subsets of the population with PD. According to this study, African Americans received significantly fewer DBS procedures than members of other racial groups. This trend likely reflects a combination of access to care, cultural beliefs, socioeconomic status and trust in the medical community. Further studies are needed to better delineate the roles of these factors in order to help improve access to DBS.

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Probabilistic mapping of Deep Brain Stimulation in Parkinson's disease

T. Dembek, J. Roediger, V. Visser-Vandewalle, L. Timmermann, M. Barbe (Cologne, Germany)

Objective: To find the neuroanatomical origins of Deep Brain Stimulation (DBS) induced effects using probabilistic mapping.

Background: While DBS of the subthalamic nucleus (STN) and the ventral intermediate nucleus of the thalamus (VIM) are well-established therapies for Parkinson's disease (PD), open questions remain regarding the neuroanatomical origin of beneficial motor effects as well as of stimulation-induced side-effects. **Methods:** We generated probabilistic maps from a DBS dataset consisting of monopolar reviews of 25 PD patients with a total of over 500 stimulation settings. Patients were implanted either in the STN or the VIM. The dataset contained information about symptom improvement as well as side-effect occurrence under DBS. Electrode positions were determined and transformed into a common neuroanatomical space using MRI coregistration. Probabilistic maps was performed to find clusters of voxels with symptom suppression or side-effect elicitation significantly higher than the average of the dataset. Clusters were then validated using a non-parametric permutation algorithm.

Results: Distinct clusters were detected for the suppression of rigidity, bradykinesia and tremor but cluster locations varied depending on the examined symptom. Rigidity was best suppressed in the dorsal parts of the STN, while the cluster for bradykinesia improvement was located at the lateral border of the STN. Tremor improvement was associated with more posterodorsal stimulation of the zona incerta and the ventral intermediate nucleus of the thalamus. Some but not all observed DBS-induced side-effects also showed distinct clusters, which were often but not always in line with neuroanatomical hypotheses about side-effect origins.

Conclusions: Our method of probabilistic mapping revealed distinct topographies for symptom suppression as well as for certain DBS side-effects. Larger datasets from multiple centers will be needed to confirm these results.

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Comparison of subthalamic and pallidal Deep Brain Stimulation in treatment of Parkinson's disease: a 5year follow-up study

A. Gamaleya, A. Tomskiy, A. Dekopov, E. Bril, A. Poddubskaya, N. Fedorova, V. Shabalov (Moscow, Russia) **Objective:** To assess and compare the long-term motor and functional outcome of subthalamic (STN) and pallidal (GPi) Deep Brain Stimulation (DBS) in treatment of patients with advanced Parkinson's disease (PD). **Background:** DBS STN and GPi are effective for treatment of levodopa-responsive symptoms, motor fluctuations and dyskinesias in advanced PD. Several previous trials delivered ambiguous results concerning comparison of motor and functional outcomes as well as possible affective and cognitive complications following both methods. **Methods:** We evaluated 40 patients with advanced PD (Hoehn&Yahr stage 3.4±0.6). 25 patients received DBS STN (age at surgery 53.4±7.3 years; disease duration 12.0±3.6 years). 15 patients received DBS GPi (age at surgery 54.2±13.4 years; disease duration 11.3±5.4 years). Groups had no significant differences in clinical scoring. LEDD and L-dopa dose in DBS STN were higher. We assessed clinical outcome (UPDRS), quality of life (PDQ-39), antiparkinsonian medication regimen (levodopa dose and L-dopa equivalent daily dose) under continuous DBS at the time point of 1, 3 and 5 years postoperatively.

Results: Both DBS STN and GPi improved significantly PD symptoms in off-medication state and reduced complications of L-dopa therapy up to 3-year follow-up. Absolute decrease in UPDRS motor score was higher in DBS STN group (28.8 ± 14.7 and 45.5% vs. 15.3 ± 14.6 and 26.5%, p<0.05). DBS GPi was less effective in long-term follow-up; off-state UPDRS III score in the 5th year approached preoperative. Motor improvement (off) in DBS STN remained significant during entire follow-up. In DBS GPi, motor symptoms in on-medication state deteriorated significantly over the time. In DBS STN, on-state was initially improving with further slight decline not exceeding preoperative level. DBS STN provided stable reduction in LEDD (- $35.5\pm32.8\%$ after 5 years). In DBS GPi, LEDD tended to increase ($25.3\pm31.1\%$ after 5 years). PDQ-39 quality of life remained improved to the 5th year in DBS STN (11.3%). In DBS GPi, PDQ-39 score was ameliorated only in the first year of follow-up.

Conclusions: DBS STN should be regarded as an advantageous method in advanced PD patients with severe motor fluctuations, high L-dopa dose, and excellent L-dopa response. DBS GPi might be still an option in patients with less L-dopa response or severe dyskinesias at low L-dopa dose. In the long-term, quality of life is crucial.

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The DBS response ratio: An individual benchmark parameter of DBS quality

L. Lange, M. Reich, R. Nickl, F. Steigerwald, C. Matthies, J. Volkmann (Würzburg, Germany) **Objective:** The aim of this study is to define a simple clinical benchmark parameter for assessing the quality of STN-DBS outcome in PD.

Background: Despite being a well-established treatment option in PD, STN-DBS shows a significant individual outcome variability. This includes patient/disease related factors, variable responsiveness of different PD symptoms

to DBS, as well as differences in lead placement and clinical DBS programming. The levodopa response correlates significantly with the DBS stimulation response and is therefore used as a DBS eligibility criterion. Here we propose to use a ratio between best levodopa response and DBS response as a benchmark for individual DBS outcome quality.

Methods: We reevaluated 15 PD patients with STN DBS (Øage 63,1 years, ØUPDRS III(off): 49,8) 6-60 months after implantation. Motor symptoms control (reduction in UPDRS III) by STN-DBS and Levodopa challenge were assessed after an overnight medication (+1h stim off) washout. When DBS implantation was <12 months we used the preoperative Levodopa challenge. The DBS response ratio (DBSrr) was defined as stimulation effect / levodopa response. Patients were categorized into two groups (good/suboptimal) based on a threshold of <0,7. Additionally, active contact (aC) location within the different STN subsegments was determined by fusing postoperative CT with preoperative MRI and Yelnick atlas (1) registration using Suretune® (Medtronic Sapiens, NL).

Results: 6 suboptimal responders (median DBSrr: 0,50) had only 5/12 aC placed within the sensorimotor segment of the STN, 4 aC were in the limbic subpart and 3 outside of the STN. An aC location outside of the sensorimotor STN unilaterally was found in 3/6 subjects (median DBSrr: 0,56) and bilaterally in 3/6 subjects (median DBSrr: 0,57). In 9 good responders (median DBSrr: 1,02) 18/18 aC were located within the sensorimotor segment of the STN. Lead revision after failed reprogramming attempts was indicated in all 6 patients.

Conclusions: STN-DBS is a effective treatment for PD on a group level, but there is an increasing concern about DBS "failures", in whom postoperative outcomes do not match the preoperative expectations. An excellent motoron after a levodopa challenge is the best predictor of DBS outcome. Here, we have used the ratio between stimulation and levodopa response to eliminate patient and disease related factors of outcome variability and to create an individual benchmark for the DBS outcome.

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Postoperative delirium after Deep Brain Stimulation surgery for Parkinson's disease

F. Sasaki, G. Oyama, M. Ito, S. Sekimoto, R. Nakamura, T. Jo, Y. Simo, A. Umemura, N. Hattori (Tokyo, Japan) **Objective:** To investigate the potential predictive factors of postoperative delirium after Deep Brain Stimulation surgery for Parkinson's disease (PD).

Background: Subthalamic nucleus Deep Brain Stimulation (STN-DBS) is an effective treatment for medically refractory PD patients. Postoperative delirium (POD) is one of the common complications of STN-DBS surgery and often leads to further problems.

Methods: A retrospective database and chart review of patients with PD implanted bilateral STN-DBS in our hospital between August 2015 and November 2016 was conducted. Diagnosis of POD was retrospectively made based on chart review or the Delirium Rating scale (DRS) at postoperative day one. Patients were classified into two groups based on presence of POD, and preoperative scores of the Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB), Japanese Version of The Montreal Cognitive Assessment (MoCA-J), Hamilton Depression Rating Scale (HDRS), the United Parkinson Disease Rating Scale (UPDRS), and Levodopa equivalent daily dose (LEDD) were compared between two groups. A two-tailed t-test was applied for statistical analysis. **Results:** Forty-eight patients (23 male and 25 female) were included in this study. The average disease duration and average age were 13 ± 4.0 years and 62 ± 7.9 years, respectively. From this cohort 17 patients developed POD (35%). Patients with POD showed significantly lower MoCA-J score (p<0.05). Age, disease duration, preoperative LEDD, FAB, MMSE, HDRS, UPDRS PartIII ON-state and OFF-state were not significantly different between two groups.

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Electrode impedance as a marker for "on" and "off" states in a Deep Brain Stimulation cohort: A pilot study *W. Deeb, J. Shute, M. Okun (Gainesville, FL, USA)*

Objective: To determine the possible use of electrical impedance as an easily measured surrogate measure for clinical changes in patients with Parkinson's disease (PD) with DBS.

Background: The mainstay of symptomatic treatment in PD is the use of dopaminergic medications. The functional and biochemical effect of these agents is referred to as the "ON" state. As the effect of these agents decreases there may be recurrence of the PD motor symptoms – referred to as the "OFF" state [1]. Unfortunately, currently, there is no objective assessment of the fluctuations between the "ON" and "OFF" states except with lengthy "day-visits" and observations. These can be cumbersome to patients and not available in most centers due to time and resource constraints. Identifying easy to obtain objective measures for the clinical "ON" and "OFF" states in PD DBS patients could be clinically relevant to care. Voltammetry allows measurement of dopamine concentration by

altering the redox state of dopamine, inducing an electric current [2]. Impedance, a measure of resistance, is inversely related to current. We hypothesize that impedance is modulated by the dopamine concentration at the site of the DBS electrode.

Methods: A prospective single center pilot study was conducted. Patients with already implanted Medtronic Activa DBS presenting for their yearly DBS visit were selected. Patients presented in the "OFF" state withholding dopaminergic medications for at least 12 hours. Patients were asked to take their regular dopaminergic medication dose (time 0). Serial impedance measurements were recorded at times 0, 10, 20, 30, 40, 50 and 60 min. At each time point, patients rated the dopaminergic medication "on" effects using a visual analog scale.



832

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828

826

824

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Results: The study is ongoing and 3 patients have been recruited. Preliminary analysis reveals a trend towards a negative correlation between impedance and the patient's impression of medication effects (figure 1). We will present the updated data at the meeting.

Conclusions: These preliminary results are encouraging as they show a trend toward negative correlation between impedance (easily measured in DBS patients) and the patient's impression of dopaminergic medication effects. We expect an improvement in statistical significance as we recruit a higher number of patients (given the large number of patients at our center we expect a much higher number by the time of the MDS meeting).

369

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0

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Clinical 3

20

30

40

Impedance 3 Linear (Impedance 3)

50

Meta-analysis of mortality following subthalamic and pallidal Deep Brain Stimulation for patients with Parkinson's disease

A. Negida (Zagazig, El-Sharkia, Egypt)

Objective: The aim of this meta-analysis is to compare mortality after subthalamic (STN) and pallidal (GPi) Deep Brain Stimulation (DBS) for patients with Parkinson's disease (PD).

Background: DBS is a surgical treatment for patients with advanced PD. STN and GPi are the most common stimulation targets for DBS in patients with PD. Postoperative complications might limit the use of DBS, however, till the moment, there is no head to head comparison between DBS STN and DBS GPi in terms of mortality after surgery. In this meta-analysis, we are comparing the risk of mortality between the two groups using data from prospective clinical trials.

Methods: We searched PubMed through September, 2016 for prospective controlled studies comparing STN DBS and GPi DBS for PD patients. Records were screened for prospective controlled trials comparing STN DBS and GPi DBS for PD patients. Data were extracted by the study reviewers independently and quality of included studies was assessed by the Cochrane risk of bias assessment tool. Frequency of mortality in both groups were pooled as risk ration between the two groups in a fixed effect model meta-analysis. In case of multiple reports, we analysed data

from the most recent data set. We introduced subgroup analysis according to the follow up duration to investigate whether the effect size differed from different time periods. Heterogeneity was assessed by visual inspection of the forest plots and measured by I-square and Chi-Square tests. We used RevMan 5.3 for windows.

	STN		GPi			Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl		
Anderson 2005	1	12	0	11	6.1%	2.77 [0.12, 61.65]			
Follet 2010	11	147	5	152	57.7%	2.27 [0.81, 6.39]	+-■		
Moro 2010	24	68	2	37	30.4%	6.53 [1.63, 26.11]	— —		
Okun 2009	1	26	0	26	5.9%	3.00 [0.13, 70.42]			
Total (95% CI)		253	_	226	100.0%	3.64 [1.68, 7.87]	-		
l otal events	37 1 50 36 7		1	~~					
Heterogeneity: Unit = 1	1.52, 01 = . 7 - 2.20 /5	3 (P = (J.68); I*= 24)	0%			0.005 0.1 1 10	200	
restior overall effect.	Z = 3.28 (F	r = 0.01)))				Favours STN DBS Favours GPi DBS		
	STI	N	GP	i		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl		
1.8.1 <12 months									
Anderson 2005	1	12	0	11	2.8%	2.77 [0.12, 61.65]			
DBS group 2001	4	68	2	37	13.9%	1.09 [0.21, 5.66]	_		
Okun 2009	1	26	0	26	2.7%	3.00 [0.13, 70.42]			
Subtotal (95% CI)		106		74	19.4%	1.60 [0.44, 5.79]			
Total events	6		2						
Heterogeneity: Chi ² = (0.48, df = 2	! (P = 0	.79); I ^z = I	0%					
Test for overall effect: 2	Z= 0.71 (P	= 0.48)						
4.0.2.24 months									
1.8.3 Z4 monuts			-	450	~~ ***	4 05 10 55 4 0 11			
Follet 2010 Subtotal (05% CI)	8	14/	5	152	26.4%	1.65 [0.55, 4.94]			
Sublotal (95% CI)		147	_	152	20.4%	1.05 [0.55, 4.94]			
Lotaregeneiti: Notion	ð Jisshla		5						
Test for everall effect: 2	7 – 0 00 /P	- 0.27	`						
restion overall ellect. 2	L = 0.30 (F	- 0.37	,						
1.8.4 36 months									
Rodriguez-Oroz 2005	14	68	2	37	13.9%	3.81 [0.91, 15.86]			
Weaver 2013	11	147	5	152	26.4%	2.27 [0.81, 6.39]	+ - -		
Subtotal (95% CI)		215		189	40.3%	2.80 [1.21, 6.47]	◆		
Total events	25		7						
Heterogeneity: Chi ² = ().33, df = 1	(P = 0	.56); I² = I	0%					
Test for overall effect: 2	Z = 2.42 (P	= 0.02)						
1.8.5 5-6 years									
Moro 2010	24	88	2	37	13.0%	6 53 11 63 76 111			
Subtotal (95% CI)	24	68	2	37	13.9%	6.53 [1.63, 26.11]			
Total events	24		2				-		
Heterogeneity: Not and	ulicable .		-						
Test for overall effect: Z = 2.65 (P = 0.008)									
Total (95% CI)	c -	536		452	100.0%	2.78 [1.63, 4.76]	●		
i otal events	63	-	16						
Helerogenerity, Crinters, Sou, Grie (1990); (Fellow) (1000)								1000	
Testfor overall effect 2 = 3.75 (P = 0.0002) Favours STN DBS Favours GPI DBS									
restion subdroub dille	rences; C	nr = 2.	ສ3,ui≓ 3	.(≓ = U	.40), F = L	170			

Results: Four trials (7 full text articles) were included in the final analysis with a total of 479 patients (STN 253 patients, and GPi 226 patients). Follow up duration ranged from 6 months in COMPARE trial to 6 years in the study of DBS group 2001. The overall risk ratio favoured GPi DBS than STN DBS with RR 3.64, 95% CI (1.68 to 7.87). This results suggests more than 3-fold increase in mortality following STN DBS than GPi DBS. **Conclusions:** Death was more common after STN DBS than GPi DBS in PD patients. But most of death cases were

Conclusions: Death was more common after STN DBS than GPi DBS in PD patients. But most of death cases were due to postoperative complications and were not related directly to stimulation. Our results highlight the importance of considering postoperative complication while choosing surgical target for PD patients.

Battery consumption and need for replacement in patients with Parkinson's disease treated with interleaved Deep Brain Stimulation

L. Deuel, J. Pilitsis, A. Ramirez-Zamora (Albany, NY, USA)

Objective: To evaluate battery life in patients managed with unilateral or bilateral subthalamic nucleus (STN) interleaved Deep Brain Stimulation (DBS).

Background: DBS is a common surgical treatment for patients with Parkinson's disease (PD), and interleaved stimulation (ILS) is a relatively new technique that involves alternating programs on the same lead, with a goal of optimizing symptom control and minimizing adverse effects. While ILS has been evaluated for efficacy and tolerability in small populations, it is unclear what effects this programming may have on battery life, as there are several theoretical concerns about increased consumption. Increasing frequency of battery replacements may subsequently increase morbidity and procedural costs.

Methods: We conducted a retrospective review of ten patients with fifteen total implanted leads treated with ILS at our institution, and evaluated the need for battery replacement. Premature replacement was defined as battery replacement prior to 36 months post-operatively.

Results: Half of the patients (5/10) had unilateral DBS (four in the left STN and one in the right); the remaining half had bilateral STN DBS. Of fifteen total leads, eleven (73%) were set to unipolar stimulation prior to initiation of ILS. Most leads (12/15; 80%) were transitioned to ILS within six months of the initial surgery. Nine leads in six patients required premature battery replacement, while six leads in four patients did not. One patient required one lead/battery replacement due to infection, not as a direct result of battery depletion. In all other patients, charge per second (uC/s) was calculated based on the formula by Miller et. al (2016). uC/s was =27 in eight leads requiring premature battery replacement, while uC/s was =22 in the other six. At an average of 51 months of follow-up post-operatively, eleven leads in seven patients remained in ILS.

Conclusions: In ten patients with PD treated with ILS, all leads with premature battery depletion were noted to have increased total charge per second based on their final settings. As charge per second is directly related to amplitude and pulse width, these may be independent factors resulting in early battery depletion and replacement, not the use of ILS itself. In addition, ILS appears to be efficacious and well-tolerated, as the majority of patients remained on this programming even after battery replacement.

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UPDRS III score and RS latency can determine the possible neuromodulative role of STN DBS in Parkinson's disease (PD) patients

S. Szlufik, A. Przybyszewski, J. Dutkiewicz, P. Habela, T. Mandat, D. Koziorowski (Warsaw, Poland) **Objective:** The aim of this study was to evaluate the impact of STN DBS on the changes of UPDRS scale and RS parameters (OFF phase) in 3 PD groups: early-DBS STN (DBS-group), late-DBS STN (POP-group) and one that obtained only medication therapy (MED-group).

Background: Subthalamic nucleus Deep Brain Stimulation (STN DBS) has been claimed to change the progression in animal models, but there are lacking information about the possible neuromodulative role of STN DBS in humans.

Methods: DBS-group consisted of 20 PD patients (7F,13M) who underwent bilateral STN DBS. POP-group consisted of 15 post-DBS PD patients (6F,9M) in median 24 month-time after surgery. Control group (MED-group) consisted of 24 patients (13F,11M) who did not underwent surgical intervention. UPDRS III scale and RS parameters (latency, amplitude, duration, peak of velocity) were measured during 3 visits (V1, V2, V3) in total OFF phase. The mean period between visits was 9±3months.

Results: We have observed the comparable UPDRS III gain in V3/V2/V1 MED-group and POP-group (p<0,05) but not V3/V2 (p>0,05) vs V2/V1 (p<0,05) DBS-group. There was also interesting relation between RS latency and DBS treatment: the only change in V2/V1 DBS-group vs no change in MED-group and POP-group (p>0,05). **Conclusions:** The strongest effect of STN DBS on RS parameters was during first 6 postoperative months whereas the most influential effect of STN DBS treatment on UPDRS III OFF score was observed during 6-12 months after surgery (but not in longer post-DBS periods).

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STN DBS can temporarily improve balance disorders in Parkinson's disease (PD) patients

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Objective: The aim of this study was to evaluate the impact of STN DBS on balance disorders in PD patients. **Background:** Subthalamic nucleus Deep Brain Stimulation (STN DBS) can influence on balance and gait disorders, but there are some conflicting information.

Methods: DBS-group consisted of 20 PD patients (7F,13M) who undergo bilateral STN DBS. POP-group consisted of 15 post-DBS PD patients (6F,9M) in median 24 month-time after surgery. Control group (MED-group) consisted of 24 patients (13F,11M) who did not underwent surgical intervention. UPDRS III scale and balance tests (UpAndGo Test, Tandem Walk Test) were measured during 3 visits (V1, V2, V3) in total OFF phase. The mean period between visits was 9±3months.

Results: We have observed the improvement in balance tests (UpAndGo, TWT) in V2/V1 DBS-group period (p<0,05) which was not observed in other (MED, POP) groups. The effect was not observed in V3/V2 DBS-group period. The comparable UPDRS III changes were also observed in V2/V1 (p<0,05) vs V3/V2 (p>0,05) DBS-group periods whereas V3/V2/V1 in MED-group and POP-group UPDRS III OFF scores were statistically changed (p<0,05).

Conclusions: STN DBS can temporarily improve balance disorders in PD patients, with the strongest effect during first 6 postoperative months.

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The battery longevity of implantable pulse generators (IPG) in Parkinson's disease (PD) is affected by IPG model, number of previous IPG replacements and stimulation energy delivered

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Objective: To determine the effects of stimulation parameters, IPG model and the number of previous IPG replacements on IPG battery longevity.

Background: For some patients rechargeable batteries is not an option. It is known that total electrical energy delivered (TEED) and stimulation modi can affect battery longevity. There have also been reports that the certain targets and certain conditions may also result in higher battery drain (e.g., pallidal DBS for dystonia) but this may be secondary to higher stimulation parameters. We have observed a decreasing battery longevity with each successive IPG replacement.

Methods: Sixty-two PD patients (37 male), treated with bilateral subthalamic DBS, Kinetra or Activa PC, 59.1 ± 9.8 years-old, with at least one IPG battery replacement, in total 80 Kinetra and 23 Activa IPGs, were identified from a database of patients followed up at the Movement Disorders Institute, Sheba Medical Center. In order to take into account stimulation parameters we created a model to predict battery longevity using the trendline tool in Excel. The best goodness of fit (R²>0.57) was achieved by assuming a power relationship. We used the data from the largest subgroup (Kinetra, only the first IPG per patient). The TEED-longevity curves for these IPGs and for all Activa PCs are shown in Figure 1. We used percentage change in observed battery longevity versus that predicted by the TEED as the outcome measure.'





Results: The mean and standard deviations of the age of the age of the first operation, TEED and battery longevity and percentage change from predicted battery longevity are presented in Table 1. Battery longevity decreased from 57.6 months to 30.7 months from the 1st Kinetra to the 3rd Kinetra and the percentage change from the predicted battery longevity drooped from 0.8 to -26 and from -36 to -46 in Kinetras and Activas respectively from the 1st to the 3rd replacement. The main effect for IPG model was $p<10^{-6}$ and for IPG number was $p<10^{-3}$.

IPG number	IPG model	n	Longevity (m)	TEED (μ)	Percentage change from predicted longevity (%)	Age at 1st operation (y)
1	Kinetra	55	57.6 ± 14.1	241 ± 134	0.8 ± 17.2	59.3 ± 11.5
	Activa	7	36.8 ± 9.9	256 ± 135	-36 ± 13	64.5 ± 6.8
2	Kinetra	22	47.3 ± 14.5	288 ± 190	-13 ± 18	56.8 ± 10.7
	Activa	10	38.1 ± 11.7	259 ± 106	-30 ± 18	59.8 ± 5.3
3	Kinetra	2	30.7 ± 14.0	519 ± 251	-26 ± 19	52.9 ± 4.8
	Activa	5	26.0 ± 6.1	322 ± 70	-46 ± 9	53.6 ± 18.2
4	Kinetra	1	31.6	524	-18	49.5
	Activa	1	15.8	696	-54	56.2

Conclusions: We show here that independently of stimulation parameters there is an effect of both IPG number and IPG model. There are potential clinical implications to these findings which may influence the choice of IPG as well as stimulation parameters.

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Expectations and perceived outcomes following DBS for PD: A Case Series

D. Coughlin, M. Hernandez-Con, M. Pavon, M. Spindler, L. Chahine (Philadelphia, PA, USA) **Objective:** To examine effect of preoperative expectations on postoperative satisfaction in individuals with PD treated with DBS

Background: While clinical trials of DBS in PD have demonstrated a clear benefit on motor function in appropriately selected patients, improvement in motor function does not necessarily translate to perceived benefit by the patient or improved quality of life (1). Expectations of DBS outcome are among the most important factors that contribute to self-reported patient satisfaction with DBS (2).

Methods: Data was abstracted from the Penn Parkinson's Center Specialty Assessment and Evaluation for DBS (SAFE-DBS) clinic database. At the University of Pennsylvania Parkinson's Disease and Movement Disorders Center, DBS candidates are seen in a multidisciplinary clinic preoperatively. They complete a questionnaire about expectations prior to evaluation, which is subsequently reviewed with them in detail. In cases of unrealistic expectations, extensive counseling is provided to educate the patient. For patients enrolled in the database, follow up questionnaires, including the PDQ-8, are administered post-operatively at 1 year to assess satisfaction with multiple symptoms and overall quality of life. Improved cognition, balance, and speech were considered unrealistic expectations whereas improvements in tremor, gait, dyskinesias, quality of life, and medication reduction were considered realistic expectations.

Results: 9 patients (mean age 59.3 y; range 50.29-72.07; 2 female, 8 with bilateral STN implants and 1 bilateral GPi implants, median disease duration 8 y) completed baseline and 1 year postoperative assessment and were included. 3 patients had at least one unrealistic expectation at baseline but of these patients, PDQ-8 improved in 2/3 (66%). Of items assessed pre and post-operatively, 14/18 (78%) realistic expectations were met at the 1y followup and 2/2 unrealistic expectations were unmet. Two patients had realistic expectations that were unmet, one of which had a reduction in PDQ-8 at 1 year. Overall 6/9 (66%) had stable or improved PDQ-8 scores 1 year postoperatively [table 1].
Table 1

Patient #	Expectations to Improve:	Expectations Met at 1y	Expectations Not Met at 1y	PDQ-8 Baseline	PDQ-8 1y
1	Realistic: Dyskinesias, Motor Fluctuations		Realistic: Dyskinesias, Motor Fluctuations	8	11
	Unrealistic: (Fatigue)*				
2	Realistic: Tremor, Medication Reduction	Realistic: Tremor, Medication Reduction		25	16
	Unrealistic: Speech		Unrealistic: Speech		
3	Realistic: Tremor, Rigidity, Quality of Life**	Realistic: Rigidity	Realistic: Tremor	15	14
4	Realistic: Tremor	Realistic: Tremor		11	15
5	Realistic: Medication Reduction, Gait	Realistic: Medication Reduction, Gait		12	5
6	Realistic: Dyskinesias, Medication Reduction, Quality of Life	Realistic: Dyskinesias, Medication Reduction, Quality of Life		4	3
7	Unrealistic: Cognition		Unrealistic: Cognition	24	17
8	Realistic: Tremor, Rigidity, Dyskinesias	Realistic: Tremor, Rigidity, Dyskinesias		6	10
9	Realistic: Tremor, Medication Reduction	Realistic: Tremor, Medication Reduction		6	6

** Patient 3 did not respond regarding post operative quality of life

Conclusions: In PD patients undergoing DBS, unrealistic baseline expectations do not necessarily translate to negative perceived outcome. The role of preoperative counseling/education in mitigating negative impact of unrealistic preoperative expectations may be helpful and deserves further study.

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Action tremor control with Deep Brain Stimulation in patients with Parkinson's disease: Specific target associations

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Objective: To determine the effects of Deep Brain Stimulation (DBS) on action tremor in Parkinson's disease (PD) and to identify if there are specific target associations.

Background: DBS is an effective therapy for the control of PD tremor. Subthalamic nucleus (STN) and globus pallidus internus (GPi) are frequent DBS targets in PD, however there is no consensus over tremor outcomes using these targets. Although rest tremor is more prevalent in PD, action tremor, observed in 40-50% of patients, is a major contributor to functional disability. Previous research has mostly examined the effects of DBS on rest tremor and other motor features of the disease.

Methods: In this single-center retrospective study, we identified PD DBS patients who presented specifically with moderate-to-severe action tremor in their dominant hand. Patients were included if they scored = 2 on item 21 of the Unified PD Rating Scale (UPDRS) part III. Item 20 scores (rest tremor) were noted as well. Action and rest tremor assessments were performed before surgery (off medication) and 4-6 months after surgery (off medication-on stimulation). Univariate analysis was performed using Chi square for categorical variables and Wilcoxon Mann-Whitney for non-parametric continuous variables. Comparison of baseline to postoperative outcome for each target was performed using Wilcoxon signed rank. All statistical analyses were performed in SAS 9.4.

Results: Fifty-two patients (39 STN, 13 GPi) with significant action tremor were analyzed. The two groups were similar in age (STN 61.5 \pm 10.6; GPi 66.2 \pm 8.1; p = 0.4) and gender (STN 31 males; GPi 9 males; p = 0.4). Baseline mean action tremor score for STN (2.5 \pm 0.7) and GPi (2.4 \pm 0.5) were not statistically different (p = 0.8). With stimulation, the post-operative action tremor score decreased by an average of 1.9 points in the STN group (p <0.001) and by 1.5 points in the GPi group when compared to baseline (p < 0.001). A similar decrease was seen for mean rest tremor score (STN 1.7, p < 0.001; GPi 1.5, p < 0.001). The mean improvements in action (p = 0.3) and rest (p = 0.5) tremors were not target dependent.



Figure Legend

Figure: Action tremor score (item 21 on UPDRS motor scale) before surgery and foursix months after DBS lead placement and activation. Data shown as mean \pm SEM, for GPi and STN targets. Compared to preoperative baseline scores, there is significant improvement of tremor for both targets *p<0.001.

Conclusions: DBS effectively controlled action PD tremor regardless of the STN vs. GPi location. Prospective studies on tremor outcomes will perform an accurate and direct comparison.

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Combined surgical therapies for optimal management of advanced Parkinson's disease

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Objective: We report a case of a patient with advanced PD who began LCIG for refractory motor fluctuations while continuing longstanding STN-DBS.

Background: LCIG and DBS are device therapies with established efficacy for motor fluctuations in advanced PD. There is little data to guide decision-making for patients who develop refractory symptoms with one device in place. A review of the literature reveals only 2 prior reported cases of combined LCIG and DBS.¹ Patients on DBS can require concomitant oral Levodopa and are therefore dependent on the motility and function of the GI tract. Consequently, dysautonomia and gastroparesis can lead to improper response to oral medication. We propose that there may be a rationale for adding LCIG to DBS for patients with GI symptoms impeding oral drug delivery. **Methods:** The patient's medical records were reviewed from 2008-2016. Data was extracted on UPDRS motor scores, subjective symptoms, DBS settings, and medications.

Results: We present the case of a 61-year-old man treated with LCIG and DBS. His PD was diagnosed at 49. 6 years later, he developed refractory "offs" and underwent bilateral STN-DBS. His symptoms were controlled for 4 years on STN-DBS and oral Levodopa. His UPDRS motor score improved from 31 to 12, daily Levodopa declined from 1700 to 1250 mg, and he no longer needed pramipexole and apomorphine. 5 years later, he developed bothersome peak-dose dyskinesias and gastroparesis refractory to Domperidone and trimethobenzamide. Over the next 2 years, despite changes to DBS settings and medication, his symptoms progressed to persistent dyskinesias, biweekly falls, and deep "offs." His UPDRS increased by 8-12 points. He required rotigotine and developed ICD. He began LCIG nearly 7 years after DBS. His DBS was continued, though turned down, as he remained responsive with UPDRS uptrending though significantly below his pre-DBS baseline. Oral Levodopa was discontinued. His daily Levodopa on LCIG ranged from 1050-1500 mg. He reported resolution of bothersome dyskinesias and reduction in falls to 2 in 6 months. His UPDRS motor score declined by 6 points. He no longer required rotigotine and ICD resolved.

Conclusions: This is the first reported case from the U.S. of combined LCIG and DBS, and third overall. We are the first to describe a patient with DBS with added LCIG due to gastroparesis.¹ This case demonstrates that combined device therapy may be an option for patients whose symptoms have become refractory to one device. LCIG may be an option for patients on DBS requiring Levodopa who develop worsening motor fluctuations in the setting of gastroparesis. The addition of LCIG to longstanding DBS is a logical sequence of therapies given that DBS can be

performed in younger patients who are better neurosurgical candidates, with option to begin LCIG at a later date if needed. Further research is warranted on the safety, efficacy, and optimal usage of combined device therapies.

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Long term tremor benefit from cyst formation as a complication of DBS surgery in a patient with Parkinson's disease

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Objective: To describe the unexpected, beneficial effects of cyst formation as a complication of sub-thalamic nucleus (STN) Deep Brain Stimulation (DBS) surgery in a patient with Parkinson's disease (PD) and treatment refractory tremor.

Background: DBS is a very effective surgical intervention to improve motor function and tremor in appropriately selected patients with PD. The most frequent complications of DBS surgery include infection, bleeding, seizures, and migration of leads. CSF cyst formation is a relatively rare complication of DBS surgery, with only case-reports found in the literature.

Methods: Case Report

Results: A 59 y/o male with PD had a left STN deep brain stimulator placed for refractory right arm tremor. Within a month of electrode placement and optimization of stimulation parameters, he had significant improvement in his right sided tremor. Unfortunately, two months after his surgery, he developed new onset gait impairment, sensory symptoms involving the right face, and a predominantly expressive aphasia. The DBS stimulation was turned off without any change in symptoms. He underwent further evaluation, including a CT and MRI of the head with contrast. The imaging revealed a cystic lesion at the tip of the DBS electrode in the left STN with no rim enhancement to suggest infection or hemorrhage. His DBS electrode was subsequently removed with gradual improvement in the deficits but no return of tremor in the right arm. He gradually developed worsening of his left sided PD symptoms over time which required treatment with antiparkinsonian medications but, to this date eight years later, the right sided tremor has not recurred.

Conclusions: This abstract demonstrates that the rare DBS complication of cyst formation after electrode placement in the STN for PD resulted in enduring control of tremor, despite removal of the electrode. The cyst formation may have acted as a permanent lesion to the STN, providing long-term symptomatic benefit.

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Feedback Controlled DBS in Parkinson's disease using Electrocorticography

N. Swann, C. de Hemptinne, A. Miller, W. Chen, I. Tamir, R Gilron, J. Ostrem, P. Starr (San Francisco, CA, USA) **Objective:** To provide a proof of principle implementation of closed loop DBS in an office setting using narrowband ? and β power as modulatory signals for DBS therapy.

Background: Deep Brain Stimulation (DBS) therapy is a common treatment for Parkinson's disease (PD) and other movement disorders, but suffers from several limitations. Existing DBS devices continuously stimulate target structures regardless of changes in motor function, often resulting in stimulation-induced adverse effects, short battery life, and the need for labor-intensive programming by a clinician. DBS treatment could be improved by automatically adjusting stimulation parameters based on brain signals that reflect the patient's clinical state (closed loop DBS). We and others have identified brain signals related to motor impairments of PD in both motor cortex and subthalamic nucleus (STN). Dyskinesia is associated with a narrowband y oscillation at 60-90 Hz. Akinesia is associated with excessive neuronal synchronization in the β band (13-30 Hz).

Methods: Closed loop DBS in two patients (both male, 59 and 62 years old at time of surgery) implanted with a novel bidirectional neural interface for at least a year were studied. This device allows chronic recording and stimulation. We utilized electrocorticography (ECoG) over motor cortex as a signal to adjust DBS voltage, delivered in STN, within a neurologist-specified range. Short sessions (less than 10 minutes) were performed with either data streaming to an external computer to perform calculations and update DBS, or algorithms directly uploaded to the internal pulse generator for totally implanted control.

Results: We showed that stimulation updates were appropriately triggered based on ECoG power for both sessions utilizing external streaming or totally implanted approaches. Patients and investigators did not report any adverse stimulation effects.

Conclusions: We have demonstrated the feasibility of implementing closed loop DBS in clinic based on cortical narrowband ? and ß power. This approach has the potential to trigger DBS updates based on changes in dyskinesia and akinesia/rigidity and represents the first step towards closed loop DBS to improve treatment efficacy, reduce

side effects and reduce battery consumption. The next step will be to assess potential clinical benefit during a longer closed loop DBS session (1 week) before undertaking a long-term trial of closed loop DBS.

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Dynamic of symptoms of dopamine dysregulation syndrome after deep brain stimulation in patients with Parkinson's disease

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Objective: Assessment of the dynamics of dopamine dysregulation syndrome in patients with Parkinson's disease after deep brain stimulation of the subthalamic nucleus compared with the control group of patients who performed only pharmacotherapy, aimed at correcting the motor and affective disorders.

Background: Dopamine dysregulation syndrome (DDS) is a complication of dopaminergic therapy of Parkinson's disease (PD), manifested compulsive intake of dopaminergic drugs. Deep brain stimulation may improve, worsen or have no effect on existing clinical symptoms of DDS. Furthermore, it can first occur postoperatively.

Methods: We observed 24 patients with advanced PD. The main group consisted of 8 patients PD after DBS STN, who in the preoperative period had clinical signs of DDS. The control group consisted of 16 patients with PD DDS, who received only conservative medical therapy. The average age of patients-54.5+12.5 and 64+7.4 years, disease duration-9.7+3.4+2.6 and 12 years, the average dose of levodopa-1570 + 922 and 1323+300 mg/day and average duration of treatment-8.7+3.2 and 10.5+3.4 years, respectively, in patients of main and control group. Neurological and behavioral evaluation included the following scales: Unified Rating Scale of Parkinson's Disease, quality of life scale in patients with Parkinson's disease (scale PDQ-39,1987) and the Schwab & England activities of daily living scale (Schwab JA, England AC,1969), Part IV of the UPDRS, the definition of the equivalent daily dose of levodopa (LEDD, Smith et al., 2010), Spielberg scales for assessment of anxiety (STAI, Spilberger Ch.D., 1972) and the Hamilton depression Rating scale (HDRS, 1952).

Results: Follow-up observation of PD patients of the main group confirmed the possibility of a substantial reduction LEDD daily dose with a full regression compulsive taking the drugs for two years of observation, as well as improving the quality of life, activities of daily living, reducing the severity of motor fluctuations and drug dyskinesias of advanced PD. Patients in the control group tended to increase significantly the dose of dopaminergic therapy and preservation of clinical signs of the DDS with low adherence to therapy.

Conclusions: Based on our data, we can conclude that DBS STN can lead to regression of symptoms of DDS, possibly due to a significant reduction in doses of drugs due to improved motor manifestations of PD.

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Asymptomatic and transitory postoperative hypodense lesion around deep brain stimulation electrode

M. Sousa, F. Moreira, N. Canário, O. Brito, R. Pereira, M. Rito, C. Januário (Coimbra, Portugal) **Objective:** To report the case of a patient that developed a post-operative asymptomatic, transitory, non-infection hypodense lesion around DBS lead, literature review and discussion of its management.

Background: There are few published reports of transient, non-infectious, hypodense lesions surrounding the DBS electrode. Its etiology remains debatable in most clinical reports, and may have a wide spectrum of manifestations, with some passing unnoticed and other being severely symptomatic with need to invasive interventions.

Methods: A 47 years-old male patient, with young onset Parkinson's disease, was submitted to bilateral STN-DBS surgery without acute complications and the DBS system was programmed 1 week after system implantation with a good clinical response (MDS-UPDRS-III off medication/off stimulation: 57; off medication/on stimulation: 32; on medication/on stimulation: 8). One month later a hypodense lesion in superior-frontal region, around right DBS electrode, was noticed in routine brain CT [Figure 1]. This lesion did not show enhancement after contrast administration. The patient at this moment presented no focal neurological symptoms, no worsening of parkinsonian symptoms or infectious symptoms, namely suggestive of central nervous system infection.



Results: Control brain CT, 2 days after being admitted were similar and the patient remained asymptomatic, and did not present changes in blood inflammatory markers. The patient was discharged at that moment and repeated brain CT after 3 weeks. In that exam, the lesion was less hypodense and has smaller dimensions comparatively to the first exam [Figure 2]. The patient remained clinically asymptomatic with no worsening of parkinsonian symptoms. **Conclusions:** Despite of the benign course of the lesion described in this case report, the pathophysiology of these post-operative lesions remains unknown. In literature, the impact of these lesions is highly variable with some patients requiring invasive measures and sometimes with neurological sequelae.



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Drug-induced movement disorders: Not a typical problem

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Objective: To characterize patients with neuroleptic drug-induced movement disorders (DIMD) referred to a single academic center Movement Disorders clinic, their causative medications and the indications for their use. **Background:** First-generation antipsychotic medications that block dopamine receptors (DRBA) are associated with a significant risk of DIMD. The introduction of second generation, or so-called atypical DRBAs decreased the incidence of tardive dyskinesia by half. Thus, a plethora of new second generation DRBAs have been used for increasingly broader indications. Nevertheless, recent studies suggest that the incidence of DIMD has not decreased since the introduction of newer DRBAs.

Methods: We conducted a retrospective medical records review of patients with a diagnosis of DIMD at the Movement Disorders Clinic of the Yale School of Medicine from July 2014 to July 2016. Clinical and demographic information was extracted, including age, gender, comorbidities, phenomenology of the movement disorder, causative agent, and indication for its use. We classified each indication as *on* or *off label* based on FDA guidelines. Descriptive statistics were generated for all variables.

Results: A total of 72 patients were included in the study, 44 were females and 28 males. The mean age was 55.22 (\pm 14.61). 43 patients had been exposed to atypical DRBAs, 12 to typical DRBAs, 2 were exposed to metoclopramide and 1 to bupropion. 14 patients had a history of both typical and atypical antipsychotic use. Aripiprazole and risperidone were the 2 atypical DRBAs most frequently used. Drug-induced parkinsonism was the most frequent DIMD diagnosis (n=33) followed by tardive dyskinesia (n=17) and tardive dystonia (n=8). The most frequent indications for use were bipolar disorder (n=23), schizophrenia (n=18) and depression (n=18). 19 of the 72 patients had an off-label indication (26%). Depression was the most common indication for off label use, followed

by bipolar disorder. Combination of typical and atypical antipsychotics were most frequently used off label (n=5). The atypical antipsychotic most frequently used off-label was risperidone.

Conclusions: Atypical DRBAs were most frequently associated with DIMD in this single center study. 26% of patients had an off-label indication of use. Patients and caregivers should be well-informed about the possibility of irreversible neurological side effects from these medications, especially when used in an off-label fashion.

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Dopamine agonists and postural disorders in Parkinson's disease

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Objective: To evaluate the relationship between treatment with DA and the development of postural disorders (CC, PS and AC) in patients with PD.

Background: Stood posture, camptocormia (CC), Pisa syndrome (PS) and anterocollis (AC) are the most frequent postural disorders in PD and they generate disability, pain and reduce quality of life. Muscle weakness, dystonia, complications of surgical procedures and pharmacological treatments have been postulated as possible causes of such postural disorders. However the relationship between postural disorders and DA was not demonstrated to date.

Methods: We performed a case control study. Controls were PD patients without postural disorders. Medical charts were reviewed retrospectively. Information regarding gender, age, disease duration, medical history, cardiovascular risk factors, history of orthopedic disease, family history and PD features, was collected. Wilcoxon rank sum test and logistic regression models were used for comparisons between groups.

Results: 62 patients with PD and postural disorders (36 CC, 34 PS and 8 AC) and 101 controls were included. There were no differences in the treatment with levodopa between cases and controls (p=0.54). Regarding DA, 49 (78%) subjects that developed postural disorders had received this agents, while only 55 (54%) of controls were treated with these drugs (p=0.003). When analyzing drugs individually, while pramipexole (OR=1.51, p<0.001) and piribedil (OR=2.9, p=0.01) were associated with postural disorders, there was no significant effect for ropinirole (OR=0.9, p=0.06). Cases receiving concomitant treatment with amantadine showed higher risk of developing postural disorders (OR=2.2, p=0.01). Additionally, compared to controls, patient with postural disorders had older age (72.5±1.1 vs 67.3±1.0, p=0.001), higher H&Y (2.8±0.9 vs 1.9 ± 0.8 , p<0.001) and longer disease duration (8.1±7.8 vs 4.2 ± 3.7 , p<0.001). As well, cases when compared to controls had more falls (p=0.01), higher cognitive impairment (p<0.001), orthostatic hypotension (p<0.001), and urinary incontinence (p=0.02), in those patients that developed postural disorders.

Conclusions: Our results suggest a significant association between the use of DA and the development of postural disorders in PD, and potential risk factors including elderly, advanced disease, and concomitant treatment with amantadine. Prospective series will be crucial to confirm these associations.

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Imbalance between dopaminergic and cholinergic neurotransmission following rotenone administration suggestive of Parkinson's-like symptoms in male rats

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Objective: In the present study we analyzed rotenone-induced gait abnormalities, muscular weakness and locomotor deficits in rats. The study also evaluated the effects of rotenone on acetylcholinesterase (AChE) activity and relationship between brain dopamine (DA) and acetylcholine (ACh) levels and their association with Parkinson's-like symptoms.

Background: Rotenone (widely used as an organic pesticide and specific inhibitor of mitochondrial complex I) produces features in rats that recapitulate behaviorally, biochemically and neurochemically the symptoms of Parkinson's disease (PD). However, some aspects remain indistinct regarding the effects of rotenone as an animal model of PD.

Methods: In the study, adult male rats were administered intraperitoneally with rotenone at a dose of 1.5 mg/kg/day for eight days. Motor activity and muscular strength were monitored by the inclined plane test, footprint test, beam walking test, pole test and Kondziela's inverted screen test. Animals were decapitated after behavioral analysis and brains were dissected out for biochemical estimation such as antioxidant enzyme activities and acetylcholinesterase (AChE) activity and neurochemical estimation was also performed by HPLC-EC.

Results: Results showed that the level of DA and its metabolite were significantly decreased (figure 1) which was in turn reflected by significant impaired motor coordination in rotenone treated rats in all observed behavioral parameters (table 1). Along with these the level of reduced glutathione (GSH) and superoxide dismutase (SOD)

activity declined significantly which ultimately increased lipid peroxidation (LPO) (figure 2). Moreover, AChE activity was significantly decreased and ACh levels significantly increased in brains of rotenone administered rats (figure 1).



Table 1

Effects of intraperitoneal injection of rotenone on muscular strength and motor coordination.

		Control (n=6)	Test (n=8)	
Pole test	6 th day	38.33±11.2	29.20±8.4	p>0.05
Time to descend (sec)	7 th day	19.16±3.93	8.45±2.08	<i>p</i> <0.01
Konziela test	6 th day	87.85±16.5	62.59±13.2	<i>p</i> <0.05
Time of falling (sec)	7 th day	99.83±29.3	45.62±13.5	<i>p</i> <0.01
Inclined plane test	% Cataleptic score	2.03±0.44%	12.23±3.1%	p<0.01
	Time to scroll down (sec)	17.33±1.03%	37.44±6.02%	<i>p</i> <0.01
	Frozen body posture score	0±0	4.25±0.46	<i>p</i> <0.01
Beam walking test	Latency to cross (sec)			
	3 cm beam	9.8±2.15	36.53±8.6	p<0.01
	2 cm beam	4.1±0.98	32.07±6.2	<i>p</i> <0.01
	1 cm beam	7.8±2.1	46.43±9.0	<i>p</i> <0.01
	Number of slips			
	3 cm beam	0±0	2.75±0.7	<i>p</i> <0.01
	2 cm beam	0±0	1.3±0.26	<i>p</i> <0.01
	1 cm beam	1.8±1.1	4.6±1.30	<i>p</i> <0.01
Footprint	Forelimb stride length (cm)	9.91±0.5	7.62±0.5	<i>p</i> <0.01
	Hind limb stride length (cm)	10.06±0.6	7.72±1.2	<i>p</i> <0.01
	Front base width (cm)	5.47±0.31	5.48±0.13	P>0.05
	Hind base width (cm)	5.30±0.48	6.53±0.71	<i>p</i> <0.01
	Right overlapping (cm)	1.26±0.2	1.76±0.3	<i>p</i> <0.01
	Left overlapping (cm)	1.46±0.3	1.55±0.4	p>0.05



Conclusions: In conclusion, this study further provides indication that rotenone administration in rats produces PD-like symptoms which is evident by behavioral, neurochemical and biochemical changes (figure 3). This study also highlights the rotenone-induced imbalance between dopaminergic and cholinergic modulation which is exhibited in PD.

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Motor dysfunctions in rats following repeated exposure to stress on the neurotoxicity of lambda-cyhalothrin *R. Shukla, R. Gupta, A. Pant, V. Khanna (Lucknow, India)*

Objective: To investigate the targets associated in regulating motor functions following subsequent exposure to stress on the neurotoxicity of lambda-cyhalothrin in rats.

Background: Stress that intensifies the toxicity of environmental chemicals has been reported in number experimental studies although the exact mechanism associated with is not clearly understood. The present study has therefore been carried out to investigate the impact of forced swim stress (FSS), a physical stressor on the neurobehavioral toxicity of lambda-cyhalothrin (LCT), a new generation type-II synthetic pyrethroid is used to control insects, pests and ectoparasites in agriculture and veterinary practices including public health programmes. **Methods:** Rats were treated with FSS (placed in glass cylinder filled with water for 3 min/day) for 28 days or treated with LCT (3.0 mg/kg body weight, p.o.) for 3 days (on days 26, 27 and 28) or pre-exposed to FSS for 28 days followed by LCT treatment for 3 days. Effect on motor performance was assessed by standard protocol. Plasma corticosterone and biogenic amine levels in corpus striatum were estimated by RP-HPLC. The sensitivity of striatal dopamine receptor and related signaling was also assessed.

Results: Pre-exposure to FSS followed by LCT treatment in rats resulted to increase plasma corticosterone levels and disrupt the blood brain barrier permeability. Further, decrease expression of DA-D2 receptors, alteration in levels of DA, DOPAC and HVA in corpus striatum along with impaired in motor activity have also been observed in these rats as compared to rats exposed to either FSS or treated with LCT alone. Interesting to it, no significant effect on neurotransmitter levels of DA, DOPAC, HVA and DA-D2 receptors in corpus striatum including plasma corticosterone levels, blood brain barrier permeability associated with spontaneous locomotor activity and motor coordination has been observed in rats exposed to either FSS or treated with LCT alone as compared to controls. **Conclusions:** The results demonstrated that stress significantly synergises the neurotoxicity of LCT through DA-D2 receptors singling which regulates the motor functions.

D2 receptor mediated DARPP32/PP1a signaling is responsible for cadmium induced Parkinson's like behavioral alterations in rats

R. Gupta, R. Shukla, V. Khanna (Luckno, India)

Objective: To identify the specificity of dopamine D2 receptor mediated signaling in cadmium mediated motor alterations

Background: Cadmium, a heavy metal, is to known to exert the toxicity in human body because of its wild industrial and anthropogenic applications. Human exposure to cadmium may therefore occur both in occupational and non-occupational settings and poses a serious risk to health and associated problems. Epidemiological and experimental studies carried out also suggest the role of cadmium in the progression of neurodegenerative diseases like Alzheimer's and Parkinson's. The studies carried out mechanism and the targets associated with this have not clearly been understood. The present study has therefore been aimed to investigate the mechanism of cadmium induced motor dysfunction.

Methods: Male Wistar rats were exposed to cadmium at a dose of 5.0 mg/kg, bw, p.o. for 28 days. Motor assessment in rats was done by using open field activity test, Rota rod and grip strength test. The other parameters were assessed by using the specific western blotting, RTpcr and IHC studies the specific radioligand technique was used to asses the integrity of Dopamine D2 receptors. Further, computational studies were also carried out using the auto dock4.2.

Results: A decrease in the motor activity and motor coordination was significantly observed in rats exposed to cadmium. The transcriptional and translational changes in DA-D2 receptors were found to be decreased with no changes in DA-D1 type receptors in cadmium exposed rats. Further the specific radioligand technique carries out using the Spiperone also confirm the finding of involvement of DA-D2 receptor in cadmium mediated motor alterations. A change in the DARPP32/PP1a also found to target the CREB which are found to be associated with functional changes.

Conclusions: The results of the present study significantly inhibit the involvement of DA-D2 type receptors mediated signaling in regulating the Parkinson's like motor dysfunctions in rats.

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Risk of Parkinson's disease in zolpidem user: A systematic review and meta-analysis

S. Hussain, A.K. Najmi, D. Anil (New Delhi, India)

Objective: To explore the association between zolpidem use and risk of Parkinson's disease.

Background: Zolpidem is commonly prescribed for the treatment of sleep disorder. Epidemiological studies presenting conflicting evidence between the zolpidem use and the risk of developing Parkinson's disease(PD). **Methods:** An extensive literature search was carried out in electronic databases (Pubmed, Embase and Cochrane central) from inception to 30^{th} , November 2016. Keywords used were "zolpidem" AND "Parkinson's disorder" to retrieve the relevant article. Articles were screened for inclusion on the basis title and abstract by two independent reviewers. Quality assessment of included studies was done by using Newcastle-Ottawa Scale (NOS). Cochrane Q (p >0.10) or I² test (>50%) was used to assess the heterogeneity. Depending on the heterogeneity random effect or fixed effect model was used. All analyses were performed using Review Manager software version 5.3 (RevMan 5.3).

Results: Two cohort studies including 116,524 participants of which 45,132 patients belong to the zolpidem user group were included. Characteristics of the included studies were shown in Table|1. Both the included studies were from Taiwan and of high quality judged by the score attainment on NOS (Table|2). Fixed effect model was used as no heterogeneity was observed. The overall relative risk of zolpidem versus non-zolpidem use was 2.585 (95% CI, 2.302 – 2.903). Thus the overall risk of PD in patients receiving zolpidem was 158% greater than the non-zolpidem user (Fig.1).

Table.1. Characteri	stics of cohort stu	udies			
Author, Year (country)	Cohort name	Cohort size	Follow-up period	Number of zolpidem user	Number of PD cases
Yang et al., 2014 (Taiwan)	NR	101,719	5 years	42,171	809
Huang et al., 2015 (Taiwan)	NR	14,805	10 Years	2,961	157

Tabel.2. Quality assessment of the study by using New Castle-Ottawa scale									
Author (Year & Country)	Selection	Comparability	Outcome	Total score	Quality of the study				
Yang et al., 2014 (Taiwan)	****	**	***	9	High Quality				
Huang et al., 2015	****	**	***	9	High Quality				

	Zolpiden	n user	Non-zolpide	m user		Risk Ratio		R	sk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, I	ixed, 95% (3		
Huang et al, 2015	157	2961	240	11844	28.7%	2.62 [2.15, 3.19]				-		
Yang et al, 2014	522	42171	287	59548	71.3%	2.57 [2.22, 2.96]						
Total (95% CI)		45132		71392	100.0%	2.58 [2.30, 2.90]				•		
Total events	679		527									
Heterogeneity: Chi ² =	0.02, df =	1 (P = 0.) /P = 0.00	88); I ² = 0%				0.1	0.2 0.5	1	2	5	10
restion overall effect.	Z = 10.91	(F < 0.00)001)					Zolpidem favoura	le Zolpide	em not favou	urable	

Conclusions: Zolpidem use increases the risk of Parkinson's disease. However, to confirm this association and make the evidence robust more observational and well designed randomized controlled trial is needed.

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The accreditation and certification of the movement disorders subspecialty

S. O'Shea, L. Gutmann, L. Faulkner (New York, NY, USA)

Objective: The purpose of our study was to assess the sentiments of Movement Disorders fellowship program directors regarding the accreditation and certification of their subspecialty. Our study also explores potential benefits and barriers to pursuing the accreditation and certification of this subspecialty.

Background: The subspecialty of Movement Disorders does not have an accredited fellowship program in place. There is also no form of certification of trainees who graduate from these fellowship programs by the ABPN or the United Council for Neurologic Subspecialties (UCNS). Many specialties have pursued accreditation and certification to ensure uniformity and quality in residency and fellowship training.

Methods: A 15-question survey was distributed to 43 Movement Disorders program directors. The survey included questions that addressed not only program director's sentiments regarding accreditation and certification, but also addressed Movement Disorder fellowship program size, curricula, didactics, and research requirements. The program directors were selected from the San Francisco Match website. Two follow-up emails were sent to the program directors. The response rate was 67.4%.

Results: Our study suggested that 48.3% of program directors are in favor of accreditation and 51.7% are in favor of pursuing a certifying examination. 37.9% of program directors did not favor accreditation and 34.5% of program directors did not favor certification. The remaining respondents were indifferent to pursuing both accreditation and certification. Our study also reveals that lack of uniformity amongst Movement Disorders fellowship programs and lack of funding for such programs are the most concerning barriers to pursuing accreditation and certification. **Conclusions:** Our study supports that sentiments towards accrediting and certifying the Movement Disorders subspecialty are bimodal in distribution. Our study confirms that the field of Movement Disorders education is lacking in terms of standardization, and regardless of the accreditation or certification status, standardization is important to the advancement of the subspecialty.

Using the power of a network to accomplish a countrywide review of acute Parkinson's disease management *E. Peter, B. Mohamed, C. Thomas (Bridgend, United Kingdom)*

Objective: To undertake a review of acute Parkinson's disease management across different sites in Wales, a country that is part of the United Kingdom with a population of over 3 million. Investigate if guidelines for management of acute Parkinson's disease are in place across multiple health boards in WalesExplore future development of standardised guidelines across all health boards in Wales

Background: Acute in-hospital management of People with Parkinson's disease (PwP) is challenging and often complicated by missed and delayed medication doses. Having standardised guidelines would help with overall management and help drive up the care of PwP admitted to Parkinson's disease.

Methods: As a Parkinson's disease Excellence Network project, the authors used an existing network of Geriatric Medicine registrars working in acute hospitals across Wales to collect information on acute management of Parkinson's disease including nil by mouth guidelines, reasons for admissions, appropriate prescribing of Parkinson's disease medications and missed doses across a 6 week period. We also explored the existence of guidelines for management of acute Parkinson's disease across Welsh health boards.

Results: Data on 81 patients collected across Wales sampling every major region with an acute admitting unit.81% of acutely admitted patients admitted under a Medical Specialty. 33% referred to Parkinson's disease team as inpatient. 36% of admissions were directly related to Parkinson's disease. Only 52% Parkinson's disease medications prescribed accurately.First dose of medication missed for 31%.39% of patients missed 2 or more doses in first 24 hours. Over half of patients did not have timings of their Parkinson's disease medication accurately documented.

Conclusions: The All-Wales survey showed considerable work needs to be undertaken to establish guidelines in some health boards and further improvements in adherence to guidelines where one is present. It is notable that a countrywide review of acute Parkinson's disease management has been achieved utilising a pre-existing network of trainee physicians. This should provide a template for further works of research and service improvements.

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Hemidystonia associated with Alexander disease

D. Vijayakumar, R. Lewis, G. Fuller, S. Dhar, K. Machol, L. Robak, J. Jankovic (Houston, TX, USA) **Objective:** To describe an uncommon movement disorder phenotype of Alexander disease (AD). **Background:** AD is a rare autosomal dominant disorder that causes progressive leukodystrophy, especially in the frontal lobes. Mutations in the gene coding for glial fibrillary acidic protein (*GFAP*) are found in all variants of AD. Rosenthal fibers in astrocytes of brain and spinal cord are the morphologic hallmark of AD. There are MRI criteria for diagnosis of AD, but genetic testing has become the preferred diagnostic modality. There are three clinical variants of AD: infantile, juvenile, and adult onset forms. The infantile form typically manifests as rapidly progressive macrocephaly and seizures; the juvenile form has a slower progression, with bulbar signs, ataxia, spasticity, and ocular motor abnormalities; and the adult form frequently presents with ataxia, ocular motor abnormalities, and palatal myoclonus.

Methods: This 35-year-old woman presented with progressive difficulty walking and using her left hand. She has had progressive vision loss since age 8, with retinal features of classic retinitis pigmentosa, and progressive ophthalmoparesis. She has also had personality and cognitive changes. She was found to have a right frontal mass and porencephalic cyst, which were resected. At that time, a histopathologic diagnosis of pilocytic astrocytoma (PA), WHO grade I was rendered. Serial brain MRIs showed variable enhancement in the left middle cerebellar peduncle, hypothalamus, and thalamus. On examination, she had spastic ataxic gait and dystonic posturing of the left arm and leg. She has been repeatedly treated with botulinum toxin injections for hemidystonia, with moderate improvement.

Results: Whole exome sequencing (WES) revealed a heterozygous c.989G>C (p.R330P) novel variant of uncertain significance (VUS) in the *GFAP* gene. Another change in the same amino acid (Arg330Gly) has been described in another family with AD. The "frontal tumor and cyst wall" pathology slides when re-examined, showed profuse Rosenthal fiber formation in astrocytes and, in addition, distinctive Rosenthal fiber-like granular inclusions in astrocytic cell bodies, characteristic of AD and not seen in PA. While WES showed a VUS, it is thought to be causative of her disease given her phenotype and histologic features. Hence, the diagnosis was changed from PA to AD.

Conclusions: This case of hemidystonia broadens the spectrum of movement disorders in AD beyond ataxia and palatal myoclonus.

Genetic and clinical analysis of cerebral calcifications

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Objective: Genetic and clinical analysis in primary cerebral calcification.

Background: Cerebral calcification is associated with a variety of disorders of different aetiologies. To date, the primary form of cerebral calcification is thought to be a genetically and clinically heterogeneous disease with variable penetrance within and between families. There are currently four known genes responsible for primary familial brain calcification, *SLC20A2* being the most prevalent one. However, almost half the patients with primary familial brain calcification remain without a genetic diagnosis.

Methods: In-depth, phenotype-genotype and radiological analysis of patients with cerebral calcifications. Genetic testing was performed using Whole Exome Sequencing. Visual calcification rating of total calcification scores (TCC) was performed by two separate investigators.

Results: We analysed 58 cases of brain calcifications suggestive of Fahr's syndrome of which 72% presented with primary brain calcification and 28% had secondary forms. Whole exome sequencing was performed in 32 patients and identified a causal mutation in 17.4% of cases. The most frequent gene in this cohort was *SLC20A2*. In the familial form, movement disorders (65%), psychiatric (60%) and cognitive symptoms (56%) were most common clinical presentation with high familial and interfamilial variability. In the secondary forms, 12.5% of cases had a mitochondrial disorder presenting with cerebral calcification and 15.5% were due to other pathology. One case presented with isolated, heavy pontine calcification. TCC scores were highly variable even within family members and there was no correlation with age or progression .

Conclusions: The largest UK series of genetic and clinical analysis of cerebral calcification shows high phenotype variability and calcification patterns, absence of calcification score correlations and contributes with novel mutations. Less than one third of the patients with primary familial brain calcification were found to have a genetic cause suggesting further thorough genetic studies are necessary with potential for the discovery of new causal genes.

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Reviewing the clinical and mutational spectrum of SLC20A2 mutations in primary familial brain calcification (PFBC) for MDSgene

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Objective: Following the MDSGene protocol, we here present the clinical and mutational spectrum of *SLC20A2* mutations, thereby adding the first gene found to be mutated in patients with primary familial brain calcification (PFBC) to MDSGene.

Background: The recently launched MDSGene database (www.mdsgene.org) currently summarizes genetic and phenotypic information on >500 mutations found in >1000 patients with various movement disorders reported in the literature.

Methods: A systematic literature screen for *SLC20A2* in PubMed yielded 57 original articles. We identified 29 articles that reported at least one mutation-positive individual with PFBC and provided clinical information on mutation carriers. Mutations were included if they had a minor allele frequency <1% (based on the ExAC Browser, dbSNP or unaffected control individuals screened in the publication). We extracted radiological data and 70 other phenotypic features for 134 clinically affected and unaffected mutation carriers.

Results: 134 mutation-positive, symptomatic or asymptomatic individuals with PFBC from 41 families were included in our review. They carried 36 different heterozygous *SLC20A2* mutations (17 missense and 9 frameshift). General motor signs were the most frequently reported clinical feature in 63 individuals (47%) including parkinsonism and dystonia (both 13%) and speech disturbance (12%). A considerable proportion of patients also displayed non-motor signs, such as cognitive deficits (26%) or headache (10%). Examples of other rare manifestations are seizures, chorea, and ataxia (6-7%). Thirty-seven mutation carriers were described as clinically asymptomatic (28%). The age of onset (AOO) of clinical features ranged from 1-82 years with a mean of 32.2 years. Detailed cranial computed tomography (CCT) data was available for 82 patients (62%), showing that brain calcification was most common in the basal ganglia (80%). Overall, there was a large percentage of missing (unspecified) data (e.g. parkinsonism 35%; seizures 43%; headache 51%; AOO 62%).

Conclusions: *SLC20A2* mutations lead to PFBC of mostly the basal ganglia with high phenotypic variability and reduced penetrance of clinical signs. Our review will complement the PFBC section of MDSGene by adding the most common known gene for this condition and, as for previous entries, identifies major data gaps in the present literature, especially for non-motor symptoms.

Association analysis of single nucleotide polymorphisms near the DYT3 locus to dystonic symptoms in X-linked dystonia-parkinsonism

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Objective: We aimed to elucidate whether single nucleotide polymorphisms within the XDP locus affect the phenotypic expression of XDP.

Background: X-linked Dystonia-Parkinsonism (XDP, DYT3, *Lubag* Disease, OMIM # 314250) exhibits variability with respect to age at onset and with symptoms that range from very mild signs to severe forms of the disease. The considerable phenotypic variability seen in XDP suggests the presence of disease modifiers, such as genetic factors influencing disease expression.

Methods: 280 genetically confirmed XDP patients were included in the study. Logistic regression analysis was done to evaluate the association between phenotypes and four SNPs of interest: ChrX:71102421C>G, rs41484056, rs41438158 and ChrX:71653235C>T. Student's *t*-tests were used to compare continuous quantitative outcome measures while *Z*-test was used to compare proportions of patients.

Results: The ChrX:71102421C>G polymorphism had a significant effect on the presence of neck/shoulder dystonia (p=0.000). Logistic regression analysis showed that none of the SNPs influence age at onset of illness. Likewise, there was also no association seen between any of the SNPs and the initial symptom (whether dystonia or parkinsonism) and the region of initial dystonic manifestation.

Conclusions: Significant association was seen between ChrX:71102421C>G and the presence of neck/shoulder dystonia. This finding may indicate that genetic factors influence disease expression in XDP and hence, the phenotypic variability.

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Characterization of GNB1 mutations as a cause of global developmental delay in combination with dystonia, ataxia, or chorea in children

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Objective: To investigate the phenotypic and genotypic spectrum of GNB1 (guanine nucleotide-binding protein, beta 1) mutations and to functionally evaluate their pathogenicity.

Background: Global developmental delay (GDD) is a severe, clinically and genetically highly heterogeneous childhood-onset disorder which is often accompanied by intellectual disability, seizures and other features. In cases in which genetic causes have been identified, *de novo* mutations in neuronally expressed genes are a common scenario. *De novo* mutations in the *GNB1* gene, encoding the GB1 subunit of heterotrimeric G proteins, have recently been identified as a novel genetic cause of GDD. Of note, several of the patients also had dystonic features including a patient with severe generalized dystonia.

Methods: We searched the in-house database of 4,361 exome datasets at Centogene AG for rare variants in GNB1. Missense changes were functionally tested for their pathogenicity by assaying the impact on complex formation with G? and resultant mutant Gß? with Ga. Signaling properties of G protein complexes carrying mutant Gß1 subunits were further analyzed for their ability to couple to dopamine D1R receptors by real-time Bioluminescence Resonance Energy Transfer (BRET) assays.

Results: The pediatric patients presented with intellectual disability, seizures, nystagmus, muscular hyptonia, ophthalmoplegia, abnormal myelination, craniosynostosis, cerebellar hypoplasia, ataxia, chorea, and dystonia. First symptoms occurred at a mean age of 5.3 ± 2.8 (range: 1-12 years). We identified 14 different novel variants (2 splice site, 2 frameshift, and 10 missense changes) in GNB1 in 16 patients. One mutation (R96L) was recurrently found in three ethnically diverse families with an autosomal dominant mode of inheritance. Ten variants occurred de novo in the patients. BRET studies revealed altered functionality of the missense mutations R52G, G64V, A92T, P94S, P96L, A106T, and D118G but not for L30F, H91R, and K337Q.

Conclusions: We demonstrate a pathogenic role of *de novo* and autosomal dominant mutations in *GNB1* as a likely cause of GDD in combination with and movement disorders and provide insights how perturbation in heterotrimeric G protein function contributes to the disorder.

Whole exome sequencing in essential tremor

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Objective: To discover novel gene variants associated with essential tremor (ET) using whole exome sequencing (WES).

Background: ET, one of the most common movement disorders, affects about 5% of the population older than 65 years of age. Although family history is common in ET, the responsible genes have largely proven elusive. Many genes, including *LINGO1*, *SLC1A2*, *SCN4A*, *HTRA2*, *SORT1*, *FUS*, *TENM4*, *STK32B*, and *CTNNA3*, have been implicated in ET. Polymorphisms in *LINGO1* have been independently replicated in some studies (Kuhlenbäumer et al. 2014) but not in others (Müller et al. 2016).

Methods: We included families and singleton cases on our ET WES cohort. Our analyses initially focused on related subjects from 3 families, and identified shared variants, consistent with segregation. Several filters were next employed to prioritize the most likely responsible gene mutations from among all non-synonymous variants, including (1) brain expression, (2) minor allele frequency < 0.01 in public databases, and (3) predicted pathogenicity based on several algorithms.

Results: Our familial ET WES cohort of 20 cases (55% female) includes 6 subjects from 3 families (2 related subjects per family), and the remaining 14 subjects are singleton cases (1 subject per family). The median age at tremor onset is 19.5 years (range 4-57 years) and the median age at enrollment was 52.5 years (range 38-75 years). All ET pedigrees show at least 2 consecutive affected generations, and have an apparent autosomal dominant inheritance pattern. Following application of filters, we identified multiple, promising shared variants within novel gene candidates for each of our 3 ET families. Additional putative damaging variants in selected genes were detected among the 14 singleton exomes, consistent with genetic replication.

Conclusions: WES is a promising tool for ET gene discovery. The genes and variants identified in our study are excellent candidates for further segregation analysis in ET families and for replication studies in additional ET cohorts.

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Variations in ANO3 gene in patients with cervical dystonia

V. Han, V. Habalova, L. Klimcakova, J. Zidzik, M. Skorvanek, Z. Gdovinova (Kosice, Slovakia) **Objective:** The aim of our study was to establish prevalence of variants in the gene for anoctamin 3 (ANO3) in a population of patients with cervical dystonia.

Background: Cervical dystonia is a hyperkinetic movement disorder characterized by contractions of cervical musculature that lead to abnormal movements or abnormal posture of the head. Combination of both genetic and epigenetic factors plays role in development of the disease. List of genes associated with dystonia is constantly expanding, although prevalence of gene variants and diversity of phenotypic spectrum is not yet well understood. Our study was focused on the incidence of variants in one of these genes - ANO3, located on chromosome 11, consisting of 27 exons, and with particularly high expression in the striatum.

Methods: After obtaining informed consent, 32 consecutive patients (5 men, 27 women, mean age 59.0 ± 14.7 years) from a specialized neurological clinic focusing on the treatment of dystonia were enrolled. The average age at onset of dystonia was 43.1 ± 15.0 years (min. 13, max 66 years). DNA was analysed using direct Sanger sequencing. All 27 exons with adjacent intron and 5'-UTR and 3'-UTR regions were screened. Significance of the observed variations was predicted by the MutationTaster® software.

Results: We did not reveal any of the 13 missense mutations located in exons referred up to date in our sample. However, few very rare (frequency of minor allele <0.01) or yet undescribed variants in intron regions were detected. One of these intron's variants (NM_031418.3:c.693-10_693-9insT; rs753255476) was located in the splicing area at the border of exon and intron, and has been evaluated by predicting software as a potential diseasecausing variation. Rare variants found in the 3'-UTR region are located in the hypersensitive region of DNase I that affects transcriptional activity.

Conclusions: According to our preliminary findings, not only rare exon variants, but also variants in introns and UTR regions of the ANO3 gene might contribute to the ethiopathogenesis of dystonia. Further extensive studies and functional analyses are needed to verify these findings.

The predominant parkinsonian phenotype in beta propeller associated neurodegeneration (BPAN)

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Objective: Describe three BPAN patients with two different phenotypes and explore the phenomenology of patients reported in the literature.

Background: De novo mutations in WD repeat domain 45 (*WDR45*) are causative of beta-propeller proteinassociated neurodegeneration (BPAN). The phenotype is characterised by early developmental delay followed by a secondary period of cognitive and motor decline in adulthood with predominant generalised dystonia-parkinsonism. A T1-hyperintensity halo with hypointense centre in the substantia nigra is universal. A prominent parkinsonism in the second deterioration stage has been reported in only in a subset of patients.

Methods: Pubmed, Embase, Google Scholar search articles published from 2013 to October 2016 using terms *beta-propeller protein-associated neurodegeneration*, *WDR45* and *static encephalopathy of childhood with neurodegeneration in adulthood* as limits. We categorised patients in prominent parkinsonian phenotype when this was specified as symmetrical or asymmetrical parkinsonism with or without dystonia. Patients that not described with these features were categorised as predominant dystonia with parkinsonism.

Results: We included literature (n=43) and three of our patients with BPAN and movement disorders (Figure 1 and 2). Age at BPAN diagnosis was 33.95 ± 8.5 years (range; 15-52) and 93.47% were female patients (Table 1). The collated patients had a combination of predominant dystonia with parkinsonism (n=40) or predominant parkinsonism (n=6). The group with predominant parkinsonism had characteristically bradykinesia, gait

impairment, rigidity and altered postural reflexes. Of the reviewed literature, two patients had asymmetry but only one had rest tremor. In the parkinsonian group, only two (current study patients) were combined with focal dystonia. In contrast patients with prominent dystonia, 33 had combined parkinsonism and 7 only had dystonia alone. A trial of levodopa was performed in 20 patients, 19 of which were reported to have improvement of symptoms. In the six patients with predominant parkinsonism, the mean levodopa equivalent daily dose was 433.3 ± 312.51 mg.



	Dystonia predominant	Parkinsonian
	BPAN (n=40)	predominant BPAN
		(n=6)
Age at examination in adulthood	33.92 ± 9.0	35.3 ± 3.4
Age at second decline in adulthood	26 ± 5.41 *	33.8 ± 2.9
(years)		
Preserved ambulation after second	1/15 (6%)	6/6 (100%)
decline		
Epilepsy	23 (57%)	3 (50%)
Atypical Rett syndrome	11/36 (30.5)%	0/6
Corticospinal signs	10/13 (76.92%)	4/6 (66%)
Response to levodopa	19/20 (95%)	6/6 (100%)
Levodopa induced dyskinesia	14/15 (93%)	2/6 (33%)



Levodopa-induced dyskinesias were reported in 93% with predominant dystonia vs 33% in the parkinsonian group. **Conclusions:** Predominant parkinsonism with moderate to excellent levodopa response, older age at second decline and preserved ambulation suggest a distinctive BPAN phenotype

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Case of myotonic dystrophy

A. Jusupova (Bishkek, Kyrgyzstan)

Objective: Myotonic dystrophy (dystrophia myotonica, DM) is the most frequently inherited neuromuscular disease of adult life.

Background: Classical DM (DM1) has been identified as an autosomal dominant disorder associated with the presence of an abnormal expansion of a CTG trinucleotide repeat on chromosome 19q13.3.

Methods: Patient D, 46 y.o, complains: weakness of distal part of limbs, muscle contractions of hand at the beginning of active movement, voice changing, backaches and impossibility to straighten up walking, absense of vision from the right side, heart aches. Onset of disease in 2007 (at the age of 40), when he firstly feel weakness of distal muscles of legs, backaches, difficulties in standing up, muscle spasms of hands. In 2008 appears dysphonia. From 2009 begins vision worsening. From 2011 he mentioned increasing of weakness of limbs and muscle spasms of hand.

Results: Expressionless, mask-like face. Involuntary posture, flexed in lumbar part. He gets about on crutches. Hypotrophy infraspinatus muscles, muscle hypotonia, muscle power in distal part 3-3,5, and in proximal part -4 score, positive stairs symptom. He cannot suddenly open a clenched fist. Tendon reflexes are absent. Disembriogenetic stigmas such as gothic palate, pigmented nevus on back. ECG: Sinus rhytm, heart rate -54 per min. Electrical axis deviated to the right. AV blockade first degree, right bundle-branch block. Myocardiac cardiosclerosis. EMG: Myotonic discharges. Ophthalmologist: Total cataract ?D, immature cataract ?S. Genealogical analysis has revealed that grandparents had marriage of close relatives (they were cousins on mother right), such symptoms was revealed in every generation equally in boys and girls. Similar symptoms have elder brother and younger sister.



Conclusions: Our case is DM1, symptoms become evident from the fourth decade of life, with a slow progression over time. The key feature of the disease is myotonia, progressive muscular weakness (dystrophy) and wasting are also typical findings; facial, axial, semi-distal, and distal compartments are predominantly involved. DM1 is a multisystem disorder; indeed, patient has abnormalities of other organs and systems including the eye and the heart. We would like to draw attention to this multisystem disorder and note that in developing countries where DNA analysis is not available yet, diagnosis can be based only on neurological examination, careful anamnesis and genealogical analysis.

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Spasmodic Dysphonia in Hereditary Spastic Paraplegia Type 7

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Objective: To describe a case of spasmodic dysphonia associated with hereditary spastic paraplegia (HSP) type 7. **Background:** HSP is a heterogeneous group of inherited disorders characterized by lower limb predominant spasticity with or without weakness. HSP can be classified as uncomplicated or complicated based on the presence of other neurological or systemic features. HSP7 is an autosomal recessive disorder caused by a mutation in the *SPG7* gene on chromosome 16q. HSP7 is usually complicated, with cerebellar ataxia as the most frequent additional feature. Dystonia is rarely seen in HSP7; to date only cervical dystonia has been reported.

Methods: We describe a case of a 26-year-old man who presented with a progressive gait disorder and abnormal speech. At age 17, he began to toe-walk. Over time, he developed a limping, unsteady gait with leg stiffness and falls. At age 25, his voice became progressively hoarse and strangulated without dysphagia. His parents are first cousins and a paternal uncle has global developmental delay. Examination revealed normal strength, diffuse hyperreflexia in the arms and legs, bilateral positive Hoffmann's reflexes, increased spastic tone in the legs with bilateral ankle clonus and upgoing toes. He had pronounced foot plantar flexion when walking. His gait did not change when running or walking backwards. His voice had a strained quality with occasional breaks on voice phonation. His voice quality normalized when laughing and the strain and breaks resolved with whispering. **Results:** A brain MRI was normal. A cervical spine MRI revealed mild flattening of the cord. Nerve conduction studies and electromyography were normal. Laryngovideostroboscopy revealed normal laryngeal function with occasional spasm with connected speech. Trio whole exome sequencing detected a homozygous, previously reported pathogenic nonsense variant, p.L78X (c.233T>A), in the *SPG7* gene. Clinical Sanger sequencing confirmed the presence of the homozygous variant in the patient.

Conclusions: He is being treated with botulinum toxin injections to the larynx for spasmodic dysphonia and to the bilateral gastrocnemius for gait dysfunction, thought to be a combination of spasticity and dystonia. The injections

and voice therapy successfully improved his voice. We believe this is the first description of spasmodic dysphonia, a focal dystonia of the laryngeal muscles, in association with a SPG7 mutation.

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The neural correlates of apathy in premanifest and manifest Huntington's disease: A cross-sectional multimodal imaging study

S. Martinez-Horta, J. Perez-Perez, F. Sampedro, M. Carceller, A. Horta-Barba, J. Pagonabarraga, J. Kulisevsky (Barcelona, Spain)

Objective: To delineate the brain correlates of apathy severity by means of glucose metabolism (18-FDG PET), grey-matter (GM) and white-matter (WM; FA-DTI) changes and relations with clinical measures in preHD and manifest HD (mHD).

Background: Apathy is a common and disabling neuropsychiatric symptom in Huntington's disease (HD). It is already found in premanifest mutation carriers (preHD) and linearly worsens as disease progresses. However, little is known about sub-serving neural correlates of apathy in HD.

Methods: 60 gene-mutation carriers (21 preHD/39 mHD) were enrolled. Clinical-sociodemographic data comprised age, sex, education, CAG repeats, disease burden score (DBS), UHDRS-TMS, functional capacity, cognition, apathy severity and other neuropsychiatric symptoms (PBA-S). Apathy severity was used in a vowel-wise regression analysis with age, sex, DBS, PBA-S and UHDRS-TMS as covariates. Relative metabolic uptake (SUVr) and grey-matter volume (GMV) were quantified in ROIs to explore associations with clinical measures. Significance was set at p<0.001 and k=50.

Results: Apathy correlated with DBS and cognition. Decreased 18-FDG metabolism in ACC, orbital/ventro-medial PFC, insula, superior temporal and lingual gyrus was associated with apathy in both groups, being more circumscribed in preHD. SUVr in ACC and insula were respectively associated with less inhibitory control and word-reading in mHD. GMV reduction was found in the ACC, orbital/ventro-medial PFC, insula, putamen, amygdala, fusiform, temporal cortex, SMA and occipital lobe in mHD, with changes in preHD limited to the SMA and temporal cortex. GMV in amygdala and occipital lobe contributed to lower cognitive performance in mHD, whereas in preHD, the occipital and ACC contributed to lower set-shifting and psychomotor speed. In mHD, FA was decreased in forceps minor, anterior limb of internal capsule, posterior thalamic radiation, cingulum, stria terminalis and sagittal stratum. In preHD in superior longitudinal fasciculus, posterior limb of internal capsule and splenium.



Conclusions: Apathy in HD is associated with metabolic abnormalities in critical reward, emotional and cognitiverelated territories. The propagation of metabolic alterations from preHD to mHD is associated with GM and WM decreases in multiple fronto-temporal, limbic and posterior regions also associated with lower cognitive performance.

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Screening of cognitive impairment in Huntington's disease with the Parkinson's Disease – Cognitive Rating Scale (PD-CRS)

S. Martinez-Horta, A. Horta-Barba, J. Perez-Perez, J. Pagonabarraga, J. Marin-Lahoz, J. Kulisevsky (Barcelona, Spain)

Objective: To explore the psychometric properties of the PD-CRS as compared to two commonly used measures (the MMSE and the UHDRS Cognitive score) for detecting cognitive impairment in HD and discriminating cognitive profiles and disease-stage.

Background: Cognitive impairment is an essential feature of Huntington's disease (HD) and causes an enormous impact on quality of life. In the context of HD, comprehensive assessment batteries are time consuming and impractical as outcome measure in clinical trials, and short assessment scales for global cognition have generally shown limited specificity over the cognitive characteristics of HD. The PD-CRS, an instrument specifically designed to capture disexecutive and posterior cortical deficits in PD, might also prove valid, reliable and practical in HD. **Methods:** Forty-one symptomatic gene-mutation carriers ranging on disease-stage between 1 and 4 were enrolled.

The Clinical Dementia Rating scale (CDR) sum-of-boxes was used as gold-standard and to classify participants as cognitively preserved (CDR = 0), MCI (CDR = 0.5) or demented (CDR > 0.5).

Results: With a sensitivity 90% / specificity 81%, the PD-CRS cutoff = 81 showed the highest discriminative power (AUC=0.896; 95% CI 0.78 – 1) detecting cognitive impairment. The MMSE = 26 showed a sensitivity of 88% / specificity 68% (AUC=0.793; 95% CI 0.63 – 0.94) and the UHDRS-Cogscore = 180 a sensitivity 77% / specificity

63% (AUC=0.753; 95% CI 0.57 – 0.93). The PD-CRS cutoff = 55 differentiated dementia from MCI with a sensitivity 87% / specificity 85%, the MMSE = 24 with sensitivity 74% / specificity 50%. The UHDRS-Cogscore was not computable due to extreme floor effects in demented patients. All instruments captured significant differences between stages 1 - 2 and 1 - 3. The PD-CRS showed the strongest correlation adjusted for age/education with disease-stage (r=-0.709; p<0.000).



Conclusions: The PD-CRS appears as an appropriate instrument to assess cognitive impairment in HD based on its excellent psychometric properties and superiority compared to other common tools. Further studies will explore sensitivity to change over time, discriminative properties in premanifest HD population and, whether the addition of more HD-specific sub-tests can improve the psychometric properties of the present version of the scale.

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Predictors for psychosis in Huntington's disease: preliminary analysis of the Enroll-HD database.

N. Rocha, E. Furr-Stimming, A. Teixeira (Houston, TX, USA)

Objective: To evaluate predictors for psychosis in HD.

Background: Behavioral problems are present across all stages of HD, even preceding the development of the motor symptoms. While not so frequent in HD, psychosis can be very distressful for both individuals with HD and

their caregivers. Psychotic symptoms have been underinvestigated in HD, and it remains to be established their predictors.

Methods: This study included 2303 manifest patients with HD from the Enroll-HD database (December 2015). First, we performed univariate analyses in order to investigate differences between HD patients with and without medical history of psychosis. Then, all variables that presented p<0.20 in the univariate analysis were included in a multivariate analysis (Binary Logistic Regression).

Results: Nearly 11% (N=248) of patients with HD presented history of psychosis. Among HD patients with medical history of psychosis, 55.3% were pre-morbid (i.e., the age of psychosis symptoms preceded the age of clinical diagnosis of HD) and 31.6% have current psychosis (i.e., PBA-s psychosis score = 1). The CAG trinucleotide repeat length was not associated with psychosis. Patients with a history of psychosis presented with a higher frequency of behavioral problems and worse motor, functional capacity and cognitive scores than patients without a history of psychosis. A logistic regression was performed and patients with HD presenting medical history of alcohol use disorders, depression, violent/aggressive behavior, preservative/obsessive behavior and previous suicidal ideation were more likely to exhibit psychosis. Moreover, poorer performance in the Symbol Digit Modalities Test (SDMT) was associated with an increase in the likelihood of psychosis history (table 1). The logistic regression model was statistically significant (?2 = 225.755, p = 0.000). The model explained 23.0% of the variance in psychosis history and correctly classified 90.9% of cases. [table 1]

-						100		
							95% CI f	or Odds
							Rat	tio
	В	SE	Wald	df	p Value	Odds Ratio	Lower	Upper
Age	005	.007	.530	1	.466	.995	.980	1.009
Mother affected	268	.167	2.583	1	.108	.765	.551	1.061
Alcohol use disorders	.668	.244	7.512	1	.006	1.951	1.210	3.147
Drugs abuse	.161	.268	.363	1	.547	1.175	.695	1.986
Depression	1.014	.265	14.669	1	.000	2.757	1.641	4.632
Initability	.192	.242	.628	1	.428	1.211	.754	1.947
Violent/aggressive behavior	.660	.189	12.254	1	.000	1.935	1.337	2.800
Apathy	.278	.202	1.887	1	.169	1.320	.888	1.962
Perseverative / obsessive behavior	1.058	.192	30.392	1	.000	2.881	1.978	4.198
Cognitive impairment	.088	.198	.199	1	.655	1.092	.741	1.609
Previous suicidal ideation	.439	.176	6.239	1	.012	1.552	1.099	2.190
TMS	.005	.005	.941	1	.332	1.005	.995	1.016
SDMT score (total correct)	029	.010	8.699	1	.003	.971	.953	.990

Table 1. Logistic regression model to predict psychosis history in Huntington's disease.

Conclusions: Behavioral problems, previous suicidal ideation and poorer cognitive performance were significant predictors for psychosis in HD. Psychosis seems to occur in patients with HD that already have a burden of other non-motor symptoms. Further analysis in the larger database will allow refining the precision of predictors.

Examining central cognitive processing speed as an early marker of Huntington's disease (HD) onset *A. Nathan, S. Park, P. Gilbert, J. Corey-Bloom (La Jolla, CA, USA)*

Objective: To examine central processing speed as an early marker of Huntington's disease (HD) onset using the Computerized Test of Information Processing (CTiP).

Background: The CTiP, administered on a laptop, is a relatively simple and useful tool for evaluating the extent to which neurological conditions affect cognitive processing speed. It consists of three computerized reaction time (RT) subtests that progressively increase in task complexity - Simple RT (SRT); Choice RT (CRT), with an added decisional component; and Semantic Search RT (SSRT) with an added conceptual component.

Methods: Gene carriers (n=77) were categorized using the UHDRS Total Functional Capacity and Penny Burden of Pathology score as early pre-manifest, transitional (i.e. individuals close to disease onset or with very mild HD), or moderate HD. Subjects were administered the CTiP in addition to traditional cognitive assessments commonly used in HD. Central processing speed was measured using motor-corrected CRT and SSRT values. A one-way ANCOVA adjusting for age was used to compare group performance on the RT subtests.

Results: Moderate HD subjects showed significantly slower reaction times in all conditions (p<0.001), as compared to NC. Importantly, even transitional subjects showed significantly slower reaction times on the CRT (p<0.01) and SSRT (p<0.01), and in central cognitive processing, compared to NC. [table1] [table2]





Conclusions: Our results suggest that the CTiP may be a useful and early marker of deficits in central cognitive processing in individuals with, and transitioning to, HD.

Huntington's disease: determinants for cognitive disease progression - A proposed model

N. Gonçalves, J. Mendes, J. Ferreira, C. Sampaio (Lisbon, Portugal)

Objective: To develop a conceptual model to determine the rate of cognition impairment in Huntington's disease manifest patients and to identify the factors that influence the progression rate.

Background: Huntington's disease is an inherited autosomal dominant neurodegenerative disease caused by a gene mutation, which results in progressive deterioration of the motor and cognitive abilities. The nature and extent of cognitive impairment is not clearly identified because in-between of the prodromal phase and the late stage there is lack of information on how it progresses. There is evidence that cognition impairment can be affected by functional and motor conditions, CAG repeats, education level and sex.

Methods: A theory-driven longitudinal structural equation model was developed. Cognition was measured by six indicators: Symbol Digit Modality Test, Stroop Word Reading, Stroop Color Naming, Trail Making Test part A and B, Verbal Fluency Test and Strop Interference Test. Longitudinal data from Enroll-HD public dataset (December 2016) was used to validate the model. The full model was estimated in R with package semPLS. The measurement model was validated trough reliability and validity measures.

Results: 134 HD manifest participants were considered with 4 years of follow up, 58% male, mean age 53.5 ± 11.6 yo; 58% have a ISCED level higher than 3. Mean CAG repeats was 43.4 ± 3.6 and motor onset 47.1 ± 10.8 yo. Motor score was 26.9 ± 13.5 , TFC score 9.5 ± 2.9 and FAS score 21.1 ± 4.4 . The reliability of the model was higher than 0.90 and convergent validity above 0.5 for all the latent variables; the average R² was 0.79. The rate of cognition decline is low in the first 2 years (1%), increasing to 9% between the third and fourth year. Indicators for attention and integration of information do not have impact on cognition after three years of evaluation. Except for sex, all other variables do not have a significant impact on cognition impairment. The rate of progression in women is higher than the global average between the third and fourth year (20%), and also when compared with men rate of progression.



Conclusions: The conceptual model for cognition impairment was validated and sex was identified as a relevant factor for cognition decline. The characteristics of the manifest population studied may influence the rate of progression and therefore the model should be validated using other HD datasets.

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Behavioral changes on the ucsd Huntington's disease behavioral questionnaire (HD-BQ) distinguish patients transitioning to manifest Huntington's disease (HD)

S. Park, S. Nam, A. Nathan, A. Haque, A. Haque, P. Gilbert, J. Corey-Bloom (La Jolla, CA, USA) **Objective:** To utilize the UCSD Huntington's Disease Behavioral Questionnaire (HD-BQ) to assess behavioral changes that distinguish HD gene carriers transitioning to manifest HD.

Background: Behavioral changes, including apathy, depression, irritability, anxiety, and difficulty prioritizing and initiating activities, are characteristic features of HD and may serve as an early marker of disease onset. The UCSD HD-BQ consists of 30 items with a 3-point rating scale (0-3), and takes about 5 minutes to complete. The maximum score is 90 with higher scores indicating greater severity.

Methods: Gene positive subjects (n=118) were stratified using the UHDRS Total Functional Capacity and Penny Burden of Pathology score as early pre-manifest (EPM); transitional (i.e. individuals close to disease onset or with <u>very</u> mild HD); or mild-moderate manifest HD. The UCSD HD-BQ was administered to 22 normal control (NC); 29 EPM; 27 transitional, and 62 HD subjects. We used one-way ANOVA/Tukey Posthoc to compare groups on dependent variables and effect sizes to quantify the mean difference between each group.

Results: Mean MMSE, TFC, and TMS scores were 28.9, 12.8, and 1.7 respectively for NC; 28.2, 13.0, and 1.6 respectively for EPM; 27.3, 12.4, and 7.6 respectively for transitional; and 24.1, 8.2, and 35.6 respectively for manifest HD subjects. Although statistically significant differences were not seen between transitional or EPM subjects and NC with regard to these cognitive, functional and motoric measures, statistically significant differences were seen with regard to the HD-BQ between transitional (mean HD-BQ=32.3; p=0.000) and, more surprisingly, EPM (mean HD-BQ=22.8, p=0.011) subjects and NC (mean HD-BQ=5.7). HD showed the largest effect size (0.620) compared to transitional (0.611) and EPM (0.481) subjects. Highest scoring symptoms among transitional and EPM subjects comprised anxiety, difficulty concentrating, and memory.

Conclusions: The HD-BQ is a brief, reliable instrument for screening behavioral changes in individuals at risk for, and transitioning to, HD. Behavioral disturbances are important in HD and may serve as an early marker of disease onset.

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Juvenile Huntington Disease (JHD) subjects' stratification according to the mutation-length

M. Marano, M. Marano, S. Migliore, S. Maffi, F. Consoli, A. Ciammola, E. Gatto, F. Squitieri (Rome, Italy) **Objective:** To identify clinical and genetic markers to differ JHD from adult Huntington disease (HD) and to monitor JHD progression

Background: JHD is a HD variant with onset >20 years of age. Such classification was based on a clinical observation before the mutation discovery. After that, several articles reported young cases associated with heterogeneous and atypical phenotypes and variable size of mutations, sometime overlapping the size of adult presentations. Considering the rarity of JHD, the obvious difficulty in assessing young children and the still missing validated scales, no longitudinal studies for comparison with adults neither clinical trials, are available **Methods:** We stratified JHD cases according to mutation length, i.e. patients with high CAG expansion =60 [HE, mean=76.6 (60-120), n=22] and with low CAG expansion <60 (LE, mean CAG=51 (43-57), n=13), with a total of 35 cases. A subgroup of 10 HE patients completed a total motor score (TMS) assay with a 3-year follow-up from a basal visit for comparison to an adult HD cohort. Life span and adult HD data were available from our Registry and Enroll-HD databases. JMP12 software was adopted for statistics

Results: HE-JHD patients had an infantile onset (before the age of 10) in 54% cases, paternal inheritance occurred in 95% of them. Cognitive impairment (i.e. developmental delay in younger cases) largely featured HE patients (68%), that were affected by parkinsonism or dystonia since onset (36 and 27% respectively) or during follow-up (31 and 54% respectively), predominating on other motor manifestations. Compared to an adult HD sample, HE patients presented a higher mean TMS unit increase per year (p<0.05) at a longitudinal analysis and a lower life span in year (p<0.05). All LE patients had adolescent onset (between 11 and 20 years, 92%) and presented paternal inheritance in 75%. They manifested with predominant parkinsonisms (46% at motor onset) with chorea in 53% cases during the follow-up. Obsessions were frequently and constantly reported since the onset (69%) **Conclusions:** JHD cases with large expansions may manifest a worsen HD progression, with atypical, non-adulthood, manifestations (i.e. psychic and motor developmental delay, missing chorea). A correct stratification of JHD cases based on mutation size, in addition to age at onset, may offer new clues on detecting biomarkers to transfer into clinics in such ultra-rare condition

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Progressive microstructural abnormalities of the occipital cortex in Huntington's disease

O. Odish, R. Reijntjes, S. van_den Bogaard, R. Roos, A. Leemans (Leiden, Netherlands) **Objective:** To investigate the rate of longitudinal microstructural alterations in the occipital cortex in patients with different stages of Huntington's disease (HD) compared to healthy controls, with the aim of assessing biomarker potential.

Background: Finding sensitive biomarkers characterizing disease state and progression in HD is an active area of research, essential to objectively assess potential effects of proposed therapeutics. Using diffusion MRI, we sought to quantify the rate of longitudinal microstructural alterations in the occipital cortex of patients in different stages of HD and to compare these to rates in matched healthy controls. The choice for this region was driven by mounting evidence of the involvement of the occipital cortex in HD neuropathology.

Methods: Twenty-two premanifest (preHD) (43.6 ± 8.7 years), 10 early manifest HD (50.2 ± 9.3 years) and 24 healthy control subjects (49.0 ± 8.2 years) were included. The preHD group was split into far (preHD-A) and near (preHD-B) to predicted disease onset groups. All completed baseline and two year follow-up diffusion tensor imaging (DTI) scans. An automated atlas-based DTI analysis approach was used to obtain the mean, axial and radial diffusivities of the occipital cortex. Cognitive tests were administered.

Results: The longitudinal rate of diffusivity change in the superior occipital gyrus (SOG), middle occipital gyrus (MOG), and inferior occipital gyrus (IOG) was significantly higher in early HD compared to both preHD and controls (all p's = 0.005). In preHD, only the change rate in the diffusivity of the MOG could significantly discriminate between preHD-B compared to preHD-A and the other groups (all p's = 0.04). An inverse correlation was found between the Stroop Word Reading task only and diffusivities in the SOG and MOG (all p's = 0.01). **Conclusions:** These results suggest that automated atlas-based DTI measures obtained from the occipital cortex can serve as a sensitive longitudinal biomarker for disease state and progression in HD. This in turn could be used to assess the effects of proposed disease modifying therapies.

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A modified model for prediction of Huntington disease age of onset based on length of CAG repeat expansion *Y. Seliverstov, E. Shulgina, S. Illarioshkin, M. Belyaev (Moscow, Russia)*

Objective: We aimed to search for a possibility to modify Langbehn et al. model (LanM) for prediction of Huntington disease (HD) age of onset based on length of CAG repeat expansion using multidimensional optimization technique on the third Enroll-HD study periodic dataset (PDS3).

Background: Among a number of statistical models which establish relationship between CAG expansion length and HD age of onset, LanM appears to be the most accurate to date. However, it is applicable for those HD mutation carriers only with 36-56 CAG repeats, being the most accurate for 41-56 CAG repeats.

Methods: PDS3 database comprises the clinical data from 8,714 participants, including 3,598 from the European REGISTRY study that preceded Enroll-HD. We took data for all manifest HD mutation carriers with verified CAG expansions of at least 36 (n=4789). The median for CAG repeats was 43, ranging from 36 (min) to 71 (max). We used least squares method (LS) implemented to the SciPy library to determine the best curve fit based on data analyzed. The model has the following form: $age = exp(x_0 * CAG + x_1) + x_2$. In this model, "*age*" is the date of clinical HD diagnosis, "*CAG*" is the number of CAG repeats, and "x" is the vector of model's parameters. We took LanM's coefficients for the initial guess on independent variables (-0.146; 9.556; 21.54, respectively). We applied mean squared error (MSE) as an average quality measure for all subjects and for 3 specified subgroups: subjects with 36-39 (subgroup A), 40-56 (subgroup B), and those who have 57 CAG repeats and more (subgroup C), respectively.

Results: After processing, we received the following modified model (ModM): age = exp(-0.084*cag + 7.292) + 9.406. In general, MSE for the LanM (MSE-L) was 67.75, whereas with application of ModM (MSE-mod) = 63.83. For the subgroups we obtained following results. Subgroup A: MSE-L = 447.98; MSE-mod = 285.57. Subgroup B: MSE-L = 60.20; MSE-mod = 59.20. Subgroup C: MSE-L = 38.91; MSE-mod = 28.20 (see [figure1]). However, on closer examination, we found that for carriers of 57-66 CAG repeats ModM is less accurate: MSE-L = 18.54, MSE-mod = 28.8.



Conclusions: The results suggest that the ModM is more accurate for 36-39 CAG repeats carriers in comparison with LanM. For 40-56 CAG repeats carriers, the ModM has similar accuracy to LanM. This allows to consider ModM as an alternative to LanM for prediction age of HD onset for 36-56 CAG repeats carriers.

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Myths and misconceptions regarding Huntington's disease in Peru

A. Vishnevetsky, M. Illanes-Manrique, M. Inca-Martinez, M. Cornejo-Olivas (Philadelphia, PA, USA) **Objective:** To explore the understanding and conceptualization of Huntington's disease (HD) genetics and pathology among HD patients and family caregivers in Peru.

Background: HD is an autosomal dominant, late-onset incurable neurodegenerative disease. HD-affected patients and families in the developed world typically have extensive disease education and genetic counseling. In contrast, there are no genetic counselors in Peru, and disease education is conducted by the neurologist during patient visits. Little is known about HD disease understanding amongst HD families in this context.

Methods: Individuals with HD and their family caregivers were recruited for participation at the Neurogenetics Research Center of the Instituto Nacional de Ciencias Neurológicas (INCN) in Lima, Peru, and at rural neurology campaigns conducted in Cañete province. Study participants were recruited as part of a larger study on HD quality

of life. Qualitative, semi-structured interviews were conducted with 13 patients and 25 caregivers. All interviews were recorded, transcribed, and analyzed in Spanish by two co-investigators using thematic analysis. **Results:** The key disease misconception among interviewees involved a "genetics plus" explanation of HD: the disease is "genetic" or "hereditary" but at the same time due to causes as varied as trauma, alcohol, smoking, malnutrition, or curiously, contact with Koreans (due to confusion over the term, "Huntington's Chorea"). The misconceptions frequently cause increased guilt, regret, and distress among patients and families for past actions that are perceived as having led to HD. The second main finding of the study relates to "HD disease risk calculation errors": some interviewees thought that since the disease was genetic, offspring were guaranteed to have the disease, while others estimated their risk at around 2-5%. Others thought that the disease only affected a single gender, or that they could not transmit the disease if they were still asymptomatic.

Conclusions: Many patients and caregivers affected by HD in Peru have an incomplete understanding of the cause and transmission of HD. In environments where it is not feasible to train specialized genetic counselors or provide extensive personalized education on HD, a brief disease education guide for use and local cultural adaptation by physicians or other allied health professionals would be useful to address misunderstandings surrounding the cause and genetics of HD.

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Cerebrospinal fluid biomarkers in Huntington's disease - a longitudinal study

V. Niemelä, J. Sundblom, A.-M. Landtblom, S. Herman, K. Kultema, D. Nyholm, K. Blennow (Uppsala, Sweden) **Objective:** To validate the role of NFL as a marker of disease progression and to discover new biomarkers in HD. **Background:** Neurofilament light chain (NFL) is an important protein in the cytoskeleton, and it is generally accepted as a marker of neuronal damage. It has gained clinical use as a prognostic marker in other neurological diseases, but is also suggested to be a good marker of disease stage in Huntington's disease (HD). There is a lack of validation of "wet" biomarkers in HD. Proteomic CSF studies have so far yielded conflicting results but with more advanced techniques we hope to validate and discover new proteins involved in the pathophysiology of HD. **Methods:** The study was conducted in accordance with the declaration of Helsinki and was approved by the local research ethics committee in Uppsala, Sweden. All participants signed an informed consent before study entry. A standardized protocol for lumbar puncture was applied. The subjects were assessed with UHDRS total motor score, the cognitive-s test battery and Total Functional Capacity to characterize disease stage. NFL was quantified by ELISA and a liquid chromotography-mass spectrometry analysis was performed.

Results: The study enrolled manifest HD-patients (n=13) and premanifest HD-gene expansion carriers (n=12). Repeated samples after 1-4 years were obtained (n=10). Healthy control samples (n=5) along with neurological controls (eg. Tension type headache cases) (n=40) were matched with cases for sex and age. The concentrations of NFL were significantly higher in the manifest HD patients compared with the premanifest gene expansion carriers after adjustment for age (p = 0.003). There was a significant correlation between NFL and disease burden score (r = 0.69, p < 0.01). NFL correlated with 5-year probability of disease onset in the premanifest gene expansion carriers (r = 0.72 p = 0.0153). Longitudinal NFL and Proteomics results will be available in early spring.

Conclusions: This is a longitudinal study of CSF biomarkers in HD, a design which has not been published in this field before. The results strengthen the case for NFL as a dynamic marker of disease progression.

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Longitudinal study of cortico-striatal functional connectivity In Huntington's disease measured with High-Field functional MRI.

M. Kronenbuerger, M. Kronenbuerger, J. Hua, X. Mia, P. Unschuld, P. van Zijl, C. Ross (Baltimore, MD, USA) **Objective:** To assessed functional connectivity by using functional Magnetic Resonance Imaging (fMRI) at 7 Tesla as baseline and one year thereafter.

Background: Our previous study showed reduced cortico-striatal functional connectivity at rest in Huntington's disease (HD) at 3 Tesla (Unschuld et al. Neurosci Letter 2012) and at 7 Tesla (Kronenbuerger et al. work in progress). Little is known about changes of cortico-striatal functional connectivity in HD over time.

Methods: 9 HD subjects [age 46+/-12 years, CAG repeat 43+/-3, Unified Huntington's disease Rating Scale (UHDRS) motor score -14+/-18, estimated years to symptom onset (YTO) 5+/14 according to Langbehn et al. Clin Genet 2004], and 8 healthy controls [age 47+/-12 years] were studied. The functional connectivity between the striatum and several cortical areas were analysis. Two tailed t-test was applied.

Results: Functional connectivity between striatum and premotor area was impaired comparing all HD subjects with controls at baseline (p<0.01) and the one year follow-up (p<0.01) (Table 1). HD patients showed greater decline of

functional connectivity between striatum and premotor area over time, with a trend to statistical significance (p=0.09). All other comparisons did not reveal statistical significance differences.

Table 1. Cortico-striatal functional connectivity (excerpt of results)

		premotor corte	x - striatum	motor cortex -	striatum
		baseline	1 year follow up	baseline	1 year follow up
Huntington subjects	n=9	0.006+/-0.03	0.05+/-0.04	0.03+/-0.04	0.04+/-0.09
Healthy controls	n=8	0.03+/-0.03	0.03+/-0.03	-0.02+/-0.04	-0.03+/-0.03
t-test (two tailed)		<0.01	<0.01	0.2	0.8

The table shows an excerpt of the results of the contico-striatal functional connectivity in Huntington subjects and healthy controls at baseline and at 1 year follow-up measured with 7 Tesla Magnet Resonance Imaging. Values are mean+/-standard deviation.

Conclusions: These data confirm impairment of functional connectivity between striatum and premotor area in HD compared to healthy controls. In this small sample, worsening with time in HD is suggested. We plan to examine a larger number of subjects in the follow-up to assess if the impairment of functional connectivity between striatum and premotor area is worse in premanifest compared to manifest HD, and to determine if there is longitudinal progression progresses over time.

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Hung up knee jerk reflex in Huntington's disease: A clinical and neurophysiological study

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Objective: Evaluate the presence of Hung-up Knee jerk reflex (HUKJR) in premanifest and symptomatic Huntington's disease (HD) patients and its neurophysiological correlate.

Background: The HUKJR is a classical clinical sign specific of HD that can be observed at physical examination along the disease course. HUKJR happens when testing the knee jerk reflex if the extended leg does not relax straightaway and remains elevated. This singularity of HD, known as "Gordon's reflex phenomenon", is due to a sustained contraction of the quadriceps femoris muscle and its origin is still unknown. Electromyography register shows a high sensibility detecting the abnormal continuous quadriceps contraction that follows the knee-jerk examination in HD, even if the HUKJR is not seeing at physical examination. As far as we know, the presence of HUKJR has never being evaluated systematically in premanifest individuals.

Methods: Prospective study of the knee-jerk reflex in genetically confirmed HD patients compared to controls. Patients were classified as premanifest (preHD) if their total motor score, measured through the Unified Huntington's Disease Rating Scale (UHDRS), was <5 and symptomatic if their UHDRS was =5. Controls were enrolled from partners of HD patients. The presence of HUKJR was evaluated by 2 neurologists at physical examination during a needle electromyography register, performed at the quadriceps muscle. We achieved 10 trials in each leg, including Jendrassik maneuver to facilitate the Knee-jerk reflex. We classified the individuals according to the different clinical and electromyography patterns observed.

Results: We included 35 individuals, 24 genetically confirmed patients -14 preHD, 10 HD- (median age 43 ± 6 years, 6 males, CAG 42 ± 3) and 11 controls (41 ± 4 years, 4 males). HUKJR was present at physical examination in 14% of preHD, 80% of HD and none of the controls; 2 HD also presented a contralateral HUKJR while exploring the presence of ipsilateral HUKJR. We could identified 3 different electromyography patterns: monophasic (controls n=11, preHD n=5); dichrotic (preHD n=7, HD n=1) and sustained (preHD n=2, HD n=9). Patients with the sustained pattern also presented the HUKJR at physical examination.

Conclusions: HUKJR is frequent in HD and it can be observed in premanifested individuals. Electromyography can detect changes many years before motor phenoconversion and could be used as a marker of disease progression.

Imaging of phosphodiesterase 10 A (PDE10A) enzyme levels in the living human brain of Huntington's disease gene expansion carriers and healthy controls with positron emission tomography.

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Objective: The objective of this study was to examine the loss of Phosphodiesterase 10A enzyme (PDE10A) across a broad spectrum of Huntington's disease (HD) stages.

Background: PDE10A is enriched in striatal medium spiny neurons and is involved in signal processing within the cortico-striato-thalamic circuit. PDE10A in the striatum is decreased in HD gene expansion carriers (HDGECs) and has the potential to serve as a disease or pharmacodynamic marker.

Methods: Forty-five HDGECs (10 early pre-manifest (disease burden =250), 7F, $39\pm7y$; 15 late pre-manifest (disease burden =275), 9F, $39\pm7y$; 15 stage I, 4F, $50\pm10y$; and 5 stage II 3F, $56\pm15y$) and 45 age- and sex-matched healthy controls (HCs; 23F, $44\pm11y$) were examined with PET using the radioligand ¹⁸F-MNI-659 (PDE10A). Partial volume effect correction was applied to PET data using 3T MR images. The outcome measure was the binding potential (*BP*_{ND}) estimated with the 2 tissue compartment model using the cerebellum as reference region. Differences in ¹⁸F-MNI-659 *BP*_{ND} values in the caudate, putamen and globus pallidus between HDGECs and HCs were assessed using multivariate ANOVA. Associations between *BP*_{ND} values and disease burden scores were examined using linear regression.

Results: 89 participants (44 HDGECs/45 HCs) were included in this per protocol analysis. Very strong evidence in support of a difference in BP_{ND} values between HDGECs and HCs was observed in each region of interest ($p_s < 0.0001$). BP_{ND} values were lower in HDGECs relative to HCs. In HDGECs, strong evidence in support of a main effect of both HD stage (p < 0.0001) and region (p < 0.0001) was observed for BP_{ND} values. Statistically significant but weaker evidence was observed for an interaction between stage and region (p < 0.0296). An effect of disease burden on BP_{ND} was observed in each brain region (p < 0.0001).

Conclusions: ¹⁸F-MNI-659 BP_{ND} values are lower in HDGECs relative to HCs in the caudate, putamen, and globus pallidus; BP_{ND} values differ between HD stages with lower values typically observed as disease stage severity increases; BP_{ND} values are associated with disease burden score.

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Prescription pattern of treatment in Mexican patients with Huntington's disease

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Objective: To describe the prescription pattern for the treatment of HD in a sample of Mexican patients from a tertiary referral center.

Background: Huntington's disease (HD) is autosomal dominant neurodegenerative disorder. The clinical picture is compromised by motor and neuropsychiatric symptoms. The treatment depends on the predominance and severity of these symptoms. The American Academy of Neurology guidelines and the International Parkinson's and Movement Disorder Society recommendations differ significantly in regards to the pharmacologic drugs of choice. In addition, prescription patterns may be influenced by socioeconomic factors.

Methods: A cross-sectional study was carried out. Patients with molecular diagnosis of HD attending the outpatient clinic of the National Institute of Neurology and Neurosurgery in Mexico City were included. The data collected included main clinical features as well as the type of drug. Descriptive analysis was performed in terms of percentages.

Results: A total of 185 patients were included in the study (48.1% men and 51.9% women). The mean age was 50.8 ± 13.2 years. Age at HD diagnosis was 38.5 ± 12.9 years. The most common used drugs were antipsychotics. Typical antipsychotics used were haloperidol prescribed in 78 Patients (42.2%), sulpiride in 1.6%, amilsupride and levopromazine in only one patient each. On the other hand, atypical antipsychotics prescribed included risperidone in 35 patients (18.9%) olanzapine in 16 patients (8.6%), quetiapine in four patients (2.2%) and clozapine in six

patients (3.2%). A tot	al of 18 (9.7%) were or	i tetrabenazine. [Table 1]
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Table 1

Treatmeant	Numbers of patients	%
TBZ*	N=18	9.7
Typical Antipsychotics		
Haloperidol	N=78	42.2
Sulpiride	N=3	1.6
Amilsuloride	N=1	0.5
Levonromazine	N=1	0.5
Atunical antineuchotics		0.0
Risperidone	N=25	18.9
Olanzanine	N=15	86
Clozanine	N=6	3.2
Ouetiapine	N=4	22
Benzodiazenines		E.L
Clonazenam	N=39	21.1
Alorazolam	N=3	16
Lorazenam	N=2	1.1
SSRI**		
Fluoxetine	N=33	17.8
Citalopram	N=13	7
Sertraline	N=17	9.2
Paroxetine	N=4	2.2
Escitalopram	N=3	1.6
Venlafaxine	N=3	1.6
Trazadone	N=1	0.5
Duloxetine	N=1	0.5
Milnacipram	N=1	0.5
Tricyclic antidepressants		
Mitarzapine	N=8	4.3
Amitriptyline	N=4	2.2
Antiparkinsonians		
Amantadine	N=10	5.4
Biperiden	N=7	3.8
Levodopa	N=3	1.6
Trihexyphenidyl	N=3	1.3
Cholinesterase Inhibitor		
Donepezil	N=4	2.2
Galantamine	N=1	0.5
Anti NMDA***		
Memantine	N=8	4.3
Anticonvulsant		
Valproic Acid	N=26	14.1
Magnesium Valproate	N=4	22
Carbamazenine	N=2	11
Lamotrigina	N-2	1.1
Lamotrigine	N=Z	1.1
Coopers Old		
Coenzyme Q10	N=21	11.4
Probenicia	N=5	2.1
Vitamins	N=2	1.1
Butolinic Toxin	N=1	0.5
Melatonin	N=1	0.5

*Tetrabenazine

**Selective serotonin reuptake inhibitors

***N-methyl-D-aspartate

Conclusions: In Mexico, typical antipsychotics are more commonly used than atypical ones. Overall, haloperidol is the most common drug used. Other drugs, such as tetrabenazine, may be used less mainly due to economic reasons. A cost-utility and cost-effectiveness analysis may be warranted.

Prevalence of substance abuse in Huntington's disease patients and its relationship with neuropsychiatric symptoms

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Objective: To describe the prevalence of substance abuse and its relationship with neuropsychiatric features in Huntington's disease (HD).

Background: Substance abuse is not well established in HD. In Mexico, overall frequency of alcohol abuse is 49.1%, tobacco use 18.4 % and marijuana use 17.8%. All more in men (68%). To our knowledge, the prevalence of substance abuse in HD is not widely reported in literature. Moreover, alcohol and drug abuse are associated with suicidal ideation. Only four studies have explored the relationship between substance abuse and HD age of onset, with conflicting results, but the association with neuropsychiatric symptoms was not assessed.

Methods: Subjects diagnosed with HD were included. Data collected included: age, age of onset, sex, and education. Substance abuse History (alcohol, tobacco, marihuana/cocaine), presence of apathy, anxiety, insomnia, aggressiveness, irritability, suicidal ideation, obsessive or compulsive symptoms.

Results: A total of 185 subjects were included (48.1% men). Use of tobacco was reported in 40%. No association was found with neuropsychiatric symptoms (Table 1). Use of alcohol was reported in 41%. A trend of alcohol use and anxiety was found (p=0.059). Moreover, alcohol use was associated with insomnia (p=0.027) and irritability (p=0.02). Finally, drug abuse was reported in 4.9 % of the sample. Had anxiety (p=0.019), 6 patients had insomnio (p=0.027).

Substance abuse and neuropsychiatric symptoms

	Alcohol (+)	Alcohol (-)	p	Tobacco (+)	Tobacco (-)	p	Drugs (+)	Drugs (-)	Р
Age	50.95	50.82	0.947	51.57	50.41	0.560	45.67	51.14	0.22
Age of onset	39.92	38.28	0.395	40.49	37.93	0.188	39.33	38.93	0.228
Men	50	39	0.00	46	43	0.002	7	2	0.68
women	26	70		28	68		2	94	
Apathy	12	15	0.701	11	16	0.932	2	25	0.506
Anxiety	23	20	0.059	20	23	0.32	5	38	0.019
Insomnio	32	29	0.027	30	31	0.074	6	55	0.027
Agressiveness	27	37	0.824	26	38	0.9	3	61	0.935
OC	5	10	0.525	7	8	0.582	0	15	0.361
Depression	34	56	0.374	33	57	0.368	6	84	0.268
Irritability	38	36	0.02	31	43	0.668	3	71	0.676
SI	12	15	0.70	10	17	0.734	2	25	0.506

OC: Obsessive / Compulsive symptoms SI: suicidal ideation

Conclusions: In our sample of subjects with HD tobacco use was higher than in general population. Conversely, alcohol and marihuana/cocaine use was less frequent. A relationship between tobacco use and insomnia and irritability was found. Drug use was related with insomnia and anxiety. No association with suicidal ideation or HD age onset was found for any substance use.

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Evidence-based Brazilian Physicaltherapy Guideline for Huntington's Disease

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Objective: Identify the Evidence based Physicaltherapy available for HD and provide recommendations to physicians.

Background: In Huntington's Disease (HD) Chorea is usually presented in any phase of disease and other motor impairments appears dystonia and hypokinesia and rigidity and increase the dependence level. Even with the ideal

medical and surgical treatment, HD patients still present problems with functional activities, gait and balance. Physicaltherapy is often prescribe for this propose.

Methods: We reviewed the literature 2000 to 2016 for pertinent evidence using Grading of Recomendations Assessment, Development and Evaluation Process and include randomized clinical trial, patient series and expert opinion.

Results: The Main goals of physicaltherapy targeted on HD, were divided on 4 different stages. Pre-Manifest – Support for maintenance of an independent exercise program. No evidence to treatment. Early stage the motor functions should be assessed by a physical therapist. There were a few protocols of exercises addressed to people with HD. They suggest some strategies to training gait, balance, functional activities and multi-sensory stimulation. Aerobic exercises are recommended in a frequency of 3-5/week, intensity of 65-85%. Exergaming, Yoga, Pilates, taichi and relaxation are also suggested. The benefits of regular physical activity for people with HD are widely recognized. Mid stage - facilitate independence (in activities of daily life and optimize participation in family, work, leisure) by education and specific advice on safety and risk management, modification of activities or environments, or the provision of assistive devices or wheelchairs. As the disease progresses, physiotherapy is frequently directed toward maintaining or retraining the reach to grasp movement, bed mobility, transfers, and walking. The prescription of gait aids may be useful for people with HD but the difficulty if chorea isn't severe. Late stages Assistance to complete. Maintain Postural adjustments, mobility and prevention contractures; as well to teach the person how to clear sputum and cough effectively. Caregivers should be trained to assist airway clearance techniques such as deep breathing, postural positioning and supported coughing are used.

Conclusions: The efficacy of physiotherapy, randomized control studies in the published for HD is few, but there is evidence that exercise may be useful in specific impairments in each stage.

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Factors Influencing Completion of Predictive Testing for Huntington's Disease (HD)

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Objective: To determine if the new simplified testing protocol led to an increase in completion rate of predictive testing for HD, and to study some factors influencing testing process.

Background: HD is an autosomal dominant disorder with CAG triplet repeats at HTT gene presenting with motor, cognitive and psychiatric symptoms which are highly disabling. The knowledge of the causative gene has made it possible to test at-risk individuals (=have family history of HD but unknown inheritance of CAG expansion {which is 50% }), before clinical symptoms develop. International Huntington Association (IHA) and World Federation of Neurology (WFN) Research Group on Huntington's Chorea made recommendations in 1994 regarding predictive testing. Testing process for HD is psychologically stressful. Some studies found up to 40% incompletion rates; others have shown that only 15% at-risk population undergo predictive testing.

Methods: In January 2014, testing protocol at University of Alabama (UAB) HD clinic was changed to make a new streamlined protocol requiring 3 in-person visits, with genetic counseling on phone and psychiatric evaluation via mailed questionnaire as compared to 5 visits previously. Study population consisted of all patients who began predictive testing for HD at UAB HD clinic between Aug 2009 and Oct 2015 (n=46). A chart review was done to collect age, sex, distance from clinic, when patient began testing, number of relatives with HD, if completed testing and motivation for testing. Anonymous patient based survey was emailed to all patients for whom email addresses could be found (n=11). It included questions pertaining to above along with satisfaction with testing and testing completion (reasons if not completed).

Results: 54.35% patients completed the testing before protocol change and 48.83% completed after protocol change. [Table 1] and [Table 2] summarize the results of chart review portion and patient survey portion respectively. No statistical significance was achieved for any of them.

Variable	Completion Rate	P-value (Fisher's Exact)
Overall	54.35%	N/A
Time of testing (n=46)		
Before protocol change	63.64%	0.2528
After protocol change	45.83%	
Sex (n=46)		-
Male	50%	0.7640
Female	57.14%	
Age (n=42)		
18-29	53.33%	>0.9999
30+	51.58%	
Distance from Birmingham (n=30)		
<76 miles	46.15%	
76-150 miles	33.33%	0.5195
>150 miles	62.5%	
Living relatives with HD (n=36)		
0	55.56%	0.4697
1*	40.74%	
Motivation for testing (n=15)		
Curiosity	50%	>0.9999
Family members	25%	0.5692
Family planning	33.33%	>0.9999
Future	100%	0.0769
Multiple reasons	33.33%	>0.9999

Table 1. Percentage of patients who completed testing based on chart review, stratified by question response.

Variable	Completion Rate	P-value	
Overall (n=7)	85.71%	N/A	
Education level (n=7)			
Some college	66.67%	.4286	
College/graduate degree	100%		
Marital Status			
Married	85.71%	N/A	
Motivation for testing (n=7)			
Family planning	66.67%	.4286	
Curiosity	100%		
Primary caretaker			
No	85.71%	N/A	
Told family (n=7)			
No	100%	>0.9999	
Yes	83.33%		
Family Support			
Yes	83.33%	N/A	

Table 2. Percentage of patients who completed testing based on patient survey, stratified by question response.

Conclusions: Primary hypothesis that the completion rate would be increased after protocol change was rejected. Primary motivation for testing and proximity of residence to clinic (secondary hypotheses) were not statistically significant. This study is limited because of small scale and loss to follow up; more studies like this are needed to determine if national guidelines for HD testing need to change for more accessibility to patients.

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Sensory modulation of postural control in Huntington's disease

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Objective: To characterize sensory modulation of postural control in Huntington's disease (HD); and to identify postural metrics that are sensitive in the prodromal stage of HD.

Background: In manifest HD (mHD), there is progressive decline of postural control. The Modified Clinical Test of Sensory Interaction and Balance (mCTSIB) is a common bedside balance test for postural control. In prodromal HD (pHD), the root mean square (RMS) is sensitive in revealing postural deficits. It is unclear whether other postural metrics are sensitive in pHD and mHD during mCTSIB.

Methods: Our sample included 10 control (mean age: 43.7y), 14 pHD (mean age: 46.38 y), and 10 mHD (mean age: 50.5 y). Subjects performed the mCTSIB: eyes open-firm surface; eyes closed-firm surface; eyes open-foam surface; and, eyes closed-foam surface. An accelerometer collected data in anteroposterior (AP) and mediolateral (ML) directions. Postural sway was assessed based on sway jerkiness, time-based, and frequency-based domains. To examine within-group differences across conditions, Friedman's ANOVA with multiple comparisons was used. To examine between-group differences and to identify metrics sensitive to pHD, Kruskal-Wallis test was used. **Results:** Sensory modulation of postural control differed significantly in all groups across sensory conditions as measured by sway jerkiness domain (jerk), time-based domain (total sway area, RMS sway, mean distance, and mean velocity), and frequency-based domain (frequency in AP (mHD) and in ML (all groups). Generally, the greatest decrements were observed during standing with eyes closed on foam for all groups. To maximize the potential in revealing postural deficits in pHD, between-group analysis focused on standing eyes closed-foam surface. Both pHD and mHD had significantly worse sway than controls in AP and ML directions based on jerk, all

time-based domain measures (except for mean velocity in ML direction), and one frequency-based domain measure (total power). Mean frequency was not a sensitive metric of postural deficit for HD.

Conclusions: Manipulation of sensory input during mCTSIB reveals postural control deficits in pHD and mHD. Metrics that are sensitive to pHD are jerk, several time-based domain measures, and total power; thus suggests multiple independent balance constructs may be impaired early in the course of HD.

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Admission Diagnoses and Eventual Discharge Dispositions for Hospitalized Huntington's Disease Patients: Results of a Nationwide Survey

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Objective: To better understand the causes of acute illness and its consequences for subsequent inpatient care in patients with Huntington's disease (HD).

Background: HD is a genetic neurodegenerative disorder that is slowly progressive and thus primarily managed in the outpatient setting. There is little understanding of the outcomes of hospitalization in patients with HD. Drawing from a large national database of patients hospitalized in the United States, this study sought to understand the causes and outcomes of hospitalization in this patient population.

Methods: The Nationwide Inpatient Sample (NIS) data sets from 2003 to 2013 were used to identify HD patient admissions based on presence of ICD-9-CM code 333.4 as well as the associated diagnoses of each admission. These cases were grouped by primary diagnosis as cause for admission based on Clinical Classification Software (CCS) codes. Patients were also stratified by known source of admission and subsequent discharge disposition. **Results:** From 2003 to 2013 as reported in the NIS, there were 6,913 patients with a diagnosis of HD in this analysis. Primary diagnoses on admission due to infectious and respiratory diagnoses were most common (20.5% and 18.2% respectively) with a large proportion of psychiatric diagnoses (12.9%) as well [table1]. 50.5% of all HD patient admissions had a discharge to either skilled nursing facility (SNF) or nursing home/long-term care facility (LTCF). Of all HD elective admissions, only 40.2% were discharged home or similar level of care [table2].

DXCCS Codes	N (%)	Description
Infection		
2	715 (10.3)	Septicemia
3-8, 76	47(0.5)	Other Infections
159	302 (4.4)	Urinary Tract Infection
246	51 (0.7)	Fever of Unknown Origin
238	152 (2.2)	Infectious Complication of Surgical Procedure
197	154 (2.2)	Skin and Subcutaneous Infections
Total	1421 (20.5)	
Respiratory		
122	405 (5.9)	Pneumonia
123	13 (0.2)	Influenza
125	27 (0.4)	Acute Bronchitis
127	80 (1.2)	Chronic Obstructive Pulmonary Disease
128	34 (0.5)	Asthma
129	572 (8.3)	Aspiration Pneumonia
131	126 (1.8)	Respiratory Failure
Total	1257 (18.2)	
Psychiatric		
657	490 (7.1)	Mood Disorders
659	216 (3.1)	Schizophrenia and other Psychotic Disorders
653	63 (0.9)	Delirium, Dementia, and other Cognitive Disorders
650-652, 654, 656, 658, 660 - 670	126 (1.8)	Other Psychiatric Disorders
Total	895(12.9)	
Trauma		
226	92 (1.3)	Hip Fracture
233	164 (2.4)	Intracranial Injury
225, 227-232, 234-236, 239, 244	255 (3.6)	Other Traumatic Injury
Metabolic		
55	187 (2.7)	Fluid and Electrolyte Disorders
Gastrointestinal		
153	103 (1.5)	Gastrointestinal Hemorrhage
155	98 (1.4)	Other Gastrointestinal Disorders
Total	201 (2.9)	
Neurologic		
109	97 (1.4)	Acute Cerebrovascular Disease
83	95 (1.4)	Epilepsy
Total	192 (2.7)	

 $\label{eq:table_table_table} \begin{array}{l} \textbf{Table 1} \mbox{ Most common admission diagnoses among patients with HD. DXCCS: Diagnosis Clinical Classification Software} \end{array}$

Sources of Admission	Routine	Transfer from	SNF/LTCF	Home	Died
		another hospital		Health	
Elective	40.80%	2.90%	40.20%	12.50%	2.50%
Transfer from Another Hospital	26.50%	2.90%	44.90%	14.70%	7.40%
ED	28.30%	2.50%	54.30%	10.30%	3.20%
SNF/LTCF	8.30%	0.00%	83.40%	2.00%	6.30%
Overall Discharge Disposition	31.20%	2.40%	50.50%	11.40%	3.40%

Table 2: Comparative discharge disposition based on the source of admission. HD: Huntington's Disease; SNF: Skilled Nursing Facility; LTCF: Long Term Care Facility; ED: Emergency Department.

Conclusions: Despite its slow progression, HD remains a highly morbid condition, prone to multiple complications often leading to hospitalization. Primary reasons for admission are more likely to be medical than neuropsychiatric. Despite this, hospitalization of HD patients is very likely to result in discharge to SNF/LTCF. Compared to a prior examination of these trends from 1996 to 2002, there are higher rates of hospitalization resulting in long term care placement, though slightly decreased mortality in the current sample[1]. This study reinforces the need for better
understanding of factors leading to hospitalization of HD patients and also design better measures to delay or prevent LTCF placement and improve overall quality of life.

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Depression among Inpatients with Huntington's Disease: Patient Characteristics and Outcomes

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Objective: To better understand the relationship between Huntington's disease and depression. **Background:** Huntington's disease (HD) is an uncommon genetic neurodegenerative disorder in the United States that is frequently characterized by significant psychiatric and behavioral comorbidities, including depression. Drawing from a large database of patients hospitalized with HD, the current study provides a preliminary comparison of patients with and without a comorbid diagnosis of depression in terms of key demographic, length of stay (LOS), cost and discharge disposition.

Methods: The National Inpatient Sample database was queried for the period of 2003-2013 for patients discharged with a diagnosis of HD, ICD-9 Code 333.4. HD patients with comorbid depression were identified using Agency of Healthcare Research and Quality (AHRQ) criteria. We compared age, LOS, total hospital charges between HD patients with and without depression, as well as association between depression and patient race, sex, and discharge/disposition status.

Results: From 2003-2013, a total of 159,329 HD patient discharges were identified. Analyses revealed that 18.8% of the sample met criteria for depression. Comorbid depression was associated with more advanced age (mean 56.45 years versus 55.14 years, p=0.002), female gender (20.3% versus 17.1%, p<0.001) decreased length of stay (6.36 days versus 8.05 days, p<0.001) and lower total cost of admission (32,059 versus 37,159 p=0.011). However, HD with comorbid depression was associated with lower rates of being discharged home (28.2% versus 31.7%, p=0.001). Of HD patients with depression, 55.8% were discharged to a Skilled Nursing Facility (SNF) while only 49.8% of those without depression went to a SNF (p=0.001). [table1]

	Depression	No Depression	P Value
Age (mean, in years)	56.45	55.14	0.002
Race			<0.001
Caucasian	20.4%	79.6%	
African American	11.4%	88.6	
Hispanic	12.0%	88.0%	
Asian	12.1%	87.9%	
Other	19.8%	80.2%	
Gender			<0.001
Female	20.3%	79.7%	
Male	17.1%	82.9%	
Length of stay (days)	6.36	8.05	< 0.001
Total Charges (dollars)	32,059	37,159	0.011
Patient Disposition			0.001
Routine (Home)	28.2%	31.7%	
Short-term Hospital	2.6%	2.2%	
Skilled Nursing Facility	55.8%	49.8%	
Home Health Care	9.7%	11.9%	
Against Medical Advice	1.0%	0.8%	
Died	2.6%	3.4%	

Table 1. Characteristics of HD patients based on existent diagnosis of depression.

Conclusions: These results demonstrate that depression is a significant comorbidity in HD patients. Current findings point to race and gender disparities in HD patients diagnosed with depression. The presence of depression also correlated interestingly with decreased length of stay and lower cost to the patient, but with disposition to a higher acuity of care than patients without depression. While more rapidly discharged, these patients may have worse levels

of function hence require higher levels of care. Further research is warranted to delineate the true impact of depression on HD patients.

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Skin nerve phosphorylated a-synuclein deposits in idiopathic REM sleep behavior disorder

E. Antelmi, V. Donadio, G. Plazzi, R. Liguori (Bologna, Italy)

Objective: Here we tested if p-syn deposits can be detected with the same approach in patients affected with idiopathic RBD (iRBD), as an early histopathological marker of impending synucleinopathy.

Background: Searching for phosphorylated a-synuclein (p-syn) deposits by means of skin biopsy has been reported to be an extremely sensitive method in Parkinson's disease.

Methods: Proximal (cervical) and distal (legs) samples of skin biopsy have been obtained in 12 patients with polysomnographic-confirmed iRBD and 55 sex and age-matched healthy controls (HC). P-syn deposits were assessed by a monoclonal antibody against phosphorylated a-synuclein at Serine 129, disclosed by an immunofluorescence method. Patients underwent also an extensive work-up in order to search for non-motor symptoms and neuroimaging findings usually associated with impending neurodegeneration and to exclude subtle motor or cognitive signs.

Results: P-syn deposits were detected in 9 (75%) out of 12 patients affected with iRBD and none of the HC. In iRBD, p-syn deposits showed a rostro-caudal gradient of sensitivity, with the highest positivity at the cervical site (67%) and the lowest one at the leg site (58%).

Conclusions: Our preliminary findings suggest that skin biopsy in patients with iRBD might be a safe and sensible procedure in order to detect p-syn deposits in the pre-motor stage of synucleinopaties.

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Longitudinal study of freezing of gait in patients with Parkinson's disease

M. Sawada, K. Wada-Isoe, S. Tagashira, K. Nakashima (Tottori, Japan)

Objective: We conducted a prospective hospital based cohort study to investigate the incidence of Freezing of gait (FOG) and variables associated with onset of FOG in Japanese Parkinson's disease (PD) patients.

Background: FOG is one of the motor symptoms that disable and affect the quality of life of PD patients. There have been few studies examining the longitudinal course of FOG in PD patients.

Methods: 133 idiopathic PD patients were enrolled at baseline evaluation and followed prospectively over one year. The Japanese version of New Freezing of Gait Questionnaire (NFOG-Q) was administered to evaluate FOG, which has a cutoff for a gait freezer at =1 points. Hoehn-Yahr stage (HY stage), Unified Parkinson's Disease Rating Scale (UPDRS) part 3, Levodopa equivalent daily dose (LEDD), cognitive function including the Mini Mental State Examination (MMSE), the Japanese version of Montreal Cognitive Assessment (MoCA-J) and the Frontal Assessment Battery (FAB), and non-motor symptoms including depression, apathy, fatigue and sleep disorders were also assessed.

Results: At baseline, 77 patients (57%) had FOG with a mean age of the freezer of 69.9 (SD: 9.2) years, mean disease duration of 7.5 (5. 6) years and a mean HY stage of 2.4(0.87). At the follow-up evaluation (mean follow-up duration was 12.7 (2.8) months), prevalence of FOG increased to 62% of patients. Twelve patients who were non-freezer at baseline developed FOG (incident freezer), while six patients who were freezers at baseline became non-freezers. Compared to the non-freezer group, the age at evaluation was significantly higher and the FAB score at baseline was significantly lower in the incident freezer group. There were no significant differences in UPDRS part 3 and HY stage at baseline between the two groups. At the follow-up evaluation, the scores of UPDRS part 3 and HY stage were significantly higher in the incident freezer group compared to the non-freezer group. While the tremor sub-score of UPDRS did not change, the sub-scores of bradykinesia, rigidity and postural instability gait difficulty (PIGD) were significantly worsened in the incident freezer group.

Conclusions: Although the etiology of FOG in PD remains uncertain, our study indicates that in addition to frontal lobe dysfunction, motor exacerbation may contribute to the occurrence of FOG in PD patients.

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Axial signs in early-stage Parkinson's disease: an influence of the genotype?

G. Baille, D. Devos, V. Huin, T. Perez, B. Sablonniere, L. Defebvre, C. Moreau (Chru Lille, France) **Objective:** To assess the association between the genotype and the axial signs.

Background: Regarding the onset of axial signs in Parkinson's disease (PD), heterogeneity has been highlighted. In fact, in early-onset PD patients dysarthria, swallowing disturbance and respiratory muscles dysfunction can be observed. Due to their impact on the outcome and quality of life, evidencing risk factors of these symptoms is essential to optimize the follow-up of our patients.

Methods: MAPT haplotypes and COMT polymorphism were tested in 31 PD patients (mean age= 61.4 years ± 6.5) of the Prodigy-Park 1 cohort with a mean disease duration of 1.1 years (± 1.1). Neurological, swallowing and voice and pulmonary function testing evaluations were performed.

Results: A valine homozygous polymorphism (n=11) was associated with a significantly higher sniff nasal inspiratory pressure (SNIP) in comparison with methionine homozygous (n=7) and heterozygous polymorphism (n=13) (78% \pm 14.2 vs. 60.9% \pm 19.8 - p=0.02). Regarding MAPT gene, patients with a H1/H1 haplotype (n=21) had a significantly higher severity of their dysarthria assessed by a French adaptation of the Frenchay Dysarthria Assessment (4 \pm 2.7 vs. 1.4 \pm 2.2 - p=0.02).

Conclusions: The onset of dysarthria or inspiratory muscle weakness might be associated with the genotype. Dopamine might impact on the ventilatory function and MAPT H1 haplotype could lead to a pseudobulbar palsy. We need to be confirmed these results in a larger cohort to assess the influence of MAPT haplotypes or COMT polymorphism in the other features of the axial signs (such as the swallowing disturbance).

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Increased and symmetric expression of rigidity in early Parkinson's disease with abnormal REM sleep without atonia

M. Petrucci, S. Amundsen Huffmaster, C. Lu, P. Tuite, M. Howell, C. MacKinnon (Minneapolis, MN, USA) **Objective:** The purpose of this study was to compare the level and bilateral expression of upper arm rigidity between people with early stage Parkinson's disease (PD) with and without abnormal elevation of rapid eye movement (REM) sleep without atonia (RSWA).

Background: People with PD and REM sleep behavior disorder (characterized by increased RSWA) typically present with an akinetic-rigid subtype of disease, are less responsive to medications, and may have faster disease progression (Postuma et al. 2008). This study tested the hypothesis that earlier and more extensive degeneration in nigrostriatal and brainstem systems may be expressed by worsening and increased asymmetry of rigidity.

Methods: Clinical (MDS-UPDRS) and quantitative assessments of rigidity were obtained in 15 individuals with PD with either abnormally increased (RSWA+) or normative (RSWA-) muscle tone during REM sleep (based on polysomnogram). Quantitative measures of forearm rigidity were obtained using a robotic manipulandum that passively moved the forearm through a 80 deg. sinusoidal trajectory about the pronation-supination axis. Two movement frequencies (1.0 and 1.5 Hz) and resistance conditions (passive and active facilitation during contralateral forearm tapping) were tested. Two-way repeated measures ANOVAs were performed to test differences between groups and sides (more vs. less-affected) in both resistance conditions and movement frequencies.

Results: There were significant (p < 0.05) main effects of group and side x group interaction effects. Post hoc analysis showed that rigidity was significantly increased in the RSWA+ vs. RSWA- groups. Interactions effects showed that rigidity was reduced on the less-affected compared with the more-affected side in the RSWA- group (consistent with asymmetric presentation of disease), but the rigidity in the RSWA+ group was similar across both sides.

Conclusions: These findings suggest that not only is rigidity increased in people with early stage PD and abnormal RSWA, but abnormal tone is present more symmetrically. The bilateral disruption of muscle tone regulation in both REM sleep and normal waking suggests brainstem involvement in both symptoms.

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The nature of postural tremor in Parkinson's disease

M. Dirkx, H. Zach, M. Hallet, R. Helmich (Nijmegen, Netherlands)

Objective: To identify dopaminergic mechanisms underlying postural tremor in Parkinson's disease.

Background: Parkinson's tremor classically occurs at rest, but many patients also have a postural tremor. The nature of postural tremor, which is clinically diverse, remains unclear: besides re-emergent tremor, postural tremor may reflect co-occurring essential tremor, enhanced physiological tremor, or dystonic tremor.

Methods: We used electrophysiology and clinical assessments in 74 tremor-dominant Parkinson's patients, both OFF-medication and after levodopa-benserazide 200/50 mg. First, we divided patients into four groups based on two orthogonal criteria: (1) presence/absence of a 1.5 Hz frequency difference with rest tremor; (2) presence/absence of

tremor suppression upon posturing (Figure 1 & 2). Second, across groups we tested for levodopa-induced tremor reduction and for an association with clinical features.

Results: Of 60/74 (81%) patients with postural tremor, 68% had re-emergent tremor (amplitude suppression, frequency difference <1.5 Hz) and 12% had pure postural tremor (no amplitude suppression, frequency difference >1.5 Hz); 20% had "in-between" tremor (Figure 2 & 3). Levodopa reduced re-emergent tremor, but not pure postural tremor (Figure 4A). The dopamine response of the in-between groups was binomially distributed, indicating two underlying phenotypes. The power and dopamine response of re-emergent and resting tremor were highly correlated (Figure 4B & C). Pure postural tremor was not associated with signs of essential tremor or dystonia, and was not influenced by weighing.





Conclusions: Postural tremor in Parkinson's disease can be divided into two phenotypes. Re-emergent tremor is continued resting tremor during stable posturing ("tremor of stability") and has a dopaminergic basis. Pure postural tremor has a central origin and is inherent to Parkinson's disease, but has a non-dopaminergic basis.

Does cerebellar dysfunction contribute to tremor in Parkinson's disease?

E. Batzianouli, M. Pagliaro, D. Benninger (Lausanne, Switzerland)

Objective: This study aims to investigate the potential role of cerebellar dysfunction in the pathogenesis of tremor in Parkinson's disease (PD).

Background: Rest tremor in Parkinson's disease (PD) is disabling and responds often incompletely to conventional therapy. The pathogenesis remains largely unknown. Functional imaging, neurophysiology and structural studies, and stereotactic surgery point to an involvement of the cerebellum and the cerebello-thalamo-cortical pathway, but the precise nature remains unknown. These functional changes in the cerebellum may include pathological and compensatory mechanisms.

Methods: Cerebellar function can be tested by the eyeblink classical conditioning (EBCC), a form of associative motor learning, which depends on the integrity of the cerebellum and the olivo-cerebellar circuit. Fifteen PD patients with tremor (PD+tremor) and fifteen without (PD-tremor) were investigated compared to age-matched healthy controls. We assessed the associative motor learning in a delayed classical conditioning paradigm.

Results: Our findings suggest an impaired EBCC both in the PD-tremor and PD+tremor compared to healthy controls, which do not differ regarding tremor. The rate of associative motor learning ranges widely from being preserved to complete abolition which appears to correlate rather with the disease progression.

Conclusions: There is an impaired associative motor learning in PD suggesting a potential cerebellar dysfunction, which does not contribute to tremor pathogenesis. This cerebellar dysfunction may progress along with the neurodegenerative process in PD, which needs to be further explored.

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Modeling Parkinson's disease pathology by combined injection of fibrilar and monomeric a-synuclein in rat brain

P. Thakur, L. Breger, M. Lundblad, O. Wan, B. Mattsson, K. Luk, V. Lee, J. Trojanowski, A. Björklund (Frankfurt, Germany)

Objective: Development of a fast and progressive Parkinson's disease (PD) model in rat.

Background: a-Synuclein is a common link between sporadic and familial PD. Rodent PD models based on asynuclein overexpression have been extremely helpful in elucidating the molecular pathology of disease. However, most of these models are extremely slow to develop and require unrealistically high amounts of a-synuclein to elicit disease features.

Methods: Female SD rats were injected with a low dose of AAV6-a-syn in substantia nigra (SN) to express monomeric a-synuclein. After 4 weeks, when the a-synuclein is fully expressed, sonicated pre formed fibrils of a-synuclein were injected in same spot. Some rats received either fibrils or AAV6-a-syn only. These rats were histologically evaluated at 3, 12 and 24 weeks post fibril injection.

Results: Fibrils and AAV6-a-syn alone group showed only 10-30% loss of TH positive cells in SN at 3 and 12 weeks. It took either of them 24 weeks to escalate this loss to 50%. However, the combination significantly accelerated this cell loss displaying 55% decrease in just 3 week. Further worsening of this cell loss was relatively slower and reached around 65% after 24 weeks. In contrast, TH fiber density in striatum decreased more gradually changing from 60% at 3 weeks to 40% at 24 weeks in the combination group. Similar to cell loss, fiber density loss was much slower in the fibrils or AAV6-a-syn alone groups. Further, a large number of neurons in the combination group expressed phosphorylated a-synuclein (p-syn), which is a marker for aggregated a-synuclein. These aggregates were dense, mature and spread through the nucleus, cytoplasm and dendrites at all time points. In comparison, AAV6-a-syn only group displayed diffuse cytoplasmic occurrence and small puncta in nucleus. Fibrils only group displayed far fewer aggregates occurring mostly in cytoplasm. This combination also elicited neuroinflammation, causing 2-fold increase in the number IBA-1 positive glial cells, which was not observed in other groups.

Conclusions: Ability of fibrils seeds to nucleate the aggregation of monomeric a-synuclein enhanced the pathological process both in time and intensity. Activation of neuroinflammation could be the additional mechanism acting to enhance pathology.

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Information transfer between subthalamic area and forearm muscles during tonic muscle activity in Parkinson's patients

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Objective: We compare information transfer between forearm muscles and two subthalamic regions, namely the subthalamic nucleus (STN) and the zona incerta (ZI), during an isometric hold condition in Parkinson's patients. **Background:** For Parkinson's patients, more causalities have been found for connections from electromyographic activity (EMG) of forearm muscles to STN local field potentials (LFP) than in the opposite direction (Florin et al., 2010). However, since a linear technique derived from Granger causality was used, we speculate that nonlinear techniques might capture a slightly different picture of information transfer between the subthalamic area (SA) and forearm muscles. It has been shown that the posterior SA, including the ZI might be a better target for deep brain stimulation (DBS) than the STN (Plaha et al., 2006). Therefore, we hypothesize that information transfer between ZI and forearm muscles might be more pronounced and modulated to a stronger degree by voluntary movement than between STN and forearm muscles.

Methods: Transfer entropy was used to capture information transfer and quantify information transmission delays between three different contralateral forearm muscles and either STN or ZI. TE is a nonlinear, model-free implementation of Wiener-Granger causality. We included 19 akinetic-rigid Parkinson's patients in this study. At two recording heights, namely 5-6 mm dorsal of the STN and within the STN, at least 20 sec of LFP and EMG activity, during a tonic hold condition of the contralateral forearm, followed by at least 30 sec of a rest condition were measured. Data was preprocessed offline using a low-pass filter at 320 Hz and a high-pass filter at 2 Hz. **Results:** For LFP recorded in the ZI, we found a bidirectional significant increase of causalities from the rest to the hold condition. During rest and independent of the direction, more causalities were found between STN and muscles than between ZI and muscles. Only at rest, interaction delays from muscles to LFP were significantly shorter than in the opposite direction.

Conclusions: Using nonlinear techniques, our results indicate a more distinct role of the ZI in voluntary movement modulation than of STN, which might explain better therapy effects observed when stimulating this area. Interaction delays for afferent connections to the SA indicate direct proprioceptive feedback, which is in line with previous findings.

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Potential of non-invasive brain stimulation to ameliorate freezing of gait in Parkinson's disease: A deep repetitive TMS randomized, double-blinded, cross-over pilot study

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Objective: To investigate the impact of deep transcranial magnetic stimulation (TMS) of the medial prefrontal cortex (mPFC) on freezing of gait (FOG) in Parkinson's disease (PD).

Background: FOG is common among patients with advanced PD and is often unresponsive to medications. FOG is frequently triggered during task switching (e.g., gait initiation, turns), processes which have been linked to the mPFC.

Methods: Nine PD patients participated in this pilot study. We applied real and sham deep repetitive TMS using an H3 coil at 10?Hz, over the mPFC. Each patient was assessed before and after 4 weeks of intensive stimulation (3 sessions per week) and 4 weeks of maintenance (once a week) of real and sham TMS. The primary outcome was the score on a FOG-provoking test. The secondary outcomes consisted of the UPDRS-III, the freezing of gait questionnaire (FOG-Q) and spatiotemporal gait parameters. All testing were conducted in the "on" state. **Results:** Scores on the FOG-provoking test improved significantly ($?=-4.14\pm3.98$; p=0.027) after the intensive real TMS treatment; the gains persisted after the maintenance treatment ($2=-6.00\pm6.66$; p=0.046). The UPDRS-III also improved after real-intensive treatment (?=-7.86±6.54; p=0.028), however this effect was not maintained. Conversely, scores on the FOG-provoking test and the motor part of the UPDRS were not significantly affected by the sham treatment. Gait speed variability was reduced from $8.37\pm3.59\%$ at baseline to $5.25\pm1.05\%$ after real treatment (p=0.028). Similarly, stride length variability decreased from $7.46\pm4.35\%$ at baseline to $4.46\pm1.00\%$ after real treatment (p=0.046); step time variability decreased from $6.20\pm1.92\%$ to $4.69\pm1.25\%$ after real treatment (p=0.028) and swing time variability decreased from $8.87\pm2.88\%$ to $5.99\pm1.85\%$ (p=0.028). In contrast, no significant differences were found after the sham stimulation, p>0.05. The FOG-Q scores did not improve. Due to unexpected arm movement and pain during treatment, two patients dropped out and eventually the study was halted. **Conclusions:** This study provides initial cause-and-effect evidence of the role of the PFC in FOG in PD using TMS. Due to the small sample size and subject pain, the findings should be interpreted with caution. Future work and other non-invasive brain stimulation techniques are needed.

Neuroinflammation in the substantia nigra is triggered by synucleinopathy and precedes nigral degeneration *M. Duffy, T. Collier, K. Luk, M. Tansey, K. Paumier, D. Fischer, N. Polinski, C. Kemp, C. Sortwell (Grand Rapids, MI, USA)*

Objective: To determine the relationship between synucleinopathy, neuroinflammation and nigrostriatal degeneration using the rat a-syn PFF model.

Background: No therapy exists to halt or slow nigrostriatal degeneration in Parkinson's disease (PD). Neuroinflammatory markers are observed in *post mortem* PD brains, and longitudinal PET imaging reveals early microglial activation in the basal ganglia of PD patients. However, whether microglial-mediated neuroinflammation acts as a *contributor* to dopamine (DA) neuron loss or manifests as a *consequence of* nigrostriatal degeneration is debated. Our lab recently characterized a rat model in which intrastriatal injection of alpha-synuclein (a-syn) preformed fibrils (PFF) seed endogenous a-syn conversion into a pathological hyperphosphorylated form resulting in widespread, Lewy-body like pathology and ~40% nigral dopamine neuron degeneration over six months. **Methods:** Male Fischer 344 rats received unilateral intrastriatal injections of mouse a-syn PFFs or vehicle. Cohorts of rats (total n= 96) were euthanized at monthly intervals up to six months. Outcome measures at each time point include quantification of nigral dopamine neurons, phosphorylated a-syn (pS129) aggregates, microglial density (Iba-1) and major histocompatibility complex-II (MHC-II) antigen-presenting microglia.

Results: Significantly higher numbers of MHC-II-immunoreactive microglia were observed in the substantia nigra (SN) of a-syn PFF-injected rats compared to control rats, indicating that the neuroinflammation observed is pSyn inclusion-specific and not related to injection damage. Nigral MHC-II immunoreactivity peaked when: 1) phosphorylated a-syn accumulations were most abundant and 2) dopaminergic neurons began to lose their phenotype, events that occur prior to overt degeneration.

Conclusions: These results suggest that pathological a-syn accumulation drives microglia-associated neuroinflammation prior to overt nigral degeneration and may serve as a contributor to nigral degeneration in PD. Future studies aimed at identifying specific inflammatory mediators will lead to greater understanding of the relationship of neuroinflammation to pathological a-syn misfolding and may identify future therapeutic targets for intervention

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Characterizing the Bcl-2 Associated Athanogene 5 Interactome

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Objective: Characterizing the Bcl-2 Associated Athanogene 5 (BAG5) interactome will uncover the molecular pathways with which BAG5 associates and further elucidate its role in dopaminergic neurodegeneration. **Background:** Monogenic PD is caused by heritable mutations to the genes encoding proteins such as a-synuclein, LRRK2, PINK1 and Parkin. BAG5 has been shown to interact with several of these proteins and to enhance protein aggregation and neurodegeneration in the substantia nigra. The pathological effect of BAG5 is thought to be due to its inhibitory effect on the chaperone proteins Hsp70 and CHIP, which normally antagonize protein aggregation. However, BAG5 may also contribute to neurodegeneration by modulating the cellular processes responsible for maintaining mitochondrial health: a function independent of its association with Hsp70. The precise role of BAG5 in the pathobiology of PD is still unclear.

Methods: The BAG5 interactome was characterized by immunoprecipitating BAG5 from a tetracycline inducible SH-SY5Y stable cell line and identifying co-immunoprecipitated proteins via mass spectrometry. To minimize the effects of random genomic integration, the BAG5 transgene was inserted into the AAVS1 genomic safe harbor. To assess which BAG5 interactions are dependent on its association with Hsp70, the same procedure was performed with a mutated form of BAG5 [BAG5(mut)] incapable of binding Hsp70. The relative affinity of interacting proteins for either BAG5 or BAG5(mut) was gauged using isobaric tags.

Results: The interactome analysis revealed 288 high confidence BAG5 interacting proteins, including a-synuclein, LRRK2 and several other proteins commonly mutated in familial PD. Both Hsp70 and CHIP were found to preferentially associate with BAG5 relative to BAG5(mut), which was expected based on previous reports. GO term enrichment and KEGG pathway analysis revealed that BAG5 is associated with a number of diverse cellular processes including mRNA processing in the nucleus, microtubule dynamics and response to misfolded proteins. **Conclusions:** This characterization of the BAG5 interactome validated previously known PD relevant BAG5-protein interactions and revealed novel interactions that may be important for further investigation into the molecular mechanisms of PD.

Neuroprotective Potency of Tetrahydroisoquinoline a Novel Ayurveda Molecule in Experimental Parkinson's Disease

R. Banerjee, D. Nthenge-Ngumbau, R. Singh, P. Jaisankar, K. Mohanakumar, S. Biswas (Kolkata, India) **Objective:** Tetrahydroisoquinoline (TIQ) an identified alkaloid from ancient Indian '*Ayurveda*' medicine for Parkinson's disease (PD) was tested for neuroprotection in a cellular system and a preclinical mouse PD model. **Background:** PD treatment remains symptomatic with disabling side-effects. *Ayurveda* describes treatment for '*Kampavata*' or PD and novel herbal molecules might be neuroprotective.

Methods: Co-cultures of murine neuronal (Neuro2a), microglial (EOC20) and astrocytic (C8D30) cells were challenged with MPP+ a potent dopaminergic neurotoxin. TIQ (0.1-10 μ M) incubated for 24 h post-MPP+ were subjected to MTT cell viability or Live Dead assays. Neuro2a cells, dbcAMP-differentiated to dopamine neurons were cultured in indirect contact with astrocytes and microglia through inserts. Mitochondrial superoxide radical accumulation in dopaminergic neurons was determined by MitoSOX dye flow cytometry. Adult C57/BL6 mice were acutely intoxicated with the MPTP parkinsonian neurotoxin (16 mg/kg dose, 4 times at 2 h intervals) and TIQ was gavaged (200 mg/kg body weight, bi-daily) for 7 days post MPTP intoxication. Control mice were PBS injected or fed with TIQ alone. Striatal dopamine levels on 7th day post-MPTP were measured by HPLC electrochemical detection. Striatal tyrosine hydroxylase (TH) enzyme expression was assayed by immunoblotting.

Results: *In vitro*, TIQ (10 μ M) treatment significantly attenuated MPP+-induced loss of total cell viability. Live Dead Assay confirmed a significant (37%) increase in the number of live (Calcein AM-positive) differentiated neurons compared to MPP+ alone incubated for 24 h. Further, MPP+-induced mitochondrial accumulation of toxic superoxide radicals in dopamine neurons was significantly reduced (30%) by TIQ (10 μ M). *In vivo*, TIQ ameliorated dopaminergic neurotoxicity in mice by causing a significant 16% increase in MPTP-induced striatal dopamine loss with 1.2-fold upregulation of the reduced expression of TH at the striatal terminals.

Conclusions: The anti-parkinsonian neuroprotective potential of TIQ is revealed in MPP+-exposed cell co-culture and in MPTP mice. TIQ protects through reduced toxic mitochondrial superoxide radicals, recovery of striatal dopamine levels and tyrosine hydroxylase expression. Molecular basis for TIQ's dopaminergic neuroprotection could translate into therapeutic benefit in PD patients.

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High-mobility group box 1 from astrocytes upregulates TH expression to maintain dopaminergic neurons via JNK pathway in human Parkinson's disease patients and MPTP induced mouse model

S.J. Kim, M.J. Ryu, J. Han, Y. Jang, J. Kim, M.J. Lee, I. Ryu, X. Ju, W. Chung, E. Oh, G.R. Kweon (Daejeon, Korea) **Objective:** Supporting by glial cells could be reinforced the function of dopaminergic neurons against extracellular insults in Parkinson's disease (PD) development. However, we do not understand the molecular pathway that how they modulate the dopaminergic neurons via the actions of activated astrocytes and cytokines. We focused on the dopaminergic neurons and investigated underlying mechanism of tyrosine hydroxylase (TH) modulation in acute methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model.

Background: High-mobility group box 1 (HMGB1) can be actively secreted from inflammatory cells and is known to both promote inflammation and protect against disease propagation. Also, HMGB1 act as a mediator of neuroinflammation in subacute PD animal model.

Methods: Male C57Bl/6 mice were intraperitoneal injections of sterile saline or MPTP administered as 4 times injections of 20mg/kg at 2h intervals and were sacrificed at selected time points after the last injection (1, 3, 5 and 7 days). We measured by enzyme-linked immunosorbent assay (ELISA) that detects HMGB1 in human PD patient serum and U87MG cells (human a glioblastoma, astrocytoma cell line).

Results: The staining intensities of HMGB1 and Receptor for advanced glycation end product (RAGE) are higher in the nigral area of MPTP-treated mice, a toxin-induced PD like model, compared to saline-treated controls. HMGB1 was found to principally localize to astrocytes, and could affect the neighboring dopaminergic neurons, due to co-localization of RAGE with TH-positive cells. Treatment of a dopaminergic neuron cells with HMGB1

simultaneously induced JNK phosphorylation and TH mRNA expression. A JNK inhibitor was found to block the HMGB1-induced upregulation of TH expression.

Conclusions: Our results suggest that increased HMGB1 in astrocytes upregulates TH expression to maintain dopaminergic neuronal functions in acute MPTP mouse model. And HMGB1 could be a new research target for modulation of dopaminergic neurons.

Interaction between PLK2 (Polo-like kinase-2) and alpha-synuclein in the non-human primate MPTP model of Parkinson's disease

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Objective: The objective is to determine the levels and interactions between PLK2 and one of its main substrates, synuclein, in the non-human primate MPTP model of Parkinson's disease (PD)

Background: The molecular mechanisms leading to the loss of specific neuronal populations of dopaminergic cells have not been delineated yet in PD, but several pathogenic pathways have been identified. One of these pathways involves mitochondrial dysfunction and dysregulation of reactive oxygen species. Matsumoto and colleagues identified the PLK2 as a gene that is highly expressed in cells with defective respiration and increased oxidative stress. Furthermore, several studies have demonstrated that PLK2 can also phoshphorylate and promote selective autophagic clearance of synuclein (SCNA), the major component of Lewy bodies.

Methods: 15 *Macaca fascicularis* were included in the study. 10 monkeys received one weekly intravenous injection of MPTP until they developed bilateral parkinsonian features. Animals were sacrificed and perfused with saline buffer. Punches from the *Substantia Nigra* (SN) and cerebellum were collected. For quantitative analysis of PLK2 and SCNA gene expression, real time PCR was performed. Western blotting was performed using primary antibodies, against PLK2 and synuclein.

Results: In the SN of MPTP monkeys a 1.8-fold increase was observed in the PLK2 mRNA level related to untreated monkeys. Regarding SCNA expression, we found a decrease of mRNA levels nearly to 60% compared to untreated monkeys. Besides, both expression levels were negatively correlated (R=-0.76). In the cerebellum, no changes were detected and no correlation between the expression patterns was found (??Ct=0.56±0.12). To evaluate if these changes were only at RNA level, we also performed Western Blot analysis. In the SN, we found a decrease of 45% in alpha-synuclein protein levels of MPTP monkeys. A fold increase of 1,5 was found in PLK2 protein level. No changes in the cerebellum were found.

Conclusions: We demonstrate for the first time that an upregulation of PLK2 exists in the brain of MPTP-monkeys, and that this upregulation is only circumscribed to the SN. Furthermore, this upregulation correlates negatively with synuclein expression, confirming previous studies that suggested the selective autophagy clearance of synuclein by PLK2 and its role in PD pathophysiology.

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Impacts of CSF kynurenine pathway on neuroinflammaion in patients with Parkinson's disease

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Objective: To investigate the interaction between the KYN pathway and the neuroinflammation in PD. Background: In Parkinson's disease (PD), some pathologic mechanisms are reported such as mitochondrial dysfunction, inflammatory reaction and oxidative stress. Inflammatory cytokines are noticed as one of an important mediator of inflammatory reaction in the central nervous system (CNS). Kynurenine (KYN) pathway is also known to play an important role for degradation of oxidative stress in the CNS. Disproportion of KYN pathway can act neurotoxically and induce several neurological diseases including PD. In metabolites produced from this pathway, 3-hydroxykynurenine (3-HK) and quinolinic acid are as neurotoxic and kynurenic acid (KYNA) is neuroprotective. Methods: We could recruited 20 patients with PD (age; 57-80 y, median; 69.5 y) and 13 controls (age; 23-83 y, median; 75.0 y). Clinical severity was evaluated with Hoehn and Yahr staging. Samples of the cerebrospinal fluid (CSF) were obtained between 9:00 and 10:00AM after overnight bed-rest and before breakfast in PD patients. Control CSF were corrected from normal pregnant women on their lumbar anesthesia ante partum who had no neurologically abnormal condition confirmed by neurological examination and neuroimagings in advance. All CSF samples were promptly cryopreserved in a deep freezer (-80 ?). CSF levels of KYN or 3-HK were measured using with the high-performance liquid chromatography coupled with the electrochemical detector. CSF levels of IL-6, IL-16, TNF-a and IFN-? were also measures using with an ELISA. Statistical analysis was performed and the significance level was set at p < 0.05. This study was carried out after approval in our university ethical review board and written informed consents from all participants.

Results: CSF levels of KYN in PD and control were 22.6 to 90.3 nM (median; 49.0 nM) and 9.5 to 51.4 nM (30.5 nM), respectively. CFS levels of 3-HK were 0.2 to 13.3 nM (4.25 nM) and 0.001 to 3.96 nM (1.55 nM), respectively. These were significantly higher in PD than in control (p<0.05). These were still statistically significant after normalization to CSF levels of triptophan(p<0.05). There was a positive correlation between the CSF levels of 3-HK and TNF-a (r=0.54,p=0.055).

Conclusions: We could suggest that elevated CSF levels of KYN and 3-HK and positive correlation between 3-HK and TNF-a in patients with PD is associated with neuroinflammation in the CNS.

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Motor effects induced by D1- or D2-like receptor agonists in experimental parkinsonism

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Objective: We set out to compare movement patterns induced by systemic administration of l-dopa versus D1- or D2-class DA receptor agonists in mice with unilateral 6-OHDA lesions of the nigrostriatal pathway.

Background: Dopamine (DA) replacement therapy in Parkinson's disease (PD) is often initiated using DA receptor agonists, which are less dyskinesiogenic than l-dopa. Mice with unilateral 6-OHDA lesions are often used to discover new symptomatic or antidyskinetic treatments for PD, but the effects of DA agonists in this animal model have not been characterized.

Methods: Mice sustained unilateral 6-OHDA injections in the medial forebrain bundle, and were divided in three groups to receive treatment with increasing doses of skf38393, quinpirole, or 1-dopa. Abnormal involuntary movements (AIMs) were rated using a validated scale. Rotational, horizontal and vertical activity was evaluated using a videotracking system returning measurements of distance travelled, rearing events, rotations, and movement speed.

Results: An overall analysis of total axial, limb and orolingual (ALO) AIM scores revealed no major differences between the three treatments: ALO AIMs had increased in a dose-dependent manner. However, when different AIM subtypes were analyzed individually, we found that quinpirole had induced a dramatic increase in axial AIMs while markedly reducing horizontal and vertical activity. By contrast, skf38393 had mainly increased orofacial AIMs and induced a large increase in horizontal and vertical activity (with a similar effect magnitude to 1-dopa).

Conclusions: These results indicate that the pharmacological activation of D1 and D2 receptors activation produces strikingly different movement patterns in hemiparkinsonian mice. Their relative contribution to the genesis of dyskinesias may determine the choice of antidyskinetic treatment in the future.

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Targeted overexpression of A53T-alpha-synuclein induces progressive neurodegeneration and electrophysiological changes of noradrenergic locus coeruleus neurons – a preclinical model of Parkinson's disease

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Objective: In our present study, we developed a new mouse model to study the time dependent effects of cellular A53T-a-synuclein overexpression in the locus coeruleus, regarding the toxicity caused by a-synuclein accumulation, the alteration in electrophysiological properties and noradrenergic cell loss.

Background: Dysfunction of the noradrenergic locus coeruleus (LC) is an early hallmark of Parkinson's disease (PD). The extensive loss of noradrenergic LC neurons in PD is responsible for a large amount of non-motor symptoms that occur in early stages of the disease. However, the mechanisms that render LC neurons prone to a-synuclein accumulation and neurodegeneration are still unclear.

Methods: Serotype 1/2 recombinant adeno-associated viral vectors (rAAV) carrying the genome for A53T-asynuclein or luciferase were unilaterally injected in the right LC of C57Bl/6 wildtype mice to induce continuous protein overexpression. At 1, 3, 6 and 9 weeks post injection, eight animals overexpressing either A53T or luciferase were sacrificed for immunohistochemical analysis. In addition, four animals per group and timepoint were used to study the biophysical characteristics of LC neurons by patch-clamp recordings in acute brainstem slices. **Results:** We show, that targeted overexpression of A53T-a-synuclein in the LC of wildtype mice caused progressive a-synuclein accumulation and significant loss of noradrenergic LC neurons in the injected side in a time dependent manner, starting 3 weeks post-injection. Aggregated forms of a-synuclein were confirmed by Proteinase K resistance and Ser129 phosphorylation. Furthermore, overexpression of a-synuclein led to a progressive increase of astro- and microglia density in the injected LC region. In our model, neurodegeneration of LC cells was associated with significant changes of their electrophysiological properties. Time dependently, A53T-a-synuclein overexpression induced alterations in action potential shape and an acceleration of the pacemaking frequency. **Conclusions:** Our data indicate that overexpressed A53T-a-synuclein accumulates steadily in LC neurons, while simultaneously induces neuroinflammation and major changes in electrophysiological properties, which might be responsible for the observed cell death of LC neurons.

Increased bilirubin levels in Parkinson's disease from southern Spain

D. Macias Garcia, D. Macias Garcia, C. Mendez Barrio, S. Jesus, M.A. Labrador Espinosa, M. Bernal Escudero, L. Vargas Gonzalez, A. Adarmes Gomez, F. Carrillo, M. Carballo, P. Gómez-Garre, P. Mir (Seville, Spain) Objective: To evaluate serum bilirubin concentration in Parkinson's disease (PD) compared to healthy controls (HC) and to investigate its associations with motor and non-motor features in our population from southern Spain. Background: Oxidative stress is one of the main pathways studied in PD etiopathology and heme oxygenase (HO) is an important enzyme which regulates oxidative balance. HO converts heme molecules in carbon monoxide, iron and biliverdin/bilirubin and it is described HO upregulation in dopaminergic cells exposed to oxidative stress. Increased levels of bilirubin have been found in PD patients compared to controls and are interpreted as a consequence of oxidative enzymes overexpression in central nervous system.

Methods: We included 401 PD patients (48% males, 63 ± 12 years) and 309 HC (48% males, 58 ± 16 years), and total bilirubin plasma levels was measured. We excluded subjects on treatment with statins or chemotherapy, liver disease and hemolytic anemia. Demographic data were collected in both groups as well as clinical manifestations and complications of dopaminergic therapy in PD patients. We evaluated severity of PD with Hoehn & Yahr scale. To compare bilirubin levels between groups we analyzed data with binary logistic regression and multivariante analysis adjusted by age and gender. In PD group, bilirubin levels were also correlated with clinical characteristics. **Results:** Bilirubin levels were significantly higher in PD patients than HC subjects (PD: 0.58 ± 0.27 mg/dl, HC: 0.43 ± 0.2 mg/dl; p<0.005). In PD patients we demonstrated a negative correlation between bilirubin levels and Hoehn & Yahr stage (p<0.05) with increased levels in early stages of PD. We identified higher bilirubin levels in PD patients with dysphagia, falls and visual hallucinations (p<0.05) but no other significant differences were found regarding the clinical manifestations.

Conclusions: Increased bilirubin levels might be related to PD etiopathology as a serum biomarker of oxidative stress dysregulation. In early stages of disease, with lower Hoehn & Yahr stage, these higher levels might translate overexpression of oxidative enzymes.

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Exploratory Clinical study of role of cerebral dopamine neurotrophic factor (CDNF) mediating endoplasmic reticulum stress (ERS) in Parkinson's disease

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Objective: 1: To identify and measure endogenous CDNF levels in peripheral whole blood of healthy control subjects and to examine CNDF expression development profile across the life span of humans ; 2: To investigate differential CNDF mRNA expression in whole blood, platelets and lymphocytes and whether the changes in CNDF expression is specific for PD subjects.

Background: There is growing evidence for the neuroprotective and neurorestorative effects of CDNF secreted by the endoplasmic reticulum selective for dopamine (DA) neurons. CDNF modulate neuroinflamamtion, protein folding and mitigates excessive ER stress and faciliates alpha-synclein aggregates clearance. CDNF infusion rescues behavioral neural repair in PD.

Methods: Part 1)For characterizing CDNF development, we recruited three groups of healthy controls: 1) children (1-18 yrs : 2) adults (18-50 yrs); 3) elderly adults (> 50 yrs). Part 2) For PD subjects, we recruited PD subjects diagnosed by research neurologists, along with normal age-matched healthy subjects and stroke patients. Venous blood was collected, lymphocytes and platelets were isolated for RNA extraction for reversed transcriptase rRT-PCR assays for both Part 1 and part 2.

Results: We found a statistically significant (p < 0.05, one-way ANOVA ; Tukey ;posthoc test) decrease in CDNF mRNA expression in whole blood in the transition from the childhood/adolescence [n=7] to the yound adulthood [n=22], with progressive trend of significant decline in CDNF from childhood to elderly group [n=16 mean age 63 yrs] (p < 0.05), suggesting downregulation of CDNF mRNA expression with aging. We found that a significant increase in CDNF mRNA expression in PD patients [n=13 mean age: 72.8 yrs] compared with stroke patients [n=8 mean age: 71.5 yrs] and normal healthy control subjects [n=15, mean age: 66.8 yrs], as determined by one-way ANOVA (F(2,33)=4.89, p, 0.014) across the three groups. No significant difference was found in the lymphocytes. Whole blood CDNF mRNA was reduced in stroke patients compared with control but not for PD patients. **Conclusions:** Our findings of specific paradoxical increase in platelet CDNF mRNA expression for PD , and decline of CDNF mRNA with age, suggest compensatory CDNF to counteract ER stress may be the emerging potential therapeutic target in PD.

Listen to your heart: Ordinal pattern statistics reveal altered cardiac rhythm dynamics in LRRK2nonmanifesting carriers

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Objective: To assess the complexity of heart rate variability (HRV) dynamics in *LRRK2*-nonmanifesting carriers compared to healthy individuals.

Background: Cardiovascular autonomic dysfunction is an early feature of Parkinson's disease (PD) and manifests as a reduction in the magnitude and complexity of HRV. Dysautonomic symptoms have been reported in PD patients who carry the G2019S mutation in the *LRRK2* gene, although our previous work has found that HRV magnitude was not reduced in *LRRK2*-PD or in *LRRK2*-nonmanifesting carriers. However, no previous investigation has assessed the complexity of HRV in *LRRK2* G2019S mutation carriers.

Methods: Shannon entropy (ShE) and permutation entropy (PE), including ordinal patterns statistics (OPS), from 5 min cardiac interbeat interval series, were analyzed in 16 *LRRK2*-nonmanifesting carriers and 15 healthy individuals. For PE analysis different embedding dimensions (3-4) and time delays t (1-20) were considered. Differences between groups were assessed controlling for age, sex, and mean heart rate (HR). A forward stepwise discriminant analysis was carried out for estimating the classification functions based on OPS. Sensitivity (Se), specificity (Sp), and positive and negative predictive values (PPV and NPV, respectively) were calculated following a K-fold cross-validation strategy (k=10).

Results: There was no significant difference in PE or ShE between *LRRK2*-nonmanifesting carriers and healthy individuals. However, we observed a correlation between ShE and HR in *LRRK2*-nonmanifesting carriers such that ShE was significantly lower in those with a HR>65 bpm. This correlation was absent in healthy individuals. Furthermore, some OPS were significantly different between groups, especially those describing the HRV dynamics between 4-10 s or 0.1-0.3 Hz (t=4). A three-dimensional feature space discrimination, represented through the classification functions, reached 93.8% Se, 86.7% Sp, 88.2% PPV, and 92.9% NPV.

Conclusions: The dynamics of cardiac rhythm determined by both sympathetic and parasympathetic autonomic branches might be selectively altered in LRRK2-nonmanifesting carriers. Replication in larger and independent samples is required to elucidate the effectiveness of OPS for the detection of early perturbations in cardiac autonomic regulation in *LRRK2*-nonmanifesting carriers and prodromal PD.

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Beneficial and protective effects of withania Someniferais on mice brain: A therapeutic potential drug for Parkinson's disease

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Objective: Objective of our study was evaluate effect of Withania Someniferais leaves on Parkinson's brain of mice.

Background: Parkinson's disease (PD), an age-related disorder, is accompanied by the symptoms, tremor, bradykinesia, rigidity, stooped posture and instability. The disease progresses slowly and may ultimately produce complete akinesia. The neuropathology of the disease is based on the depigmentation and cell loss in the dopaminergic nigrostriatal tract of the brain with the corresponding decrease in the striatal dopamine concentration and the presence of eosinophilic inclusions called Lewy bodies. Withania Someniferais (WS) retard brain aging and help in regeneration of neural tissues besides producing antistress, adaptogenic and memory enhancing effect.

Methods: In present study 6-hydroxydopamine (6-OHDA) model of PD mice were used. The symptoms of PD such as tremors, akinesia, rigidity, catalepsy, and vacuous chewing movements (VCMs) were evaluated. The methanolic extract of WS was administered at doses of 200 mg and 500 mg/kg body weight followed by stress. The combination of L-dopa and carbidopa was used as a standard drug. Behavioral studies such as locomotor activity and grip strength were determined, and oxidative stress was evaluated in mice brain. ANOVA was used followed by post hoc Turkey test.

Results: Brain was used for biochemical and histopathological study. Animal exposed to stress showed significant decrease in Superoxide dismutase (SOD), Catalase (CAT), Glutathione (GSH) and total protein. This was accompanied by simultaneous increase in Thiobarbituric acid reactive substances - TBARS evel. Treatment with Withania Somenifera had no significant but moderate effect on antioxidant enzyme (SOD and CAT). Pretreatment with WS (200 and 500 mg/kg) significantly reduced the intensity of muscular rigidity, duration of catalepsy, akinesia, the number of tremors, and increase fighting behavior. The locomotor activity and grip strength were

significantly increased by WS. Treatment with WS significantly reduced LPO level and restored the defensive antioxidant enzymes SOD and CAT in mice brain.

Conclusions: Present study provides evidences that oral administration of alcoholic extract of WS leaves have shown anti-aging effect in stress.

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Parkinson's disease disrupts motor skill learning that requires improvement of a speed-accuracy trade-off *C. Kim, A. Zimnik, U. Kang, P. Mazzoni (New York, NY, USA)*

Objective: 1) To test whether PD reduces the ability to improve motor acuity (speed-accuracy trade-off performance) in goal-directed movements; 2) To examine the effect of PD on exploration during practice of these skilled movements.

Background: The striatum is thought to make specific and crucial contributions to certain types of motor skill learning, possibly due to dopamine's role in synaptic plasticity at corticostriatal synapses. Studies of motor skill learning in patients with Parkinson's disease (PD), a condition that reduces striatal dopamine, however, have yielded mixed results that depend on the motor task learned. Because of striatal dopamine's presumed role in driving exploration in reinforcement learning, we hypothesized that a specific type of motor learning that might be affected by PD should be motor skill learning that requires improvement in the speed-accuracy trade-off. This type of motor learning allows exploration of the balance between practicing faster and less accurately, vs. practicing slowly and more accurately.

Methods: Participants with PD in the operational off-medication state (PD group) and participants without neurologic or musculoskeletal disorders (CLT group) made wrist movements that guided a screen cursor through a semicircular arc channel (PMID 22514286) and obtained points for moving faster while keeping the cursor in the channel. Motor acuity was tested before and after practice in testing blocks that imposed matched speeds. Practice occurred in a separate block that allowed self-directed exploration of various speeds.

Results: PD subjects had the same accuracy as CTL in baseline testing, and practiced at similar speeds as CTL, but exhibited reduced motor skill learning, i.e. they achieved smaller gains of motor acuity after practice. They also exhibited less trial-to-trial variation of trajectories during practice.

Conclusions: PD disrupts motor skill learning that requires improvement in the speed-accuracy trade-off, independently of its effects on movement execution speed or accuracy. This disruption may be due to reduced trial-to-trial variation of movements during practice. Such a mechanisms would be consistent with a possible role of striatal dopamine in guiding exploration of movement parameters in the search for increased reward, analogously to dopamine's better-established role in reinforcement learning of simple behavioral choices.

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Inhibition of mitochondrial complex I synthesis by chloramphenicol mitigates dopaminergic neuronal cell loss in PQ-induced parkinsonism

S.J. Kim, J. Han, Y. Jang, J. Kim, M.J. Lee, I. Ryu, X. Ju, M.J. Ryu, W. Chung, J.Y. Heo (Daejeon, Korea) **Objective:** To find the potent drug for prevention of PD, we screened with above 1000 drugs in the PQ treated cells which currently used drug in clinics and hospitals. Among those drugs, chloramphenicol (CP) showed most powerful inhibitory effect.

Background: Paraquat (PQ), an herbicide regarding as an environmental factor for Parkinson's disease (PD) occurrence, induce dopaminergic neuronal loss via inhibition of mitochondrial complex I and III. Most patients of PQ-induced PD is affected by chronic exposure and need to preventional strategy for modulation of the disease progression.

Methods: We assessed the change of mitochondria complex expression using real time PCR, western blotting and immunohistochemistry in dopaminergic neuronal SN4741, mitochondrial DNA-depleted Rho cell and primary dopaminergic neuron . And to evaluate the function of mitochondria, we measured mitochondrial oxygen consumption rate using Seahorse bioscience XF24 analyzer. Also, we confirmed the ameliorate effect of CP in MPTP induced parkinson's disease mouse model.

Results: Administration of PQ after CP pretreatment has more increased cell viability in SN4741 cells and primary cultured dopaminergic neurons from rat than control group. Furthermore, reactive oxygen species (ROS) production with PQ treatment also reduced by CP pretreatment which imply the mitochondrial complex I as a target of CP. Decreased activity of mitochondrial complex I by reducing synthesis of ND1 protein with CP treatment lowered the PQ-recycling, which is mechanism of ROS production, resulting prevention of cell death and those CP effect did not

observed on the Rotenone pretreatment and Rho cells. Consistent with in vitro and ex vivo results, MPTP treated mice has also ameliorate the dopaminergic neuronal cell loss and glial reactivation with CP pretreatment. **Conclusions:** Our finding indicate that inhibitory action of mitochondrial complex I with CP treatment for protecting the dopaminergic neurons may provide a presentational strategy in prevention of neurotoxin induced PD.

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Alpha-synucleinopathy and mitochondrial dysfunction in a cell based model of neurodegeneration: Implications in the pathogenesis of sporadic Parkinson's disease

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Objective: To elucidate the role of a-synuclein, parkin and mitochondria in a cell-based model of neurodegeneration relevant to Parkinson's disease pathogenesis.

Background: The suggested mechanisms of PD pathogenesis have been deciphered using various experimental models, mainly the toxin-based models, which have questionable relevance in explaining the pathogenesis of sporadic PD. Thus, a model of neurodegeneration in cultured cells relevant to PD employing toxic effects of endogenous molecules like dopamine (DA) and iron would be relevant.

Methods: SHSY5Y neuroblastoma cells were treated with varying concentrations of iron (20-100 μ M) and dopamine (10 - 50 μ M) for a variable period of time. Cell death was assessed by trypan blue dye-exclusion test and lactate dehydrogenase release assays. The nature of cell death was analyzed by examining nuclear morphology after PI and Hoechst staining. Mitochondrial parameters were analyzed using JC-1 dye and ATP synthesis assays. a-Synuclein, parkin and Bax expressions were analyzed by Western blotting and qRT-PCR for mRNA. a-synuclein and parkin knockdown was carried out by using specific siRNA.

Results: Both DA and iron causes dose-dependent and time-dependent cell death.10 μ M DA over a period of 96 h produces nearly 40% cell death along with decreases of mitochondrial membrane potential and ATP synthesis but the degree of cell death by iron was much lower. However, similar intra-cellular accumulation of a-synuclein took place in both conditions. When parkin expression levels were compared between DA-treated and iron-treated cells, a significant increase of parkin expression were noticed after iron, but not DA exposure suggesting a protective action of parkin against dysfunctional mitochondria. We are currently verifying this protective role of parkin by knock-down experiments. The nature of cell death appears to be apoptosis and secondary necrosis. The involvement of Bax in DA or iron mediated cell death will also be explored.

Conclusions: The results strongly suggest that oxidative stress mediated by DA or iron can initiate neurodegeneration through the involvement of a-synuclein and mitochondria. Parkin may play a protective role against neurodegeneration by preventing dysfunction of mitochondria. An increased accumulation of a-synuclein and downregulation of parkin in sporadic PD brain have been documented.

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Anti-synuclein alpha antibodies and IL-1ß at Parkinson's disease (PD)

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Objective: Determine a correlation between the levels of anti-synuclein alpha antibodies and IL-1ß at serum and CSF of patients with PD.

Background: PD is a progressive neurodegenerative disorder with impact of immune reactions on the pathogenesis. Recent studies revealed that abnormal aggregation and accumulation of synuclein has implicated in PD development. Higher level of SNCA at plasma and lower concentration of SNCA at CSF than at healthy control were revealed at PD. IL-1ß plays an important role at regulation of immune and inflammatory responses. Methods: Serum and cerebrospinal fluids (CSF) were obtained from 31 patient with PD (M:F=0,94:1; age=63,7±10,3 SD) - main group (MG) and 8 subject (M:F=3:1; age= 64±8,2 SD) with planned minor surgical operations under peridural anesthesia (herniotomy or pelvic plastic) - control group (CG). Non-parametric methods of statistical analysis were used. Investigation was approved by local ethic committee. All subjects signed informed consent form before including in the study. Anti-synuclein alpha antibodies (SNCA) and IL-1ß concentration were determined using ELISA kits (Anti-SNCA Cloud-Clone Corp., US and Vector-Best, Russia, respectively). **Results:** Anti-synuclein alpha antibodies at serum were detected at all samples of MG and at 6 (75%) samples of CG. At CSF positive results were at 10 (32,3%) samples of MG and only at 1 (12,5%) sample of CG. IL-1ß was detected at all samples of both groups. Median levels of anti-synuclein alpha antibodies were at MG (serum - 5,06 ng/ml [2,82; 8,82], CSF - 0.0 ng/ml [0,0; 0,61] and at CG (serum - 3,29 ng/ml [0,34; 3,84], CSF - the single result was 0,61 ng/ml). Median levels of IL-1ß were at MG (serum – 2,04 pg/ml [1,65; 3,04], CSF – 2,48 pg/ml [2,09; 2,95] and at CG (serum – 2,68 pg/ml [2,1; 2,98], CSF – 2,97 pg/ml [2,42; 4,48]. Only difference for anti-synuclein

alpha antibodies at serum between MG and CG was statistically significant (Mann-Whitney test, p=0,02). No correlation was found between serum levels of anti-synuclein alpha antibodies and IL-1ß of MG with use of Spearman Rank Order Correlation (R=0,18, p=0,3).

Conclusions: The level of anti-synuclein alpha antibodies may be useful for the diagnose of PD. Level of antisynuclein alpha antibodies is not connected with non specific immune and inflammatory response.

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Admixing augments nigral dopaminergic correlates during development to impart resistance to MPTPtoxicity at adulthood

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Objective: Establish the developmental basis for varying nigral dopaminergic (DA) correlates in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) susceptible C57BL/6, MPTP resistant CD-1 and their resistant crossbred mice.

Background: Asian-Indians are less vulnerable to Parkinson's disease (PD) than the Caucasians. Interestingly their admixed population is at much lesser risk. Studying this phenomenon through mice strains with differential MPTP susceptibility revealed variations in nigral DA neuronal number along with other cytomorphological features in assigning resistance/susceptibility.^{1,2}

Methods: Postnatal day 2 (P2), P6, P10, P14, P18, P22 and adults of C57BL/6, CD-1 and their reciprocal crossbred mice were studied. Tyrosine hydroxylase (TH) immunostained midbrain sections were evaluated for nigral volume and DA neuronal number by planimetry and stereology, respectively. TH expression and the neuronal morphological development was examined, alongside overall nigral development.

Results: Nigral volume and DA numbers were lesser in C57BL/6 compared to CD-1 and the crossbreds at birth and remained so throughout the development. A significant increase in number and nigral volume was observed in all the strains till P14. However, a drastic fall was seen thereafter only in C57BL/6 before stabilising at adulthood. Interestingly, CD-1 and the crossbreds retained their numbers from P14 to stabilize with supernumerary DA neurons at adulthood. Neuronal size significantly increased from P2 to P10 and then attained their adult morphology in CD-1 and the crossbreds, whereas it continued to increase in C57BL/6, only to stabilize at P22. TH expression and nigra attained its adult architecture at P14 in CD-1 and the crossbreds, whereas at P22 in C57BL/6.

Conclusions: We provide the first unbiased stereological estimation of nigral DA number during postnatal development in mice. CD-1 and the crossbreds by birth acquire resilient cytomorphological features; evidenced by higher number of DA neurons at P2. Absence of neuronal loss in these strains after P14 as seen in C57BL/6 indicates lesser developmental cell death. Faster maturity of DA neurons and nigral architecture provide further evidence for superior developmental characteristics, which might render MPTP resistance at adulthood. This demonstrates that variable MPTP susceptibility and heterogeneity in PD pathogenesis may arise early during development.

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Dopamine substitution restores effective connectivity between prefrontal and premotor areas in Parkinson's disease

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Objective: To assess influences of dopamine deficiency on the causal interplay within the motor network during bimanual finger tapping in Parkinson's disease (PD) patients.

Background: Bimanual coordination relies on a complex orchestration of neuronal information within distinct brain areas, including supplementary motor area (SMA), lateral premotor cortex (IPM), primary motor area (M1) and prefrontal cortex (PFC) [1]. Disruption of functional integration of these areas due to dopamine deficiency is thought to underlie impaired motor control in PD [2]. Alterations of causal interplay within this network, however, remain to be elucidated.

Methods: 33 patients diagnosed with idiopathic PD and 32 age-matched controls performed complex bimanual tappings while a 128-channel EEG was recorded. PD patients completed variations of the task 12 hours post withdrawal of their regular dopaminergic medication and following the intake of a standardized dose of L-dopa. Behavioral data was analyzed with regard to error rates and performance time. Subsequently, dynamic causal modelling (DCM) for induced responses was employed to characterize changes of oscillatory coupling between predefined regions of interest. Coupling values were extracted and correlation analysis was performed to relate motor function with effective connectivity.

Results: Behavioural analysis revealed that PD patients off medication made more mistakes compared to healthy participants (PD Off: 42.9 % vs. Control: 29.4 %, p = 0.012), whereas no difference in error rates could be detected for patients in the On-state (PD On: 38.0 % vs. Control: 29.4 %, p = 0.098). Bayesian model selection favored a fully connected model in all groups. Second level analysis revealed no significant coupling between left PFC and premotor areas in the Off-state, whereas left PFC to left IPM coupling was present in the control. In the On-state, however, left PFC to left IPM and SMA coupling was present. Additionally, a significant negative correlation between left PFC to left IPM and SMA coupling with performance time was detected for PD On (Rho = - 0.600, p = 0.011).

Conclusions: Our results suggest that bimanual coordination as well as prefrontal to premotor coupling is affected in PD. Levodopa seems to restore effective connectivity between left PFC and premotor areas and the presence of this influence can be associated with better motor performance.

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Expression of late cell cycle markers in Parkinson's disease and Lewy body dementia

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Objective: The objective of this study is to determine the expression of late cell cycle markers in Parkinson's disease (PD) and Lewy Body Dementia (LBD)

Background: Mechanisms that initiate and cause PD and LBD neuronal death are not fully understood. Several studies have shown that degenerating neurons, under certain stress conditions, can activate the program that normally guides cells to mitotic division. In these post-mitotic cells, the re-entry into the cell cycle will not end with neuron replication but with the activation of unknown mechanisms that will trigger neuronal death. Several studies have described abnormal expression of cell cycle markers in degenerating neurons. Furthermore, evidence for a completed S phase in PD brain, raises the question of what factors are missing in the adult neurons that lead to neuronal death just before the neuron enters mitosis.

Methods: We examined 3 brains of PD, 3 brains of LBD and 3 controls brains. Sections from *Substantia Nigra* (*SN*), *locus coeruleus (LC)*, cerebellum, frontal and temporo-occipital cortex were immunostained using antibodies against PLK1 pSer 137, PLK1 pThr210, Aurora A, cyclin B and synuclein pSer 129. Double immunofluorescence techniques against the previous markers were performed. Interactions were analyzed using proximity ligation assays. **Results:** We examined the expression of Aurora A and PLK1. PLK1 is crucial to regulate mitotic entry. This event depends on Aurora-A phosphorylation of PLK1 Thr 210. Besides, dephosphorylation of PLK1 Ser-137 is required for execution of cytokinesis. PLK1 pSer 137 was upregulated in all the regions both in PD and LBD brain but no in controls. Immunoreactivity against PLK1 pThr210 was found only in the *LC* in the PD brains, and in the *LC*, cerebellum, frontal and occipital cortex in the LBD brain. No expression was found in controls. All neurons immunostained against Aurora A were also immunoreactive against PLK1 Thr-210. Cyclin B1 immunoreactivity was only circumscribed to the cytoplasm, indicating that these neurons are in a late G2 phase. Cyclin B1 immunoreactive.

Conclusions: This work describes for the first time the overexpression of two kinases involved in the G2/M transition, PLK1 and Aurora, whose over expression correlates with the severity of the pathology. These new PD targets could lead to the discovery of new pathways involved in neuronal death.

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Salivary alpha-synuclein in aging

G. Vivacqua, A. Fabbrini, A. Suppa, R. Mancinelli, G. Fabbrini, C. Colosimo, A. Berardelli (Rome, Italy) **Objective:** We measured alpha-synuclein total (a-syn_{total}) and alpha-synuclein oligomers (a-syn_{olig}) concentration in 70 healthy subjects, of different ages (from 18 to 88 years old) to detect if salivary a-syn concentration is influenced by aging.

Background: The pathological hallmark of PD is a-syn deposition leading to the formation of Lewy bodies. A-syn can be detected in biological fluids including saliva. A-syn_{olig} exerts a crucial neurotoxic effect in PD. In PD patients we detected lower salivary a-syn_{total} and higher a-syn_{olig} than healthy subjects. Previous studies have shown that a-syn neuronal aggregates increase during aging.

Methods: Subjects have been divided into 5 groups of 14 subjects each one. The I group includes subjects from 18 to 26 years old (YO), the II group includes subjects from 30 to 36 YO, the III subjects from 40 to 46 YO, the IV subjects from 50 to 65 YO and the V includes subjects from 70 to 88 YO. Samples of saliva were collected following the protocol reported in previous study (Vivacqua et al., 2016). ELISA analysis was performed using two

specific ELISA kits: SensoLyte 55550 for a-syn_{total} and MyBioSource MBS043824 for a-syn_{olig}. Statistical significance was evaluated by Mann-Whitney U test.

Results: No significative differences have been found in the concentration of $a-syn_{tot}$ and $a-syn_{olig}$ between the first four groups (p>0,05). The mean concentration of $a-syn_{olig}$ is respectively: 0,10±0,081 ng/ml in the I group, 0,17±0,13 ng/ml in the II group, 0,19±0,16 ng/ml in the III group and 0,14±0,14 ng/ml in the IV group. Salivary a-syn_{total} was significantly lower, whereas $a-syn_{olig}$ was significantly higher in the subjects of the V group confronting with the others (p<0,05). A-syn_{olig} concentration in the V group was 0,96±0,15 ng/ml. No significative correlations have been detected between a-syn concentration and age in the five groups.

Conclusions: In the subjects of the V group, decreased salivary concentration of $a-syn_{total}$ may reflect the reduction of a-syn monomers ($a-syn_{mon}$), leading to the formation of insoluble intracellular inclusions during aging process. This is supported by the increased concentration of $a-syn_{olig}$ in the same group. Moreover, the similar concentration of $a-syn_{olig}$ in PD patients and in aging healthy subjects suggests that measurement of a-syn in saliva might be a useful method for help the diagnosis of PD especially in the early stages of the disease.

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Neuroprotective effect of a-Mangostin in restoration mitochondrial function in MPTP-induced Parkinson's disease in mice

A. Prakash, A.B. Majeed, K. Ramasamy, M. Hasan (Baltimore, MD, USA)

Objective: The aim of the present study was to explore the protective effect of alpha-mangostin against mitochondrial oxidative stress in MPTP treated mice.

Background: It has been reported that mitochondrial oxidative stress plays a pivotal role in neurodegenerative disease like Parkinson's disease (PD). Recently, medicinal plant extracts acted as traditional, complementary and potential medicine for PD. Alpha-mangostin (AM) is the main xanthone purified from mangosteen known as anti-oxidative properties.

Methods: MPTP was administered repeatedly on 1st, 7th and 14th day intranigrally for the induction of PD in mice. AM (3 and 6mg/kg) and Selegiline (10 mg/kg) were given intraperitonially, after induction of PD for 14 days. Different behavioral performances were carried on 1st, 14th, 21st, 28th days and biochemical parameters were estimated on 28th day.

Results: Central administration of MPTP showed significant impairment of motor behavior and marked increase of mitochondria oxidative damage and neuro-inflammation in mice. However, post treatment with AM (3 and 6mg/kg) significantly and dose dependently improved the motor deficits and attenuated the oxidative damage indicating decreased rise of LPO and nitrite concentration and restored the decreased activities of endogenous antioxidant enzyme (Glutathione, Catalase, SOD) and mitochondria enzymes (NADPH dehydrogenase, Succinic dehydrogenase and cytochrome oxidase) as compared to selegiline effects. In addition AM also attenuates the pro-inflammatory cytokines like TNF-a and IL-ß in striatum region of MPTP induced PD in mice.

Conclusions: These results suggested that AM exhibit Neuroprotective effect by mediating brain antioxidant defense mechanism and by up regulating of dopaminergic pathway

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Eight contact LFP recordings in the subthalamic region localize beta source to the dorsal STN

I. Tamir, C. de Hemptinne, J. Ostrem, P. Starr (San Francisco, CA, USA)

Objective: The aim of this study was to investigate the electrophysiological characteristics of intra and extra STN LFPs in PD to better locate the source of these oscillations.

Background: Enhanced beta band oscillations and their entrainment of neuronal spiking are an electrophysiological hallmark of Parkinson's disease (PD). Beta band synchronization is modulated by both dopamine medications and DBS in a manner that correlates with clinical outcome. Although STN spiking activity and LFP recordings suggest that STN beta activity is most prominent in the dorsolateral STN, the LFP characteristics beyond the assumed borders of the STN remain unknown.

Methods: Eight PD patients were bilaterally implanted in 11 STNs with an 8 ring-contact DBS lead (Boston Scientific Corporation). Subcortical LFPs were recorded intra-operatively from each contact in the off medication-awake-rest-eyes open state. Each contact was localized relative to STN borders based on microelectrode recordings. The contact array covered ventral and dorsal STN, Zona Incerta (ZI) and lateral thalamus or white mater. Signals were sampled at 3 kHz, and referenced to the adjacent contact. Power spectral density was computed for each contact pair, averaged across multiple frequency bands (theta, delta, alpha, low beta, high beta and broadband gamma). Phase distributions of beta range band-pass filtered signals were computed for every contact pair.

Results: Oscillatory activity in the beta band was found in all contact pairs covering the dorsal STN. In 8/11 STNs, beta peak was bi-phasic, having one peak at low and the other at high beta range. Similar beta power was also found in the ventral STN. The phase of the filtered beta signal seemed to exclusively reverse across contacts located in dorsal, but not ventral STN. The contact pairs covering ZI had significantly lower beta power. Very low beta power was found in contacts that cover white matter or thalamus. Other frequency bands were not altered significantly, in terms of power, across contact pairs.

Conclusions: We found the largest beta power and phase-reversal of beta signals to be localized to the dorsal STN. These findings support the dorsal STN as the primary source of beta oscillations in the subthalamic region, and argue against the hypothesis that STN beta activity represents volume-conducted cortical activity.

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Phosphodiesterases and striatal pathways in Parkinson's disease

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Objective: To use phosphodiesterase (PDE)10A ([¹¹C]IMA107) and PDE4 ([¹¹C]Rolipram) positron emission tomography (PET) molecular imaging combined with diffusion tensor imaging (DTI) based probabilistic tractography to explore the expression of PDE10A and PDE4 in striatal output pathways in healthy controls and patients with Parkinson's disease (PD).

Background: PDE10A and PDE4 are enzymes hydrolysing cyclic nucleotides that play a critical role in modulating striatal neuron output and movement regulation. Preliminary human PET studies have demonstrated a loss of PDE10A and PDE4 in patients with movement disorders.

Methods: We studied 24 subjects (12 PD) who had [¹¹C] IMA107 and [¹¹C] Rolipram PET, and DTI scans. MIAKATTM was used to generate parametric images of [¹¹C] IMA107 nondisplaceable binding (BP_{ND}) and [¹¹C] Rolipram volume of distribution (V_T) from the dynamic PET data using the simplified reference tissue model and Logan plot, respectively. FMRIB's diffusion toolbox (FDT) was used to perform probabilistic tractography on each subjects' diffusion data to functionally parcellate the striatum according to cortico-striatal, direct sensorimotor striatonigral (substantia nigra [SN]/globus pallidus internus [GPi]) and indirect sensorimotor striatopallidal (globus pallidus externus [GPe]) projections.

Results: In healthy controls, [¹¹C]IMA107 BP_{ND} and [¹¹C]Rolipram V_T were more highly expressed in the indirect sensorimotor striatopallidal projections compared to direct sensorimotor striatonigral projections ([¹¹C]IMA107 BP_{ND}: 18%, p<0.001; [¹¹C]Rolipram V_T: 6%, p<0.05). PD patients had higher loss of [¹¹C] IMA107 BP_{ND} in the direct sensorimotor striatonigral projections compared to indirect sensorimotor striatopallidal projections (13%; P<0.01); whereas loss of [¹¹C] Rolipram V_T was similar between the direct striatonigral (24%; P<0.05) and indirect (22% and P<0.05) sensorimotor striatopallidal projections.

Conclusions: Our findings show: (a) Preferential expression of PDE10A and PDE4 in indirect striatal pathways in humans, in line with animal data; (b) Loss of PDE10A is prominent in the direct striatal pathways; whereas loss of PDE4 expression in both direct and indirect striatal pathways in patients with PD; providing new insights in the pathophysiology of PD which may have relevance to the development of targeted treatments.

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Objective gait parameters as a noninvasive biomarker for freezing of gait in Parkinson's disease patients *J. Shah, T. Virmani (Little Rock, AR, USA)*

Objective: To determine if steady-state gait parameters in Parkinson's disease (PD) patients could serve as a predictive biomarker for freezing of gait (FOG).

Background: FOG is a debilitating, late motor complication of PD that occurs in 50-80% of patients. It decreases mobility and increases falls thereby significantly worsening the quality of life. In separate studies, patients with FOG have been shown to have an increase in stride length variability, cadence, and asymmetry in stride.

Methods: PD patients and healthy controls (HC) were enrolled after IRB approval. Patients with more than 1 fall/day or a Montreal Cognitive Assessment (MoCA) score <10 were excluded. Subjects walked at their normal pace for 8 rounds on a 20x4 foot pressure-sensor mat (Zeno Walkway, Protokinetics, Havertown, PA). Data was collected and analyzed using PKMAS software (Protokinetics) and statistical analysis performed using SPSS 22 (IBM).

Results: 70 age-matched subjects (21 PD FOG, 26 PD no-FOG, and 23 HC) were enrolled. Disease duration was similar between PD FOG and no-FOG groups (8.9±5.6 vs. 7.5±6.5; p=0.43). Mean Giladi FOG-Q scores (11.4±3.6 vs. 2.6±2.9; p<0.001) and Hoehn & Yahr scores (2.2±0.6 vs. 1.7±0.5; p<0.005) were higher, and MoCA scores

 $(25\pm3.3 \text{ vs. } 26.5\pm2.8; p=0.11)$ were not significantly different in the PD FOG vs. no-FOG groups. Mean stride length and stride velocity were significantly lower in both PD no-FOG and FOG groups compared to HC while stance percent and total double support percent were significantly higher, but only stride length and stride velocity were statistically significant between PD FOG and no-FOG groups $(111.2\pm21.3 \text{ vs. } 127.7\pm16.9 \text{ cm}; p<0.01 \text{ and} 104.0\pm19.2 \text{ vs. } 114.8\pm15.2 \text{ cm}; p=0.05 \text{ respectively})$. Percent coefficient of variation (%CV) was also significantly different between the PD FOG and no-FOG groups in stride length ($5.1\pm1.6 \text{ vs. } 3.7\pm1.2 \text{ cm}; p<0.005$) and stride velocity ($6.5\pm2.1 \text{ vs. } 5.1\pm1.4 \text{ cm/s}; p<0.05$), but not total double support or stance percent.

Conclusions: PD patients with FOG had decreased stride length and stride velocity and increased variability in stride length and stride velocity, but not total double support or stance percent. This differential regulation suggests that objective gait assessment could provide a way to predict FOG in PD.

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Increased appendicular lean body mass is associated with increased cerebral cholinergic innervation in Parkinson's disease

J. Chua, M. Müller, M. Beaulieu, S. Nejad-Davarani, N. Bohnen (Ann Arbor, MI, USA)

Objective: The main aim of this study was to examine the effect of cholinergic nerve terminal integrity in the brain on measures of sarcopenia.

Background: Sarcopenia can accompany Parkinson's disease (PD) as an apparent peripheral muscular symptom that typically is attributed to increased sedentariness and aging. However, it is unclear whether central mechanisms may also play a role.

Methods: 37 PD patients (age=66.3±5.9 years, Hoehn and Yahr stage 2.4±0.6) underwent whole body tissue absorptiometry using a Hologic DEXA scanner and cholinergic brain PET imaging of the VAChT using [¹⁸F]FEOBV. Appendicular lean body mass (kg/m²) was calculated. [¹⁸F]FEOBV was synthesized following standard methods and a short (30 minutes) dynamic scan (every 5 minutes) was obtained 3 hours after bolus injection. Distribution volume ratio (DVR) was determined for MR based volumes of interests (using Freesurfer) with the supratentorial white matter as the reference region.

Results: Mean appendicular lean body mass was 7.73 ± 1.61 kg/m². Mean cortical ¹⁸F]FEOBV was 1.14 ± 0.1 . Increased appendicular lean body mass was associated with increased cortical VAChT activity (R=0.38, P= 0.019). Similar results were obtained when using lean body mass normalized to age-matched data.

Conclusions: Appendicular lean body mass correlates with cerebral cholinergic innervation in PD independent of age. This finding suggests a disease specific effect. Further research is needed to determine whether cerebral cholinergic denervation is associated with parallel loss of spinal cord motor neuron cholinergic activity, leading to weakened peripheral muscular function.

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Vitamin D in the Parkinson's associated risk (PARS) study

M. Fullard, S. Xie, K. Marek, M. Stern, D. Jennings, A. Siderowf, A. Chen-Plotkin (Philadelphia, PA, USA) **Objective:** The purpose of this study was to evaluate vitamin D levels in a population at risk for developing Parkinson's disease (PD).

Background: Vitamin D deficiency is common in PD, especially in advanced disease, and has been implicated as a potential risk factor for the development of PD. Within the PD population, lower levels of vitamin D have been linked to relative impairment in balance, motor function, mood and cognition. Findings from epidemiologic studies, however, have been inconsistent, with the most recent Atherosclerosis Risk in Communities (ARIC) study finding no association between baseline vitamin D levels and risk of PD 17 years later. No study has explored vitamin D levels in subjects with pre-diagnostic PD on the cusp of diagnosis.

Methods: The Parkinson's Associated Risk Study (PARS) is a well-characterized cohort of participants at risk for developing PD. Serum vitamin D levels were measured from samples collected at baseline using the gold standard liquid chromatography tandem mass spectrometry. We examined correlations between vitamin D levels and (1) dopaminergic system integrity (putaminal dopamine transporter (DAT) uptake), as well as (2) cognitive performance in the PARS cohort.

Results: PARS study individuals with serum samples available for analysis (n=198) comprised a group at high risk for PD based on hyposmia and DAT putaminal uptake <80% of age-expected (n=56) vs. all others (n=142). Mean vitamin D levels did not differ between the two groups, with a level of 27.8ng/ml [SD=12.0] in the high-risk group vs. 24.7ng/mL [SD=9.0] in all others (p=0.09). The high risk group demonstrated poorer performance on executive domain cognitive testing (p=0.02), but there were no other significant differences in cognition. Using partial

correlations, there was no association between vitamin D level and putaminal DAT uptake, controlling for age, sex and season of blood draw. Additionally, there were no correlations between vitamin D levels and cognitive performance.

Conclusions: Vitamin D levels did not differ between PARS participants at high risk for Parkinson's disease compared to controls, and vitamin D level was not associated with cognitive function or with dopaminergic system integrity.

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Evaluation of CSF cytokine profiles in people with Parkinson's disease and age-matched controls

G. Crotty, D. Vaughan, G. Moloney, G. O'Keeffe, S. O'Sullivan, A. Sullivan (Cork, Ireland)

Objective: To investigate the levels of cytokines in the cerebrospinal fluid of subjects with Parkinson's disease (PD) and matched healthy controls.

Background: Neuroinflammation is thought to be play a role in the pathogenesis of PD. As such it is possible that there are alterations in the balance between pro- and anti-inflammatory cytokines in the brain that may be reflected in the CSF profiles of patients with PD. Though a number of studies have examined the expression of CSF cytokines in people with PD, results have varied significantly across studies highlighting the need for further studies in this area.

Methods: Participants included 20 people with PD and 20 healthy controls. Basic demographics including age, gender and cognitive status were recorded. CSF was collected as per standard protocols and stored at -80 until it was analysed. CSF then underwent multiplex ELISA analysis for the cytokines Interleukin (IL)4, IL6, IL8 and IL10; TNF-alpha and Interferon-gamma. Data on amyloid-beta 42, total tau and phosphorylated tau levels were also available from previous testing. Data was analyzed using graph pad prism.

Results: 20 PD subjects and 20 controls were analyzed. Mean age was 64.13 years (range 45-89 years) and 64.55 years (range 52-85 years) for control and PD groups. CSF levels for IL6 were 1.51 ± 0.41 pg/ml and 0.98 ± 0.09 pg/ml in the control and PD groups, respectively (p=0.22). CSF levels for IFN-gamma were 0.28 ± 0.07 pg/ml and 0.20 ± 0.04 pg/ml in the control and PD groups, respectively (p=0.33). CSF levels for IL10 were 0.08 ± 0.03 pg/ml and 0.06 ± 0.01 pg/ml in the control and PD groups, respectively (p=0.67). CSF levels for TNF-alpha were 0.04 ± 0.01 pg/ml and 0.046 ± 0.01 pg/ml in the control and PD groups, respectively (p=0.67). CSF levels for TNF-alpha were 79.85 ± 0.73 pg/ml and 79.85 ± 0.8 pg/ml in the control and PD groups, respectively (p=0.996). IL4 was undetectable in the CSF of controls and PD subjects.

Conclusions: Although cytokines were detectable in the CSF, they were present at very low levels, with the exception of IL8 whose expression was significantly greater than the others tested. We found no significant differences in cytokines between the two patient groups. Further review of potential confounding variables and methodological differences in our study compared to other similar studies is ongoing, but our data suggests that there is not a pro-inflammatory CSF profile in people with PD.

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Alpha-synuclein protein homeostasis and oligomerization in iron-overloaded cells expressing mutant HFE

Y. Kim, J. Connor, M. Stahl (Hershey, PA, USA)

Objective: Study the direct and indirect effects of iron overload on alpha synuclein homeostasis in a genetic model of hemochromatosis (*HFE*)

Background: Parkinson's disease (PD) is characterized by the presence of alpha synuclein-containing Lewy bodies with selective vulnerability of particular neuronal populations, especially the dopaminergic neurons in the substantia nigra (SN). Increased levels of iron and ferritin in the SN also appear to be consistent features of the disease, but it remains unclear whether this accumulation is pathologic and if it relates to synuclein aggregation. Population genotype studies have returned conflicting results in regards to correlation between polymorphisms in iron metabolism genes (transferrin, transferrin receptor 1, HFE, frataxin, and lactoferrin) and PD. Nevertheless, a direct effect on synuclein can be postulated due to the known effect of metal ions on protein aggregation in vitro, the presence of a putative iron responsive element (IRE) in the 5'- untranslated region of the alpha synuclein messenger RNA, and the effects of iron on synuclein disposal via autophagy and proteasome activity.

Methods: Human neuroblastoma SH-SY5Y cell lines with stable transfection of two common *HFE* mutations (C282Y and H63D) were used to study alpha synuclein in iron-overloaded states. Total synuclein protein was assessed by Western analysis, while oligomers were studied using blue native PAGE. Autophagic flux was assessed via Western blot for LC3 and proteasome activity via effects on a artificial fluorescent/luminescent substrates. Transcripts were measured using RT-PCR.

Results: Western blot analysis showed that H63D and C282Y *HFE*-expressing cells had higher levels of total alpha synuclein compared to wild type. Addition of the iron chelator deferoxamine had varying effects on the intracellular labile iron pool and alpha synuclein levels. The impact of the *HFE* mutants on transcription of alpha synuclein, autophagic flux and proteasome activity and ultimately the levels of higher molecular weight alpha synuclein oligomers was also assessed.

Conclusions: These findings support the concept that iron may play a synuclein-mediated role in PD neurodegeneration.

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Effectiveness of lead position with MER to determine STNs: A study of MER with DBS for quantifying the effects of DBS in Parkinson's disease

V. Rama Raju, R. Borgohain (Hyderabad, India)

Objective: To quantify the effectiveness of MER with DBS, characterize Parkinson's disease symptoms/extract MER signal features of STN

Background: Parkinson's disease targeting CNS, causing group of neurons in one area of brain to begin dying off, triggering tremors and shakes. PD is characterized by progressive loss of dopamine cells in SNp of mid brain. Sending targeted pulses to this area can help whip living neurons back into shape and stop Parkinson's 4 cardinal signs

Methods: 46 patients executed (12considered for computation). Five electrodes were introduced into brain. Recording started from 10mm above the target, extended 10mm below. Stereotactic targets were acquired using CRW. Targeting performed according to Lozano's method –2mm sections are taken parallel to the plane of anterior comissure posterior commissure line at the level with maximum volume of red nucleus, STN is targeted at 3mm lateral to antereo anterior lateral border of red nucleus. Stimulation(130Hz), 70 μ s pulse width. Response was seen with increasing amplitude. Best responded channel was chosen. STN was detected by a high noise with a larger baseline, irregular discharge patterns of multiple frequencies. PCA applied

Results: STN was clearly distinguished from the dorsally located zona incerta and lenticular fasciculus(fieldH2) by a sudden increase in background noise level and increase in discharge rate typically characterized by rhythmic bursts of activity with a burst frequency between 20 to 35Hz. ?2computation for *f*-distribution, patterns of *F*-ratios showed good results (Tables1,2). With a ?2(9.21) with 2 degree of freedom at 5% (p<0.0095)highly-significant. The effects of DBS were quantified by examining those PCs in a lower dimensional feature space. The scatter plot of first two scores showed 80% variance(Fig1,Table2). Coherence seen(4/12patients,Figs2,3).

Table 1

Hypothesis	centra	l anterio	r poster	ior	medial	lateral	On the whole
					(5×12 = 60)		
χ ²	1.5	4.3	1.5	1.5	4.3	8.771	
(%)	5%	5%	5%	5%	5%	5%	
Significance	**NS	* S	NS	NS	s		HS
†df	1	1	1	1	1		2
Р	0.2	0.03	0.2	0.2	0.03	0.0029	

Table 1: χ^2 distribution of f-significance of all 60 STNs.

** Not significant, * Significant, HS – Highly significant, *Degree of freedom; (5×12 patients = 60); Note: chisquare (χ^2) and p-values bolded are highly significant.

Table 2: Analysis of variance (anova) for means

Source	SS/10 ⁴	df	MS/10 ⁴	⁵ F—rati	o *df of F-i	ratio p-Va	lue
Patients	0.1978	11	0.0180	1.9270	11.99	0.0466	5
STN Ne	urons 1	.5134	9	0.1682	18.0226	9.99	0.0000
Error	0.9237	99	0.0093				
Total	2.6349	119	-	-	-	-	

* degree of freedom



Fig 1. | Scatter diagram showing the plot of the First Two P.C. Scores (explaining about 80% of variation).



Fig 3. Frequency (X-axis) with Coherence Greater Than 0.75 (Y-Axis) of the patient 1



Fig 4. Coherence frequency of above patient 1

Conclusions: The data analysis showed significant findings which led to attempts at more sophisticated analyses using multivariate techniques MER signal recordings leading to effective data summarization and measures of dissimilarity between patients as reflected in the signals recorded, consequent possible clustering among them. However, the analysis did not lead to meaningful clinical inferences. These analyses could possibly be applied to longitudinal follow ups and correlations with controls in the future.

Effects of different intensity exercises on motor function of PD rats as well as the regulation of DA

X. Liu, P. Chen, D. Qiao, M. Wang (Beijing, People's Republic of China)

Objective: This paper research the intervention effect of the different intensity treadmill exercise on motor function of Parkinson's 's diseases (PD) model rats, and explore the most suitable intensity treadmill exercise intervention for prevention and treatment of PD.

Background: Parkinson's disease (PD) is the second most common progressive, irreversible neurodegenerative disorder in the World. Leads to difficulty with activities of daily living (ADLs) and decline in quality of life (QOL). Treatment options for PD are limited to pharmacologic management and surgery. Less invasive alternatives, such as exercise, have captured the attention of scientists and clinicians as possible adjunctive therapy.

Methods: Clean level male SD rats were randomly divided into Control group, PD group, PD+6Ex group, PD+11Ex group and PD+16Ex group. PD model rats were established by injection of 6-OHDA in right medial forebrain bundle single point. Control groups rats received same dose of saline. The exercise groups were intervened by 4 weeks of treadmill exercise at 24 hours after the surgery, the corresponding running speed of each group is 6m/min,11m/min and 16m/min,30 min/day,5day/week.

Results: Cylinder test showed that, the effect of the intervention became more and more obvious with the time prolonged. Grid test results showed, after 4 weeks exercise intervention, compared with PD group of rats, the slip times of PD+11Ex group significantly reduced. Immunohistochemical results showed that, compared with PD group, the expression of TH and D2DR in striatum of PD+11Ex group and PD+16Ex group rats increased significantly .The variation trend of the results of Western Blot was in accordance with the results of immunohistochemistry. The expression levels of TH and D2DR in striatum in low intensity exercise group rats have low correlations with the changes of motor ability ;but in medium intensity exercise group rats have high correlations with the changes of motor ability.















Conclusions: Four weeks treadmill exercise intervention can reduce movement dysfunction of PD model rats, and significantly increased TH and D2DR expression level in striatum. This suggests that DA systems involved in the regulation of motor function in rats; and the neurobiological mechanisms of exercise intervention reduced the motor dysfunction in PD model rats may related to the regulation effect of TH and D2DR.

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Explicit movement control in functional movement disorders is characterized by reduced lateralized beta desynchronisation

T. Teodoro, A. Meppelink, S. Little, A. Macerollo, R. Grant, M. Edwards (London, United Kingdom) **Objective:** To test whether beta power remains abnormally raised during motor preparation in functional movement disorders (FMD) patients. **Background:** Excessive attention towards movement control is considered a key pathophysiological feature of FMD. Patients tend to perform worse when a movement can be highly predicted. Beta oscillations decrease before normal movements and provide an index of motor attention. Therefore, here, we aimed to test whether beta remains abnormally raised during motor preparation as a marker of this excessive attention in FMD.

Methods: We analyzed beta-frequency cortical oscillations during a pre-cued choice reaction time (RT) task with varying cue validity (50% or 95% congruence between preparation and go cues) and focused on action preparation prior to the go cue. At baseline, we compared FMD patients with healthy controls (HC). FMD patients then underwent physiotherapy-based treatment. At follow-up, we compared FMD "responders" with "non-responders" to physiotherapy.

Results: In contrast to the HC group, FMD subjects showed no speed improvement in the predictable cueing condition (95% congruence) as compared with unpredictable cueing condition (50% congruence). Furthermore, during action preparation, FMDs showed less beta desynchronisation than HC. Importantly, in 95% congruence conditions, HC showed faster contralateral beta desynchronisation [slope -0.045 (95CI -0.057 -0.033)] relative to the ipsilateral side [slope -0.033 (95CI -0.046 -0.021)] (p-value < 0.001), and also a trend for reaching lower absolute contralateral beta power [mean -0.482 (95CI -0.827 -0.137)] relative to the ipsilateral side [mean -0.328 (95CI - 0.673 0.016)] (p-value 0.069). Crucially, this was not the case for FMD, or for 50% predictable trials. At follow-up, FMD responders were faster than FMD non-responders. Importantly also, only these responders showed beta desynchronization during motor preparation.

Conclusions: Persistent beta synchronization and lack of lateralized beta desynchronization during motor preparation are signatures of abnormal explicit movement control in FMD. We propose that abnormal self-directed attention in FMD, which is associated with an explicit mode of motor control, might interfere with beta desynchronization and impair motor performance.

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Multivariate analysis of writer`s cramp: A study with advanced multi-channel microelectrode recording system

V. Rama Raju, R. Borgohain (Hyderabad, India)

Objective: To quantify difference in WC patients with Concordant mirror movements(MMs) from those with Discordant MMs.

Background: Invasive methods are encouragive for quantitative analysis. The most established scale for assessing WC is WC rating scale (WCRS,Wissel.J,1996) which is subjective. Quantitative analysis is used for objective reason.

Methods: 12 patients (M:F=11:1) with WC included in the study(mean age38.5±3Yrs, disease

duration104±126.3months were studied). They were asked to write with right hand(RH) for 4 minutes with left for 4 minutes. During latter phase, they were inquired to maintain RH resting on table flexed on elbow in a semi pronated position, wrist in a neutral position, with fingers being kept relaxed in a semi flexed position. RH was observed for MMs while writing with LH. WC signals recorded, videotaping was done. A close up of signal recording shown(Fig1). PCA, canonical correlation analysis between RH writing signal(RHWS), LH writing signals(LHWS) for each patient was carried out.

Results: Data are centered, dispersion matrix computed for each of these matrices. Eigen vectors give the weightages to be given for 10means/SDs as the case may be, to construct 10scores as combinations of 10means/SDs for each patient. These scores are such that they have variability's in decreasing order and uncorrelated. The variances/10000 for the case of means(Fig2) are(PC₁:9.5056,PC₂:0.9306 .0000 out of a total of11.215). Canonical variates defined for 2sets of variates observed on same "individuals" are pairs of linear combinations of the two sets, which are correlated maximally with each other, but uncorrelated with other such sets. No significant patterns could be discerned on comparing coherence patterns in C, D groups. In D group both LHWS RHWS showed significant coherence in ECR, 5thmuscle comparison 3/4 patients. This was seen in 6/8, 4/8 patients in C group (Table1).

Table 1: Frequency of coherence in Left Hand Writing Signal (LHWS)

Group	Coherent	Non		
		coherent		
С	6	2	8	
D	3	1	4	
	9	3	12	

with a $\chi^2 \simeq 0$ with 1 degree of freedom (df), which is not significant at 5%.





Conclusions: This study showed significant quantifiable differences in the signals seen while writing with R and L hands between those WC patients with concordant MMs (C group) versus those with discordant MMs (D group). Analyses showed significant findings which led to attempts at more sophisticated analyses using multivariate techniques leading to effective data summarization, measures of dissimilarity between patients as reflected in the signals recorded and consequent possible clustering among them.

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Glut-1 deficiency: A case report

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Objective: To report the case of a patient with refractory seizures who was diagnosed with Glut-1 deficiency. **Background:** Although Epilepsy is commonly diagnosed by child neurologists, glucose transporter-1 deficiency (GLUT1D) has recently been identified as an important cause of generalized epilepsies in childhood. A heterozygous mutation in the SLC2A1 gene compromises glucose transport into the brain, leading to insufficient glucose levels for brain metabolism. The clinical picture is characterized by refractory epilepsy, developmental delay, hypotonia, spasticity and complex movement disorder consisting of ataxia, dystonia or a combination of both. **Methods:** We report the case of a patient with refractory seizures who was diagnosed with Glut-1 deficiency. **Results:** The patient was born following a normal pregnancy labor and unremarkabledelivery, with normal Apgar scores. No history of consanguinity was mentioned. At 3 months of age he started with muscles spams. His EEG was abnormal due to disorganized background activity. He also presented with global developmental delay. When he started to walk wat 2 years, new clinical symptoms were observed: episodes of asthenia during physical activity associated with hypoglycemia. Dietery changes were made to no avail. In his first evaluation with a neurologist, he was diagnosed with possible congenital myasthenia and Mestinon was initiated. His symptoms worsened progressively until he was 13 v/o, when a new neurological evaluation revealed dystonia, ataxia, maintenance of seizures and severe intellectual disability with deficits in adaptive functioning. Due to significant clinical worsening a new work-up was done and CSF biochemistry found reduced levels of glucose. A genetic evaluation (MLPA analysis) showed a heterozygous deletion of the SLC2A1 gene, compatible with GLUT1 deficiency syndrome. Ketogenic diet was adopted and an excellent control of symptoms was achieved. The patient improved considerably his clinical condition with complete control of seizures and a remarkable reduction of the severity of the neurological disabilities.

Conclusions: Recognition of GLUT 1 deficiency as a possible cause of refractory epilepsy of childhood is important, since it is a treatable condition. Ketogenic diet can significantly reduce neurological disabilities.

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Putaminal atrophy gradient in X-linked dystonia-parkinsonism

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Objective: To better understand striatal pathology in X-linked Dystonia-Parkinsonism (XDP) by combining T1 and Magnetization Transfer (MT) Imaging.

Background: XDP is a neurodegenerative disorder characterized by severe adult-onset dystonia followed by parkinsonism over the course of the disease. Post-mortem and quantitative MR analyses revealed severe striatal and pallidal atrophy even in early disease stages. MT imaging is a sensitive method to reveal microstructural alterations of tissue integrity and may be helpful to differentiate between demyelination (very low MT ratio (MTR)) and edema (slightly reduced MTR).

Methods: T1-weighted and MT images were acquired from 10 male XDP-patients (age: M= 42.6, SD= 7.6; mean disease duration: 3.4 years, range: 1-6 years) and 16 ethnicity-matched male healthy controls (age: 35.6, 7.3) at 3 Tesla. To detect a pattern or gradient of neurodegeneration, three regions of interest (ROI) were defined (rostral, central and caudal putamen), reflecting functionally divergent regions of the putamen. Mean voxel intensity and MTR values were extracted with FSL. To test for statistical differences a mixed model ANOVA using SPSS was performed.

Results: In line with previous findings, putaminal voxel intensity as a marker of gray matter pathology was significantly lower in the patient group (p<0.001). Here, the reduction of voxel intensity followed a caudo-rostral gradient (caudal (-14.41%), central (-38.55%), and rostral putamen (-46.30%)). In contrast to these distinct abnormalities throughout the entire putamen, MTR values were reduced in the central putamen only and not in the other parts of the putamen. [figure1]



Whereas voxel intensity differs significantly in all parts of the putamen (rostral/central: p<0.001; caudal: p=0.002), MTR is only significantly different in the central putamen (caudal p=0.127, central p=0.003, rostral p>0.9). There is a significant interaction of group and putamen for voxel intensity (F(1.03, 22.65)=94.78, p<0.001) and MTR (F(1.43, 31.44)=9.5, p=0.002) (both Greenhouse-Geisser corrected).

Conclusions: Putaminal atrophy in XDP is severe even after relatively short disease duration. T1 and MT imaging depict different aspects of neurodegeneration in XDP. In the rostral putamen, similar MT ratios in the presence of distinct atrophy upon T1 images may indicate a terminated neurodegenerative process whereas neurodegeneration is still ongoing in other parts of the putamen. Given the predominant motor phenotype of XDP, the observed caudo-rostral atrophy gradient is in contrast to the hypothesized preferential degeneration of the caudal sensorimotor putamen. Further multimodal imaging of the basal ganglia is warranted to better understand these findings and to interpret the significance of MT imaging in XDP.

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Saccadic impairment in patients with Gaucher's disease type 3

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Objective: To characterize saccades in patients with chronic neuronopathic Gaucher's disease (GD3) in relationship to their neurological and cognitive status using a computer-based eye-tracking technique.

Background: GD3 is relatively frequent in northern Sweden. Besides multiple other neurological symptoms, horizontal gaze palsy, sometimes described as oculomotor apraxia, is common in GD3.

Methods: Horizontal and vertical reflexive saccades as well as antisaccades of nine GD3 patients (4M/5F; 41.1 \pm 11.0y; mSST: 9.3 \pm 5.4; MoCA: 24.0 \pm 4.2) and age-matched controls were analyzed using EyeBrain T2, a head-mounted binocular eye-tracker. Systematic clinical assessment included the modified Severity Scoring Tool (mSST)1, a valid tool for monitoring the neurological progression in GD3, and Montreal Cognitive Assessment (MoCA).

Results: In GD3 patients, the average velocity of horizontal saccades was reduced $(106.4^{\circ}/s \pm 42.6 \text{ vs}. 283.9^{\circ}/s \pm 17.0; p=0.0009)$ compared to healthy controls. The vertical and horizontal saccadic latency was increased (295.8ms $\pm 37.0 \text{ vs}. 236.5\text{ms} \pm 22.4; p=0.005)$ while the gain remained unaffected $(0.95 \pm 0.06 \text{ vs}. 0.94 \pm 0.03; p=0.8)$. The latency of horizontal reflexive saccades correlated to the mSST score (R2=0,83; p=0.003). GD3 patients made more errors in the antisaccade task $(3.9 \pm 2.8 \text{ vs}. 0.7 \pm 0.7; p=0.02)$ and the error rate tended to correlate to the cognitive function measured in MoCA score (p=0.06).

Conclusions: The mean age of 41 years of our GD3 cohort reflects the increased life expectancy of patients in the Norrbottian area compared to other GD3 cohorts. Marked impairment of horizontal saccades was evident in all patients while impaired vertical saccades were linked to more advanced stages of the disease. Saccadic latency was correlated to the severity of neurological symptoms and antisaccade errors were linked to cognitive impairment. The assessment of saccades provides diagnostic markers for neurological and neuropsychological involvement in Norrbottian GD3 and may be used as an outcome measurement in treatment studies.

Atypical and slowly progressive FTDP-17 caused by MAPT p.R406W mutations - similarities to AD and PSP E. Ygland, D. van Westen, E. Englund, R. Rademakers, Z. Wszolek, K. Nilsson, C. Nilsson, O. Hansson, L. Gustafson, A. Puschmann (Lund, Sweden)

Objective: We compiled clinical data of a new kindred with the MAPT c.1216C>T (p.Arg406Trp; R406W) mutation and systematically reviewed previously described cases with this mutation.

Background: MAPT R406W is a known cause of frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) with Alzheimer's disease (AD)-like clinical features.

Methods: Patients were enrolled when symptomatic and followed for up to 22 years. Neuropathological examination was performed in three family members. Exome sequencing revealed MAPT R406W heterozygosity in the family. Clinical, radiological and neuropathological data in previously described R406W cases were systematically reviewed, yielding an assessment of 70 R406W heterozygotes and three confirmed homozygotes in total.

Results: Ventromedial temporal lobe atrophy was present early in the new kindred and was at first observed around the collateral sulcus, with ensuing atrophy of the parahippocampal gyrus. Neuropathological examination of three family members showed tauopathy with neurofibrillary tangles (NFTs), more distinct in the ventromedial temporal lobe. Mild concomitant alfa-synuclein pathology was present in one of these patients and there was widespread TDP-43 pathology in another. In previously described cases and also in the new kindred combined, impaired memory was the most frequent symptom, behavioral disturbance and language impairment were less common and Parkinsonism was rare. Overall median age of onset was 55 years and median disease duration 13 years. The most frequent clinical diagnosis was AD. Previously reported R406W homozygotes had lower age at onset and higher frequency of behavioral symptoms and Parkinsonism, compared to R406W heterozygotes.

Conclusions: The disease course of R406W patients is most often slow, and reminiscent of AD but with a risk of developing behavioral symptoms or language impairment at any disease duration. We postulate the ventromedial temporal lobe to be atrophic at all stages of R406W associated disease and an early focus not only for AD pathogenesis but also for R406W associated neurodegeneration. The same tau isoforms and ultrastructure are aggregated into NFTs in R406W associated disease and AD. We hence hold R406W-associated disease as an interesting crossing of tauopathies, AD and the debated primary age-related tauopathy, spanning the whole spectrum from neuropathology to clinical disease.

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FXTAS, PD, and ET subjects demonstrate distinct gait, balance and tremor deficits under normal, environmentally challenging, and dual-task conditions

E. Robertson, D. Hall, A. McAsey, M. Swanson, A. Bery, C. Huml, E. Berry-Kravis, J. O'Keefe (Chicago, IL, USA) **Objective:** To compare FXTAS, PD, ET and controls using quantitative measures of gait, balance, and tremor. **Background:** Fragile X-associated tremor/ataxia syndrome (FXTAS), a neurodegenerative disease that affects carriers of a 55-200 CGG repeat expansion in the fragile X mental retardation 1 gene, may be misdiagnosed as PD or ET due to overlapping motor symptoms. It is critical to characterize distinct phenotypes in FXTAS compared to PD and ET to improve diagnostic accuracy. Environmentally challenging and dual-task (DT) paradigms can reveal subtle gait and balance impairments, and tremorography correlates with clinical tremor rating scale scores. **Methods:** Subjects with FXTAS (n = 10; mean age 69.70 ± 6.81 years), PD (n = 15; mean age 70.87 ± 7.97 years) and ET (n = 9; mean age 69.56 ± 7.35 years) and controls (n = 12; mean age 64.42 ± 7.12 years) underwent gait and balance testing with an inertial sensor system (APDM; Oregon). Instrumented Timed Up and Go (i-TUG) and 2-minute walk (i-WALK) tests were used to test gait, and the i-SWAY to test balance. DT conditions included a verbal fluency task. Subjects also underwent tremorography using the ETSenseTM system (Kinesia HomeViewTM; Great Lakes NeuroTechnologies Inc.).

Results: On the i-TUG, FXTAS subjects had increased sit-to-stand peak velocity compared to PD subjects (p=0.04). On self-selected speed and DT i-WALKs, they had increased stride length (p=0.03 and 0.04, respectively), and during self-selected and fast i-WALKS they had reduced cadence (p=0.03 and 0.04, respectively) compared to PD subjects. On the i-SWAY, both FXTAS and ET subjects had increased jerk (m^2/s^5 ; smoothness of path sway) compared to PD subjects during the foam, feet apart, and eyes closed condition (p=0.01 and 0.04, respectively). On tremorography, FXTAS subjects showed reduced rapid alternating movement amplitude compared to PD subjects (p=0.0045), and PD subjects showed reduced rapid alternating movement amplitude and speed compared to ET subjects (p=0.0002 and 0.0115, respectively).

Conclusions: This pilot data demonstrates that FXTAS, PD, and ET subjects exhibit distinct deficits in gait, balance and tremor under normal, environmentally challenging and DT conditions. This suggests that these quantitative measures may be sensitive to distinguish FXTAS from PD and ET.

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Cerebrotendinous xanthomatosis without tendon xanthoma: a diagnostic challenge

S. Souki, L. Vasconcellos, M. Spitz, J. Pereira, V. Marussi, A. Carrié, P. Couvert (Rio de Janeiro, Brazil) **Objective:** To describe the case of Cerebrotendinous xanthomatosis (CTX) without tendon xanthoma, highlighting the diagnostic challenge due to its rarity, as well as the importance of neuroimaging.

Background: CTX is a rare autosomal recessive disease caused by mutation in the CYP2A1 gene, encoding the mitochondrial enzyme sterol 27-hydroxylase. This enzyme participates in bile acid synthesis and cholesterol and other sterols metabolism, so that its reduction results in cholesterol and cholestanol deposit in several tissues, especially tendons, nervous system and crystalline lens.

Methods: A 52 year-old Caucasian woman that developed seizures and delayed psychomotor development at the age of 5. At the age of 24 she underwent cataracts surgery. One year later she developed dystonic movements (predominantly craniocervical), as well as dysarthria, dysphagia and ataxia. There was progressive worsening of motor function, so that she became wheelchair-bound at the age of 30 and bedridden at 49. She has had no effective interaction for the past 3 years and she is under exclusive gastrostomy feeding.

Results: Laboratory workup revealed cholestanol of 19.6 mmol/L (Reference: 2-12 mmol/L) increased cholestanol/cholesterol rate of 4.55 (Reference: 0.16 +/- 0.05) and increased cerebrospinal fluid albumin of 24.4 mg dL (Reference: up to 3.5). Brain MRI showed diffuse cortical atrophy, multiple signal changes affecting the posterior limb of the internal capsule, brain peduncles, pontine median raphe, upper and middle cerebellar peduncles, medullary pyramids and cerebellar white matter. Spinal MRI revealed extensive longitudinal signal alteration (hyperintensity on T2) of the posterior and lateral funiculi and corticospinal tracts of the cervical and thoracic spinal cord. Achilles tendon MRI was normal. Genetic test with analysis of CYP27A1 gene revealed that the patient is a homozygous carrier of a late nonsense mutation, which is diagnostic of CTX.



Fig 1. Brain MRI. A: Hyperintense signal on T2 in dentate nucleus and white matter in the cerebellar hemispheres. B: Signal increase in spinal corticospinal tract and periventricular white matter on FLAIR.

Conclusions: Early suspicion of rare and potentially treatable diseases is of great importance in medical practice because it changes the natural history of the disease and, consequently, the clinical outcome of the patients. The neuroimaging is essential in the diagnostic investigation of XCT. It should be noted that up to 30% of patients with XCT do not present with tendon xanthomas, as in the case reported.
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Deferiprone combined with phlebotomy for aceruloplasminemia

L.H.P. Vroegindeweij, J.G. Langendonk, J.H.P. Wilson, A.J.W. Boon (Rotterdam, Netherlands) **Objective:** To evaluate the efficacy and safety of chelation therapy with deferiprone combined with phlebotomy in reducing iron stores and neurological progression in aceruloplasminemia.

Background: Aceruloplasminemia is a rare form of Neurodegeneration with Brain Iron Accumulation (NBIA). No treatments have yet been reported giving sustained clinical benefit at a neurologically symptomatic stage of the disease (1). Deferiprone is the only chelator available which might act beyond the blood brain barrier, and is capable of redistributing iron to hematopoietic tissues by transferring it to transferrin. Phlebotomy is a more effective iron remover than deferiprone alone. The combination of deferiprone and phlebotomy has not yet been reported. **Methods:** Four Dutch patients with homozygosity for G631R in the *CP* gene (2) received deferiprone to a maximum dose of 65 mg/kg/day in combination with phlebotomies of up to 500 ml blood/2 weeks. Safety and tolerability were monitored. Neurological function was quantitatively assessed by the Unified Parkinson's Disease Rating Scale (UPDRS III-Motor Section) and the Scale for the Assessment and Rating of Ataxia (SARA), every 3 months for the first year of treatment and every 6 months thereafter. Systemic iron stores were measured by ferritin levels and brain MRI was performed yearly to evaluate cerebral iron deposition.

Results: Deferiprone combined with phlebotomy was well tolerated in case 1 and 2; in the other cases the treatment regimen was early discontinued [table 1]. After 30 months of treatment motor features had gradually worsened in case 2; case 3 showed stable neurological disease. Case 1 and 4 died during follow-up [figure 1]. Ferritin levels decreased from 3523- to 113 ug/l and 2938- to 605 ug/l in case 1 and 2, respectively; in case 3 and 4 serum ferritin remained normal. Conventional MRI of the brain showed no obvious changes in iron distribution in case 2 and 3; in case 1 progressive iron accumulation was found.

Table 1. Clinical characteristics of the patients at start of combined chelation therapy and during follow-up

Case/gender/age			Base	ine characteristics			Follow	-up	
	Neurological phenotype	Serum ferritin (ng/ml)	Haemoglobin (g/dl)	Disease duration (years)	Previous treatment, years		Duration of treatr	nent (months)	
				0.0		Deferiprone	Side effects*	Phlebotomy	Side effects
Case 1/M/50	Orofacial dyskinesia, chorea,	3523 H	15.0 N	2	(-)	17	-	17	-
Case 2/M/56	dysarthria, gait disturbances	2938 H	153 N	2	-	30	_	30	
cuse 2mm bo	behavioral changes	2750 11	10.0 11	-				00	
Case 3/M/61	Stress related tremor, slightly	266 N	11.6 L	19	Deferoxamine, 13 [†]	30	-	1	Anaemia
Case A/F/63	diminished facial expression Orofacial dyskinesia, chorea	145 N	9.8 1	12	Deferovamine 0 5	3		1	Ansemia
Case 4/1705	gait disturbances, cognitive	140 18	5.0 E	12	Deferasirox, 4.5 ²		/igitalitioey tosis	1	2 Machina
	impairment, character changes								

Abbreviations: II, high; N, normal; L, low

Serious adverse events leading to discontinuation of treatment. [†]Deferoxamine was initially continued in combination with deferiprone and phlebotomy; after 17 months of combined chelation therapy, only deferiprone was continued, because of persistent low haemoglobin levels after two venesections. ^{}Both chelators were discontinued due to severe nausea.



Figure 1. Neurological rating scales of the cases at baseline and during follow-up. A: UPDRS III. B: SARA. † Case 1 and 4 died after 19- and 5 months of follow-up, respectively. Motor function tests were not performed during their last months of life (dotted line).

Conclusions: Deferiprone combined with phlebotomy proved to be safe and effective in reducing serum ferritin in two non-anaemic aceruloplasminemia patients. Phlebotomy should not be tried in combination with deferoxamine or in the presence of anaemia. The progression of neurological disease despite biochemical effectiveness in patients with advanced manifestations underlines the importance of early diagnosis and prompt initiation of treatment.

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An unusual presentation of tyrosine hydroxylase deficiency

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Objective: To discuss a case of tyrosine hydroxylase deficiency presenting with resolution of symptoms on levodopa except for a dynamic segmental dystonia.

Background: Dopa-responsive dystonia (DRD) has largely been associated with autosomal dominant mutations in the GCH1 gene leading to GTP cyclohydrolase 1 deficiency (1). More recently, a deficiency in tyrosine hydroxylase (TH) has been recognized to cause DRD. This is a rare disorder resulting from a genetic mutation in the TH gene on chromosome 11 (2). The phenotype ranges from DRD with complete resolution on levodopa to infantile parkinsonism and encephalopathy only partially responsive to levodopa (2).

Methods: We report a man with an usual presentation of dystonia. He grew up in rural Myanmar with limited medical care. Childhood was normal except for episodic illness with difficulty moving and speaking. At 18 years he

developed difficulty writing. At 21 years he could not speak, walk, or write and was taken to a city hospital. Multiple medications were tried without benefit until carbidopa/levodopa, to which he had a miraculous response. Since then he has attempted to come off medication, however his symptoms return after several weeks. On presentation to us at 31 years he was taking 450mg levodopa/day and 4mg trihexyphenidyl/day. He had a dynamic dystonia in his neck and trunk, subtle at rest and prominent with walking. He exhibited a sensory trick when touching his hand to chin; improvement occurred to a lesser degree when he imagined this, and to an even lesser degree when the examiner touched his chin. He had no parkinsonism.

Results: He underwent genetic testing, revealing a homozygous variant mutation in the TH gene (p.Thr494Met) leading to a diagnosis of autosomal recessive tyrosine hydroxylase deficiency.

Conclusions: TH deficiency can cause a broad range of clinical symptoms and severity. As more cases are discovered, the phenotype expands. Here we describe a unique case of TH deficiency DRD that does not show complete response to levodopa with residual symptoms behaving like an idiopathic segmental dystonia which is task specific and responds to a sensory trick. In addition, while the history is limited, it is possible he may have had childhood episodes similar to "lethargy-irritability crises" seen in more severe cases. As more TH deficiency cases are discovered it is important to clearly identify distinguishing features to allow for proper diagnosis and treatment.

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Phenotype of PLP1-related disorder caused by novel mutation: A case report

N. Kresojevic, I. Petrovic, V. Dobricic, A. Tomic, M. Svetel, V. Kostic (Belgrade, Serbia) **Objective:** To illustrate phenotype of PLP1-related disorder caused by a novel mutation. **Background:** Phenotypes of X-linked PLP1-related disorders vary from severe forms of hypomyelinating

leukodystrophy-Pelizaeus–Merzbacher disease, clinically characterized by nystagmus, spastic quadriplegia, ataxia, dystonia and developmental delay, to mild forms of hereditary spastic paraplegia type 2.

Methods: Patient with an unremarkable family history was born following uncomplicated pregnancy and delivery, but was floppy baby with delayed psychomotor milestones. He achieved independent walking at the age of 23 months, however, his gait was spastic and ataxic. Over the time gait slowly worsened: at the age of 12 he needed walking stick and was wheelchair bound at the age of 20. The first dystonic feature was writer's cramp observed early at primary school. Thereafter, dystonia slowly generalized. Vision has been poor from childhood. He finished primary school with personal assistance help. Parents noticed significant progression of cognitive decline and behavioural disturbances. From the age of 16 he has had urinary urgency. Brain CT at the age of 3 revealed global but mild atrophy of cerebral cortex and vermis. He was diagnosed with mild optic atrophy at age of 4. On the last examination (26 years), he had vertical gaze palsy (particularly on upward gaze), pronounced delay on saccadic initiation, head and voice tremor, dysarthria, generalized dystonia, spastic paraplegia, and stimulus sensitive myoclonus. Intention tremor was present on finger-to-nose test. Somatic examination was unremarkable. Interestingly enough, nystagmus has never been observed.

Results: Brain MRI revealed diffuse hypomyelination, global brain atrophy, thin corpus callosum and atrophy of the cerebellum, especially vermis [figure1]. A hemizygous variant in the PLP1 gene, c.354del (p.Gly120Alafs*27) was detected. This new mutation creates a shift in the reading frame starting at codon Gly120. The new reading frame ends in a STOP codon 26 positions downstream.



Conclusions: We reported a patient with new PLP1 mutation, characterized, in addition to typical findings, with the presence of stimulus sensitive myoclonus and vertical gaze palsy, lack of nystagmus during the disease course and cerebellar atrophy on MRI examination.

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Non-motor symptoms in ACDY5-associated disease

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Objective: To describe non-motor symptoms in a case of ACDY5-associated disease.

Background: The hereditary dyskinesia syndrome caused by an ACDY5 mutation was first described in 2001. To date, 46 patients with 6 different mutations have been described in the literature. Patients present during childhood or adolescence with choreiform movements, facial myokymia, dystonia, gait abnormality, abnormal saccadic eye movement and developmental delay.

Methods: We conducted a review of the literature by using the search terms "ACDY5," "movement disorders," "tics," "cognition," and "behavior" on PubMed. We report the case of a patient with an ACDY5 mutation who exhibited, in addition to the classical movement disorders phenotype, a broader spectrum of symptoms including tics, oppositional behavior and neuropsychological deficits with depression and cognitive impairment. **Results:** The 11-year old boy with ACDY5 mutation presented since age 3 with mixed hyperkinetic disorder marked by choreatic movements of the extremities and the trunk as well as facial myokymia. His paroxysmal, mostly spontaneous attacks lasted 30s to 9min with dystonic and clonic movements of the extremities and oral movements without loss of consciousness or EEG findings. At age 10, his condition was complicated by motor and vocal tics. He started repeating words multiple times, stamping his feet, hitting the table with his hands, and using insulting words. His symptoms worsened with stress or lack of sleep. He also developed depression and disturbed social behavior. His social behavior disorders were marked by, among other, stealing, lying, aggression against siblings and classmates or breaking car glasses. He showed a delayed motor and speech development complicated by cognitive impairments requiring intensive support at school. Two different intelligence tests were performed, a SON-R at age 6 with average results within normal limits and a WISC at age 10 with a result of 65.

Conclusions: ADCY5 mutations are the cause for a rare hereditary dyskinetic syndrome with a broad spectrum of movement disorders. Cognitive impairments may complicate the condition; however, it is unclear to which extent ADCY5 plays a role in cognitive development. Intellectual disabilities were reported in 10% and delayed language development in 30% of patients. We further expand the spectrum of motor and non-motor symptoms in ADCY5-associated diseases, as tics and behavior disorders have not yet been reported in the literature.

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Congenital mirror movements: When the left hand doesn't know what the right is doing

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Objective: To report on two non-related cases of congenital mirror movements (CMM).

Background: Mirror movements (MM) are involuntary symmetrical movements of one side of the body that mirror intentional movements of the other side, making the person affected unable to perform a purely unimanual task. They are common in early childhood when motor mirroring is presumed to stem from incomplete myelination of the transcallosal tract and insufficient interhemispheric inhibition. Their persistence into adulthood is pathological and may occur either as an 'essential' movement disorder with no other neurological features (CMM) or as part of a syndrome (Kallmann, Joubert, Wildervanck, Klippel-Feil etc). Their re-emergence in later life (acquired MM) is commonly seen during the course of neurodegenerative diseases such as PD. CMM is a very rare disorder, with an estimated prevalence of less than 1:1,000,000. The severity of the MM is defined on a scale from 0 (no MM) to 4 (MM equal to that observed in the intended hand). CMM is generally inherited in an autosomal dominant (AD) manner, with heterozygous pathogenic variants identified in about 35% of affected individuals/families in either the *DCC* or *RAD51* gene. The identified genes have roles in axon guidance at the midline of the corticospinal tract. **Methods:** Clinical and family history, examination, video assessment, blood tests to screen for syndromic causes of MM, smell test (UPSIT), brain and cervical spine MRI. Screening for mutations in DCC and RAD51 genes was performed through next-generation sequencing (NGS).

Results: Case 1 (M.B.) and case 2 (A.A.) were both otherwise healthy, right-handed 16 year-olds who had exhibited mirror movements of both hands since early childhood, which had become problematic as they had begun performing more complex bimanual tasks. There was no relevant family history; the clinical examination was unremarkable except for repetitive sustained MM of both hands in which the nonvolitional hand followed smoothly and closely the movements of the volitional hand (video). MM score was 3. Blood tests and olfaction were normal.

M.B's MRI revealed non-specific developmental changes in the brain, and A.A.'s neuroimaging showed no abnormalities. NGS for M.B. revealed a pathogenic missense mutation in the DCC gene.

Conclusions: CMM remains an underdiagnosed entity. After evaluation of difficulties with ADLs, adaptation of the school/home environment is recommended.

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Perceptual decision making and reflection impulsivity in drug naïve and treated patients with restless legs syndrome

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Objective: To investigate perceptual decision making and reflexion impulsivity in patients with restless legs syndrome (RLS) with and without dopamine replacement therapy.

Background: Detailed neuropsychological tests using tasks specifically designed to assess impulsivity have not been performed in drug naïve RLS patients so far.

Methods: A total of 20 drug naïve and 15 RLS patients treated with dopaminergic replacement therapy without augmentation or impulsive behaviours were included in this study. All patients underwent detailed neuropsychological testing. Furthermore, we used two information sampling tasks to assess cognitive impulsivity, specifically reflection impulsivity and perceptual decision making. The results were compared to 22 healthy controls.

Results: Both RLS patient groups gathered less evidence in the beads task before making a decision than healthy controls (p<0.001). Patients with dopaminergic replacement treatment drew fewer beads than untreated patients (p=0.026). Moreover, both patient groups made more choices against the evidence than healthy controls (p=0.001), but there was no difference between the two patient groups (p=0.88). In the perceptual decision making tasks untreated RLS patients responded slower than both controls and treated patients (p<0.001), but there was no difference between treated patients and controls (p=0.6). There was also no difference in total error rates (p=0.67).

Conclusions: These results suggest that jumping to conclusions and irrational decision making are common in both drug naïve as well as treated RLS patients which may be due to a dysfunction of brain networks responsible for cortical inhibition. Whether dopaminergic medication improves perceptual decision making in RLS needs to be confirmed in further studies.

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Abnormal activity in reward system in Parkinson's disease patients with rapid eye movement sleep behavior disorder

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Objective: To study the mesocorticolimbic reward system in Parkinson's disease (PD) patients with and without REM sleep behavior disorder (RBD).

Background: RBD is a parasomnia observed in up to 60 % of PD patients. A greater risk of impulse control disorders (ICD) has been reported in PD with RBD, suggesting a more severe mesocorticolimbic impairment in these patients (1).

Methods: Sixty six participants were included: 22 PD with RBD (PD-RBD); 22 PD without RBD (PD-noRBD) and 22 healthy volunteers, age and sex matched [Table 1]. RBD was diagnosed by video polysomnographic recording according to the ICSD-3 criteria. Subjects with ICD, depression or apathy were excluded. We compared brain activation in the three groups using a functional MRI paradigm named "monetary incentive delay task" [Figure 1]. The latter explore the reward system during anticipation and reception of a monetary reward. Brain activation was measured by the BOLD effect, voxel by voxel in the whole brain and in regions of interest (ROI) within the reward system. ROIs are chosen from independent whole brain analysis (2): midbrain, striatum, insula, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC).

Results: In whole brain analysis, reward system were found to be less activated in PD-RBD patients when a reward was anticipated or received. Significant différences were observed in the ACC, the parahippocampal gyrus, and the caudate (p <0.001 uncorrected). ROI analysis showed lower activation of reward system in PD-RBD group during the two different phases of reward. During monetary anticipation, caudate nucleus, insula, ACC and OFC were less activated in PD-RBD group than both PD-noRBD and healthy control (p<0.03) [Figure 2]. For reward outcome, nucleus accumbens and OFC were less activated in PD-RBD group (p<0.02) compared to the other groups [Figure 3].



Figure 1 : Monetary incentive delay task. Subjects first saw a cue informing them about the intensity (size of pictogram dallars) and probability (pie chart) of an upcoming reward. Two cases are represented here: a chance of 25 % of receiving a large amount of money (top), and a sure chance of getting nothing (control trials, bottom). Then cue was replaced by a question mark, symbolizing a delay period during which a pseudorandom draw was performed according to the announced probability. Following this anticipation phase, participants had to perform a target discrimination task within< 1s. The target was either a triangle (left button press require) or a square (right button press required). Both their performance and the result of the pseudorandom draw determined the nature of the outcome. In rewarded trials, subjects saw a monetary amount displayed on a safe (high or low amount, top). In non-rewarded and control trials, subjects saw a scrambled picture (bottom).



Figure 2: Percent signal change for monetary reward anticipation phase for each group (No RBD, RBD and Volunteers) in each ROIs. ANOVA and post hoc test between the three groups. Percent signal change was extracted is the different ROIs: Nacc = nucleus accumbens, NCaudate = caudate nucleus, insula, ACC = anterior cingular cortex, COF = orbito frontal cortex and midbrain. The error bars indicate SEM. Asterisks denote significance (*p<0.05, **p<0.01).



Figure 3: Percent signal change for monetary reward outcome for each group (No RBD, RBD and Volunteers). ANOVA and post hoc test between the three groups.Percent signal change was extracted is the different ROIs: Nacc = nucleus accumbens, NCaudate = caudate nucleus, insula, ACC = anterior cingular cortex, COF = orbito frontal cortex and midbrain. The error bars indicate SEM. Asterisks denote significance (*p<0.05, ** p <0.01).

Table 1 : Main demographic, clinical and neuropsychological features of the subjects included in the study

	PD-RBD (n=22)	PD-No RBD (n=22)	Total PD (n=44)	Controls (n=22)	PD-RBD vs PD-NoRBD (p)	Patients vs Controls (p)
M/F (% Male)	13/9 (59,1)	13/9 (59,1)	26/18 (59,1)	13/9 (59,1)	ns	ns
Age (yrs)	64,6 ± 7,9	63,5 ±9,2	64,1 ± 8,4	63,4 ± 8,0	ns	ns
Education level (yrs)	18,6 ± 3,4	19,0 ± 4,1	18,8 ± 3,7	13,8 ± 3,4	ns	< 0,001
Age of onset PD (yrs)	58,4 ± 9,0	57,9 ± 9,2	. .		ns	(-)
Duration of PD (years)	6,2 ± 4,1	5,6 ±2,4	34		ns	
Hoehn & Yahr	1,25 ± 0,6	0,9 ± 0,5	12	-	ns	340
MDS UPDRS 1 score	6,0 ± 3,5	5,4 ± 3,9	82	120	ns	-
MDS UPDRS 2 score	6,5 ± 3,8	7,0 ± 3,8	12	-	ns	-
MDS UPDRS 3 score	15,5 ± 7,5	14,9 ± 9,8	2 <u>0</u>	121	ns	121
MDS UPDRS 4 score	1,6 ± 2,4	0,6 ± 2,3	57	1070	ns	1.7
LEDD (mg)	654,3 ± 379,1	599,2 ±554,0	-	-	ns	-
Mean DA-LEDD (mg)	245,6 ± 552,7	113,9 ± 108,3	-		ns	
MOCA score	27,54 ± 1,6	27,45 ± 1,4	27,5 ± 1,5	27,9 ± 2,0	ns	ns
Depression (BDI)	8,6 ± 4,7	8,1 ±4,0	8,4 ± 4,3	5,8 ± 4,7	ns	0,04
Apathy (LARS)	-25,7	-27,1	-26,4	-28,6	ns	0,09
Impulsivity (UPPS)	87,1 ± 15,6	89,1 ± 15,2	88,1 ± 2,3	90,7 ± 2,7	ns	ns
ICD (QUIP)	0,2 ± 0,5	0,3 ±0,6	0,27 ± 0,5	0,09 ± 0,3	ns	ns
RT mean (ms)	596 ± 88	597 ± 82	596 ± 83	589 ± 65	ns	ns

The quantitative variable are shown as the mean and standard deviation (SD). M = male; F = female; PD = Parkinson's disease; RBD = REM sleep Behaviour Disorder; yrs = years; LEDD = levodopa equivalent daily dose; DA = dopamine agonist, MDS UPDRS = Movement disorder society-Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; BDI = Beck Depression Inventory; LARS = Lille Apathy Rating Scale; UPPS = Urgency Premeditation Perseveration Scale; ICD = Impulse Control Disorder; RT = Reaction Time.

Conclusions: The present study found a hypoactivation of the reward system in PD patients with RBD compared to those without RBD. These abnormalities may play a role in the increased risk for ICD previously observed in PD patients with RBD, further supporting the notion of an association between RBD and ICD in PD.

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Gait, freezing of gait and falls detection using wearable sensors: A systematic review

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Objective: An overview of the use of wearable systems to assess gait, freezing of gait (FOG) and falls in patients with Parkinson's disease (PD).

Background: Despite the large number of studies that have investigated the use of wearable sensors to detect gait and gait disturbances such as FOG and falls, little consensus has been achieved regarding device usage methodologies.

Methods: A systematic search in the PubMed and Web of Science databases was performed using a group of concept key words. The final search was performed in November 2016, and articles were selected based upon a set of eligibility criteria, and data extraction was performed using a predefined table.

Results: In total 39 articles were selected. Of those, 21 related to FOG, 14 to gait and 4 to falls. FOG studies were performed in either laboratory or home settings, with the shin as most preferable location and accelerometer as the most used sensor type. Validity measures ranged from 73-100% for sensitivity and 67-100% for specificity. Falls and fall risk articles were all home-based, mostly using one sensor containing accelerometers, in various positions. Most articles assessing gait consisted of pre-structured tasks performed in a laboratory environment. Gyroscopes and accelerometers were most commonly used, placed at the shin and/or axial body locations. Gait was detected with a sensitivity of 84-100% and specificity of 75-99%. By quantifying gait into parameters, some systems were able to detect differences between groups (PD-ON/PD-OFF and PD/non-PD).

Conclusions: Despite the promising validation initiatives reported in these studies, they were all performed in a relatively small sample sizes, and there was a lack of consistency in outcomes measured and results reported. Given these limitations, the validation of sensor-derived assessments of PD features would benefit from increased collaboration among researchers, aligning data collection protocols, and merging dataset.

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Measuring temporal irregularity in spiral drawings of patients with Parkinson's disease

S. Aghanavesi, M. Memedi, J. Westin (Borlange, Sweden)

Objective: The aim of this work is to evaluate clinimetric properties of a method for measuring Parkinson's disease (PD) upper limb temporal irregularities during spiral drawing tasks.

Background: Basal ganglia fluctuations of PD patients are associated with motor symptoms and relating them to objective sensor-based measures may facilitate the assessment of temporal irregularities, which could be difficult to be assessed visually. The present study investigated the upper limb temporal irregularity of patients at different stages of PD and medication time points.

Methods: Nineteen PD patients and 22 healthy controls performed repeated spiral drawing tasks on a smartphone. Patients performed the tests before a single levodopa dose and at specific time intervals after the dose was given. Three movement disorder specialists rated the videos of patients' performance according to six items of UPDRS-III, dyskinesia (Dys), and Treatment Response Scale (TRS). A temporal irregularity score (TIS) was developed using approximate entropy (ApEn) method. Differences in mean TIS between two groups of patients and healthy subjects, and also across four subject groups: early, intermediate, advanced patients and, healthy subjects were assessed. The relative ability of TIS to detect changes from baseline (no medication) to later time points when patients were on medication was assessed. Correlations between TIS and clinical rating scales were assessed by Pearson correlation coefficients and test-retest reliability of TIS was measured by intra-class correlation coefficients (ICC).

Results: The mean TIS was significantly different between healthy subjects and patients (P<0.0001). When assessing the changes in relation to treatment, clinical-based scores (TRS and Dys) had better responsiveness than TIS. However, the TIS was able to capture changes from Off to On, and the wearing off effects. Correlations between TIS and clinical scales were low indicating poor validity. Test-retest reliability correlation coefficient of the mean TIS was good (ICC=0.67).

Conclusions: Our study found that TIS was able to differentiate spiral drawings drawn by patients from those drawn by healthy subjects. In addition, TIS could capture changes throughout the levodopa cycle.TIS was weakly correlated to clinical ratings indicating that TIS measures high frequency upper limb temporal irregularities that could be difficult to be detected during clinical observations.

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Assessing Parkinson's disease motor symptoms using supervised learning algorithms

P. Angeles, Y. Tai, N. Pavese, R. Vaidyanathan (London, United Kingdom)

Objective: Implantable brain stimulators are now an established method of treating Parkinson's disease (PD). Determination of optimal neural stimulation parameters is complex and clinically demanding. The goal of this work is to develop a wearable sensor system to determine the optimum amount of treatment that should be given based on the severity of their symptoms. A necessary step in optimising the amount of treatment is to firstly quantify the severity of symptoms.

Background: Sensor-based assessments for one or two of the primary symptoms of Parkinson's disease have been documented but a sensor system that quantifies three of the primary symptoms using supervised learning and that has been tested on patients has yet to be explored [1]. The system uses two motion sensors, two muscle activity (mechanomyographic, MMG) sensors and one force sensor [Figure 1].

Methods: Trials were conducted on 13 PD subjects receiving DBS treatment and 3 healthy subjects. Subjects sat with the system attached to one of their arms (the most severely affected arm for PD subjects). The arm was then assessed and each assessment during this trial was repeated 3 times. The following assessments (demonstrated in [Figure 2]) were used: Rigidity - Cogwheel movement of the arm by the clinician (5 repetitions); Bradykinesia - Pronate and supinate the wrist (5 repetitions); Kinetic tremor - Index finger on nose to clinician's finger and back (5 repetitions); Postural tremor - Hold arm straight out for 10 seconds; Rest tremor - Rest arms on lap for 10 seconds. A clinician fed back the UPDRS score for each assessment. The UPDRS score was used to draw correlations from the severity of the subject's symptoms and the sensor data collected. Simple trees, linear support vector machines and fine k-nearest neighbours were used to assess correlations. A cross-validation with 5 folds was used to validate the models created.













Symptom	UPDRS range	Features	
Rigidity	0,1,2,3	(a) mean force (b) mean MMG from both MMG sensors	
Bradykinesia	0,1,2,3	 (a) mean angular velocity of both IMUs (b) standard deviation of angular velocity of both IMUs (c) standard deviation of quaternions of both IMUs 	
Kinetic Tremor	0,1,2,3	(a) standard deviation of quaternions of both IMUs (b) standard deviation of accelerations of both IMUs (c) mean accelerations of both IMUs	
Postural Tremor	0,1,3	 (a) standard deviation of quaternions of both IMUs (b) standard deviation of accelerations of both IMUs (c) mean accelerations of both IMUs 	
Rest Tremor	0,1,2,3	 (a) standard deviation of quaternions of both IMUs (b) standard deviation of accelerations of both IMUs (c) mean accelerations of both IMUs 	
Symptom	Simple Tree (%)	Linear SVM (%)	Fine KNN (%)
Rigidity	(a) 56.5 (b) 50.7	(a) 55.1 (b) 44.9	(a) 66.7 (b) 49.3
Bradykinesia	(a) 52.9 (b) 70.0 (c) 60.0	(a) 52.9 (b) 65.7 (a) 60.0 (b) 91. (c) 44.3 (c) 81.4	
Kinetic Tremor	(a) 84.3 (b) 81.4 (c) 82.9	(a) 87.1 (b) 87.1 (a) 98.6 (b) 97.1 (c) 87.1 (c) 100	
Postural Tremor	(a) 69.9 (b) 65.8 (c) 74.0	(a) 69.9 (b) 72.6 (a) 98.6 (b) 76.7 (c) 75.3 (c) 90.4	
Rest Tremor	(a) 85.9 (b) 77.5 (c) 85.9	(a) 88.7 (b) 80.3 (a) 94.4 (b) 87.3 (c) 81.7 (c) 100	

Results: The UPDRS score was used as the response for the models. The range of UPDRS and predictors (features) used for each symptom are given in [Table 1] and the validation results from the models are given in [Table 2]. **Conclusions:** The sensor system has so far been tested on 16 subjects and results show that the system is able to relate sensor data to UPDRS scores through machine learning models. The k-nearest neighbours model usually performed best (average 85.1 % successful classification).

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Using measurements from wearable sensors for automatic scoring of Parkinson's disease motor states *I. Thomas, F. Bergquist, R. Constantinescu, D. Nyholm, M. Senek, M. Memedi (Falun, Sweden)*

Objective: The aim of this study was to investigate the concurrent validity of an objective gait measure for assessment of motor states in advanced Parkinson's disease (PD) patients.

Background: Five million people suffer from Parkinson's disease (PD) worldwide. The use of wearable sensors could help monitor disease progression and medication efficacy.

Methods: A single center, single dose, open label clinical trial was conducted in Uppsala, Sweden in 2015. Patients repeatedly performed a walk task while wearing 3D accelerometry and gyroscope sensor units on all four limbs. Assessments were made once before dose administration, once at time of administration, and at pre-specified timepoints until the medication effect had worn off. Each test took approximately 15 seconds and consisted of a 2.5 meter straight walk, which was repeated three times by making 2 U-turns in the process. The patients were also

video recorded and the videos were rated by three movement disorder experts according to a Treatment Response Scale (TRS), ranging from -3 (very Off) to +3 (very dyskinetic) and a Dyskinesia Rating scale (DysRS), ranging from 0 (no dyskinesia) to 4 (severe dyskinesia). For the predictive modelling, 32 features from each sensor were extracted together with 24 features that quantified the differences in symmetry between the sensors (152 total features). Principal component analysis was employed on the features of each sensor and the principal components of the four sensors together with the symmetry features were used as predictors in two separate support vector machine (SVM) models. One model mapped the features to the TRS scale and the other to the DysRS scale. **Results:** Preliminary results from 7 patients showed good predictive ability of the SVM models in a leave-one-individual out cross-validation setting. The predictions on the TRS scale had correlation of 0.79 to the experts' mean ratings and Root Mean Square Error (RMSE) of 0.70. The predictions in the DysRS scale had correlation of 0.79 and RMSE of 0.47. The results for the seven patients can be seen in figure 1.



DysRS. The raters' mean values are colored in red and the models' predictions are colored in blue.

Conclusions: The results of the study indicate that the use of wearable sensors when performing walking tasks can generate measurements that have a good correlation to subjective expert assessments. This could be useful during individualized evaluation of symptoms and treatments.

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Assessment of graphomotor impairment in patients with Spinocerebellar ataxia and Parkinson's disease *M. Thomas, A. Stezin, A. Lenka, N. Thota, P. Pal, R. Yadav (Bengaluru, India)*

Objective: The study aimed to assess the kinematic characteristics of handwriting in patients with Spinocerebellar ataxia (SCA) and to compare it with patients with Parkinson's disease (PD) and healthy controls (HC). **Background:** Handwriting abnormalities are commonly observed in patients with Parkinson's disease (PD) and Spinocerebellar ataxia (SCA). Digitizing tablet technology has revolutionized the study of kinematic variables of

handwriting. Although several studies have explored the kinematic properties of handwriting in PD, similar studies in patients with SCA are few. As handwriting analysis may help in measuring the response to treatment, it is essential to identify the basic kinematic abnormalities of handwriting these disorders.

Methods: Thirty patients each with SCA and PD, and 30 age-gender matched HC were studied. Severity of motor symptoms were measured by the Scale for the Assessment and Rating of Ataxia (SARA) for patients with SCA and by the Unified Parkinson's Disease Rating Scale (UPDRSIII) for patients with PD. The subjects performed five standardized handwriting tasks on a digitizer (Wacom Intuos CTL-470). The data was collected and analysed using MovAlyzeR, a handwriting analysis software.

Results: Compared to the HC, handwriting of both PD and SCA groups were: (1) slower, as measured by absolute velocity (p < 0.01), (2) more dysfluent, as measured by number of peak acceleration points (p < 0.01), (3) smaller in size, as measured by the trace length of the writing (p < 0.01). The trace length of writing was significantly less in SCA (1.4 ± 0.5 cm) compared to PD (1.5 ± 0.6 cm) whereas the average velocity was significantly decreased in PD (2.0 ± 1.5 cm/s) compared to SCA (2.5 ± 1.3 cm/s).

Conclusions: Handwriting abnormalities in SCA and PD include disturbances in velocity, fluency and size. Our results suggest that micrographia, which is considered a clinical sign of parkinsonism, may also be present in SCA. Analysis of handwriting can be used as a simple and objective measure to determine disease severity in SCA and PD. These findings may also have relevance while designing rehabilitative interventions aimed at preserving the quality of life in patients with these debilitating diseases.

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PDSS: a novel mobile-based Parkinson's disease severity score

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Objective: To propose a novel mobile-based Parkinson's Disease Severity Score (PDSS) to provide high resolution and objective severity monitoring for patients in the home setting.

Background: Currently, the principal means of assessing disease severity is assessed through subjective, episodic rating scales performed primarily in the clinic. New tools are needed to enable objective, high-frequency assessments outside the clinic.

Methods: Using the HopkinsPD app [2], 71 patients with PD who were on medication (Table 1) completed 5,800 self-administered active tests in pairs -- right before and within one hour after their first dose. The active tests are designed to measure aspects of motor function such as gait, voice, dexterity, and reaction time. A novel machine learning algorithm for disease severity score learning [1] was used to train a model that maps a vector of measurements (490 features in aggregate across all tests [2]) to a scalar severity score, the PDSS. The learning algorithm relies on the assumption that the severity ordering before and after medication is correct in the majority of training examples provided. 10-fold cross validation is used to evaluate model performance. Model accuracy is defined as the ratio of active tests in which PDSS decreases after the first dose.

Results: The average accuracy over all participants was 67%. Mainly, over 20% of individuals (Group A) show a significant severity decrease after medication (with significant defined as accuracy > 80%). Nearly 30% of individuals (Group B) did not show a significant or consistent severity decrease after medication (defined as accuracy < 60%). Figures 1 ~ 3 compare the two groups on disease duration, duration of medication, and daily dosage respectively. They suggest that patients who have a longer PD history and medication period are more likely to experience significant decreases in disease severity after medication. A detailed example of short-term and long-term severity trajectories is provided in Figure 4.





Characteristic	Parkinson disease participants (N=71)
Age (SD)	61.1 (8.1)
Percent women	38%
Percent white	100%
Percent Hispanic/Latino	8%
Percent country of residence, United States	89%
Percent with college education	96%
Disease duration, years (SD)	6.6 (4.8)
Duration taking medications for Parkinson disease, year (SD)	3.8 (4.0)

SD = standard deviation



1) roch0769 (first dose LED = 119 mg, daily LED = 712.5 mg) from Group A had a significant severity decrease after the first dose and a slight severity increase over time from May 2015 to July 2015;



2) roch0359 (first dose LED = 120 mg, daily LED = 120 mg) from Group B did not show a consistent severity decrease after the first dose and that severity was stable between November 2014 and February | 2015. (The segments connecting each red cross to green triangle yield the severity change after an individual's first dose of that day. The red and green trend lines yield the smoothed, locally weighted trajectories (LOESS) of PDSS before and after a patient's first dose, respectively.)

Conclusions: The Parkinson's Disease Severity Score provides a new way to monitor both daily severity variation and long-term progression with high granularity. Our preliminary results indicate that PDSS may be detecting changes in individuals with PD who are more likely to be fluctuators (have had longer disease and medication histories).

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Can three-dimensional visual cues delivered via smart glasses reduce freezing of gait in patients with Parkinson's disease?

S. Janssen, J. Nonnekes, B. Bolte, M. Bittner, T. Heida, Y. Zhao, R. van Wezel (Enschede, Netherlands) **Objective:** Investigate the efficacy of augmented three-dimensional (3D) visual cues delivered via smart glasses on improving freezing of gait (FOG) and gait stability in patients with Parkinson's disease (PD) and FOG (PD-FOG). **Background:** FOG is characterized by paroxysmal gait arrests preventing effective forward movement. The timing and scaling impairments involved in FOG extend to gait in between FOG episodes. External cues like transverse lines on the floor reduce FOG and improve gait parameters in a subset of patients, but their use in daily life is limited by practical constraints. Smart glasses could deliver portable, personalized cues, but their efficacy has yet to be established.

Methods: 25 patients with PD-FOG performed a walking trajectory aimed at eliciting FOG while wearing customized smart glasses that could provide augmented cues in the central visual field. Five different cueing conditions ('no cue', 'transverse bars on the floor', 'metronome', 'augmented bars' and 'augmented staircase') were compared. FOG episodes were scored from video recordings; motion data was recorded from inertial sensors attached to all four limbs, the trunk and head.

Results: Out of 25 participants [19 males, mean age 72 years, Hoehn & Yahr 2-3], 20 participants walked each cuetrajectory combination twice, 5 participants once. A total of 300 FOG episodes (222 during turning) occurred in 19 out of 25 participants. The Friedman test showed a statistically significant difference amongst all conditions for the number of FOG episodes ($?^2(4) = 9.936$, p = 0.042) and total duration of FOG ($?^2(4) = 11.414$, p = 0.022), but pairwise comparisons yielded no statistically significant difference between cues. Results were similar when imputing missing second sessions from first sessions, and when analyzing FOG during turning and non-turning separately. Participants preferred the metronome most, then the bars on the floor, the augmented bars via the smart glasses, no cue, and the augmented staircase the least.

Conclusions: Our study shows no beneficial effect of augmented 3D visual cues delivered via customized smart glasses on number and duration of FOG. Currently available smart glasses which are able to project cues in the central visual field are rather bulky and heavy. Indeed, participants considered the smart glasses uncomfortable, which might have caused distraction, interfering with the effect of all cues.

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Design and personalisation of new upper-limb dynamic orthoses for dystonia and dyskinesia

L. Garavaglia, M. Ferari, A. Lo Mauro, E. Pagliano, G. Baranello, B. Bassi, A. Aliverti, S. Pittaccio (Lecco, Italy) **Objective:** The study proposes a method to obtain anatomically- and functionally-personalised orthotics for the dynamic postural control of the upper limb.

Background: The orthotic treatment of secondary dystonia and dyskinesia is not well characterised in the literature. Some studies suggest that limiting the range of motion of some joints in the limb kinematic chain may improve overall functional performance. Personalisation of the orthosis action seems essential in order to prevent excessive constraint, hypertone and guarantee comfort, but the necessary biometric and functional assessment of the patients is often prevented by the involuntary motion caused by movement disorders (MD).

Methods: Five children (12.2±5.6 years old) with MD pictures comprising secondary dystonia and dyskinesia took part in the study. As conventional laser-scanning methods and direct moulding are difficult to use for patients with MD, due to the continual involuntary body motion, we developed a topologically structured 105-maker set-up and employed optoelectronic photogrammetry as a means to acquire upper-limb and chest wall geometry. One timeframe (0.017 ms) is sufficient to obtain the required data. Incidentally, arm kinematics is available to identify the most affected arm degrees of freedom. The marker point cloud was converted into a meshed geometry, and a positive model of the limb was obtained by milling, upon which the thermoplastic orthosis shells were shaped. Personalised fixtures were 3D-printed to hold nonlinear springs of Ni-Ti alloy, which provide a mild patient-specific dynamic joint constraint.

Results: The method is robust. The digital and physical arm models reproduce the main features of the limb and are smooth enough to allow orthosis shell moulding without any need for manual correction. The personalised fixtures and alloy characteristics endow the device with a patient-specific dynamic action (spring force and direction). Patients found the orthoses comfortable and were wearing them in excess of 6 hours a day for a month.

Conclusions: The method was found to be very useful to build personalised orthotic devices for children with extreme involuntary movements. The all-in-one-frame capture of limb surface and the orthosis processing that can be carried out almost without involving the patient, make this technique very acceptable and more time-efficient for children with dystonia or dyskinesia.

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Instrumental measurement of stepping in place - detection of asymmetry and freezing of gait

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Objective: To detect freezing of gait (FoG) and quantify movement asymmetry from markerless full body motion capture with Microsoft KinectTM during the execution of a 40 seconds "stepping in place" task.

Background: Asymmetry of limb movements is one characteristic and treatment-responsive feature of Parkinson's disease (PD). Freezing of Gait (FoG) is a frequent and debilitating symptom in those with advanced stages of the disease and has been related to reduced mobility and fall risk. However, it often evades direct observation in standard clinical assessment and thus screening for FoG mainly relies on patient history.

Methods: We used Motognosis Labs in combination with Microsoft Kinect V2 to record execution of a stepping in place task for 40 sec at self-selected speed and movement amplitude. We included 15 people with PD (PwPD) of different disease severity (UPDRS 7-55) and 50 healthy subjects (HC). Cadence [steps/min] as well as knee and hand amplitudes in anterior-posterior (a-p) direction [m] were calculated using Kinect joint time series. Gait

asymmetry was described for knee movement amplitudes as absolute differences [m] and differences as percentage of mean [%]. FoG was detected using windowed frequency analysis of knee movements.

Results: As expected, PwPD featured slower cadence (p=0.097) and smaller amplitudes of knee and hand excursions (p<0.001 and p<0.001) compared to HC. Although absolute side differences of knee excursion showed similar means and distributions in both groups, mean relative differences were increased in PwPD (15.89% (CI: -15.52 - 47.32) versus 6.54% (CI: -0.92 - 14.0) (HC), p = 0.041), consistent with movement asymmetry in independent clinical ratings. Step frequency analysis detected 7 FoG episodes in recordings from 4 PwPD but not in HC. For all patients, hesitation/freezing was also noted in independent clinical rating. [SM1]

Conclusions: Using an easy-to-use commercially available infrared sensor and a clinically applicable stepping paradigm, we were able to extract quantitative descriptors for bradykinesia, hypokinesia as well as asymmetry of movement in accordance with clinical ratings. Interestingly FoG episodes were observed in four PwPD that were also detected by analysis of kinematic signals alone.

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Final validation of an electronic diary for motor fluctuations and dyskinesias evaluation in PD patients: Comparison with paperback diary

C. Terroba, A. Medina, F. Nanni, V. Bruno, D. Cerquetti, M. Rossi, M. Merello (Buenos Aires, Argentina) **Objective:** To determine the reliability and compliance to an electronic motor diary in PD patients. **Background:** Despite paper diaries are widely used, adherence, duplication, fraudulent registry entries are frequent, data post processing and evaluation is time consuming and dyskinesias impact in life activities have not been assessed in an electronic device.

Methods: : We developed an electronic Android based open source touch screen application with medication alarms, adjustable intervals and medication dose settings to prevent retrospectively data entry to evaluate ON-OFF periods and dyskinesias. Validation of the electronic motor diary against medical examination was previously reported ^{(1).} A prospective second phase was completed with 16 consecutive patients that underwent a diary training session for a modified paper version of CAPSIT-PD and electronic diary support by the tablet. Participants were randomly assigned to start with one or other and they completed the diary during the same three consecutive days in two weeks. They selected, each 30 min periods, one of five possible states recommended for the registry of motor fluctuations by CAPSIT-PD. The UDyRS (historical section part 1 and 2) was completed when each diary were finished.

Results: Nine patients were male. The mean age and disease duration were 64.0 ± 7.1 and 12.3 ± 5.9 years respectively, mean education years was 12.5 ± 3.5 , mean MoCA was 25.2 ± 2.4 . The values of mean percentages and SD for the awake day and total sleep time for each diary categories for all patients over evaluation days were not different. There were no significant differences between both diaries in OFF, partial OFF, ON, freezing dystonia times and number of falls. However differences were found for the categories dyskinesias time and sleep time [p=0.02 and p=0.04, respectively].

Conclusions: This electronic motor diary showed to be reliable for ON-OFF states and dyskinesias identification and classification according their impact on life's activities. The logger showed no-inferiority when compared to the paper diary.

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Improved detection of gait abnormalities in Parkinson's disease using an IMU sensor-based system

B. Shiwani, S. Roy, J. Kline, M. Saint-Hilaire, C. Thomas, M. Gennert, G. De Luca (Natick, MA, USA) **Objective:** To develop an automated system that uses a limited set of IMU sensors to improve the detection of gait abnormalities in Parkinson's disease during unconstrained activities of daily living.

Background: The use of wearable sensors and automated algorithms for detecting and monitoring motor symptoms of Parkinson's disease (PD) holds promise for improving medical assessments and treatments. However, present sensors based on accelerometers alone use energy-frequency metrics that do not capture some of the more subtle abnormalities in gait such as shuffling or reduced arm swing. To overcome this challenge, we developed an approach that uses IMU sensors to capture these gait abnormalities and compare them to accelerometer metrics during wearing off.

Methods: Sensors were placed on the upper- and lower-limbs of patients with mild to moderate PD (n=6; age: 60.8 \pm 11 y; Hoehn & Yahr 1-3). Sensor and video recordings were acquired during 3-hour experiments of unconstrained activity in a simulated apartment setting. On-Off medication states and activity type (sitting, standing, and walking)

were annotated from the video by movement disorder experts. Metrics derived from the sensor data during walking were compared for accelerometer and gyroscope data.

Results: Both accelerometer and gyroscope data could be used to measure the energy and dominant frequency of walking. However, the gyroscope data provided a greater ability to capture the degree of arm swing and shuffling of steps that could not be obtained from the accelerometer. When comparing these gyroscope features with the accelerometer features, we found that the gyroscope features showed significant difference between the On-Off transitions, while features from the accelerometer did not (Figure 1).



Figure 1: Comparison of features computed from accelerometer (left) and IMU (right) signals. Significant differences between "on" and "off" medication states were only observed in IMU data.

Conclusions: The use of IMU sensors to measure not only accelerometer but also gyroscope data provides an enhanced means for detecting gait abnormalities in PD during On-Off transitions. The improved ability of the gyroscope metrics to discriminate between these transitions and identify more characteristics of gait abnormalities in PD (such as shuffling and reduced arm swing), supports the preferred use of IMU over accelerometer sensors for automated body-worn gait analysis. These advantages may be of value in early detection of PD or as an outcome measure for medication titration.

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Efficacy of smartphone-enabled active tests in automated PD severity assessment

A. Zhan, S. Mohan, M. Elson, E. Dorsey, A. Terzis, S. Saria (Baltimore, MD, USA)

Objective: To compare the efficacy of five smartphone-enabled active tests in detecting severity changes after medication, via an automated Parkinson's Disease Severity Score (PDSS).

Background: Traditional severity metrics such as UPDRS provide low-resolution assessments that can only be collected by physicians in clinic. Self-administered active tests via smartphone provide a new way to monitor the granular progression of PD severity on a daily basis out of clinic.

Methods: Using the HopkinsPD app [2], 71 individuals on medication (Table 1) record measurements from 5,800 self-administered active tests in pairs -- right before and within one hour after their first dose -- to measure aspects of motor function such as voice, postural instability, gait, finger dexterity, and reaction time. A novel machine learning algorithm for disease severity score learning (DSSL) [1] is used to train five models that map this vector of measurements to a scalar severity score, the PDSS. The algorithm assumes that the severity ordering, before and after medication, is correct in the majority of training examples provided. 10-fold cross validation is used to evaluate model performance, under the assumption that no individual appears in both the train set and test set. Model accuracy is defined to be the ratio of active tests in which PDSS decreases after the first dose. An active test is labeled effective if it is at least 60% accurate.

Results: 89% and 69% of the population had at least one and two effective active tests, respectively. Both the gait and finger dexterity tests -- the two most informative tests -- are effective in more than half of all subjects (Table 2). 17% of patients for whom 3 or more individual tests were effective had long-standing disease duration, with a mean

of 8.8 years. The 11% of patients for whom no active test was effective all had short medication histories of less than five years. Across the voice, finger dexterity, and gait tests, PDSS was at least 70% accurate on between 30% and 40% of patients (Figure 1).

Baseline characteristics of study participants

Characteristic	Parkinson disease participants (N=71)
Age (SD)	61.1 (8.1)
Percent women	38%
Percent white	100%
Percent Hispanic/Latino	8%
Percent country of residence, United States	89%
Percent with college education	96%
Disease duration, years (SD)	6.6 (4.8)
Duration taking medications for Parkinson disease, year (SD)	3.8 (4.0)

SD = standard deviation

Efficacy of smartphone-based active tests

Active Test	Voice	Postural instability	Gait	Finger dexterity	Reaction Time
Efficacy (%)	48	34	54	52	27

The table above gives the percentage of patients in the population for whom each given test was deemed effective, i.e. for whom PDSS has a 60% or greater accuracy in correctly ordering the high/low severity states.

ECDF of accuracies over the five active tests respectively



Conclusions: That PDSS, generated from measurements in smartphone-enabled active tests, is effective in tracking motor fluctuations for at least half of the population in close to 3 of 5 active tests is promising. It warrants further investigation into the feasibility of automated severity scoring in monitoring the short-term and long-term variation of PD severity.

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Patient clustering through a mobile-based PD Severity Score

A. Zhan, S. Mohan, M. Elson, E. Dorsey, A. Terzis, S. Saria (Baltimore, MD, USA) **Objective:** To demonstrate that PD patients can be clustered based on their performance on smartphone-enabled active tests. **Background:** Treatment decisions of PD require granular information about an individual's symptom profile and disease severity changes over time. Currently, severity is assessed through subjective, episodic rating scales performed primarily in clinic. New tools are needed to enable high frequency assessments out of clinic that add insight into the relationships in PD progression between similar patients.

Methods: Using the HopkinsPD app [1], 71 individuals on medication record measurements from 5,800 selfadministered active tests in pairs -- right before and within one hour after their first dose -- to measure aspects of motor function such as gait, voice, dexterity, and reaction time. A novel machine learning algorithm for disease severity score learning (DSSL) [2] is used to train five models that map this vector of measurements to a scalar severity score, the PDSS. The algorithm assumes that the severity ordering, before and after medication, is correct in the majority of training examples provided. Model accuracy is defined as the ratio of active tests in which PDSS decreases after the first dose. A biclustering algorithm is used to cluster patients on their accuracy across the 5 active tests. Common in gene expression profiling, it permutes the rows and columns of a matrix such that rows with similar characteristics across a subset of columns are grouped together.

Results: Shown in Table 1 and Figure 1, 71 patients were clustered into six different groups based on their performance across the 5 smartphone-enabled tests. The darker the region, the more effective PDSS was in detecting motor fluctuation for that patient. While we notice individuals for whom all tests were effective (roch0338), there are others for whom none were (roch1034). Moreover, relationships exist at an intra-cluster level as well. Patients from Cluster 0 show strong severity fluctuation on both the finger dexterity and gait tests. Those from Cluster 5, however, experience strong severity fluctuation on the voice and gait tests instead.

Chuster	Number of	Average Accuracy (%)						
Cluster	patients	Reaction Time	Postural instability	Voice	Finger dexterity	Gait		
0	10	44	62	65	72	83		
1	20	50	57	61	73	49		
2	4	68	50	59	41	38		
3	13	55	48	65	53	62		
4	14	54	63	50	55	64		
5	10	52	45	74	68	75		

Efficacy of smartphone-based active tests

Biclustering of Patients (darker cells indicate higher PDSS accuracy)



Conclusions: That 6 unique clusters account for patient performance across the 5 tests is promising. Exploration of the relationships between intra-cluster PDSS trends will allow clinicians to study tailored treatment regimens on distinct subgroups of the population.

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A review of telemedicine for Parkinson's disease: But what's happen in Asia?

W. Rattanachaisit, P. Panyakaew, R. Bhidayasiri (Bangkok, Thailand)

Objective: To conduct a systematic review of telemedicine for Parkinson's disease.

Background: Recent literature indicates that globally significant numbers of Parkinson's disease (PD) patients have limited access to specialist care in PD. Telemedicine (TM), the use of telecommunication technologies to provide medical information and services, may be a solution to this problem.

Methods: Medline database was searched to identify relevant literature (published between January 1986-December 2016). 22 studies related to TM in PD were identified: almost all studies (21, 95.4%) utilized TM to provide remote care to PD patients, one study (4.6%) used TM as part of an educational program for healthcare providers. Study primary outcomes were classified into four main categories: 1) feasibility, reliability and validity, 2) cost and time saving, 3) effectiveness of disease management, and 4) patient's satisfaction.

Results: All TM studies were conducted in developed countries, with equal representation between the United States (43%) and European countries (43%), but no studies in Asia identified (Fig. 1). 14 out of 21(66%) studies established feasibility and validity of TM. The rest demonstrated cost and time saving benefits of TM in follow-up assessment and rehabilitation with smartphone TM applications, increasing in popularity.

-	Referen ce	literature resource (country)	TM technologies	Main results
Feasibility and validity	7,8,9,11, 15,26,28 ,33,40,4 1,52,53	USA, United Kingdom, Australia, Netherland, Spain, Finland, Sweden	IVC, online web camera, EST, Telephone-based, SMS, website, smartphone	Feasible and valid of motor assessment, speech test & therapy with LSVT, CBT, medication remider & adjustment, Apomorphine infusion, assist LCIG titration
Benefit from cost & time saving	15,22, 50,51	USA,Canada	Telehealth unit, IVC	Saved travel hours, distance, and cost in travel & lodging
Effectiveness of TM in management aspects	5,15,20 21,33,28 ,50,53	Australia, USA, Netherland	Telephone . website online Mobile phone based	TM were effective to LCIG titration and apomorphine infusion TM improved <u>CBT</u> , speech rehabilitation, No difference in QoL.
Satisfactory of PD patients to TM intervention	5,22 40, 41,51, 53	USA, Finland, Australia, Sweden	IVC, online speech therapy, telehealth unit	Partient and health care provider satified with the technology

Table of Categorized publications of telemedicine for Parkinson's disease patient care

The LSVT = Lee Silverman Voice Treatment, IVC = Interactive video conference, CBT= Cognitive Behavior Therapy, TM= telemedicine, LCIG = Levodopa Carbidopa Intestinal Gel



Conclusions: TM provides a practical solution for delivering remote assessment of PD motor symptoms and evaluation of treatment response; however, it is still not universally available. Advances in, and reduced cost of, telecommunications means it is unlikely that technology limitations are the sole reason for this deficit, particularly in Asian countries where cultural differences, and other preferences should be explored. In our opinion, TM is another option to deliver patient-centered multidisciplinary care and education when direct assessment is impractical.

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Saving veterans time, miles, and money: cost analysis of video telemedicine evaluation of deep brain stimulation (DBS) candidacy at the VA

N. Witek, S. Heath, C. Tanner, N. Galifianakis (San Francisco, CA, USA)

Objective: This study evaluated cost, time, and mileage saved utilizing video-telemedicine during the initial presurgical evaluation for deep brain stimulation as treatment for tremor at San Francisco VA Medical Center (SFVA). **Background:** The reasons for the existing disparities in surgical care amongst patient with tremor are complex, but one reason includes limited number of specialty facilities that offer the surgery. The SFVA receives referrals for DBS for the treatment of tremor from across large territory of the United States, including states as far as Minnesota, Indiana, and Michigan. The time, miles, and money spent traveling for initial in-person evaluation, and the savings incurred by using video telemedicine during initial surgical evaluation is unknown.

Methods: This study is a retrospective cross-sectional study reviewing all out-of-state referrals to the SFVA from 2008 to 2013 for DBS therapy for the treatment of tremor. Out of a total of 148 initial pre-surgical DBS evaluations completed at SFVA, there were 60 out-of-state DBS referrals identified over the six-year period for surgical treatment of essential tremor or Parkinson's disease. Of these, 24 patients underwent in-person DBS evaluation and 36 patients underwent initial consultation via video-telemedicine. Based on the patients' zip codes, the estimated hours, miles, and money spent traveling were calculated to and from appointments at the SFVA and their local VA where the video telemedicine appointment would be held.

Results: The average time, mileage, and cost of round-trip travel for a single in-person pre-surgical evaluation at SFVA per patient was 15.6 hours (range 9.5-27.8 hours), 2,938.7 miles (range 357-4,165 miles), and \$896 (range \$350-\$1,122). The average round-trip travel for a pre-surgical evaluation done utilizing video-telemedicine at patient's local VA per patient was 1.4 hours (range 16 minutes-2.6 hours), 57.4 miles (range 8.8-323.5 miles), and \$12.06 in travel cost (range \$1.72-\$16.59). Overall, the 36 patients in the video-telemedicine cohort saved an estimated total of 116,518 miles, 569.2 hours, and \$33,246 in roundtrip travel during their initial pre-surgical evaluation.

Conclusions: The use of video telemedicine during the initial pre-surgical evaluation for deep brain stimulation saved veterans time, mileage, and money in travel when compared to traditional in-person evaluation.

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Personal KinetiGraph devices assessing efficacy of continuous enteral carbidopa/levodopa infusion therapy *J. Margolesky, C. Luca (Miami, FL, USA)*

Objective: To assess the utility of Personal KinetiGraph (PKG) devices to objectively quantify difference in motor symptoms and motor fluctuations before and after the initiation of continuous enteral infusion therapy with carbidopa/levodopa (CD/LD) gel formulation.

Background: Continuous enteral infusion therapy with CD/LD is an alternative to DBS for patients with Parkinson's disease (PD) suffering from motor fluctuations associated with oral CD/LD. A PKG device is a wrist-worn accelerometer used to quantitatively assess a patient's motor fluctuations and objectively judge the efficacy of a therapeutic intervention.

Methods: Two patients wore the PKG device for 6 days prior to the initiation of and 6 days after a 3-month titration period of enteral CD/LD. PKG measures included in the assessment were: bradykinesia score (BK), dyskinesia score (DK), motor fluctuation score (FDS), percent time with immobility (PTI), and percent time with tremor (PTT). Results: Patient 1 was a 61 year-old with 6 years of PD and Patient 2, a 70 year-old with 25 years of PD. Patient 1's PKG scores before and after intervention were as follows: BK 29.4 to 21.9, DK 1.1 to 1.7, FDS 6.8 to 9.8, PTI 4.2% to 2.5%, and PTT 0.1% to 0.3%. Patient 2's PKG scores were as follows: BK 23.5 to 25.8, DK 0.6 to 0.6, FDS 8.9 to 8.6, PTI 10.4% to 12.4%, and PTT 3.2% to 5.3%. Subjectively, Patient 1 developed mild dyskinesias and Patient 2 more bothersome dyskinesias post therapy. Both patients had resolution of FOG, improved quality of life and improvement in motor fluctuations. These subjective results were not fully reflected in the objective PKG results. **Conclusions:** The experience of our 2 patients supports the efficacy of continuous enteral infusion therapy with CD/LD to improve motor fluctuations, including FOG, and to improve quality of life. These positive results were not entirely reflected in the quantitative PKG scores. Patient 1 noted mild dyskinesias and the PKG device noted an increase DK. Patient 2 noted moderate dyskinesias and the PKG device noted no change in DK, but an increase PTT, which may have reflected a misrepresentation of ongoing dyskinesias. Our small sample size does not allow for a generalization of the utility of PKG to assess motor improvement after the initiation of a therapy, but does reinforce the importance of a patient's subjective assessment and the objective clinic exam in assessing a therapeutic response.

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Patients' perspective of physicans' counseling on exercise in Parkinson's disease (Pd)

J.Y. Park, V. Shanker (New York, NY, USA)

Objective: To assess if exercise counseling during appointments translates to knowledge or action in PD patients **Background:** Aerobic activity can improve motor function, mood, cognition, and may have a neuroprotective role in PD. The American College of Sports Medicine recommends 150 minutes/week of aerobic activity in older adults, in addition to strengthening, balance work, and stretching.

Methods: Follow-up patients with PD in a movement disorders center (MDC) were identified through medical record review. Participants completed a survey which required recording exercise performed over the previous week. T-tests and Wilcoxon-rank-sum for continuous variables and chi square tests for categorical variables were performed to compare the groups who recorded = 150 minutes of aerobic activity (AA) vs. those who did not (iAA). **Results:** 103 patients were asked to complete the survey, 86 (83%) patients (29 women, 60 men; mean age 68.2 years-old) returned the survey and 63 (61%) patients completed the exercise table. Of the 63 patients who completed exercise calendars, 18 recorded = 150 minutes of aerobic activity (28.6%). There was no statistical difference between AA vs iAA when comparing age, disease duration, co-morbidities, BMI, UPDRS motor score ("old version"), Hoehn & Yahr score, assisted device use, and external or personal barriers. There was a trend for women to meet minimum aerobic requirements (44% AA vs 22% iAA, p=.08). Thirty-six percent of patients reported no counseling. There was no difference (AA vs iAA) in the perceived amount of time spent receiving counseling. More AA patients sought outside sources of education (89% vs 70%, p=.19)

Conclusions: In a MDC where exercise is routinely counseled, < 1/3 of patients complied with aerobic recommendations and $\sim 1/3$ did not recall receiving counseling. Perceived counseling did not influence whether recommended aerobic requirements were met. Routine office counseling may be an insufficient strategy for compliance. Alternative or enhanced counseling strategies should be pursued.

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Treadmill Training, Tai Chi, Dance and More: A Meta-Analysis on the Effectiveness of Different Physiotherapy Modalities in Parkinson's Disease

D. Radder, N. de Vries, M. Faber, M. van Nimwegen, S. Keus, B. Bloem (Nijmegen, Netherlands) Objective: Physiotherapy (PT) is widely recognized as an intervention for people with Parkinson's disease (PD). Many controlled trials have evaluated conventional PT, and the evidence for newer treatments such as Tai Chi or dance is increasing. Here, we evaluate the effectiveness of conventional PT, treadmill training, cueing, dance and Tai Chi, as compared to no or sham treatment.

Background: Many non-pharmacological interventions can contribute to the management of PD, and PT is applied most widely. PT consists of many different types and modalities. Their mutual main goal is to maximize the quality of movement, functional independence and general fitness, whilst supporting self-management. There is no review that summarizes the effectiveness of these treatment modalities in current literature.

Methods: As a basis for the European Guideline for Physiotherapy in PT (published in 2012), we performed a metaanalysis of the available literature on PT in PD. We have updated this meta-analysis with the latest scientific evidence, using the same search strategy. The extensive search strategy can be found at

www.parkinsonnet.info/euguideline. In total, 182 controlled clinical trials were found, of which 114 were included in the analysis. The remaining 68 studies were excluded for various reasons, mainly because the intervention was not considered to be PT (e.g. only one day of treatment or combined treatments).

Results: In table 1 we present the preliminary results. All interventions showed effectiveness for people with PD. Conventional PT significantly improved all outcomes shown in the table, except for the 6 Minute Walk Test. Treadmill training only improved walking speed. Cueing significantly improved gait parameters, while dancing was mostly effective for motor symptoms and balance measures. Finally, Tai Chi had the biggest effect on motor symptoms, balance and gait.

			Levelse to a	0	W-14116- 31
	Conventional PT	Treadmill training	Cueing (n=7)	Dancing (n=9)	Tai Chi (n=7)
	(n=64)	(n=27)			
MDS-UPDRS-	0.19 (0.07, 0.31)*	-0.01 (-0.22, 0.21)	0.14 (-0.28, 0.55)	0.59 (0.28, 0.90)**	0.36(0.17, 0.56)**
III and					
UPDRS-III					
Balance					
outcomes					
TUG	0.19 (0.04, 0.33)*	-0.16 (-0.50, -0.18)	0.57 (0.13, 1.00)*	0.58 (0.25, 0.90)**	0.44 (0.22, 0.66)**
885	0.33 (0.15, 0.51)**	0.21 (-0.13, 0.55)		0.77 (0.39, 1.16)**	0.21 (-0.07, 0.49)
Gait					
outcomes					
6MWT	0.08 (-0.06, 0.22)	0.24 (-0.02, 0.51)		-0.03(-0.55, 0.49)	
10MWT	0.46 (0.14, 0.78)*	0.01 (-0.45, 0.46)			
Walking	0.14 (0.00, 0.28)*	0.54 (0.34, 0.73)**	0.75 (0.42, 1.09)**	0.27 (-0.14, 0.68)	0.36 (0.13, 0.59)*
velocity					
Stride length	0.30 (0.06, 0.53)*	0.20 (-0.04, 0.45)	0.31(-0.25, 0.86)		0.32 (0.07, 0.56)*
Cadence	0.52 (0.28, 0.77)**	0.12 (-0.15, 0.39)	0.87 (0.38, 1.36)**		
Quality of Life					
outcomes					
PDQ-39 and	0.12 (0.02, 0.23)*	-0.09 (-0.43, 0.26)	-0.01 (-0.78, 0.76)		
PDQL					

Table 1 Outcome measures related to the type of intervention

Data as standardized mean difference (95% CI). Positive effect estimates mean positive results on each outcome measure.

Statistically significant effect, ps0.05
 Statistically significant effect, ps0.001

PT = physiotherapy; MDRS-UPDRS-III = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale part III; UPDRS-III =

Unified Parkinson's Disease Rating Scale part III; TUG = Timed Up and Go; BBS = Berg Balance Scale; 6MWT = 6 Meter Walking Test; 10MWT = 10 Minute

Walking Test; PDQ-39 = Parkinson's Disease Questionnaire 39; PDQL = Parkinson's Disease Quality of Life Questionnaire

Conclusions: This meta-analysis shows that a variety of PT interventions are effective for patients with PD. Based on the present results, an evidence based decision for a specific treatment modality can be made. Moreover, it gives patients and their health providers a choice and therefore these results support a more patient-centered treatment.

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Effects of Non-Invasive Electrical and Magnetic Stimulation to Improve Motor And Cognitive Function in Parkinson's disease: a Meta-Analytical Review

A. Goodwill, J. Lum, A. Hendy, M. Muthalib, L. Johnson, N. Albein-Urios, W.P. Teo (Burwood, NSW, Australia) **Objective:** This meta-analytical review aims to compare 1) the effects of non-invasive repetitive transcranial magnetic (rTMS) and transcranial electrical stimulation (tES); and 2) identify optimal stimulation parameters to improve motor and cognitive function in Parkinson's disease (PD). **Background:** There is a growing interest in the use of rTMS and tES as a therapeutic tool to improve motor and cognitive function in people with PD. PD is characterised by a state of increased hyperexcitability and impaired cortical inhibitory circuitry, and the application of rTMS and tES may serve to normalize aberrant neurophysiology that underpin motor and cognitive impairments. However, there is no evidence to support 1) the role of tES as an alternative to rTMS in treating motor and cognitive symptoms, and 2) optimal stimulation parameters to produce clinical meaningful outcomes.

Methods: Studies were searched through PubMed, EMBASE, Web of Science, Google Scholar, Scopus, Library of Congress and Cochrane library from inception through to 26th February 2016. Random effects meta-analysis was conducted to assess SMD between NBS (rTMS/tES) and control on motor and cognitive function in PD. The Q and I2 statistic assessed heterogeneity amongst the studies.

Results: 24 rTMS and 9 tES studies (*n*=33) were included. The Physiotherapy Evidence Database (PEDro) and Cochrane Risk of Bias tool showed high internal validity (7.4/10) and a low risk of bias. Overall, both rTMS (SMD=0.394, CI=0.106-0.683, p=0.007) and tES (SMD=0.611, CI=0.188-1.035, p=0.005) improved motor function, but not for measures of cognition. Subgroup analyses revealed that higher doses of stimulation (p=0.005), site of stimulation (motor and pre-frontal cortex, p=0.015), and higher stimulation intensities (p=0.003) were the strongest moderators of improved motor function for rTMS. No significant moderators were identified for TES. **Conclusions:** This meta-analysis supports the use rTMS and TES to improve motor function in PD. Higher doses and stimulation intensities produce stronger motor improvements, however safety guidelines for the maximal therapeutic dose has not been established. Evidence for cognitive improvements following NBS remains incongruent and future studies employing more comprehensive neuropsychological testing batteries are warranted.

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Pairing TMS and Physical Therapy for Treatment of Gait and Balance Disorders in Parkinson's disease: A Randomized Pilot Trial

A. Cucca, H. Migdadi, T. Biller, S. Agarwal, P. Kumar, A. Son, M. Ko, E. Gallo, S. Fisher, A. Di Rocco, M. Biagioni (New York, NY, USA)

Objective: To explore the feasibility of pairing repetitive transcranial magnetic stimulation (rTMS) back-to-back with standard of care physical therapy (PT) for posture instability and gait disorders (PIGD) in PD.

Background: PIGD rehabilitation is offered by PT programs that are standardized and tailored on patient's deficits. However, benefits are often limited. rTMS has shown potential to modulate motor learning in both healthy individuals and PD (1,2). The clinical applicability of such paired paradigms in PD, outside laboratory settings, have not been tested.

Methods: Double-blind, randomized, sham-controlled study. This is a collaborative study between our movement disorder institute and the rehabilitation institute. PD patients with PT prescription for PIGD were screened and enrolled. After each PT session, participants were directed to our Lab to randomly receive rTMS (experimental group) or sham rTMS (control group) as soon as possible. The duration of rTMS sessions was 20 minutes. Patients and PT providers were blinded to the intervention. Preliminary data of safety, tolerability and study adherence was analyzed.

Results: Demographic characteristics are detailed in [*Table1*]. A total of 41 PT sessions were performed in 5 patients. All 41 sessions were paired with rTMS (100% of rTMS compliance). One subject withdrew consent citing lack of motivation continue PT. The average time between PT and TMS/sham at the first session was 23 minutes (10 to 40 minutes) when TMS mapping and threshold were performed. At the following sessions, this was 12.7 minutes (4 to 25 minutes). Study procedures were well tolerated; there were only 2 mild adverse events (AE): neck pain and 1 fall.

DEMOGRAPHIC CHARACTERISTICS	MEAN (SD)
Sex	M4,F1
Age (years)	74 (8.6)
Disease duration (years)	9 (4.6)
UPDRS	44.2 (10.5)
Hoehn & Yahr	2-3
Mini-BESTest	19.6 (5.4)
5 Times Sit-to-Stand Test (seconds)	14.0 (3.5)
Timed Ten Meter Walk Test (meter/sec ond)	1.06 (0.27)

Conclusions: Combining rTMS therapy with prescribed rehabilitation therapies hold promise for clinical use. Some practical issues must be initially addressed to determine feasibility. Scheduling operability, were TMS neuromodulation and PT should be administered within a brief temporal window. Furthermore, tolerance and adherence of pairing PT and rTMS can be challenging for PD patients as rTMS prolongs patient's stay and might

cause mild AE. A limitation of our study is the sample size which prevents efficacy analysis. Our preliminary results show that systematic rTMS adjuvancy on multiple sessions of PT is a feasible and safe intervention. Our results grant a further efficacy study.

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Intrajejunal Levodopa Infusion (ILI) for Parkinson's Disease (PD): A Canadian Experience

P. Podgorny, P. McCann, K. Toore, G. Tremain, A. Lazarescu, O. Suchowersky (Edmonton, AB, Canada) **Objective:** To review the benefits and complications of ILI for PD in a tertiary movement disorders center in Canada.

Background: ILI has been in use in Canada since 2011 to treat advanced PD, typically when oral medications are no longer tolerated due to increasing dyskinesias and/or 'OFF times'. Long term outcomes in this patient population have not yet fully been elucidated. In Edmonton, ILI is executed by a multidisciplinary team including a neurologist, gastroenterologist, and a specialized nurse.

Methods: We performed a detailed chart review of all patients that have to-date been treated with ILI at our center. Information extracted included motor UPDRS scores, endoscopic reports, ILI pump and PEG-J tube complications. Additionally, patients and caregivers were interviewed at regular clinic follow up about their subjective experience with ILI, including overall satisfaction and complaints.

Results: 13 patients have received ILI [10M, 3F; mean age 65.6 yrs, range (51.8-79.5), PD duration 14.2yrs, range (9.1-22.0), mean follow-up 1.8yrs, range (0.2-4.8)]. Patients commonly reported improvement in motor function, decreased dyskinesias and 'OFF times' [mean motor UPDRS scores: pre-ILI 37.1, 1-6months post-ILI 27.5]; improvement persisted for the majority of patients. One patient noted return of sense of smell. Common complications included dislodgement, knotting or blockage of the jejunal tube extension requiring endoscopic reinsertion; 29 such incidents occurred across 6 patients in 5 years. Four patients discontinued Duodopa treatment, for reasons of declining cognition, inability to care for the pump, and/or minimal benefit. One patient died from unrelated causes.

Conclusions: The University of Alberta Hospital in Edmonton was the first center in Canada to enroll a patient in ILI therapy, under a research protocol; it is now available as a standard of practice. ILI is useful for the treatment of advanced PD, in patients that can care for the pump apparatus. The most common complication is jejunal tube displacement.

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Protocol for Upper-limb Kinematic Analysis In Pediatric Movement Disorders and Relative Normality Data

L. Garavaglia, E. Pagliano, A. Lo Mauro, G. Baranello, A. Aliverti, S. Pittaccio (Lecco, Italy) **Objective:** The study proposes a specialised protocol to collect and analyse kinematic data from paediatric patients affected by Movement Disorders (MD). The aim is to provide a dedicated tool to quantify the patient's clinical state and its evolutions.

Background: Upper-limb movement patterns in children with MD are very complex and difficult to interpret visually. In the absence of a quantitative description of motion through tracings and indices, motor function can only be tested using clinical scales that are likely affected by subjective factors. Patient evaluation is also difficult because the overall improvements often arise as the sum of mild segment-specific variations, which the clinical scales may not be able to score. Very few studies have addressed the problem of upper-limb kinematic analysis in the young affected by MD, and until now, there is no standard procedure. In addition, normality data for upper-limb tasks in children are scant.

Methods: Optoelectronic photogrammetry was selected as the measurement technique. A 30-marker set-up was developed to acquire the positions of fiduciary body points in time and inform a 3D model of the trunk, shoulder, upper-arm, elbow, forearm, wrist and index finger. The analysis comprises an efficient method to limit data loss in case the view of some markers by the cameras is blocked out during involuntary movements. Six healthy boys (12.6 ± 4.9 years old) took part in this study, as well as five children (12.2 ± 5.6 years old) with complex MD pictures comprising secondary dystonia and dyskinesia to check the protocol adaptability in real cases. Subjects were asked to carry out two motor tasks extracted from the Melbourne Assessment: reach forward to a target and hand-to-mouth.

Results: The displacements and orientations of each body segment have been determined in heathy and patients. Report sheets with tracings and values of relevant linear and angular quantities, and characteristic movement phase durations have been prepared. Figure 1 shows some normality and pathological curves.



Conclusions: The method presented here s suitable to record reliably the upper-limb kinematics in relevant standardized tasks. The result of movement analysis produces a set of tracings and indices with direct clinical interpretation, which can be of help in determining the performance of paediatric MD patients quantitatively and characterising changes.

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Design of a Randomized, Sham-controlled Trial of Pallidal Neurostimulation Versus Botulinum Toxin Treatment for Cervical Dystonia (StimTox-CD)

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Objective: In this trial, we will assess the efficacy and safety of pallidal deep brain stimulation (DBS) versus botulinum toxin A (BoNT A) therapy in cervical dystonia (CD). We hypothesize that DBS is safe and superior to BoNT A in controlling motor symptoms and restoring quality of life.

Background: The current mainstay treatment for CD is selective injections of BoNt A in affected muscles. Pallidal DBS is an effective therapy, but currently restricted to patients with BoNT A resistant symptoms. As BoNT A is effective but not satisfactory in a relevant proportion of patients(1), earlier DBS surgery might be advantageous in providing stable symptom control and preventing disability(2).

Methods: Within this trial, 66 subjects with =2 years of CD (severity =20 TWSTRS total) will be recruited into a double-blind comparison of pallidal DBS versus BoNT A from 12 DBS centres in Germany. Eligible patients need =25% motor score reduction 4 weeks after BoNT A injection, but are willing to undergo DBS surgery due to unsatisfactory symptom control. All patients will be implanted with an ACTIVA PC system (Medtronic Inc., Minneapolis), then randomized into 2 groups: First group will receive effective neurostimulation (best clinical practice; 90µs, 130Hz) + regular sham injections (saline) in dystonic muscles. Second group will receive regular BoNT A injections (2 cycles; best clinical practice) in dystonic muscles + sham-stimulation (0V generator output). Primary outcome: change in TWSTRS total score between baseline and 6 months of therapy. Secondary outcomes: changes in TWSTRS motor, Tsui, CDQ24, SF36. Safety will be assessed by spontaneously reported adverse effects. In-depth statistical analysis includes analysis based on ITT and PP populations, analysis based on imputation of missing values, analysis adjusting for differences in baseline TWSTRS total. After 6 months sham-controlled period all patients will receive open-label neurostimulation and follow-up for 12 months.

Results: The study has been approved by the institutional review boards and the German regulatory agency. Recruitment will start in 2017. First results are anticipated for 2018.

Conclusions: We will assess if pallidal DBS is a safe and effective alternative to BoNT A in CD, which may be offered earlier in the treatment algorithm based on patient preference.

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Diphasic Dyskinesias During Levodopa-carbidopa Intestinal Gel (LCIG) Infusion: Diagnosis and Management in Clinical Practice

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Objective: To describe the occurrence, diagnostic approach, clinical management and outcome of diphasic dyskinesias (Dyskinesias-Improvement-Dyskinesias, DID) in a large group of Parkinson's Disaese (PD) patients treated with levodopa carbidopa intestinal gel (LCIG).

Background: Levodopa carbidopa intestinal gel (LCIG), although widely adopted for treatment of Parkinson's disease (PD) motor fluctuations, still presents some limitations. In addition to the widely described device related adverse events, levodopa side effects are the main clinician concern. Evidences have suggested that LCIG is an effective treatment in overcome dyskinesias, however, no information are reported about the quality of targeted dyskinesias.

Methods: We adopted a retrospective chart review of LCIG patients seen at 4 movement disorder centers. Patients who experienced DID after LCIG titration were selected. The following data were recorded: motor diary, UPDRS IV and levodopa equivalent daily dose (LEDD) pre and post LCIG initiation, as well as strategy adopted to manage DID. The latter were categorized in order to propose a management algorithm.

Results: In our cohort 12% patients (16/131 subjects) reported DIDs after titration. All of them were treated with add-on therapies to levodopa before LCIG introduction. Biphasic dyskinesias were clinically detected at the early follow-up visit after titration, except in one case that manifested DID during the long term follow-up. The main red flag to suspect DIDs was the emergence of dyskinesias after lunch time or during the afternoon (end-of-dose). The most reported strategies adopted to overcome DID were: adopting a double flow infusion rate, decreasing/increasing the morning dose with a compensatory increase of the continuous infusion rate, infuse a higher extra dose bolus before lunch, re-establishing pre-existing oral therapies other than levodopa, and 24-hour infusion. Some of them required a caregiver intervention or multiple consultations that delayed titration time.

Conclusions: DID could significantly challenge LCIG titration and its overall outcome but their burden is still underestimated. In fact, they could also lead to treatment failure also when correctly recognized. Since a standardized tool (e.g. questionnaire) is still missing, we herein propose an algorithm that might guide clinicians towards DID recognition and treatment (Figure 1).



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Barriers to Exercise in Newly Diagnosed Parkinson's Disease

I. Argyropoulos, E. Pearson, F. Murphy, V. Queen, J. Rideout, C. Carrollq (Plymouth, United Kingdom) **Objective:** To evaluate and understand the perceived benefits and barriers towards physical activity in newlydiagnosed people with Parkinson's disease (PwP).

Background: The evidence base to support regular physical activity in the management of Parkinson's disease is increasing. Regular exercise and physical activity is now understood to play a key role in short-term symptom relief, as well as possibly slowing disease progression. A new patient pathway has been developed at Plymouth Hospitals NHS trust, an aspect of which entails providing patients with patient-centred information on how to become and/or remain physically active. This study aims to achieve a better understanding of the perceived benefits and barriers for patients in undertaking regular physical activity.

Methods: Two questionnaires, the 4-item Physical Activity Cycle of Change and 43-item Exercise Benefits and Barriers Survey, will be administered over the telephone to 30 newly-diagnosed PwP from 3 Parkinson's services in Devon. The first serves to objectively assess patients' current overall level of physical activity as well as their readiness to undertake regular exercise. The second aims to quantify patient's attitudes towards exercise, and provide data on patients' perceived benefits of and barriers to undertaking physical activity. Demographic data such as age, gender, time since diagnosis, and current pharmacological therapy (if any) will also be collected. **Results:** This project is still in the data collection phase. Multivariate analysis of the various demographic factors, and analysis of specific responses will hopefully serve to provide insight into the overall perceptions of patients towards exercise, as well as highlight any specific perceived barriers to exercise that may be prevalent in the patient population.

Conclusions: It is expected the findings will provide evidence that certain factors influence patients' perceptions towards exercise, and any specific barriers highlighted by the analysis could hold implications for the way in which healthcare professionals discuss exercise with newly-diagnosed patients. More tailored and patient-centred promotion of regular exercise for individual patients will hopefully result in an increase in patients' level of physical activity, and play an important role in the effort to improve their overall health and quality of life.

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Combined Motor and Cognitive Training Improves Motor and Cognitive Function in People with Parkinson's Disease and Freezing of Gait

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Objective: Investigate whether combined motor and cognitive training improves motor and cognitive function in people with PD and freezing of gait (FOG).

Background: FOG affects half of people with PD. There is a close association between FOG and executive dysfunction. FOG can be provoked by performing a dual-task. The mainstay of treatment is physical therapy but the cognitive association has directed attention to cognitive-based approaches. We recently showed that combined motor and cognitive training improves dual-tasking capacity in FOG¹. We hypothesize that this training could improve FOG as well as overall gait in PD and potentially cognitive function.

Methods: We recruited 20 PD patients (13 with FOG) to perform a virtual-reality (VR) based intervention (eight 20-minute sessions stepping in place navigating a complex VR maze). The intervention also included a simultaneous cognitive task (modified Stroop test) which exerted additional cognitive load while stepping. Participants underwent cognitive and motor assessments before and afterward, including analysis of temporal gait parameters (stepping time, rhythmicity, symmetry) and reaction time to the cognitive task, all under single- and dual-task conditions. A modified Timed Up-and-Go test was also performed, in addition to standard neurocognitive tests.

Results: The intervention significantly improved motor and cognitive performance during single- and dual-tasks for those with FOG (dual-task stepping time, rhythmicity and reaction time as well as single-task stepping time). The modified Timed-Up and Go Test times for the FOG group reduced significantly after the intervention and the trailmaking test improved trending to statistical significance. There was a significant improvement in Question 6 of the New Freezing of Gait questionnaire ("How long is your longest freezing episode when initiating the first step?").



Conclusions: A VR-based intervention combining motor and cognitive training in FOG showed significant improvements in motor and cognitive performance during single- and dual-tasks, improvements in cognitive flexibility, gait and self-reported FOG. The parallel improvement in gait and cognitive performance implies that combined training has effects on gait and possibly cognitive function as well as dual task capacity. However, larger randomized controlled studies are required.

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Managing Severe Dyskinesia in Parkinson's Disease using 24-hour Levodopa/Carbidopa Intestinal Gel Infusion

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Objective: We report the effective treatment of troublesome dyskinesias in Parkinson's disease (PD), unresponsive to 16-hour daytime infusions, using 24-hour Levodopa/Carbidopa Intestinal Gel (LCIG).

Background: Continuous 16-hour per day intra-jejunal infusion of LCIG is an effective advanced therapy in the treatment of Parkinson's disease (PD) associated with motor fluctuations, including troublesome dyskinesias in many patients(1). We describe our use of 24-hour LCIG in the treatment of severe dyskinesias inadequately controlled with daytime infusion.

Methods: We conducted a retrospective review of all patients treated with 24-hour LCIG for the treatment of dyskinesia within our centre. Data for patients with contemporaneous objective dyskinesia ratings before and after 24 hour LCIG transition were also included in the analysis. Side effects, total 24 hour dose, and LCIG infusion rates were compared before and after transition to 24 hour therapy and at most recent follow up.

Results: 26 PD patients were identified who had received treatment with 24 hour LCIG. 10 were receiving 24 hour LCIG for the treatment of dyskinesia, 9 with follow-up data available. 3 patients with objective ratings of dyskinesia severity and frequency after transition to 24-hour LCIG for another indication were identified. The mean age at the time of transition to 24 hour LCIG was 68.9 years (range 51-81), duration of PD 17.9 years (range 11-30). 10/12 patients were male. None of the patients analysed had a worsening of dyskinesia following use of 24-hour LCIG. Following transition to 24 hour LCIG, 9 patients had an improvement in dyskinesia with mean reduction of 1.3 points in both UPDRS 4.1 and 4.2 scores (range 1-3). In 7 of these patients this was observed despite an overall increase in the 24 hour levodopa dose, in 4 of which there was an increase or no change in the daytime continuous rate. One patient transitioned back to 16-hour LCIG because of side-effects.

Conclusions: 24-hour LCIG offers an effective treatment option for troublesome dyskinesia in advanced PD. The therapy was well-tolerated within this patient group, despite overall increases in LCIG dose in the majority of patients. The reduction in dyskinesia despite increase in 24 hour dose and, in many patients, maintenance of similar daytime rates, suggests a pharmacodynamic mechanism over and above improvements mediated via pharmacokinetic benefits in LCIG therapy.

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Exercise Trends Reported in Parkinson's Patients

P. Raje, C. Branson, M.P. de Leon, M. Saint-Hilaire, A. Hohler, S. Ning (Boston, MA, USA) **Objective:** To examine trends in type, frequency, and effectiveness of exercise in Parkinson's patients based on gender, race, and years since diagnosis.

Background: Exercise has been shown to improve symptoms for Parkinson's patients. However, it is unclear what types of exercise Parkinson's disease patients find beneficial. Information on these exercise trends will help in developing exercise programs targeting compliance.

Methods: 58 PD patients completed an exercise survey as part of their movement disorder clinic visit. Specific information on the frequency of exercise, the impact of exercise on their PD symptoms, and whether they exercise alone or with others was noted. The age, gender, race, and number of years since diagnosis were also recorded. Three patients were excluded due to incomplete surveys.

Results: Of the 55 patients included in the study, 51% were Caucasian males, 38% were Caucasian females, 7% were African American males, and 4% were of another race. 67% of patients exercise at least twice a week for at least 30 minutes at a time, and 97% feel that it improves their symptoms. 34% of patients exercise alone. Walking was the most common type of exercise reported (87%), followed by stretching (58%) and biking (25%). **Conclusions:** In our patient population, patients exercise and continue to do so over the course of their disease process. Men and women, and individuals in all stages of PD exercise. Individuals with PD are more likely to exercise several times a week with walking being the preferred type of exercise.

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Interaction of Dietary Protein With Levodopa in Parkinson's Disease

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Objective: To study the effect of dietary protein on levodopa effectiveness in Parkinson's disease (PD) patients. **Background:** Levodopa transport across the blood brain barrier is modulated by large neutral amino acids and thereby dietary protein has been suggested to interfere with levodopa effectiveness. Due to this PD patients are commonly advised to dose levodopa on an empty stomach. In a retrospective study of over 1000 patients, Virmani et al. [1] suggested that protein interaction with levodopa occurred in <15% of PD patients who had earlier disease onset and positive family history of PD.

Methods: Here we prospectively assessed the interaction between protein diets and levodopa causing motor symptom fluctuations in patients with PD. After IRB approval, subjects filled a questionnaire detailing their motor symptoms, medications used, presence and severity of motor fluctuations, and effect of dietary protein on levodopa

effectiveness. Motor fluctuations due to protein interaction with levodopa were defined as leading to (i) longer time to levodopa effectiveness, (ii) reduced benefit or duration of benefit, (iii) dose failures or (iv) earlier wearing off from a previously effective dose. Statistical analysis was performed using SPSS 22 (IBM).

Results: 44 patients participated to date, with average motor onset at 60.5 ± 12.3 years and disease duration of 8.4 \pm 6.6 years. 25% on levodopa reported motor fluctuation with high protein meals. These patients trended towards being younger at motor onset (55.9 \pm 12.9 vs 62.0 \pm 9.5; p=0.11), had started levodopa at an earlier age (57 \pm 10.2 vs 66 \pm 7.3; p<0.01), and were on equivalent maximum daily levodopa doses (857 \pm 382 vs 890 \pm 190 mg/day; p=0.78) for similar duration (2.9 \pm 5.4 vs 4.3 \pm 3.6 years; p=0.39). A higher percentage reported lifetime dopamine agonist use (82% vs 30%; p<0.05) and were also concurrently on a dopamine agonist with levodopa (50% vs 10%; p<0.05). Percent reporting family members with PD were equivalent (36% vs 39%; p=0.86).

Conclusions: In our cohort, 25% of patients with PD on levodopa reported protein interaction with levodopa and were possibly younger at disease onset, had started levodopa at an earlier age and a higher fraction had been on, and were concurrently on dopamine agonists. This suggests that counseling patients to dose levodopa on an empty stomach may not be warranted early in the disease.

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Botulinum Neurotoxin (Bont) for Treatment of Functional (psychogenic) Jerky Movement Disorders: a Randomized Placebo-controlled Clinical Trial

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Objective: To assess the effectiveness of botulinum neurotoxin (BonT) in patients with functional jerky movement disorders.

Background: At least 2–9% of patients seen in movement disorder clinics suffer from functional movement disorders and a substantial part has jerks. Botulinum neurotoxin (BoNT) has emerged as a useful therapy for several hyperkinetic movement disorders. Previous research and our own clinical experience suggest that treatment with BoNT is an effective therapy for jerky movements as well.

Methods: Fourty-eight patients with invalidating functional jerky movement disorders, present for at least one year were included in a double-blind randomized placebo controlled of 16 weeks. The primary endpoint was reached patients showed minimal to major improvement (score 1,2 or 3) on the Clinical Global Impression (CGI)-scale. This was based on videotaped sessions, assessed by two investigators blinded to the allocated treatment. Hereafter all patients received BoNT treatment during one year in order to evaluate the long-term effect. Blinded assessment was repeated at the end.

Results: In the treatment group 16 of 25 (64%) patients reached the primary endpoint, opposed to 13 of 23 patients (57%) in the placebo group. No significant difference was detected. In the open-label follow-up phase 35 of 44 (80%) of patients improved (4 patients were lost to follow-up). This also held for the secondary outcome measures assessing the severity of motor symptoms scored by the investigator as well as the patient. Secondary outcome measures including psychiatric co-morbidity, disability and quality of life failed to reach significance for the trial phase as well as the follow-up.

Conclusions: Preliminary results show no significant effect of BoNT on functional (jerky) movement disorders. However in the open label follow-up phase the majority of patients improved on motor symptoms. (Netherlands Trial Registry 2478).

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Intranasal Delivery of Insulin for the Restoration of Memory Signaling in Alzheimer Disease

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Objective: The objective of this study is to develop delivery-system to overcome BBB by employing novel, non-invasive approach via nasal route. The olfactory neural pathway provides both intraneuronal and extraneuronal pathway into brain. In present study delivery of antibody appended Insulin encapsulated carrier, PEGylated nanoparticle coated with chitosan to facilitate nasal absorption for efficient transfer to brain.

Background: Alzheimer's disease (AD), a form of dementia, is progressive, degenerative brain disease characterized by marked atrophy of cerebral cortex and loss of cortical and sub-cortical neurons. Weakening of insulin receptor signaling is involved in ageing-related brain degeneration such as AD.

Methods: PEGylated-PLGA nanoparticles were prepared by the modified Double Emulsification method and coated with chitosan by freeze drying. Characterization was done by FTIR, NMR and *in-vitro* for shape, size, and drug-entrapment. *In-vivo* study comprised biodistribution in various organs and fluorescence microscopy, estimation

of Anti-Aß antibody, PET-Imaging of Brain, Hemolytic Toxicity studies, Histopathology of Nasal Mucosa and Brain with periodic Blood Glucose Level Monitoring.

Results: Nanoparticles were spherical in shape and smooth [FigureP1], [FigureP2]. Degree of hemolysis showed PEGylated (PEG-NP's) and chitosan coated nanoparticles (cPEG-NP's) were less toxic. Blood glucose monitoring indicates reduction in blood glucose level in cPEG-NP's. Biodistribution assessment suggests nanoparticles showed maximum availability at olfactory bulb entrance. Chitosan coating increased CSF availability of drug even at initial period of administration. Uptake study shows intense fluorescence in brain revealing higher uptake of nanoparticles [figureP3]. These studies highlight possible biological significance of cPEG-NP's for delivery to brain.






Conclusions: Results from various studies suggest nanoparticles are effective delivery system for targeted delivery of insulin in brain for an extended period. Chitosan coating elicits associated benefits in addition to prolonging uptake via intranasal route. This project may provide sound platform towards employment of this modified nanoparticulate carrier for brain delivery of proteins and peptides towards intranasal delivery of insulin for restoration of memory signaling in Alzheimer patients.

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Clinical Experience with Initiation of Carbidopa/Levodopa Enteral Suspension in Parkinson's Disease Patients with Cognitive Impairment

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Objective: To assess the safety and efficacy of carbidopa/levodopa enteral suspension (CLES) in Parkinson's disease (PD) patients with cognitive impairment.

Background: As Parkinson's disease progresses, patients treated with levodopa frequently experience fluctuations from an ON state to an OFF state which can be complicated to effectively manage. Recently, a new formulation of levodopa has been developed, an enteral suspension for treatment of PD patient with motor fluctuations. There are no data regarding the safety and efficacy of initiation of CLES in patients with cognitive impairment.

Methods: PD patients from the University of Kansas Movement Disorder Database whom were initiated on CLES therapy and had MoCA scores less than 23 were selected. Demographics and UPDRS were collected at baseline, 6 months, and/or 12 months.

Results: Ten PD patients (6 men/4 women) with a mean age at time of surgery of 74.1 years (range 62.9-88.9) and a mean disease duration of 13.5 years (range 3.5 to 23) were initiated with CLES. The baseline mean MoCA score was 17.3 (range 8-22). The baseline mean UPDRS Mentation score was 4.1 (range 0-10), UPDRS ADL score was 25.1 (range 13-45), mean UPDRS Motor score was 33.7 (range 21-49). At this time, four patients have follow-up data. At 6 months (n=3), the mean UPDRS Mentation score improved by 1.4 points, the mean UPDRS ADL score improved by 8.8 points, and the mean UPDRS Motor score improved by 7.2 points. At 12 months (n=2), the mean UPDRS Mentation score improved by 4.4 points, the mean UPDRS Part IV, dyskinesia increased in 3 patients and was unchanged in 1 patient; however, OFF time was reduced in 3 of the 4 patients. All 4 patients reported marked improvement at all follow up visits per the patient global impression of change. Complications occurred in 9 of 10 patients and included: small perforation during placement requiring an open procedure (n=1), malfunctioning J-tube including accidental displacement (n=2), kinked tube (n=2) and occluded tube (n=1), cellulitis[KL1] (n=3), and replacing pump 4 times (n=1).

Conclusions: CLES therapy can safely be initiated in Parkinson's disease patients with cognitive impairment; however complications were common. Preliminary results suggest improvements in quality of life and motor outcomes.

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Parkinson's Syndrome Associated with Inositol-1,4,5-Triphosphate Receptor Antigen Type 1 (ITPR1) Antibodies

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Objective: To illustrate an unusual clinical presentation of Parkinson's disease (PD) that was effectively treated with immune adsorption.

Background: Autoimmune mediated movement disorders may be open to causal treatment options; as such early correct diagnosis is essential. ITPR 1 antibodies have been described in four cases with autoimmune cerebellar ataxia, however, their pathogenicity is still unclear¹. ITPR 1 gene mutations have been identified in recessive ataxia forms, SCA 15 and SCA 29². Here we report on a case of ITPR 1 antibodies present in a PD patient that was subsequently successfully treated by immune adsorption.

Methods: Retrospective chart review and clinical examination of the patient.

Results: This 63 year old active man was first diagnosed with Parkinson's disease in 2003 presenting with unilateral left-sided resting tremor, slight left-sided rigidity and bradykinesia. DAT scan revealed severe bilateral reduction of striatal dopaminergic uptake, more prominent on the right side. Subsequently, the disease progressed slowly over time and showed responsiveness to levodopa.In 01/2016 the patient rapidly developed progressive visual hallucinations without insight, delusional jealousy and cognitive impairment. Within a few, days the patient displayed decreasing levels of consciousness and was admitted to the intermediate care unit.Magnetic resonance imaging showed slight diffuse supratentorial atrophy and the EEG indicated severe encephalopathy. Cerebrospinal fluid analysis revealed high levels of ITPR1 antibodies (1:320), an antineuronal antibody of the IgG1 subclass type that is known to bind to Purkinje cell somata and dendrites¹. The first add on treatment approach with intravenous immunoglobulin showed no clinical effect. Following repeat immune adsorption, serum antibody levels decreased from 1:1000 to 1:320 to 1:100, along with clinical improvement (cognition, psychopathology, motor symptoms). **Conclusions:** Our case report demonstrates that reducing antineuronal antibodies in a PD patient by immune adsorption may be an effective therapy.

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A Novel Cause for Unpredictable Response to Levodopa

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Objective: To describe a novel cause for unpredictable response to levodopa

Background: A fluctuating response to levodopa is common in advanced Parkinson's disease and can often be attributed to dosing regimen, interaction with food and delayed gastric emptying. Failure to respond to levodopa is often an indication of a parkinsonism plus syndrome.

Methods: CASE: A 70 year-old man was referred because of failure to respond to levodopa and suspicion that he had some other form of parkinsonism. The subject reported that even at single doses of 400 mg, levodopa was ineffective, a fact that had been confirmed by other neurologists' post dose examinations. However, the patient described that he would sometimes have a period of mobility and dyskinesia during the day with no relation to medication intake.

Results: A challenge with 400 mg of PO levodopa in the practical off state in the clinic found that he had a minimal improvement in his rigidity an hour and a half after intake and by 3 hours had not achieved an optimal response. A referral to GI for a trial with nasojejunal administration of levodopa found a huge paraesophageal hernia with almost the entire stomach in the chest. Administration of carbidopa/levodopa gel (Duopa) by pump via the nasojejual tube gave the patient a full response to levodopa within 45 minutes each morning and he remained on most of the day. As there was insufficient stomach in the abdomen to do endoscopic placement of the jejunal tube, the patient had a jejunostomy by laproscopic surgery. He now has a predictable response to the infusions of the levodopa/carbidopa gel by pump.

Conclusions: Structural abnormalities of the upper GI tact may complicate oral levodopa treatment.

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Topography of Essential Tremor

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Objective: To explore the prevalence and clinical correlates of head and/or voice tremor in essential tremor. **Background:** Topography of tremor manifestations is poorly investigated in essential tremor.

Methods: Out of a prospectively designed registry of 972 patients, 884 patients with definite and probable essential tremor had complete information on tremor localization. Demographic and clinical characteristics were compared among four subgroups: group A (without head or voice tremor, n=619), B (with head but without voice tremor, n=155), C (with voice but without head tremor, n=47), and D (with both head and voice tremor, n=63). **Results:** In our patients, total prevalence of tremor was 24.7% for head, 12.4% for voice and 7.1% for the combination of head and voice. Logistic regression analyses showed that female gender is the major associated factor for head tremor, which was confirmed by an additional meta-analysis. Severe hand tremor was the only factor associated with voice tremor. Both female gender and severe hand tremor increase the risk for head and/or voice tremor. For males, hand tremor severity is significantly increased among those with head and voice tremor alone and in combination, but for females only for the combination. Patients with both head and voice tremor have more frequent involvement of legs and other localizations and are less responsive to β-blockers.

Conclusions: Female gender and severe hand tremor increase the risk of head and/or voice tremor in essential tremor. The risk factor hand tremor severity in males seems to be stronger for midline tremor than in females.

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Characteristics of Tremor Caused By Non-olivary Lesion of the Medulla Oblongata

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Objective: We examined the characteristics of tremor caused by lesions of the medulla oblongata, which do not affect the inferior olive.

Background: The medulla oblongata is functionally and structurally related to the cerebellum, and it is known that the inferior olive has a role in pathologic tremor generation probably through the dysfunction of the cerebellar connections. The characteristics of tremor caused by non-olivary lesions of the medulla oblongata have not been explored yet.

Methods: We analyzed quantitatively the tremor of 116 patients with brainstem and/or cerebellar lesions and here we report the results of 9 patients with dorso-lateral medulla oblongata lesion not involving the inferior olive (dlMO). Tremor was measured by biaxial accelerometry. Center frequency, frequency dispersion and tremor intensity were calculated. In 5 patients, control measurements were performed to assess the speed of recovery. Detailed analysis of the MRI data was performed by a neuroradiologist.

Results: Pathologic tremor was detected in 7/9 patients (77.8%). Three patients had isolated dlMO damage, one of these had pathologic tremor ipsilateral to the lesion. Six patients had lesions both in the dlMO and also in other parts of the brainstem or the cerebellum (Table 1). All these patients had pathologic tremor (Figure 1). The amplitude was only slightly higher than normal. Center frequency was 2.13 ± 0.36 Hz. Frequency dispersion was 0.57 ± 0.37 Hz. Follow-up measurements showed complete recovery of tremor in 4 weeks (Figure 2).



Patient ID	Signs and symptoms	Diagnosis	Location of lesions
	vertigo, tongue deviation to the		
	left, left-sided limb ataxia,		
CSI02	positive Romberg-sign	acute ischemic stroke	dorsolateral medulla oblongata
	gaze-evoked nystagmus, left-		
	sided limb ataxia,		
KK02	dysdiadochokinesia, gait ataxia	acute ischemic stroke	dorsolateral medulla oblongata
	dysphagia, dysarthria, crossed		
	hemihypaesthesia, right-sided		
	facial paresis, right-sided limb		
SJ01	ataxia	acute ischemic stroke	dorsolateral medulla oblongata
	dysarthria, dysphagia, head		
	tremor and tremor in both upper	tumor (unknown	
HGY01	limbs	histology)	medulla oblongata and vermis
HF02	dysarthria, dysphagia, tetraataxia	acute ischemic stroke	pons and medulla oblongata
	left-sided cerebellar nystagmus,		
	right-sided hypaesthesia on the		
	face, right-sided hypotonia, right-		cerebellum and medulla oblongata
MP01	sided dysdiadochokinesia, ataxia	acute ischemic stroke	(PICA-territory)
	left-sided facial paresis,		
	dysphagia, dysarthria, crossed		
	hemihypaesthesia, left-sided		cerebellum and medulla oblongata
MJ02	hypotonia	acute ischemic stroke	(PICA-territory)
	severe dysarthria, hiccup,		
	dysdiadochokinesia , intention		cerebellar hemisphere and
FZ02	tremor	acute haemorrhage	medulla oblongata
	cerebellar nystagmus, vertical		
	gaze palsy, dysarthria, right-sided		
	limb ataxia, right-sided	adenocarcinoma	cerebellum, medulla oblongata
BI02	dysdiadochokinesia	metastasis	and mesencephalon



Conclusions: Non-olivary lesions of the medulla oblongata frequently cause symptomatic tremor, which has low amplitude and low frequency. Our results suggest that in the medulla oblongata a network rather than a single structure, like the inferior olive, plays role in the generation of pathologic tremor. The tremor caused by acute medulla oblongata lesion is reversible; the recovery is usually complete within 4 weeks. The reversible nature of

symptomatic tremor highlights the differences in the pathomechanism compared to tremors caused by neurodegenerative diseases.

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Characteristics of Tremor Caused By Non-olivary Lesion of the Medulla Oblongata

A. Kovács, N. Pintér, L. Halász, A. Kamondi (Budapest, Hungary)

Objective: We examined the characteristics of tremor caused by lesions of the medulla oblongata, which do not affect the inferior olive.

Background: The medulla oblongata is functionally and structurally related to the cerebellum, and it is known that the inferior olive has a role in pathologic tremor generation probably through the dysfunction of the cerebellar connections. The characteristics of tremor caused by non-olivary lesions of the medulla oblongata have not been explored yet.

Methods: We analyzed quantitatively the tremor of 116 patients with brainstem and/or cerebellar lesions and here we report the results of 9 patients with dorso-lateral medulla oblongata lesion not involving the inferior olive (dlMO). Tremor was measured by biaxial accelerometry. Center frequency, frequency dispersion and tremor intensity were calculated. In 5 patients, control measurements were performed to assess the speed of recovery. Detailed analysis of the MRI data was performed by a neuroradiologist.

Results: Pathologic tremor was detected in 7/9 patients (77.8%). Three patients had isolated dlMO damage, one of these had pathologic tremor ipsilateral to the lesion. Six patients had lesions both in the dlMO and also in other parts of the brainstem or the cerebellum (Table 1). All these patients had pathologic tremor (Figure 1). The amplitude was only slightly higher than normal. Center frequency was 2.13 ± 0.36 Hz. Frequency dispersion was 0.57 ± 0.37 Hz. Follow-up measurements showed complete recovery of tremor in 4 weeks (Figure 2).



Patient ID	Signs and symptoms	Diagnosis	Location of lesions
	vertigo, tongue deviation to the		
	left, left-sided limb ataxia,		
CSI02	positive Romberg-sign	acute ischemic stroke	dorsolateral medulla oblongata
	gaze-evoked nystagmus, left-		
	sided limb ataxia,		
KK02	dysdiadochokinesia, gait ataxia	acute ischemic stroke	dorsolateral medulla oblongata
	dysphagia, dysarthria, crossed		
	hemihypaesthesia, right-sided		
	facial paresis, right-sided limb		
SJ01	ataxia	acute ischemic stroke	dorsolateral medulla oblongata
	dysarthria, dysphagia, head		
	tremor and tremor in both upper	tumor (unknown	
HGY01	limbs	histology)	medulla oblongata and vermis
HF02	dysarthria, dysphagia, tetraataxia	acute ischemic stroke	pons and medulla oblongata
	left-sided cerebellar nystagmus,		
	right-sided hypaesthesia on the		
	face, right-sided hypotonia, right-		cerebellum and medulla oblongata
MP01	sided dysdiadochokinesia, ataxia	acute ischemic stroke	(PICA-territory)
	left-sided facial paresis,		
	dysphagia, dysarthria, crossed		
	hemihypaesthesia, left-sided		cerebellum and medulla oblongata
MJ02	hypotonia	acute ischemic stroke	(PICA-territory)
	severe dysarthria, hiccup,		
	dysdiadochokinesia , intention		cerebellar hemisphere and
FZ02	tremor	acute haemorrhage	medulla oblongata
	cerebellar nystagmus, vertical		
	gaze palsy, dysarthria, right-sided		
	limb ataxia, right-sided	adenocarcinoma	cerebellum, medulla oblongata
BI02	dysdiadochokinesia	metastasis	and mesencephalon



Conclusions: Non-olivary lesions of the medulla oblongata frequently cause symptomatic tremor, which has low amplitude and low frequency. Our results suggest that in the medulla oblongata a network rather than a single structure, like the inferior olive, plays role in the generation of pathologic tremor. The tremor caused by acute medulla oblongata lesion is reversible; the recovery is usually complete within 4 weeks. The reversible nature of

symptomatic tremor highlights the differences in the pathomechanism compared to tremors caused by neurodegenerative diseases.

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Patients with Essential Tremor Live Longer than their Relatives

C. Akbostanci, K. Doganyigit, M. Sen, E. Onat, A. Tekinay, T. Özçelik, M. Akbostanci (Snoqualmie, WA, USA) **Objective:** The objective of this study is to compare the lifespans of patients with essential tremor (ET) with their relatives.

Background: Essential tremor is a movement disorder commonly manifesting as action tremor of the hands and the head. There is growing evidence for a hypothesis which points to longevity in ET. But there are several recent studies reporting shorter life expectancy in ET.

Methods: Present data was initially gathered for a study done to determine a genetic link to familial ET. We used the information on ET patients we had at hand and their relatives totaling to 670 individuals (326 females, 48.8%) from 64 families.

Results: Average age of death for ET patients was 76.13 years, and for cases without ET was 63.10 years. Average age of death of patients with young (0-20 years), intermediate (20-50 years), and late onset (50+ years) were 74.00, 76.27 and 76.81 consequently. Women without ET died at the age of 66.16 years (n=71), and men at the age of 60.59 years (n=72) on average. Average ages of death for cases with ET were 78.39 years for females (n=47), and 73.98 years (n=55) for males (Table 1)

	No ET	No ET	No ET	ET	ET Male	ET Total
	Male	Female	Total	Female		
Number of Cases Alive At the	54	78	132	130	161	291
Moment of Data Collection						
Number of Cases Dead At the	72	71	143	47	55	102
Moment of Data Collection						
Number of Cases Dead+Alive	126	149	275	177	216	393
Total						
Number of Young Onset Cases	NA	NA	NA	1 dead/	7 dead/	8 dead/ 99
(Alive/Dead)				36 alive	63 alive	alive
Number of Late Onset Cases	NA	NA	NA	11 dead/	22 dead/	33 dead/
(Alive/Dead)				16 alive	13 alive	29 alive
Mean Age at Death	60.59	66.16	63.10	78.39	73.98	76.13
Mean Age at Death for Young	NA	NA	NA	80	74.83	75.57
Onset Patients						
Mean Age at Death for Late Onset	NA	NA	NA	79.78	75.46	77.97
Patients						

Table 1. Lifespan Data of Patients with Essential Tremor and their Family Members.

Conclusions: Essential tremor of any age of onset could lead to longevity compared to their healthy family members, with an average of 13.03 years of improvement in lifespan. The data we have support the theory that ET patients live longer than their healthy relatives regardless of gender or their age of onset.

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Tremor in Motorneuron Disease: Central or Peripheral Origin

A. Latorre, M. Stamelou, L. Rocchi, M. Ciocca, K. Sidle, J. Rothwell, K. Bhatia (London, United Kingdom) **Objective:** To investigate whether postural/action tremor in motorneuron disease (MND) has a central origin. **Background:** MND refers to the whole spectrum of progressive degenerative diseases which differentially affect the upper and lower motor neurons. Clinical and postmortem observations demonstrate that there is considerable variability in the phenotypic expression of MND, indicating that it should be considered a multisystem neurodegenerative disease where the extrapyramidal, cerebellar, somatosensory and autonomic systems can also be affected (1). Postural/action tremor, which is often determined by cerebellar dysfunction, is present in MND patients (nearly 5% in our experience), but its pathophysiology is currently unknown. **Methods:** We recruited 6 MND patients with postural/action tremor without other extrapyramidal signs. In all of them, tremor was recorded bilaterally from flexor and extensor carpi radialis using surface EMG and a triaxial accelerometer placed on the dorsal surface of the most affected hand. Tremor was recorded without weight and with a variable weight load based on patients' muscle power (50-500 g). Power spectra of rectified EMG and accelerometric signal was calculated. Eye blink classic conditioning (EBCC) was also studied in 4 out of the 6 patients and compared with results obtained in a group of age-matched healthy subjects.

Results: Among the 6 patients, the analysis of accelerometric signal demonstrated that the frequency varied between 4.9Hz and 10.1Hz in the "no weight" condition, and between 4.6Hz and 10.1Hz in the "weight" condition. Furthermore, the EMG frequency spectrum exhibited that the frequency ranged from 4.3Hz to 9.5Hz and from 4.0Hz to 10.4Hz, respectively in the "no weight" and "weight" condition. Within each patient there was no effect of mass loading on peak frequency (all p values > 0.05) in both the accelerometer and EMG analysis (the mean absolute value of the difference in frequency were respectively: 0.2 ± 0.3 Hz and 0.6 ± 0.6 Hz). With regard to the EBCC, the number of conditioned responses in MND patients was significantly lower than healthy subjects in blocks 4-5-6.

Conclusions: Our results suggest that postural/action tremor in MND has a central origin, possibly resulting from a cerebellar dysfunction.

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Functional Lesional Neurosurgery for Tremor - a Systematic Review and Meta-analysis

S. Schreglmann, J. Krauss, J. Chang, K. Bhatia, G. Kägi (London, United Kingdom)

Objective: To evaluate the consistency and effect size as well as the incidence of persistent side effects of lesional neurosurgical interventions using radiofrequency ablation (RF), focused ultrasound (MRIgFUS) and gamma knife (GK) in the treatment of tremor due to Parkinson's disease (PD), Essential Tremor (ET) and Multiple Sclerosis (MS).

Background: The introduction of incision-less lesional functional neurosurgery by GK and MRIgFUS has again created interest in lesional treatments for tremor disorders.

Methods: Systematic review of Medline and Cochrane databases of lesional neurosurgical interventions for tremor published between January 1990 and June 2016 following PRISMA guidelines. Studies with a minimum of n=5, follow-up = 3 months and tremor quantification using a validated scale were selected for random effects metaanalysis based on standardized mean difference/Hedge's g. All studies reporting persistent side effects after unilateral interventions were included in the safety assessment.

Results: Out of 1247 abstracts screened, 84 published peer-reviewed studies homogeneous for tremor etiology, surgical target and intervention were included. Based on data from 1198 patients, effect on PD tremor was better when targeted at the ventral intermediate nucleus (V.im.) by RF (Hedge's g: -4.15; 95% CI: -5.13 /-3.17) over V.im. by GK (-2.2; -3.62/-0.78), subthalamic nucleus (STN) by RF (-1.12; -1.4/-0.84) and globus pallidus internus (GPi) by RF (-0.88; -1.19/-0.57). For ET V.im. ablation by MRIgFUS (-2.47; -2.83/-2.12) showed similar tremor reduction to V.im. ablation by RF (-2.46; -2.56/-2.35) and a stronger effect than V.im. ablation by GK (-2.13; -3.78/-0.48). For MS tremor V.im. ablation by GK (-1.96; -3.12/-0.81) had a greater effect size than by RF (-1.63; -2.56/-0.7). Rates of persistent side effects after unilateral lesions in PD were 15.9±14.7% (RF V.im.), 14.7±5.0% (RF STN), 8.3±15.1% (RF GPi), 1.6±0.8% (GK V.im.) and 4.9±6.9% (MRIgFUS V.im.). For ET rates were 6.3±7.1% (RF V.im.), 1.9±2.4% (GK V.im.) and 10.9±11.4% (MRIgFUS V.im.) and for MS 37.7±23.9% (RF V.im.). **Conclusions:** This comprehensive comparison of safety and efficacy of lesional neurosurgical interventions for tremor disorders defines the benchmark for and guides future developments of incision-less techniques. Lesion target and technique have different effects according to tremor etiology.

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Effects Of Thalamic Deep Brain Stimulation On Posture And Balance In Patients With Essential Tremor K. Lizarraga, A. Farooqi, A. Rasul, J. Jagid, C. Luca (Miami, FL, USA)

Objective: To characterize posture and balance dysfunction in patients with essential tremor (ET) after undergoing deep brain stimulation (DBS) of the thalamic nucleus ventralis intermedius (Vim).

Background: Essential tremor is characterized by progressive, symmetric, moderate-to-high frequency postural and action tremor. ET is also associated with cerebellar dysfunction including impaired gait and ataxia. Though DBS of the thalamic nucleus Vim is an effective treatment modality for medically-refractory ET, its effect on posture and balance is not clearly defined.

Methods: Eight patients with a clinical diagnosis of ET (3 pre-Vim-DBS, 5 post-Vim-DBS) underwent standardized balance assessment using body accelerometers (Mobility Lab, APDM Inc.). Sway testing was carried out with the patients standing with eyes open and closed. The following parameters were measured and averaged in both groups of patients, to then be compared with normative data: sway smoothness or JERK (m^2/s^5), sway area (m^2/s^2), RMS sway and path length (m/s^2), mean velocity (m/s), range of acceleration (m/s^2), mean distance (m^2/s^5) and total power (m^2/s^4).

Results: In pre-DBS patients, all measured balance parameters were either normal or mildly abnormal. In post-DBS patients, these parameters were moderately to severely abnormal (Table 1).

Balance	Normal	PRE-Vim-DBS		POST-Vim-DBS	
parameter	values	Eyes open	Eyes closed	Eyes open	Eyes closed
JERK (m²/s⁵)	0.087±0.05	0.11	0.22	1.4	2.4
Sway area (m²/s²)	0.002±0.001	0.003	0.005	0.034	0.04
RMS sway (m/s²)	0.059±0.025	0.07	0.10	0.12	0.17
Path length (m/s²)	4.58±1.08	5.64	7.32	16.39	22.8
Mean velocity (m/s)	0.114±0.05	0.13	0.25	0.25	0.30
Range of acceleration (m/s²)	0.314±0.11	0.38	0.51	0.98	1.10
Mean distance (m²/s⁵)	0.049±0.016	0.05	0.08	0.13	0.14
Total power (m²/s⁴)	0.51±0.6	0.93	1.68	3.79	6.27

Conclusions: While patients with ET may experience mild-to-moderate balance and postural problems as a result of disease progression, DBS of the thalamic nucleus Vim could significantly aggravate them potentially resulting in significant postural imbalance and falls.

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Cortico-thalamic Biomarkers for a Responsive Deep Brain Stimulation: an Enhanced Treatment of Essential Tremor

E. Opri, J. Shute, R. Molina, K. Foote, M. Okun, A. Gunduz (Gainesville, FL, USA)

Objective: To explore cortico-thalamic biomarkers of intention tremor and intentional movement in hand Primary Motor (M1) and Premotor (PM) Cortex, and Ventral Intermediate Thalamic Nucleus (VIM) in patients with Essential Tremor to be used to clinically validate an effective responsive Deep Brain Stimulation (DBS) treatment. **Background:** Essential Tremor (ET) is defined as a rhythmical, involuntary oscillatory movement of the limbs. Intention tremor is present in the upper limbs (slow oscillations, ~4-12 Hz) during the initiation and execution of goal-directed reaching motions, while it is absent at rest. It has currently been suggested that a synchronous pathological oscillation in a network that includes PM, M1, VIM and cerebellum is suppressed with DBS by jamming the "tremor cells" in the thalamus.

Methods: Two patients were implanted in both cortical (PM, M1) and thalamic (VIM) regions and recorded during a DBS implantation surgery. Together with inertial and EMG collected data, it was possible to explore biomarkers related to movement intention/execution, and to tremor. These biomarkers can be reliably used to responsively deliver DBS.

Results: It was shown that it is possible to achieve single trial detection of movement intention/execution from PM, M1 and Vim. Pilot data collected from cortical strips implanted for a different cohort (Tourette') show reliable detection capabilities in Medtronic PC+S devices, which will also be used in our responsive ET cohort.

Conclusions: Our results suggest that a reliable control of responsive DBS is possible with the use of a single or a combination of targeted brain areas. This enhanced DBS therapy solution would decrease the possible patient's side effects, such as balance and speech impairment, and slow down battery depletion, by being inactive during non-tremor statuses, while delivering an equally effective treatment.

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A Survey-based Analysis of Abnormal Movements in Patients with Postural Tachycardia Syndrome (PoTS) *R. Pyda, A. Hohler (Boston, MA, USA)* **Objective:** The aim of this study is to evaluate the characteristics of PoTS associated tremor. **Background:** Postural tachycardia syndrome (PoTS) is a dysautonomia most prevalent in young women and children. Its most classic presentation is an increase in heart rate of at least 30 beats per minute (bpm) within 10 minutes of standing in adults, or of at least 40 bpm in children in the absence of orthostatic hypotension. **Methods:** Thirty patients with POTS completed a 37 item questionnaire about movement disorders including tremor and dystonia. Responses were elicited on a five-point Likert scale by converting the responses into integers (strongly disagree=1, disagree=2, neutral=3, agree=4, strongly agree=5). Frequency of positive responses (strongly agree and agree), median, and interquartile ranges were calculated using Microsoft Excel and graphed using StatPlus. **Results:** Our analysis shows that approximately 53% of PoTS patients reported tremors (n=30). Thirty three percent report tremors in areas other than the hands; 10% report ocular involvement, 3% report lip tremor, 10% report arm involvement, 10% report leg involvement, 7% report foot involvement, 3% report head tremor, and 3% report general upper body tremor. Only 3% of the POTS patients reported dystonia. In addition to the twenty seven percent of patients that noted that their tremors became worse with action, another twenty percent of patients reported that their tremors were worse at rest, contradicting the findings of current (Abdulla and Rajeevan, 2016).

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
MOVEMENT					
I experience tremors					
My tremors are worse at rest					
My tremors are worse with action					
I have tremors in places other than my hands (If yes, specify where)					
I have dystonia (If yes, specify where)					

Conclusions: PoTS is primarily felt to be a disease of orthostatic intolerance. The heterogeneity of the disorder may stem from comorbidities rather than the syndrome itself (Benarroch, 2012). The movement disorders noted in this PoTS population included tremor and dystonia. The reported tremors represented a mixed picture of both rest and action tremors with and without orthostatic exacerbation. Orthostatic intolerance has been associated with tremor, light-headedness, fatigue, exercise intolerance and near syncope in upright posture (Agarwal et al, 2007; Benarroch, 2012). However, our study demonstrates movement disorders in standing as well as seated positions and also shows that these POTS tremors are not purely action tremor (Hua et al, 2004; Elble, 2013).

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Forehead Tremor: a Clinical Presentation of Ocular Myasthenia Gravis?

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Objective: The case of a patient with seropositive Myasthenia Gravis (MG), presenting with forehead tremor, is reported.

Background: The clinical presentation of MG with involuntary movements was observed in an exiguous number of cases, but the association between MG and forehead tremor has not previously described.

Methods: A 59-year-old man complained of rhythmic eyebrow movements with a fluctuating daily trend for 7 months. Neurological examination showed bilateral ptosis and forehead tremor, observable at rest and increasing in up-gaze. Single-Fiber-EMG of Orbicularis Oculi (OO) muscle documented a jitter value of 92 µs and 100% of pairs with pathological jitter. Brain-MR and chest-CT were negative. Titer of anti-acetylcholine-receptor antibodies was of 22 nmol/L. Patient also underwent facial tremor recording by surface electrodes on Frontalis (F) and OO muscles. An irregular bilateral activity of F muscles with frequency of 4-6 Hz, increasing in amplitude during up-gaze, was recorded. Antagonistic OO muscles activity was absent. Pyridostigmine 360 mg and prednisone 50 mg daily were administered with clinical improvement of ptosis and forehead tremor.

Results: The association between movement disorders and MG was firstly pointed out in 1967 with the description of palpebral tremor in a MG patient (1). The co-occurrence of MG and opsoclonus-myoclonus syndrome (2) was also reported. Forehead tremor has been very rarely described in patients with Parkinson's disease, Essential Tremor and focal dystonia. In this report, we described a patient with forehead tremor as presentation sign of MG. EMG

tremor pattern is usually featured by the presence of alternating or synchronous contraction of agonist-antagonist muscles. Antagonist muscles activity was absent in this case. The pathophysiologic process below this clinical feature is unknown. We hypothesized that typical F and OO weakness of ocular MG could explain the onset of forehead tremor as a compensatory act for keeping eyes open, clinically resembling tremor, despite neurophysiological recording was not typical of tremor.

Conclusions: To our knowledge, this is the first description of forehead tremor as clinical presentation of MG. Forehead tremor was only observed in extrapyramidal syndromes. When a patient presents with forehead tremor, with or without ocular symptoms, we should consider also MG in differential diagnosis, in order to start rapidly the adequate treatment.

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Induced Pluripotent Stem Cells Based in-vitro Modelling of Spinocerebellar Ataxia Type -12 (SCA-12)

D. Kumar, M. Faruq, A. Srivastava, M. Mukerji, O. Mukherjee (Delhi, India)

Objective: To derive neuronal lineages from patient's peripheral blood mononuclear cells (PBMCs) and exploration of disease biology.

Background: Spinocerebellar ataxia type-12 (SCA-12) is a progressive cerebellar and purely neurodegenerative genetic disorder caused by (CAG) expansion in 5'UTR of PPP2R2B gene. SCA12 is the second common genetic ataxia type and has unique prevalence in North Indian population. Transgenic or any other appropriate neuronal-cell/animal models are lacking to understand the underlying cellular perturbations in SCA12. Human-induced-pluripotent-stem cell based (HiPSC) based disease modeling overcomes the limitation of non-availability of specific cell type for studying such disorders.

Methods: Lymphoblastoid-cell-lines (LCLs) derived from patient's PBMCs were used to generate non-integrated iPSCs using episomal plasmids (Yamanaka-factors). These iPSCs were then de-differentiated into NSCs/Neuronal lineage. Appropriate cellular characterization was conducted for respective cell lines. A comprehensive candidate gene transcriptomic-profiling was conducted in cell lines and compared with appropriate controls

Results: PPP2R2B transcripts levels were found down-regulated in blood samples of patients compared to controls (N=10), however, in HiPSCs lines, we observed a significant variation of all the isoforms except brain-specific isoform-4. In neural progenitor cells (NSCs) and differentiated neurons, we observed the expression of brain-specific isoform-4. This suggest that these patient iPSC derived neuronal model are good for mechanistic analysis. We observed that CAG-containing non-coding PPP2R2B transcripts (isoform-12) significantly expressed (fc>30) lines compared to control in both NSCs and neurons.

Conclusions: We have generated patient derived HiPSCs and their differentiated derivatives to study SCA12 pathogenesis. Our preliminary data shows that HiPSC based model system can serve as model to study such adult onset complex disorders. We were able to identify expression pattern of candidate gene PPP2R2B, mimicking brain-specific transcripts. Our preliminary data shows some trend towards disease relevant transcriptional signatures.

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Blink Reflex Recovery Cycle in Patients with Genetically Determined Ataxias

S. Tunc, A. Weissbach, E. Werner, N. Baginski, J. Lubs, A. Münchau, T. Bäumer (Lübeck, Germany) Objective: To investigate the R2 blink reflex recovery cycle (BRRC) in genetically determined ataxias such as spinocerebellar ataxia (SCA), ataxia telangiectasia (AT) and Friedreich's ataxia (FRDA).

Background: BRRC is known to be facilitated (enhanced) in movement disorders with basal ganglia involvement including Parkinson's disease and isolated focal dystonias.(1, 2). The underlying mechanism though is not yet fully understood.

Methods: In an ongoing study, 22 patients (7 SCA1, 1 SCA2, 5 SCA3, 4 SCA6, 1 SCA17, 1 AT, 3 FRDA) with and without dystonia and 28 age and sex-matched healthy controls (HC) were examined. The BRRC was investigated using an air-puff stimulation at interstimulus intervals (ISI) of 200, 300, 500, 1000, and 3000 msec. EMG was recorded from the right orbicularis oculi muscle. To compare individual subjects, the area under the curve ratio values of R2 conditioned/R2 unconditioned were calculated. Clinical examination included a standardized video protocol and rating scales (e.g. scale for the assessment and rating of ataxia (SARA) and Fahn-Marsden-Score for Dystonia). For statistical analysis patients were grouped into those with (n=9) and without dystonia (n=13). **Results:** The BRRC differed significantly (p<0.001) between the five ISI with stronger inhibition at shorter ISIs. Surprisingly, patients showed a trend towards a stronger inhibition of the BRRC (29% vs. 41% for ISI 300; 53% vs. 72% for ISI 1000) compared to HC. The analysis of patients with and without dystonia revealed a significant interaction (p=0.05) of the factors group and ISI (Figure 1).



Conclusions: To our knowledge, this is the first study investigating the BRRC in genetically defined ataxia patients. So far, in patients with Parkinson's disease and isolated dystonias the BRRC was facilitated suggesting deficient inhibition of basal ganglia - brainstem interaction mediating this response. In contrast, in ataxia patients reported here, there was a significant interaction of the factors group and ISI and a tendency towards stronger inhibition of the BRRC. Our ongoing investigations will clarify, if this effect withstands to significance and whether other clinical markers such as SCA subtype or symptom severity correlate with our electrophysiological findings.

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Movement Disorders and Clinical Progression in Spinocerebellar Ataxias

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Objective: To study the prevalence and influence of movement disorder signs in SCAs.

Background: Movement disorders are common features in spinocerebellar ataxias (SCAs), but their associations with ataxia progression are not well understood.

Methods: We studied 336 participants with SCA 1, 2, 3 and 6 from the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) and assessed their movement disorder signs (dystonia, postural tremor, rest tremor, rigidity, and chorea) at baseline. We repeatedly measured ataxia progression by the Scale for Assessment and Rating of Ataxia (SARA) every 6 months for 2 years. We employed regression models to study the effects of movement disorder signs on ataxia progression after adjusting for age, sex and pathological CAG repeats. **Results:** Dystonia is most common in SCA3 (25%), whereas postural tremor, rest tremor, and chorea are most common in SCA2 (29%, 13%, and 14%, respectively). Rigidity is more prevalent in SCA2 and SCA3 (20% and 17%, respectively). SCA1, 2, 6 patients with movement disorder signs and those without movement disorder signs do not differ in their pathological CAG repeat length except that SCA1 patients with rigidity have a shorter CAG repeat length than SCA1 patients without rigidity. SCA3 patients with dystonia or postural tremor have a longer CAG repeat length, whereas SCA3 patients with rest tremor have a shorter CAG repeat length. In SCA1, postural tremor is associated with slower ataxia progression, whereas chorea is associated with faster progression. Postural

tremor and rigidity predict faster deterioration in SCA2 and SCA3, respectively. Although movement disorders are relatively rare in SCA6, the presence of movement disorder signs (dystonia, postural tremor, rest tremor, or rigidity) is associated with slower ataxia progression.

Conclusions: Movement disorder signs are common in SCAs and are associated with different rates of clinical progression. Thus, SCAs with distinct movement disorder signs might represent subtypes of diseases preferentially involved with diverse neural circuitry within and outside the cerebellum.

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The Autonomic Nervous System in Friedreich's Ataxia: Preliminary Findings

E. Indelicato, A. Fanciulli, J. Wanschitz, W. Nachbauer, W. Poewe, G. Wenning, S. Boesch (Innsbruck, Austria) **Objective:** To investigate the autonomic function in Friedreich's ataxia (FRDA).

Background: FRDA is a hereditary neurodegenerative disorder characterized by progressive gait ataxia, limb dysmetria, dysarthria and peripheral neuropathy. Further features are hypertrophic cardiomyopathy and diabetes mellitus. The disease is caused by an intronic GAA expansion in the *FXN* gene. Age at onset and disease severity strongly correlates with the length of the shorter GAA repeat (GAA1). The neurodegeneration in FRDA primarily involves the dorsal root ganglia and large myelinated fibers in peripheral sensory nerves. Recently an involvement of small unmyelinated fibers has been demonstrated in skin biopsy of FRDA and it has been correlated with disturbances in temperature and pain perception. The presence of autonomic correlates was not investigated yet in genetically confirmed cases.

Methods: Sixteen genetically confirmed FRDA patients were consecutively enrolled. Each patient underwent a general and neurological examination, laboratory work-up, ECG and echocardiography to rule out cardiomyopathy. Disease severity was quantified through SARA and ADL scales. The SCOPA-aut questionnaire was administered to evaluate autonomic symptoms. Autonomic function was investigated by means of a cardiovascular tests battery (head-up tilt, active standing, Valsalva maneuver and deep breathing) and of the skin sympathetic reflex. Results were compared to normative values of our laboratory.

Results: Mean age at examination was 42 ± 14 years while the mean age at disease onset was 22 ± 14 . The average GAA1 length was 429 ± 278 repeats. The mean SCOPA-aut score was 12 ± 6 . Six patients performed just one autonomic test because of cardiomyopathy and/or severe physical disabilities. Of the other 10 patients 40% had =2 abnormal autonomic tests including blunted deep breathing and Valsalva ratio, absent skin sympathetic reflex and delayed orthostatic hypotension in 1 case. No difference regarding age at examination, disease duration or severity, GAA1 repeats, and occurrence of impaired glucose tolerance was found in the comparison between the two groups. **Conclusions:** We observed subtle alterations of autonomic function in our FRDA cohort independently from disease severity and occurrence of diabetes. That could be attributed to multiple determinants as well as to an impairment of peripheral autonomic relays.

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Is the Cerebellum a Good Target For Neuromodulation in Movement Disorders?

C. França, M. Teixeira, D. de Andrade, R. Galhardoni, V. Barbosa, V. Silva, G. Lepski, E. Barbosa, R. Cury (São Paulo, Brazil)

Objective: To assess the effects of dentate nucleus transcranial magnetic stimulation and deep brain stimulation on patients with cerebellar ataxia of different etiologies.

Background: Cerebellar neuromodulation is a new therapeutic tendency in movement disorders. A few recent studies showed that cerebellar TMS might be a new frontier regarding the treatment of cerebellar ataxias. We previously published a case report of a patient with cerebellar stroke that had a great response to dentate nucleus TMS (DN-TMS). This same patient was then offered a dentate DBS implant, with also good response. Inspired by the results in this case, we expanded the TMS trials to a larger number of patients. We included, in addition to other stroke patients, patients with ataxia of degenerative causes in order to shed a light in which types of ataxia would perhaps benefit from this approach.

Methods: Six patients with cerebellar ataxia refractory to clinical treatment were screened for DN-TMS (patient 1, ischemic cerebellar stroke; patient 2, Multiple System Atrophy; patient 3, Spino-cerebellar Ataxia; patient 4, ischemic cerebellar stroke; patient 5, Ataxia with Vitamin E Deficiency); Patient 6, hemorrhagic cerebellar stroke. All patients were evaluated before and after 5 sections of DN-TMS with the following scales: Scale for the Assessment and Rating of Ataxia (SARA) and Fahn Tolosa Martin Tremor Rating Scale (FTMTRS). Patient 2 was not evaluated with FTMTRS. Deep brain stimulation to the left dentate nucleus was performed in patient 1.

Results: Four out of six patients had an improvement in the ataxia according to the SARA (range: 25% - 34%; patients 1, 2, 3 and 4). All patients that presented a tremor at baseline (patients 1, 4 and 5) improved according to the FTMTRS (range: 23% - 70%). Only patient 6 didn't show any sign of improvement in his symptoms. **Conclusions:** This was the first controlled, neuronavigation-guided TMS study aiming at cerebellar ataxia and tremor control. All our patients improved ataxia or tremor due to the treatment. In the patient submitted to the DBS implant, the clinical improvement remained until the last evaluation (one year). The study protocol was safe and well tolerated. As one patient did not improve in the present series, further studies (including our ongoing study) are needed to provide larger evidence on the best target population for cerebellum neuromodulation.

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How Do Ataxias with Oculomotor Apraxia Look and Look Like? A Comparative Controlled Multimodal Study of AT, AOA1 and AOA2 Focusing On Video-oculography

L.-L. MARIANI, S. Rivaud-Péchoux, B. Gaymard, M. Anheim (Paris, France)

Objective: To perform a multimodal comparison of AT, AOA1 and AOA2 focusing on video-oculography. **Background:** Autosomal recessive cerebellar ataxias (ARCAs) are heterogeneous disabling inherited neurodegenerative disorders. Their diagnostic workup remains a challenge. Identifying phenotypic supportive clues is necessary to improve diagnosis delay and accuracy.

Methods: We compared 40 patients with AT, AOA1 and AOA2, referred between 2008 and 2015 at two French tertiary adult movement disorders centers to 17 healthy subjects. Clinical examination, functional scores, video-oculography, nerve conduction studies, brain MRI, and biomarkers were studied.

Results: Video-oculography revealed complex oculomotor disorders in patients relative to controls. Constant impairments were cerebellar signs (p<0.0001) (either downbeat (p<0.01) or gaze-evoked (p<0.0001) nystagmus or hypermetric horizontal saccades (p<0.0001)), altered fixation (p<0.0001), impaired pursuit, hypometric saccades (p<0.0001) and abnormal antisaccades (p<0.001). Horizontal saccade latencies could be highly increased reflecting oculomotor apraxia in 27.5 to 40% of the patients. A higher intra- and intersubject variability of saccade latencies (p<0.05) was observed in patients. Discriminating AFP thresholds with good specificities and predictive values were determined: 7-15 μ g/L for AOA1, 15-65 μ g/L for AOA2 and > 65 μ g/L for AT patients. Other shared features were early ages at onset, severe walking disability, various movement disorders, sensori-motor neuropathy, cerebellar atrophy.

Conclusions: We show AOA1, AOA2 and AT share close, complex, highly variable oculomotor phenotypes. Video-oculography is not able by itself to differentiate between them and is not mandatory in the diagnosis workup of patients with ARCA, but an appropriate oculomotor examination remains crucial. In ARCAs' diagnosis workup, AOA1, AOA2 and AT should be considered as a peculiar group characterized by ataxia with complex oculomotor disturbances and elevated AFP. Increased AFP serum level seems to be more relevant than video-oculography in distinguishing them, which finally relies on genetic analysis. Our findings will allow reliable reverse-phenotyping, which will be mandatory to interpret the numerous variants of unknown significance provided by premature next-generation sequencing.

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The Spectrum of Composite Autonomic Severity Score in SCA1, SCA2 and SCA3 Patients

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Objective: To analyze composite autonomic severity score in patients of spinocerebellar ataxia types 1, 2 and 3. **Background:** Spinocerebellar ataxia (SCA) is a progressive neurodegenerative disorder characterized by autonomic failure. There is paucity of literature for quantification of autonomic failure applying validated score in SCA. The Composite Autonomic Severity Score (CASS) was developed for laboratory quantification of autonomic failure as a single validated score. This also standardizes for the confounding effects of age and gender. In this context, we evaluated CASS in patients of SCA1, 2 and 3.

Methods: Continuous HR and BP were recorded to determine autonomic function in genetically confirmed SCA1 (n=31, age=35.3±7.82 yrs), SCA2 (n=40, age=33.25±10.45 yrs) and SCA3 (n=9, age=37.11±9.21 yrs) patients. CASS ranges from 0 to 10 and constitutes of sudomotor (0–3), cardiovagal (0–3), and adrenergic (0–4) subscores. The analysis of CASS was done by using MATLAB (R2015a).

Results: The mean total CASS was 4.45 ± 1.69 in SCA1, 4.6 ± 1.26 in SCA2 and 3.78 ± 1.2 in SCA3. Mild autonomic failure were more in SCA3 (44.44%; 4/9) than SCA1 and SCA2. Most of the patients had moderate autonomic failure such as 80.65% (25/31) in SCA1, 85% (34/40) in SCA2 and 55.55% (5/9) in SCA3. More cases of severe failure were seen in SCA1 (2/31) than SCA2 (1/40) whereas none in SCA3 [Table].

CASS ranges (0-10)	SCA1 (n=31)	SCA2 (n=40)	SCA3 (n=9)
Mild (1-3)	4 (12.9%)	5 (12.5%)	4 (44.44%)
Moderate (4-6)	25 (80.65%)	34 (85%)	5 (55.55%)
Severe (7-10)	2 (6.45%)	1 (2.5%)	0

Table: Evaluation of CASS in the patients of SCA1, SCA2 and SCA3.

Conclusions: Our data suggests moderate generalized autonomic failure (in SCA1 and SCA2) and mild failure (in SCA3) as determined by CASS. This may be a useful index imparting the clinical diagnosis of SCA1, SCA2 and SCA3.

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Allelic CACNA1A Disorders: a Retrospective Cohort Analysis on Clinical Course and Overlapping Features *W. Nachbauer, P. Dorin, E. Indelicato, A. Eigentler, S. Boesch (Innsbruck, Austria)*

Objective: (1) To retrospectively study emerging clinical symptoms and disease course in a cohort of patients with genetically proven CACNA1A mutations and (2) to define occurrence and frequency of overlapping clinical features.

Background: The CACNA1A gene codes for the pore forming alpha 1A subunit of the P/Q-type voltage-gated calcium channel (Cav2.1). Mutations in the CACNA1A gene are known to cause the three allelic disorders spinocerebellar ataxia type 6 (SCA6), episodic ataxia type 2 (EA2) and familial hemiplegic migraine type 1 (FHM1).

Methods: Patients with genetically proven CACNA1A mutations were identified from the clinical database of the Department of Neurology at the Medical University Innsbruck. Medical records were systematically analyzed for demographics, clinical manifestations at onset and in later disease course. Characterization of episodic symptoms was carried out using a standardized protocol considering frequency, duration and associated symptoms. **Results:** 46 patients with a mean age of 50 years (range: 6 – 86) were identified from the database. Mean age of onset was 26 years with significant lower onset in EA2 and FHM1 as compared to SCA6. Frequency of attacks was highest in the EA2 group, whereas duration of attacks was considerable longer in FHM1. 14% of SCA6 patients exhibited episodic symptoms mainly short lasting vertigo and gait ataxia, which were evident in early disease and preceded the chronic cerebellar syndrome. Triggers for attacks were mainly identified in EA2 comprising emotional stress, physical exercise and caffeine. Most common ictal symptoms were gait ataxia and dysarthria, which also occurred in one third of FHM1 patients during attacks. Conversely 50% of EA2 patient had a history of migraine associated with attacks or occurring independently. Interictal cerebellar signs were observed in 85% of EA2 and 71% of FHM1 patients. Gaze evoked nystagmus therefore was the most prominent cerebellar feature. Progression of cerebellar syndrome in EA2 and FHM1 was mild over the observation period.

Conclusions: This retrospective analysis further demonstrates high phenotypic variability in allelic CACNA1A disorders. Distinctive clinical manifestations are present in some mutations. In a greater part overlap between these disorders is observed in both ictal as well as interictal symptoms and most prominent between EA2 and FHM1.

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Spinocerebellar Ataxia Type-17: An Indian Scenario

S. Shakya, P. Negi, A. Garg, M. Prasad, M. Faruq, A. Srivastava (New Delhi, India)

Objective: We aimed to investigate status of SCA17 in Indian population and tried to minimise the category of unidentified cerebellar ataxia cases.

Background: Spinocerebellar ataxia type 17 (SCA17) is an Autosomal dominant, progressive, neurodegenerative disorder. The causal mutation in SCA17 is the expansion of CAG/CAA (>41) repeats in exon 3 of *TBP* on chromosome $6q^{27}$. Genetic studies are lacking for SCA17 in India, only few case reports have been published from Indian population.

Methods: A total of unrelated 670 cases with evidence of cerebellar ataxia and genetically negative for SCA1-3, SCA6-8, SCA12, and FRDA mutation (Uk-SCAs) were screened for SCA17 mutation. CAG/CAA (*TBP*) length distribution analysis in 229 cases of genetically known SCAs other than SCA17 (K-SCA) and 820 healthy controls (HC) was also carried out. CAG/CAA (*TBP*) expansion was measured by fragment analysis and confirmed by sequencing in ABI 3130xl sequencer.

Results: We identified a cerebellar ataxia patient carrying TBP-CAG/CAA- 37/129 repeats. One patient of SCA17 carrying a homozygous-CAG/CAA-45/46 with manifestations of cerebellar ataxia, psychiatric disorder and with extrapyramidal features conforming to the SCA17 diagnosis. In addition 45 patients were found to carry repeats of alleles 41-44 in unknown SCAs however the 41-44 carriers were also found in kn-SCAs (11 Patients). The CAG/CAA length distribution showed the observed range (% alleles with >39 repeats) as following; in HC 32-43(16%), in K-SCA 35-44(42%) and Uk-SCA 32-129 (35%).

Conclusions: TBP CAG/CAA- 37/129 is the largest repeat size reported till date. SCA17 seems to be a rare SCA-subtype in India and individuals with more than 41 repeats should be followed-up periodically for assessment of SCA17 features.

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Autosomal Dominant Spinocerebellar Ataxia Secondary to CACNA1G in a Patient of German Ancestry E. Call, V. Santini (Stanford, CA, USA)

Objective: We describe the case of a male patient of German ancestry with SCA 42.

Background: Hereditary spinocerebellar ataxia (SCA) describes a heterogeneous group of disorders inherited in an autosomal dominant manner, most often characterized by ataxia, although other movement phenomenology, eye movement abnormalities, cognitive impairment, pyramidal signs, and peripheral neuropathy can also be seen. In 2015, two publications described a novel disease-causing mutation (p.Arg1715His) in the *CACNA1G* gene manifesting as SCA 42. We present a case of confirmed SCA 42 in a patient of German ancestry with slowly progressive cerebellar signs and cognitive impairment.

Methods: A 75-year-old man who was evaluated in the Stanford Movement Disorders Clinic for complaints of dysarthria and imbalance. He reported 7 years of slowly progressive slurring of speech, imbalance, cognitive decline, and clumsiness of his hands. Family history was significant for similar symptoms in his father, 2 paternal aunts, and a paternal cousin. His paternal lineage was of German ancestry. Examination was notable for moderate dysarthria, hypermetric saccades and axial>appendicular ataxia. He scored a 24/30 on the MoCA with deficits in delayed recall and language.

Results: Negative work-up included HIV, RPR, TSH, B12, MMA, SPEP, UPEP, ESR, and serum paraneoplastic antibody panel. Testing for SCA 1, 2, 3, 5, 6, 7, 8, 10, 13, 14, and 17 was negative as was testing for DRPLA, FXTAS and familial coenzyme Q deficiency. A recessive variant involving a single base pair (G>A at codon 489) on the SETX gene was thought to be unrelated to his presentation. The patient's DNA was then analyzed via the University of Chicago ataxia exome panel, revealing a disease-causing heterozygous mutation (c.5144G>A; p.Arg1715His) in *CACNA1G*.

Conclusions: SCA 42 is an autosomal dominant condition caused by a change in the voltage-sensing portion of a T-type calcium channel commonly expressed in the cerebellum, leading to a slowly-progressive cerebellar syndrome with oculomotor abnormalities and variable cognitive impairment, as was seen in our patient of German ancestry.

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Ataxia, Opsoclonus and Peripheral Neuropathy Induced by Chronic Toluene Intoxication.

L. Beltrami, T. Araujo, C. Borges, F. Germiniani,, H. Teive (Curitiba, Brazil)

Objective: To report a case of a young patient with opsoclonus, ataxia and peripheral neuropathy due to toluene intoxication.

Background: Amid the causes of secondary ataxias, the most common are due to infection, auto-immune diseases and intoxications. Opsoclonus can be a result of CNS infections, paraneoplastic syndrome, auto-immune diseases or intoxications. Thinner is a common recreational drug in Brazil; one of its main components is toluene hydrocarbonate, which can cause a number of neurological syndromes.

Methods: Case Report

Results: A 37 y/o male patient who worked as a gardener presented to the outpatient clinic complaining of a trembling vision that had begun roughly one year before, as well as dizziness and difficulty to walk unaided that developed over the last two months, becoming bed-ridden. He had been inhaling thinner, a toluene-rich chemical on a daily-basis over the last 20 years. Neurological examination disclosed opsoclonus, dismetric movements of the

upper limbs, ataxic gait, loss of tactile and pain sensations and absent deep tendon reflexes in the lower limbs. A thorough work-up ruled-out the possibility of underlying malignancy. Serological testing for infectious diseases was negative and serum levels of B1 and B12 vitamins were normal. CSF analysis was normal. Brain MRI disclosed abnormal signal abnormalities on FLAIR compromising the white matter of both temporo-parietal lobes, as well as the midbrain. CT scans of cervical, thoracic and lumbar spine ruled-out compressive myelopathy. An abnormal ENMG study was compatible with chronic sensorial neuropathy with predominantly distal axonal compromise on both lower limbs. He was treated with a pulse of 1 g/day of Methylprednisolone over five days with marked improvement of ataxia and was discharged with oral Prednisone 40 mg qd.

Conclusions: Although opsoclonus often suggests the possibility of underlying malignancy or CNS infection, toxic and metabolic causes should also be considered in the differential diagnosis.

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The Diagnostic Dilemma of Olivopontocerebellar Atrophy and Spinocerebellar Ataxia, a Comparative Analysis of Clinical Cases

S. Gazieva, O. Turgunkhujaev (Tashkent, Uzbekistan)

Objective: Clinical practice often confronts us with ambiguous and conflicting data from the "western" and "eastern" publications, which leads to misunderstandings and disagreements, so we set out to bring on a common state dilemma of contradiction in respect of hereditary ataxia.

Background: Modern scientific literature is growing rapidly as the jungle, where many secrets and rare treasures are hidden. The trend of development of medicine requires a doctor's daily analysis and processing of a dozen of new articles and abstracts.

Methods: A 54 years old man, an accountant, admitted to our clinic, with a diagnosis of "Essential hypertension, Chronic brain ischemia, Sensorineural hearing loss, Organic amnestic syndrome ", with complaints of tinnitus, which progressively grew last 5 years and has led to hearing loss. The disease began with low intensity noise, which grew over the last 5 years. No harmful habits were detected. No family history. After detailed examination we revealed saccadic pursuit, violation of postural reflexes, retropulsion, light spasticity in the legs, swallowing disorders, dysarthria. Audiometry - sensorineural hearing loss (3-4 degree) with violation of the perception of high frequency sounds. MRI - MR signs of vascular encephalopathy.

Results: Our analysis showed that, in our patient more accurate diagnosis is spinocerebellar ataxia type 36, however, olivopontocerebellar atrophy with its 5 subtypes to date are included in spinocerebellar ataxia taxonomy and multiple system atrophy, in addition olivopontocerebellar atrophy is observed in many other diseases: non-hereditary ataxia, intoxication and vascular degeneration.

Conclusions: Proceeding from the above, it is clear that the diagnosis of olivopontocerebellar atrophy is in the most syndromic, and requires a doctor's deeper view into patient's progressive ataxia. The question of necessity in verification of exact diagnosis remains open, as in bears no tactical value. But, tracking such cases and the description of them is preserved in science as one the most relevant methods for the studying of rare diseases. In our opinion the doctor should solve clinical problem of "multidiseased" patient under guidance of Occam's razor principals, one of which states - "Diversity should not be assumed without necessity."

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Cerebellar Ataxia - The First Symptom Of HIV Infection

L. Beltrami, J. Kristochik, M. Novaes, G. Tansini, F. Germiniani, H. Teive (Curitiba, Brazil) **Objective:** To describe a patient with unusual and rare initial presentation of HIV infection – a progressive cerebellar ataxia.

Background: Isolated cerebellar degeneration in an HIV patient is rare and should prompt a diagnostic work up. Cerebellar complications of HIV infection primarily manifested in ataxia, usually arise as the result of cerebellar lesions due to opportunistic infections, vasculitis or neoplastic.

Methods: Case Report

Results: A 44-year-old woman, without comorbidities, developed a progressive imbalance and gait ataxia 6 months ago. At this time behavior disorders was detected and she was treated with psychiatry, using quetiapine, fluoxetine and amitriptyline. The neurological examination showed preserved cognition, slowing saccadic eye movements, dysmetria, dysdiadochokinesia, and gait ataxia. Brain MRI was normal and abdominal ultrasound demonstrated splenomegaly. Extensive work-up was negative. In the follow-up this patient developed oropharynx whitened lesions, dysphagia and worsening gait. Serology HIV test was positive and a brain MRI showed cerebellar atrophy.

CSF exam showed hyperproteinorrachia of 51.9 mg. Viral HIV load was 24880 and CD4 count of 65. The patient starts the treatment with HAART, buspirone and sulphametoxazole-trimethoprim prophylactic. **Conclusions:** HIV infection should be considered as an etiology in clinical setting of subacute cerebellar ataxia, particularly in a young or immunocompromised patient.

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Neuroferritinopathy Pedigree in 2 Families from India

J. Kaur, G. Singh, B. Paul (Ludhiana, India)

Objective: The abstract provides description of first case report of two Indian families with Neuroferritinopathy (NFT) pedigree.

Background: NFT is a rare autosomal dominant movement disorder caused by mutations in the ferritin light chain gene. It is the only NBIA subtype, which is autosomal dominant, characterised by variable clinical presentation including chorea, athetosis, dystonia, parkinsonism, cognitive decline and psychiatric symptoms. To date, few families have been described from England and France. We describe here two families from India with NFT pedigree.

Methods: Case Report.

Results: Family 1: A 31 year old female presented with complaints of abnormal movements for last 5 years, starting in her right leg and progressing rapidly to other limbs. She had unsteadiness while walking and a recent change in her behavior. There is no history of consanguineous marriage in the family. A dominant inheritance with total 13 affected members and 4 presently living with the disease were noted in pedigree (Figure 1). Mean mini-mental examination was 21/30 with frontal dysexecutive type dementia. She has mild dysarthrophonia with generalised choleric movements. She has brisk tendon reflexes with bradykinesia. Laboratory blood tests were normal and MRI brain revealed hypointensity in the globus pallidus, substantia nigra and dentate nuclei on SWI (Figure 2). Further, her 3 other family members with similar symptoms were evaluated. (Figure 3) Family 2: 33 year old carpenter presented to us with complaints of abnormal body movements for last 4 years. He had hoarseness of voice with difficulty in swallowing and a recent change in his behaviour. With normal birth history and developmental milestones, there is no consanguineous marriage in the family. The family pedigree showed dominant pattern with 5 members living with this familial neurodegenerative disease. Higher mental function examination suggested frontal dysexecutive type dementia. Generalized choreic movements were noted with oromandibular dyskinesia, palatal tremor and dysarthrophonia. In eve movements, blepharospasm with hypometric saccades was noted. Muscle tone and strength was normal with brisk tendon reflexes and bradykinesia. MRI brain revealed symmetrical hypointensity in bilateral globus pallidus on SWI-MRI (Figure 3). Further, his cousin sister with similar symptoms was evaluated.



Characteristics	Case 1	Case 2	Case 3	Case 4
Age (years)/ gender	31/F	38/F	41/M	45/M
Age at onset (years)	26	34	28	25
Dysarthrophonia	+	+	+	*+
Orolingual Dyskinesia	+	+	-	-
EOM	Normal	Abnormal	Normal	Abnormal
Bradykinesia	+	-	-	+
Dystonia	+	+	+	+
Chorea	+	+	+	+
Power	N	N	N	N
Reflexes	brisk	brisk	brisk	brisk
Gait Abnormality	+	+	+	+
Cognitive/behavioral abnormality	+	+	+	+
MRI brain (suggestive of iron deposition)	+	+	+	+





Conclusions: To the best of our knowledge, this is the first case report of two large Indian families with NFT pedigree.

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Fentanyl Induced Chorea: A Case Report

M. Gallagher, A. Colcher, A. McGarry (Camden, NJ, USA)

Objective: To report the acute onset of generalized chorea as an adverse reaction to transdermal fentanyl **Background:** Chorea can present with degenerative conditions or in an acquired manner [1]. Here we present a case of transdermal fentanyl provoking chorea, which to our knowledge, is the first such report in the literature. **Methods:** Case report

Results: A 91-year old female with a medical history of rheumatic fever as a child presented complaining of uncontrollable, generalized movements. The movements started one month prior after she was switched to a different brand of transdermal fentanyl. Her symptoms started over a period of two days and remained constant. Laboratory evaluation included thyroid studies, Sjogren's antibody, ANA, antiphospholipid antibody, double-stranded DNA, lead, antistreptolysin antibody, renal, hematologic, and liver profiles. All were unremarkable. She had a complicated hospital course that included group A streptococcus bacteremia, presumed endocarditis, and new onset atrial fibrillation. An MRI demonstrated multiple small areas of restricted diffusion within the right precentral gyrus, the left posterior frontal, left parietal, and left superior occipital regions. Her fentanyl was stopped and she was treated with oral morphine 15 mg twice daily for her chronic pain. She was given diazepam 5 mg three times a day. The movements gradually improved. Due to her prolonged dysphagia, she had a feeding tube placed. She was

discharged and completed a 6-week course of ceftriaxone for bacterial endocarditis. After a period of 4 months, her movements had resolved. She was able to have the feeding tube removed, and returned to her prehospital level of functioning. She was seen 6 months after initial symptoms in the orthopedics office due to her continued chronic pain, and was restarted on 25 mcg of transdermal fentanyl. Choreic movements promptly returned. The medication was again stopped, with gradual resolution of symptoms.

Conclusions: Chorea is a commonly reported side effect for many medications [2]. The differential diagnosis of chorea is broad, and specific identification of causative agents can be elusive. It is important to take a detailed medication history, as there are many medications that elicit chorea. In this report, we provide case data suggesting fentanyl should be considered when alternate explanations for chorea are absent or inconclusive.

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Psychiatric Manifestations of Neuroacanthocytosis Syndromes

Z. Brahem, I. Bedoui, A. Riahi, H. Derbali, M Mansour, J. Zaouali, R. Mrissa (Tunis, Tunisia)

Objective: We seek to describe the different clinical manifestations of neuroacanthocytosis syndromes and to focus especially on psychiatric one.

Background: The term "neuroacanthocytosis" is used generally to refer to disorders in which neurological abnormalities are accompanied by the presence of thorny red blood cells, known as acanthocytes. There are four core neuroacanthocytosis (NA) syndromes: chorea-acanthocytosis (ChAc), McLeod syndrome, pantothenate kinase-associated neurodegeneration (PKAN) and Huntington's disease-like 2 (HDL2).

Methods: Four cases of neuroacanthocytosis Syndromes are described. All patients had a cerebral MRI, research of acanthocytes in blood.

Results: Three men and one woman with a mean age of 31 years, with no past history were hospitalized in our department. Three of them had ChAc and one had PKAN. Three patients had chorea and one of them had parkinsonism. All of them had Psychiatric manifestations such as self-mutilation, agitation and obsessive-compulsive behavior. The "eye-of-the-tiger" seen on MRI supports the diagnosis of PKAN in one patient and for the others cerebral MRI was normal. Acanthocytosis were found in all patients 'blood.

Conclusions: Degeneration affecting the basal ganglia is the key neuropathologic finding, thus the clinical presentations can be remarkably similar in the four neuroacanthocytosis Syndromes. The characteristic phenotype comprises a variety of movement disorders, including chorea, dystonia parkinsonism, and also psychiatric and cognitive symptoms attributable to basal ganglia dysfunction. Psychiatric manifestations include depression, self-mutilation with tongue and lip-biting, head drops, agitation and obsessive-compulsive symptoms. Sometimes, these psychiatric troubles can usher the clinical presentations and we should think about these syndromes especially in front of young patients.

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An unusual case of hemichorea in a woman with newly discovered renal cell carcinoma and inconclusive LGI-1 antibody

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Objective: We report a case of a 72 year-old woman with progressively worsening chorea of the left upper and lower extremities, who was incidentally found to have renal cell carcinoma (RCC) and an inconclusive leucine-rich, glioma inactivated 1 (LGI-1) antibody. The patient underwent a partial nephrectomy with near-complete resolution of the choreiform movements.

Background: Chorea is a movement disorder characterized by hyperkinetic, dance-like movements of the extremities. Several antibodies including LGI-1 have been identified in association with paraneoplastic chorea, however RCC is not known to be associated with LGI-1 and only rarely presents with chorea.

Methods: A 72 year-old woman presented with a seven month history of progressively worsening chorea involving her left upper and lower extremities. Exam revealed choreiform movements with clumsy and dysrhythmic rapid alternating movements in the left arm and leg, and gait instability. Magnetic resonance imaging of the brain was negative without evidence of infarcts or abnormalities in the basal ganglia. Extensive lab testing of both serum and cerebrospinal fluid was unremarkable, except for an inconclusive anti-LGI-1. Computed tomography scan of the pelvis revealed a renal mass which was identified as RCC on biopsy. A partial left nephrectomy was performed with near-complete resolution of chorea.

Results: Paraneoplastic chorea is commonly associated with CRMP-5/CV2, GAD65, CASPR2, and LGI-1 antibodies. However, LGI-1 typically also presents with encephalitis, myoclonus, and ataxia, and is primarily seen in small cell lung carcinoma, thymoma, and breast and prostate adenocarcinoma, with no described association with

RCC thus far. In a study by O'Toole et al in 2013 in which 36 patients with adult-onset chorea were studied, neither RCC nor anti-LGI-1 were identified in any of the patients, and the majority of patients exhibited generalized chorea (44%) as opposed to hemichorea (25%) (1). In addition, RCC in association with chorea is rare, and has only been described in the setting of encephalitis with generalized, severe bilateral chorea (2).

Conclusions: This case is unique in that RCC is rarely associated with chorea or LGI-1 antibodies and removal of the tumor led to significant symptom improvement, which highlights that RCC should be taken into consideration in patients with chorea.

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[11C]PK11195 PET Imaging Reveals Neuroinflammation in Dementia with Lewy Bodies: NIMROD Study

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Objective: To determine if subjects with dementia with Lewy bodies(DLB) have increased microglial activation *in vivo* compared to matched healthy controls as assessed using PET imaging of the radioligand [11C]PK11195, which preferentially binds to activated microglia, and to assess whether there are correlations with clinical features. **Background:** Evidence of neuroinflammation in the pathogenesis of Lewy body dementia continues to accumulate, with recent PET studies showing microglial activation *in vivo* in Parkinson's disease dementia that negatively correlates with cognitive ability[1]. It is unclear whether similar changes occur in DLB, though alpha-synuclein is known to activate microglia and pathology studies suggest neuroinflammation in the pathogenesis of DLB[2]. **Methods:** Using dynamic PET imaging of [11C]PK11195, we compared [11C]PK11195 binding overall and within 10 regions of interest, between 11 subjects with probable DLB and 13 age and education matched healthy controls. Binding was quantified using non-displaceable binding potential (BPND) determined with the simplified reference tissue model. We also assessed correlations between regional BPND and key clinical variables including cognition (ACE-R score) and disease duration.

Results: There was significantly increased BPND in the basal ganglia (putamen) and the occipital lobe (cuneus) in DLB compared to the control group (p<0.005, Mann-Whitney U). The BPND within the cuneus correlated positively with ACE-R scores (p<0.005, Spearman R), but there was no significant correlation with disease duration. **Conclusions:** Our results show increased [11C]PK11195 binding consistent with microglial activation in brain regions known to be affected in DLB, suggesting that neuroinflammation can be demonstrated *in vivo*. Although its significance remains unclear, the positive correlation with ACE-R scores suggests that microglial activation is elevated in mild disease and diminishes in later stages. This suggests that either inflammation is protective in DLB, or that the potential immunotherapeutic window is narrow and early in disease.

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Association of arterial stiffness with cognition in patients with Lewy body disorder

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Objective: We aimed to investigate the association between arterial stiffness and cognitive function in patients with Lewy body disorder (LBD), including Parkinson's disease (PD) and Dementia with Lewy body (DLB). **Background:** The brachial-ankle aortic pulse wave velocity (baPWV) is a marker for arterial stiffness, which is associated with cardiovascular diseases. Arterial stiffness is associated with cognitive function in the elderly and patients with Alzheimer disease (AD). Some reports showed arterial stiffness is related with autonomic dysfunction. We hypothesized that arterial stiffness is associated with cognitive function in LBD, which frequently manifested autonomic dysfunction.

Methods: We consecutively included 123 patients with PD, 10 patients with DLB and 27 AD controls. Patient with PD were divided into normal cognition (PD-NC, n=63), mild cognitive impairment (PD-MCI, n=43) and dementia (PD-D, n=17). Arterial stiffness, measured as brachial-ankle pulse wave velocity (baPWV), was compared between PD-NC, PD-MCI, PD-D, DLB and AD. In LBD, we analyzed association between arterial stiffness and cognitive domain with adjustment for age, education year, hypertension, disease duration and smoking history. **Results:** Higher baPWV was significantly associated with cognitive decline in patients with LBD (baPWV in PD-D > PD-MCI > PD-NC; DLB > PD-NC). There was no significant difference of baPWV between PD-D, DLB and AD (PD-D, 2139.8 ± 411.6; DLB, 2115.6 ± 695.3; AD, 2040.7 ± 514.4). In LBD, higher baPWV was associated with lower MMSE score ($\beta \pm SE = -0.003 \pm 0.001$, p= 0.011) and more severe dementia. Higher baPWV was associated lower performance in attention, language, visuospatial function, memory and executive function in LBD. **Conclusions:** In patients with LBD, arterial stiffness was associated with cognitive dysfunction. This can suggest vascular brain injury is associated with cognitive dysfunction in LBD.

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White matter lesions and peripheral vessel reactivity in dementia with Lewy bodies

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Objective: We aimed to assess the significance of white matter hyperintensities (WMHs) in dementia with Lewy bodies (DLB) and their contribution to phenotype of the disease.

Background: Cerebrovascular pathology often found on MRI and autopsy in DLB patients. The importance of WMHs in DLB remains poorly understood. Some authors reported that WMHs have an additive effect on cognitive decline in dementia, whereas others could not confirm this association, on the contrary, considering inverse relationship. Apparently, a possible explanation for the inconsistent associations between WMHs and clinical symptoms would be heterogeneity of the WMHs.

Methods: We examined 17 patients that fulfilled clinical criteria for probable DLB. The clinical assessment included Montreal Cognitive Assessment scale (MoCA), Addenbrooke's Cognitive Examination (ACE-R), Neuropsychiatric Inventory (NPI-4), University of Miami Parkinson's disease Hallucinations Questionnaire (UM-PDHQ), the motor section of the Unified Parkinson's disease rating scale (UPDRS), orthostatic hypotension test. Sleep-wake profile was assessed using a single-question screen for REM sleep behavior disorder (RBD1Q), the Epworth Sleepiness Scale (ESS). All subjects were performed 1,5 T brain MRI. MRI revealed moderate to severe WMHs in 10 participants. Patients were performed ultrasound assessment of endothelial-dependent and endothelial-independent flow-mediated vasodilation of the brachial artery using reactive hyperemia test. Willebrand factor and lipid profile were also evaluated.

Results: The presence of WMHs was associated with a later onset of disease, clinically significant orthostatic hypotension, more severe neuropsychiatric features (?<0,05). No relationship between the parkinsonism, presence and severity of coexistent cerebrovascular lesions was seen in this cohorts of patients. DLB without WMHs frequently had excessive daytime sleepiness and RBD, worse cognitive performance (?<0,005). There was significant decline of vessel reactivity in patients with WMHs. But it was not correlated with the serum parameters, thereby suggesting different mechanisms of endothelial dysfunction.

Conclusions: We found association of WMHs with age, cognitive, sleep, neuropsychiatric and autonomic disturbances, endothelial dysfunction. Larger prospective longitudinal studies are warranted to confirm the utility of many imaging techniques in evaluating of cerebrovascular lesions in early DLB stages.

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Cholinergic activity, mobility, and attention in mild cognitive impairment

D. Martini, K. Smulders, A. Hiller, K. Chung, J. Quinn, F. Horak (Portland, OR, USA)

Objective: The aim of this investigation is to relate cholinergic activity (CA) to objective measures of balance, gait, and attention in a MCI and control group. We hypothesize that people with Mild cognitive impairment (MCI) will have low CA, which will reduce attention and relate to worse gait and balance dysfunction, compared to controls. **Background:** MCI is defined as cognitive decline greater than expected for age and education. Although MCI refers to cognitive impairments, gait and balance dysfunction has also been observed in MCI populations. Emerging literature suggests that cognitive information is critical for motor performance, particularly for complex tasks. **Methods:** 3 MCI and 6 non-MCI subjects have been tested (80 will be recruited). Each subject completed a quiet standing and walk test, both with and without a secondary task. Balance variables: 95% ellipse sway area, jerk, and RMS sway. Gait: gait speed, percent of time in double support, and number of steps in a turn. Gait and balance variable. A computerized test of attention, The Attention Network Test (ANT), was also completed. ANT variables: alerting efficiency, orienting efficiency, and conflict resolution efficiency. Short-latency afferent inhibition (SAI), a transcranial magnetic stimulation modality, assessed CA.

Results: Preliminary data yield large Cohen's *d* effect sizes for MCI and greater DTC of the 95% ellipse sway area (MCI: 0.47 ± 0.50 ; Control: -0.10 ± 0.21 ; d = 2.00), DTC of the percent of time in double support (MCI: 0.07 ± 0.01 ; Control: 0.03 ± 0.02 ; d = 2.58), and worse SAI (MCI: 88.94 ± 33.65 ; Control: 62.98 ± 13.32 ; d = 1.25) for the MCI group. Spearman's correlations indicate a significant correlation between worse SAI and greater DTC on jerk (? = 0.73; p = 0.03) and RMS sway (? = 0.68; p = 0.04). The ANT yielded weak effect sizes between MCI groups. **Conclusions:** Effect size analyses of these data yield preliminary support for the hypothesis that MCI is associated with impaired balance and gait, especially in dual task conditions. Further, significant correlations between SAI and DTC on jerk and RMS sway indicate that CA may be a factor in balance dysfunction. The MCI group shows a trend of lower CA and greater DTC in balance and gait tasks. MCI patients with low CA could be at greater risk of gait and balance dysfunction in dual task conditions.

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Adding cues to a rat gambling task potentiates the increase in premature responding in response to chronic D2/3 agonist ropinirole without mitigating preference for risk

M. Tremblay, M. Barrus, P. Cocker, S. Kaur, C. Winstanley (Vancouver, BC, Canada) **Objective:** Investigating the effect of chronic administration of the dopamine D_{2/3} agonist ropinirole on a cued model of gambling behaviour in rats.

Background: Dopamine D_{2/3} agonists are successfully used to treat the motor symptoms of Parkinson's Disease (PD), either as adjunct to L-DOPA, or as stand alone treatments. However, these dopamine agonists may lead to impulse control disorders (ICD) including pathological gambling in some patients. We have previously observed that chronic ropinirole increased choice of uncertain options on the rat Betting Task (rBT), a paradigm that captures aspects of risk aversion. In contrast, ropinirole transiently increased premature responses, a measure of motor impulsivity observed in models of addiction, without influencing choice on the rat Gambling Task (rGT). The rGT is a rodent analogue of the Iowa Gambling Task used clinically to assess decision making under risk in which rats choose between four options, each associated with differing probabilities of reward and punishment. Repeated exposure to cues that predict reward with maximal uncertainty may sensitize the dopamine system and predispose subjects to addiction disorders such as gambling. Although win-associated stimuli are salient in casinos, they are not featured on the original version of the rGT, which may explain the lack of effect of ropinirole on choice in the uncued task. We therefore tested if chronic ropinirole would increase rats' preference for the riskier options on this task. **Methods:** Subjects were 40 male rats performing the cued rGT and implanted with an osmotic pump delivering either ropinirole (5mg/kg/day) or saline for 28 days.

Results: Ropinirole led to a larger and more long-lasting increase in premature responses on the cued rGT with no effect on choice, consistent with results on the original rGT.

Conclusions: Together with other data, our results suggest that the rGT and the rBT may model decision-making deficits linked to different disorders. Chronic ropinirole increases preference for uncertainty on the rBT, potentially akin to problem gambling behaviour, whereas this drug increases impulsivity on the rGT, which may represent an endophenotype for impulse control disorders or drug addiction.

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Neurofilament light chain levels in cerebrospinal fluid do not discriminate between patients with Prion disease and mimics

B. Roeben, E. Stransky, K. Brockmann, R. Schüle, W. Maetzler, T. Gasser, G. Machetanz (Tübingen, Germany) **Objective:** To determine whether levels of neurofilament light chain (NFL) in cerebrospinal fluid (CSF) are useful to discriminate between patients with prion disease (PrD) and patients with a diagnosis mimicking Prion disease (PrMim).

Background: NFL is a structural protein of the neural cytoskeleton, essential for axonal growth, transport and signalling. Higher levels of CSF-NFL reflect axonal degeneration. Recently, NFL was shown to also be elevated in Creutzfeld-Jacobs-Disease (CJD) compared to controls and Alzheimer's disease (AD) patients [1]. To our knowledge no data is available comparing NFL levels of patients with PrD and PrMim.

Methods: Thirty-one patients with Prion disease as a potential differential diagnosis were evaluated in our hospital between 2010 and 2016. In the diagnostic process CSF was collected using standard procedures. NFL was measured using electrochemiluminiscence immunoessay (NF-light). Total-Tau (t-Tau) was measured using commercially available ELISA kits (Innogenetics NV, Ghent, Belgium).

Results: 10/31 patients fulfilled the diagnosis of Prion disease according to consensus criteria (age 65.5y \pm 8.4, male/female=8/2) while 21/31 (66.3y \pm 12.3, 8/13) received a different diagnosis after diagnostic workup, including autoimmune encephalopathy, rapidly progressive AD, status epilepticus and frontotemporal dementia. There was no significant difference in CSF levels of NFL between the PrD group (mean 10,654pg/ml, range 3855- 44,9930pg/ml, *SD*=12,201pg/ml) and the PrMim group (10,781pg/ml, 608-50,000pg/ml, *SD*=12,347pg/ml), (Kruskal-Wallis, *p*=0.17). (Figure 1) NFL alone was not useful to discriminate between PrD and PrMim (AUC=0.48), as opposed to CSF t-Tau (PrD: mean 2554 pg/ml, PrMim: mean 1311pg/ml, Kruskal-Wallis, *p*=0.009, AUC=0.88). A combination of NFL and t-Tau levels did not improve discrimination (AUC= 0.87).





Conclusions: CSF levels of NFL are elevated in patients with PrD. However, there are no significant differences in NFL levels between patients with PrD and PrMim. In contrast to CSF levels of t-Tau, NFL is not useful to discriminate between patients with PrD and patients with PrMim. A combination of NFL and t-Tau did not improve diagnostic accuracy when compared to t-Tau alone. Increased levels of CSF in NFL appear to reflect acuity of neurodegeneration rather than a specific pathophysiological process in PrD.

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Emotion regulation and neuropsychological status in psychogenic subtypes

B. Scott, A. Strutt, P. Lundberg-Love, A. Schmitt, J. Jankovic, D. Bowers (Gainesville, FL, USA) **Objective:** To determine whether cognitive dysfunction is associated with emotion regulation strategies and psychological distress in two psychogenic movement disorder (PMD) variants: non-epileptic seizures (PNES) and other hyperkinetic motor manifestations (PMD-H).

Background: Patients with PMD have difficulties identifying and regulating their emotions, and tend to use less effective emotion regulation strategies (suppression vs. reappraisal). Recent research suggests that PNES and PMD-H may represent phenotypic variants of psychogenic disturbance. Based on previous findings of greater frontal-executive inefficiencies in PNES vs. PMD-H subtypes and independent observations that frontal-executive control is necessary for effective emotion regulation, we hypothesized that PNES patients would demonstrate poorer cognitive status, use less effective emotion regulation strategies (i.e., suppression), and have greater psychological distress than PMD-H patients.

Methods: Sixteen PNES (vEEG verified) and 16 PMD-H (F&W criteria) patients, ages18-64 years (M=42.2), underwent an abbreviated neuropsychological battery including self-report measures of emotion regulation and psychopathology. Data were analyzed using regression analyses.

Results: For the total sample, lower frontal-executive function was associated with greater use of suppression than re-appraisal strategies. In the PNES group, lower general cognition was associated with more severe symptoms of posttraumatic stress disorder (PTSD), greater suppression and lower positive emotions, whereas lower cognition was associated with more severe PTSD symptoms and greater reappraisal in the PMD-H group. When controlling for general cognition, individuals who were classified as "suppressors" had a greater number of trauma events, more

symptoms of dissociation, greater internalizing dysfunction, and more severe emotional distress than individuals classified as "re-appraisers."

Conclusions: Current findings highlight the clinical utility of examining psychogenic subtypes, rather than combining them, and the importance of examining different types of emotion regulation strategies that may mediate the relationship between cognitive function and mental health outcomes. Future investigations using a similarly integrative perspective comparing psychogenic variants may facilitate the development of symptom-specific treatment approaches.

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Difficulties in executing the MDS recommendations in the Brazilian population

E. Carreira, E. Carreira, A. Prado, N. BraZ, F. Tavares, N. Rocha, L. De souza, F. Cardoso, A. Teixeira (Belo Horizonte, Brazil)

Objective: To investigate the usefulness of the trail making test (TMT)-A and TMT-B in the cognitive evaluation of a Brazilian sample of patients with PD.

Background: Around 30-40% of patients with PD fill the diagnosis criteria for dementia. Patients with PD with dementia (PDD) usually present cognitive dysfunction and behavior variances, commonly apathy and executive dysfunction. It highlights the importance of applying a suitable evaluation of executive function in these patients. **Methods:** Forty-one patients with PD (26 male/15 female; Mean age = 64.4 ± 9.7 years; Schooling = 7.2 ± 4.2 years; MMSE = 24.21 ± 4.0) were submitted to a comprehensive clinical evaluation, including motor, cognitive and neuropsychiatry symptoms, according to the MDS recommendations [1-2]. The cognitive evaluation included the TMT-A and TMT-B

Results: Patients with PD presented with great difficulty in executing the TMT. Only 36 patients were capable of finishing the TMT-A, in 92.03 \pm 53.9 seconds. This value was above the normative data for the Brazilian population (56.4 \pm 20.1 seconds). In addition, only 32 subjects could finish the TMT-B. Here again, patients with DP took longer than the expected to complete the test, according to the normative data (172.3 \pm 150.7 and 133.1 \pm 51.8 seconds, respectively). It is worth mentioning that TMT scores were not associated with verbal fluency test, and the attention and initiative/perseveration items of the Mattis Dementia Rating Scale.

Conclusions: Our data suggest that the TMT is not appropriate for the cognitive evaluation of cognition in PD. In our sample, the performance at the TMT was not associated with attention and executive tasks. More studies are needed in this regard.

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Rapidly progressive dementia and parkinsonism caused by a cortical dural AV fistula: A case report *T. Weissfeld, D. Kremens, J. McCall (Philadelphia, PA, USA)*

Objective: To report the case of a 75-year-old woman with rapidly progressive dementia and parkinsonism caused by a cortical dural AV fistula.

Background: Vascular malformations are infrequently associated with parkinsonism. Various cases exist in the literature of AV fistulas, malformations, and aneurysms leading to parkinsonian symptoms. Most of these vascular lesions are located in deep structures including basal ganglia, thalamus, and midbrain. Cortical vascular lesions are even less associated with parkinsonism, and we report such a case here.

Methods: A case of rapidly progressive dementia and parkinsonism due to a cortical dural AV fistula is described. **Results:** A 75-year-old woman presented for evaluation of dementia and parkinsonism. Her earliest symptom was confusion over finances two years before presentation. Her daughter noticed a tremor in her voice and left leg around this time. A year later she started falling. Despite physical therapy she rapidly declined from a walker to a wheelchair. She developed hallucinations, and her confusion worsened to where she no longer recognized neighbors. She had an MRI brain without contrast that was normal, and was started on carbidopa/levodopa and rivastigmine without benefit. On neurologic exam, MOCA was 7/30 with limited attention, memory, and executive functioning. She had significant bradykinesia, rigidity worse on the left, marked postural instability, and startle myoclonus. She was admitted and had a lumbar puncture to rule out prion disease, which was normal, and ultimately had an MRI of the brain with contrast that showed abnormal signal in bilateral frontoparietal lobes concerning for an AV fistula. She underwent conventional angiography, confirming a large AV fistula with cortical venous drainage. This was partially treated with embolization of the middle meningeal artery. Post-embolization, her cognitive symptoms mildly improved, but her symptoms did not fully resolve. She will need further embolization with neurosurgery in the future to fully treat the AV fistula. **Conclusions:** While parkinsonism is infrequently associated with vascular malformations, lesions in the midbrain, basal ganglia, or even cortex can cause parkinsonian symptoms. Here we described a case of dementia and parkinsonism from a large cortical AV fistula discovered only with contrast enhanced MRI, incompletely treated with embolization, resulting in partial improvement in her symptoms.

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Cefepime-induced encephalopathy and myoclonus

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Objective: To raise awareness of cephalosporin-induced encephalopathy and myoclonus.

Background: Myoclonus occurs in 15% of antibiotic-associated encephalopathy, especially with penicillins and cephalosporins. Cefepime and ceftazidime are the most commonly implicated.

Methods: Case report with video prior to and post cefepime discontinuation.

Results: We report an 85-year-old man who was admitted for encephalopathy and myoclonus. He has complex medical history of recurrent scalp squamous cell carcinoma invading the skull with intracranial extension, requiring multiple excisions, craniectomies, cranioplasties, and radiations. Prior to his current admission, he developed intermittent right arm jerking. EEG and MRI could not be performed due to his scalp wound and mechanical heart valve. He was empirically treated with gabapentin for focal seizures, which was later switched to pregabalin. Levetiracetam was then added due to persistent symptoms. Since the CT of the brain raised the possibility of infection, he was then treated with cefepime for possible cerebritis. Within few days, he became encephalopathic, had difficulty speaking and developed bilateral upper extremity jerking. On exam, while afebrile, he was encephalopathic but able to follow some simple commands with perseveration. He had spasticity, hyperreflexia on the lower extremities with sustained clonus, and proximal weakness. Indeed, there was postural and action-induced myoclonus along with asterixis. Tactile and auditory stimuli did not trigger myoclonus treatment without success. Finally, cefepime was discontinued after a negative CSF culture. Within 24 hours after discontinuing cefepime, his mental status improved, and myoclonic frequency diminished. Complete resolution of encephalopathy and myoclonus was noted within 36 hours.

Conclusions: Cephalosporin-associated neurotoxicity is an under-recognized, highly reversible cause that should be considered as a differential in patients with encephalopathy and myoclonus. Early recognition may help decrease morbidity and mortality. Unfortunately, as in this illustrative case, it is often seen in an ICU setting, with multiple co-morbidities and concurrent psychotropic medications, making it a diagnostic challenge.

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Psychogenic abdominal myoclonus in pregnancy: Case report

D. García, P.O. Vargaz, Z. Lopez (Toluca de Lerdo, Mexico)

Objective: Movement disorders in pregnancy represent a diagnostic challenge due to the poor physiopathological understanding in the extrapyramidal system where the afferent and efferent circuits in balance of voluntary movements undergo alterations apparently without a specific etiology. Psychogenic movements during the gestational stage tend to pose a diagnostic challenge that can be elucidated by performing an adequate examination, sometimes can to be a exclusion diagnosis due to a "uknown" prevalence found in the pregnant patient should be taken as part of the spreads within the spectrum of movement disorders.

Background: A 27-year-old female with a normal-evolutionary pregnancy of 23.2 gestational weeks with a history of intrafamily violence that presents acute and sudden synchronous abdominal movements, rhythmic, at rest, paroxysmal, triggered by abdominal palpation and noise, nocturnal, with 4 hrs evolution without aggregate gastrointestinal clinic that enters the emergency department.

Methods: The patient was approached where medical-surgical abdominal and obstetric emergency was ruled out; neurological examination showed suppression of movement with distraction, increased with attention, periodical, durtion of 90-seconds, Hamilton Scale test of 24 points revealed severe depression, psychological stimulus was a discussion hours prior to the onset of the symptomatology, rest of examination was normal.

Results: Basic biochemical serum controls within physiological parameters. Electroencephalogram without evidence of epileptic activity, somatosensory potentials of normal medial and tibial nerve, MRI of brain and cervical spine without evidence of lesion, electromyography of phrenic nerves and abdominal wall musculature were normal. The psychiatric profile and the sudden clinical features with emotional trigger were diagnosed as abdominal psychogenic myoclonus, concordant with the Fahn-Williams criteria, then behavioral psychotherapy was started, with remission of movement disorder.











Conclusions: The psychogenic myoclonus is integrated, the diagnostic algorithm of Zutt et al was an angular tool to perform the approach, physiopathologically these disorders do not have a well-founded anatomical substrate although with a psychiatric phenotype that may help to make such a diagnosis classically considered as exclusion. Due to the obstetric situation, this patient could not have pharmacological treatment because of the high teratogenic potential.

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Axial Myoclonus in a patient with PSP

R. Passo, T. Clark (Portland, OR, USA)

Objective: This is a case report from the Portland VA Medical Center.

Background: PSP is a parkinsonian neurodegenerative disorder characterized by deposition of tau in the basal ganglia, brainstem, cerebellum, spinal cord, and cortex. Features include supranuclear gaze palsy, postural instability, cognitive impairment, wide-eyed stare, axial rigidity, and reduced eye blink frequency. Although there are a variety of PSP presentations, there are only three reported cases of myoclonus and no reported cases of axial myoclonus.

Methods: A 72-year-old man with PSP presented with acute onset jerking. He denied any other new symptoms or recent medication changes, injury, or infection. The diagnosis of PSP had been made two years earlier following the development of falls and cognitive decline, and MRI three months ago showed midbrain atrophy. Exam on presentation revealed a fully oriented man with mild dysarthria and no tremor or myoclonic-like quality to voice. Cranial nerve exam was significant for restricted upward and downward gaze, mild right eye dysconjugate lateral gaze, and mild hypomimia. Motor exam demonstrated mild axial rigidity, no tremor in the bilateral upper extremity, and positional, non-rhythmic myoclonic jerk movements involving the cervical, axial thoracic, and abdominal musculature that completely remitted with standing and returned after eight minutes of sitting. Reflexes were 1-2+ and symmetric throughout and sensory exam was normal.

Results: He was admitted for full spine and brain MRI without contrast to rule out spinal cord compression, which was found to be unremarkable. Per the recommendation of his outpatient neurologist, the inpatient team discontinued his levodopa/carbidopa and started amantadine. Hospital course was remarkable for one observed episode of myoclonus. The leading diagnoses were propriospinal myoclonus (PSM), specifically the slow, flexion truncal jerks exacerbated while supine and relieved while standing, and atypical presentation of PSP. The non-distractible and reproducible nature of the myoclonus lowered suspicion for a functional component.

Conclusions: The etiology of axial myoclonus in a patient with PSP is unclear. Clinically, this presentation most closely resembles PSM. Recent work on PSM using DTI with fiber tracking found microstructural abnormalities in the lemniscal posterior and corticospinal posterolateral tracts, which suggests a possible connection between PSP and PSM. This may explain this unusual presentation.

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Diaphragmatic myoclonus successfully treated with Botulinum toxin A

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Objective: To report a rare case of diaphragmatic myoclonus, which would be the first case successfully treated by injecting Botulinum toxin A (BTX) into the diaphragm under needle electromyography guidance (EMG) in the literature.

Background: Diaphragmatic myoclonus, is a typical unusual focal dyskinesias which is characterized by repetitive involuntary synchronous contractions of the diaphragm and other respiratory muscles. (Ramirez JD et al., 2015) Its various clinical manifestations and ambiguous aetiology always lead to late diagnosis and ineffective treatments. Currently, there are still no recommendation for treating diaphragmatic myoclonus.BTX has paralysis effect and It has been injected into many muscles. However, injection of BTX into the diaphragm has never published before. This report documents the first time to apply BTX into the diaphragm under EMG guidance for the treatment of diaphragmatic myoclonus.

Methods: A 51-year-old man presented with a 5-year history of involuntary abdominal movements, which influenced his daily life and mood state. These movements, showing arrhythmia and jerky twitches and spasms of abdominal wall and thorax, associated with sagittal oscillations of upper body and sounds from larynx. All past treatments with scopolamine, Baclofen, Valproate, Clonazepam, traditional Chinese medicine or acupuncture, combined with cessation of possible medicine that might cause his syndromes had no effect. Results of fluoroscopy examination and synchronized EMG signals with spontaneous abdominal movements confirmed revealed the diagnosis of diaphragmatic myoclonus, as well as involvement of the diaphragms and the rectus abdominis. Considering hyperactivity in those muscles, the patient was an appropriate candidate for BTX injection. **Results:** Following the 275 units BTX were injected into bilateral hemidiaphragms and the rectus abdominis under EMG guidance, including 50 units in the right hemidiaphragm, 25 units in the left hemidiaphragm, and 100 units BTX in each RA (Figure 1), the patient had a significant relief in the intensity and frequency of his abdominal

BTX in each RA (Figure 1), the patient had a significant relief in the intensity and frequency of his abdominal movements, without dyspnea, weakness of truncal flexion or other unexpected effects. This improvement continued at least 4 months.



Conclusions: With secure EMG monitoring, local BTX injections into the diaphragm and the rectus abdominis can be an alternative treatment in the cases of diaphragmatic myoclonus.

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Reappraisal of Progressive Myoclonus Ataxia

S. vd Veen, R. Zutt, T. De Koning, M. Tijssen (Groningen, Netherlands) **Objective:** To define the clinical, electrophysiological and etiological features of progressive myoclonus ataxia (PMA). **Background:** PMA, formerly known as the Ramsay Hunt syndrome, is a progressive encephalopathy comprising myoclonus and cerebellar ataxia. Epileptic seizures and/or cognitive decline commonly extend this 'pure' syndrome to a more complex form. However, this 'complex' syndrome is hard to differentiate from other phenotypes presenting with myoclonus, such as progressive myoclonus epilepsy. Therefore, diagnosing PMA and recognizing the underlying etiology remain challenging as the syndrome is not well defined and no comprehensive overview is available.

Methods: Patients with myoclonus and ataxia were identified using an electronic database. Clinical notes of included patients were reviewed retrospectively for the clinical, electrophysiological and etiological characteristics. **Results:** In total, 76 patients were included suffering from 'pure' myoclonus and ataxia (n=10), 'complex' myoclonus and ataxia combined with cognitive decline and/or epilepsy (n=31), myoclonus combined with cognitive decline and/or epilepsy (n=31), myoclonus combined with cognitive decline and/or epilepsy (n=22). 45/76 patients showed a progressive course; patients suffering from ataxia significantly more often compared to patients without ataxia. Comparing clinical features in patients exclusively with a progressive course showed differences between patients suffering from PMA. The presence of action provoked myoclonus, ataxia of the trunk, an ataxic gait and dysphagia were more frequent in patients suffering from 'complex' PMA compared to the 'pure' form. Furthermore, comparing electrophysiological features in the same group of patients showed differences in burst duration; patients suffering from 'complex' PMA showed a burst duration of 50-100ms, significantly higher compared to patients suffering from myoclonus with cognitive decline and/or epilepsy without ataxia. In only 28/75 of all patients an etiological cause was identified (table 1).

Myoclonus and ataxia (pure PMA)	Myoclonus and ataxia combined with cognitive decline and/or epilepsy (complex PMA)	Myoclonus combined with cognitive decline and/or epilepsy without ataxia	Myoclonus without ataxia, cognitive decline and epilepsy
In 3 of 8 patients an etiological cause was identified.	In 13 of 27 patients an etiological cause was identified.	In 4 of 7 patients an etiological cause was identified.	In 1 of 7 patients an etiological cause was identified.
North Seaprogressive myoclonus epilepsy	North Seaprogressive myoclonus epilepsy*	Dravet syndrome**	Benign hereditary chorea
Spinocerebellarataxia 13	Spinocerebellar ataxia 13	Lafora Body's disease	
	Spinocerebellar at axi a 5	Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes	
Niemann-Pick Type C	Myoclonus Epilepsy with Ragged-Red Fibers		
	Ataxia-Telangiectasia		
	Neuronal Ceroid-Lipofuscinosis type 3		
	HyperprolinemiaTypeII		
	Mitochondrial Encephalom yopathy type ESOC-Leigh-like disease		

Table 1. The etiological causes found in patients suffering from progressive myoclonus. In 21 of 49 patients with a progressive course an etiological cause was identified.

* In seven patients presenting with 'complex' PMA the genetic mutation for North Sea progressive myodonus epilepsy was found.

** In two patients the genetic mutation for the Dravet syndrome was found

Conclusions: 'Complex' PMA is characterized by a burst duration of 50-100ms and can be distinguished from 'pure' PMA by clinical features regarding the presentation of myoclonus and ataxia. The low number of differentiating clinical and electrophysiological features combined with the low rate of identified etiological causes show the necessity for a better definition and a comprehensive overview of PMA.

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Hypertrophic Olivary Degeneration

G. Moreno, K. Ng, A. Duffy (Sacramento, CA, USA)

Objective: We report the findings of a patient presenting with palatal myoclonus (PM) several months after suffering from an Intracranial Hemorrhage (ICH) in order to demonstrate the unique neuroanatomical location of PM.

Background: PM is characterized by a 1-3 Hz frequency oscillation of the palate. It can be appreciated with vocalization as well as rest. PM has been demonstrated to result from a lesion within the dentate-rubro-olivary pathway (Guillain-Mollaret triangle) due to, most commonly, a cerebrovascular or demyelinating lesion. There may be subsequent associated development of hypertrophic olivary degeneration (HOD) observed on MRI. Further motor symptoms may be appreciated depending on location of this lesion within the pathway.

Methods: 72 year old female professional opera singer presented to our clinic with complaints inability to sing, left arm tremor with associated stiffness, and slowness of movements over the past six months. Eleven months prior to the onset of these symptoms, she had a left cerebellar ICH with residual vertigo and gait ataxia. Neurological exam revealed a vibratory quality to her voice with inability to sustain vocal notes and left hand wing-beating tremor present at rest, posture, and action. Additionally, she had bilateral, left worse than right bradykinesia and rigidity. She was started on carbidopa-levodopa 25/100 mg TID with moderate improvement in her parkinsonism, however the PM did not improve.

Results: Blood count, blood chemistry including liver enzymes, and thyroid stimulating hormone were normal. LDL cholesterol level was elevated at 145 mg/dl. MRI Brain revealed a focal area of high T2 signal intensity and enlargement of the right medullary olive and an area of susceptibility on GRE of the contralateral dentate nucleus from the ICH [Figure 1]. The left ICH and enlargement of the right medullary olive suggesting hypertrophic olivary degeneration with disruption of dentato-rubro-olivary pathway [Figure 2] was thought to cause the presentation of PM, Holmes (or cerebellar) tremor, and secondary parkinsonism.



Conclusions: Disruption of the dentate-rubro-olivary classically presents with palatal myoclonus with associated features with imaging demonstrating a lesion within the pathway and secondary hypertrophy of the inferior olive. These symptoms may present from months to years after the initial insult emphasizing the importance of awareness of this delayed presentation.

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Holmes' tremor and olivary hypertrophy: lessons from this neuroanatomical correlation

R. Ellis, S. Biswas, R. Pullicino, J. Panicker, B. Hammersley, J. Farah, S. Alusi (Liverpool, United Kingdom) **Objective:** To describe the neuroanatomical correlations of unilateral versus bilateral hypertrophic olivary degeneration (HOD) in three patients diagnosed with Holmes' (rubral) tremor, secondary to midbrain lesions. **Background:** The pathogenesis of HOD is related to a unique process of transynaptic degeneration whereby neurons loss is succeeded by reactive gliosis causing hypertrophy of the affected structure rather than atrophy. Bilateral HOD is unique in that it can result from a single unilateral lesion within the triangle of Guillian and Mollaret, compromising of connections between the inferior olivary nucleus, ipsilateral red nucleus and contralateral dentate nucleus. Lesions involving the central tegmental tract result in ipsilateral HOD, whilst lesions of the dentate nucleus and superior cerebellar peduncle cause contralateral HOD. Bilateral HOD has been reported in lesions involving both the central tegmental tract and superior cerebellar peduncle.

Methods: 3 patients were identified with Holmes' tremor associated with olivary degeneration on MRI imaging. A 59 year old female developed a left sided Holmes' tremor following a right sided tegmentum plate haemorrhage. Her MRI identified bilateral HOD associated with a small haemorrhagic lesion in the pons involving the right red nucleus. A 16 year old female presented with a left sided Holmes' tremor after a haemorrhage following stereotactic surgery for a right midbrain AVM. MRI demonstrated a haemorrhagic cavity involving the right red nucleus and encephalomalacic changes in the right midbrain. Bilateral olivary degeneration is present. A 47 year old gentleman who presented with a Holmes' tremor affecting the right arm and leg. His imaging showed a large left midbrain cavernoma for which he underwent a partial excision. Ipsilateral olivary degeneration was evident. He responded well to left VIM DBS.

Results: MR imaging of the 3 patients demonstrated the presence of HOD secondary to a lesion within the Triangle of Guillian-Mollaret. The lesion location within this circuit determines the development of HOD and whether it is unilateral or bilateral.

Conclusions: In patients with Holmes' tremor unilateral HOD is associated with central tegmental tract lesions interrupting the ipsilateral rubro-olivary pathways whilst bilateral HOD is associated with lesions involving the above pathway as well as the superior cerebellar tract connecting with the contralateral dentate nucleus.

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Loss of PDE10A expression in patients with PDE10A and ADYC5 mutations

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Objective: To assess phosphodiesterase 10A (PDE10A) expression *in vivo*, using [¹¹C]IMA107 PET in patients with PDE10A and adenylate cyclase 5 (ADYC5) mutations.

Background: Cyclic adenosine monophosphate (cAMP) is an essential second messenger regulating multiple intracellular signalling pathways. In the striatal medium spiny neurons, cAMP activity is determined from the balance between its synthesis by ADYC5 and its degradation by PDE10A. Functional dysregulation of striatal cAMP signalling due to *de novo* or familial mutations in these two genes causes chorea and other hyperkinetic movement disorders.

Methods: We studied two unrelated patients with *de novo* heterozygous p.Phe300Leu PDE10A mutation (Patient 1, 61F; Patient 2, 23F); one patient with heterozygous p.Ile625Phe PDE10A mutation inherited from her asymptomatic father (Patient 3, 26F); and one patient with familial heterozygous p.R418W ADYC5 mutation (Patient 4, 38M). Patients 1 and 2 presented in childhood with progressive chorea and Patient 1 developed levodopa-responsive parkinsonism in the fifth decade. Patient 3 presented with childhood onset of paroxysmal kinesigenic dyskinesias. Patient 4 presented with childhood onset of progressive chorea and dystonia. All patients underwent one [¹¹C]IMA107 PET scan and one MRI scan. Parametric images of [¹¹C]IMA107 binding potential relative to nondisplaceable binding (BP_{ND}) were generated from the dynamic [¹¹C]IMA107 scans using the simplified reference

tissue model with the cerebellum as the reference tissue.

Results: Patients 1 and 2 showed >70% decreases in [¹¹C]IMA107 BP_{ND} in the striatum (-72% in caudate and -78% in the putamen) and 65% loss of [¹¹C]IMA107 BP_{ND} in pallidum compared to a group of healthy controls. Patient 3 showed >20% decreases in [¹¹C]IMA107 BP_{ND} in the striatum (-21% in caudate and -31% in the putamen) and 9% loss of [¹¹C]IMA107 BP_{ND} in pallidum; and Patient 4 showed >10% decreases in [¹¹C]IMA107 BP_{ND} in the striatum (-8% in caudate and -11% in the putamen) and 9% loss of [¹¹C]IMA107 BP_{ND} in pallidum; and 9% loss of [¹¹C]IMA107 BP_{ND} in pallidum compared to a group of healthy controls.

Conclusions: PDE10A expression is decreased in patients with PDE10A and ADYC5 mutations and pharmacological modulation of PDE10A could help restoring restore physiological levels of cAMP, and therefore alleviate symptoms.

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The efficacy of continuous apomorphine infusion in advanced PD patients with cognitive impairments

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Objective: To review the outcome of continuous apomorphine infusion (CAI) in advanced Parkinson's disease (PD) patients at the rehabilitation unit of the Parkinson Expertise Center (RU-PEC) Groningen.

Background: CAI is a widely used treatment in advanced PD. However, CAI is recommended for PD patients with only mild cognitive impairments, although positive effects of CAI on cognition and visual hallucinations (VH) have been reported earlier.

Methods: Advanced PD patients indicated for CAI treatment at the RU-PEC were included. Cognitive and motor function were assessed at baseline and repeated at the end of the admission. Follow-up data were obtained by reviewing patient's medical records and were analyzed retrospectively.

Results: Apomorphine was initiated in 43 PD patients who had a contra-indication for deep-brain stimulation (DBS) due to high age (>70 years; n=27), cognitive impairment (n=12) or severe neuropsychiatric symptoms (n=1), while 3 patients did not want to be treated with DBS. Clinical characteristics of patients are shown in Table 1 [table1]. The total daily dose of apomorphine was 69 ± 29 mg. Due to the addition of apomorphine the levodopa-equivalent daily dose (LEDD) lowered with 17% during the admission. At the same time the number of patients treated with clozapine and cholinesterase inhibitors almost doubled. CAI reduced daily OFF time and time with troublesome dyskinesia with 45% and 51%, respectively. The cognitive performance did not worsen during titration of CAI [table2]. Overall, 34 out of 43 patients could be referred to their homes again, whereas all patients were not able to live independently at admission. In total 7 patients required long-stay nursing home placement. The duration of CAI treatment was 36 ± 35 months [figure1]. At the end of 2016, 13 patients were still on CAI, 17 deceased during CAI treatment, 3 stopped due to lessening of therapeutic effect, 2 were lost to follow-up, while 7 patients withdrew CAI due to side-effects during the follow-up. Only 4 patients had to stop CAI after years of treatment because of worsening of VH and/or orthostatic hypotension (OH).

Male / female, n	25 / 18
Age (yrs)	70.5 ± 7.9 [50-82]
PD duration (yrs)	10.7 ± 4.8 [2-23]
History of hallucinations, n (%)	32 (74%)
Active hallucinations, n (%)	28 (65%)
PD dementia, n (%)	8 (19%)
Orthostatic hypotension, n (%)	11 (26%)

Table 1. Baseline clinical characteristics of PD patients.

	Baseline	End of stay
Motor function		
OFF time (hrs/day)	3.6 ± 2.8 [0-8.9]	2.0 ± 1.7 [0-5.4]
ON time (hrs/day)	8.5 ± 2.7 [3.4-15.7]	10.6 ± 2.9 [3.2-15.7]
Dyskinesia (hrs/day)	1.9 ± 2.4 [0-7.6]	0.9 ± 0.8 [0-2.4]
Cognition		88.85 C 10.000 (* 10.000 *
MMSE	22.7 ± 5.2 [10-29]	25.5 ± 4.2 [14-30]
FAB	11.9 ± 5.0 [1-18]	13.3 ± 2.1 [9-16]

Table 2. Effect of apomorphine on motor function and cognition.



Conclusions: This study demonstrates that CAI is an effective treatment in advanced PD patients, even in a cohort of elderly patients with VH and/or OH. Irrespective these risk factors CAI treatment could be continued during 3 years on average, in combination with optimized treatment of their existing VH and/or OH.

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Neuroticism and depression is associated with impulse control disorder in Parkinson's disease: a controlled study

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Objective: Cross-sectional assessment of personality trait, impulsivity, depression and anxiety collected prospectively in Parkinson's disease (PD) with impulse control disorders (PD-ICD) compared to a matched PD non-ICD "controls" (PD-C).

Background: ICD complicate treatment of PD with dopamine replacement therapy (DRT), particularly with dopamine agonists. Information on personality trait in ICD based on data collection from controlled studies is rare. **Methods:** PD-ICD (N=34, 59% male, mean age 66.2 ± 8.4 yrs) and PD-C (N=30, 48% male, mean age 70.3 ± 6.1) were assessed for demographic details (including duration of education), motor (Hoehn Yahr stage (HY)), depression (Geriatric depression rating scale), anxiety (State-trait anxiety inventory), impulsivity (Barratt impulsiveness scale-11 (BIS-11), the Russian validation) and the three-dimensional Eyesenck personality questionnaire (extroversion or introversion, neuroticism, lie scale (deliberate attempt to control their scores)). **Results:** PD-ICD and PD-C were matched for age, duration of dopaminergic treatment (5.91 ± 4.2 vs 6.81 ± 4.3 yrs), HY (2.2 ± 0.1 vs 2.4 ± 0.1), levodopa equivalent dose (655.6 ± 407 vs 713.4 ± 297.7 mg) and mini-mental state. None were demented. PD-ICD showed significantly worse depression (p=0.03), worse self-control (p=0,02, section 1, BIS-11) and highly significant worsening of neuroticism but no other personality trait.

Conclusions: Neuroticism (emotionality with negative affect) along with depression and poor self-control is associated with ICD. Management of ICD, therefore, needs neuropsychological support of patients.

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Mechanisms of sub-anesthetic ketamine infusions to reduce L-DOPA-induced dyskinesia: effects on striatal mTOR signaling and beta band oscillations in striatum and motor cortex

M. Bartlett, A. Flores, T. Ye, H. Dollish, K. Doyle, S. Cowen, S. Sherman, T. Falk (Tucson, AZ, USA) **Objective:** To evaluate mechanism of long-term activity of sub-anesthetic ketamine infusion to reduce L-DOPAinduced dyskinesia (LID).

Background: We have published preclinical evidence and patient case reports showing a long-term reduction of LID after sub-anesthetic ketamine infusion (Bartlett et al. 2016; Sherman et al., 2016). Although the mechanisms are unknown, data from recent literature suggest that high-frequency oscillations (HFO; >100 Hz) and beta-band oscillations (15-30 Hz) in the striatum and cortex could be involved in ketamine's effects, as well as changes in dendritic spines.

Methods: Preclinical LID model: escalating L-DOPA doses (2 weeks: 6 mg/kg + 2 weeks: 12 mg/kg) to prime unilaterally 6-OHDA-lesioned rats. To mimic a 10-hr patient infusion ketamine (20 mg/kg) was injected 5 x *i.p.* two hrs apart, L-DOPA was co-injected at the 5th injection. In a separate pilot study we conducted *in vivo* electrophysiology (1-hr baseline period followed by the 10-hr ketamine protocol) in awake freely behaving 6-OHDA-lesioned rats implanted with electrode arrays targeting dorsolateral striatum (DLS) and motor cortex (M1). **Results:** Ketamine infusion once a week reduced the development of LID and increased phosphorylation of striatal mTOR (n=9 per group, *p<0.05, ANOVA). BDNF levels and dendritic spine density in the striatum are currently investigated. In a separate pilot study TrkB receptors were blocked with ANA-12 during ketamine-exposure. Co-injection of ANA-12 did not reduce the acute, but the sustained anti-dyskinetic effect seen in ketamine-only injected LID rats after 4 days, indicating an involvement of BDNF in the sustained anti-dyskinetic effects of ketamine (n=9-10). In the PD rats ketamine induced sustained gamma (30-60 Hz) and HFO (130-160 Hz) in the DLS and M1, and reduced beta power (n=5, one way ANOVA). Ketamine triggered strong HFO coherence and a progressive reduction in coherence at bands <30 Hz in M1/DLS, illustrated by an inverse relationship between HFO and beta coherence.

Conclusions: Our pilot data indicate that the anti-dyskinetic activity of sub-anesthetic ketamine infusion is accompanied by activation of striatal mTOR signaling, and reduction of beta band activity and coherence in DLS and M1, supporting the hypothesis of ketamine acting as a "chemical DBS".

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Basal Ganglia and Limbic Striatal Regions are Differentially Affected by Pramipexole: D3 receptor – Mediated Changes in Markers of Synaptic Strength

M. Bailey, A. Persons, T.C. Napier (Chicago, IL, USA)

Objective: To determine whether pramipexole (PPX) differentially upregulates AMPA receptor trafficking in limbic vs. motor striatal regions of rats.

Background: Impulse control disorders (ICD) are a side effect of PPX, a dopamine agonist, used in Parkinson's disease and restless leg syndrome. Mechanisms that underlie these disorders are poorly understood. PPX has a high affinity for D2 and D3 receptors (D2/D3R). These receptors are expressed throughout the forebrain, but D3R are higher in limbic regions implicated in ICD, whereas D2R are higher in basal ganglia regions involved in motor control. Increases in limbic striatal AMPA receptor (AMPAR)-mediated synaptic strength is associated with addictions, which often involve impulse control. D2R/D3R signaling can involve Akt/GSK3ß, and GSK3ß promotes insertion of AMPAR into cytosolic membranes to strengthen glutamatergic synapses. We hypothesized PPX-activation of D3R will alter Akt/GSK3ß and AMPAR trafficking in limbic brain regions involved in addiction (nucleus accumbens), but not in motor-related basal ganglia regions (dorsal striatum).

Methods: Rats were administered saline or PG01037 (D3R antagonist); 30min later, saline or PPX was administered. One hour later, they were killed and striatal regions were extracted. Western blot protocols determined tissue levels of Akt/GSK3B, and surface and intracellular levels of AMPAR subunits (GluA1, GluA2). Data were analyzed using a one-way ANOVA followed by a *post hoc* Newman-Keuls test.

Results: PPX significantly reduced the ratio of pAkt (active)/Akt (total) and pGSK3ß (inactive)/GSK3ß (total) and increased the surface/intracellular (S/I) ratio for GluA1 and GluA2 in the nucleus accumbens. These effects were reversed by PG01037. In the dorsal striatum, no change occurred in pAkt/Akt, pGSK3ß/GSK3ß or GluA2 S/I. Unexpectedly, PG01037 decreased GluA1 S/I, (likely reflecting blockade of endogenous dopamine activation of D3R).

Conclusions: PPX upregulates AMPA receptor trafficking to the cytosolic membrane in nucleus accumbens (i.e., limbic striatum) via D3R-mediated Akt/GSK3ß signaling, but this does not occur in basal ganglia striatum. This may be a mechanism that underlies dopamine agonist-induced ICD.

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Piperine potentiate the neuroprotective effect of quercetin against MPTP induced neurotoxicity in rats S. Singh, P. Kumar (Moga, India)

Objective: (1) Quercetin is well tolerated bioflavonoid used as supplement for various disorders but problem is its low oral bioavailability and (2) Piperine is combined to enhance bioavailability of quercetin used as neuromodulatory, neuroprotective in movement disorders like Parkinson's disease.

Background: MPTP is a neurotoxin which cause destruction of dopaminergic neurons, produces Parkinson's like manifestations both in human and animals. Quercetin possesses good antioxidant and neuroprotective activity but major complication is its poor oral bioavailability. So to overcome this hindrance the present study was designed to investigate the effect of quercetin along with bioenhancer piperine against MPTP induced neurotoxicity in rats.

Methods: Rats were administered MPTP (100 μ g/1 μ L bilaterally) for 3 days (i.e. 1st, 4th and 7th). Quercetin (25 and 50 mg/kg) and combination of quercetin (25 mg/kg) with piperine (2.5 mg/kg) was administered daily for 21 days starting from the 7th day of 1st MPTP injection. Body weight and behavioral observations (locomotor, Rotarod, Grip Strength and Narrow beam walk performance) were recorded at weekly intervals after MPTP treatment. On the 22nd day, the animals were sacrificed and the rat striatum was isolated for the estimation of biochemical parameters (lipid peroxidation, glutathione and nitrite), determination of pro-inflammatory cytokine levels (TNF-a, IL-6 and IL-1b) and neurochemical analysis (Norepinephrine, 5-HT, GABA, glutamate, dopamine).

Results: The present finding had showed that chronic quercetin treatment for the 14 days significantly ameliorated the MPTP induced motor deficit, biochemical and neurochemical alterations in rats. Moreover combination of piperine (2.5 mg/kg) with quercetin (25 mg/kg) significantly potentiates the protective effect as compared to curcumin alone treated group.








Catecholamines level 90 Т ng/mg tissue sample b,c,d 60 120 b,c b b,c,d 30 b,c b,c,d a+ rato. b I a b Š 王 0 NE Dopamine Serotonin Control 3 MPTP (100 μg/1μl) MPTP + QC (25) $\blacksquare MPTP + QC (50) \blacksquare MPTP + PP (2.5) + QC (25)$





Table.1

Treatment (mg/kg)	MDA (nmol/mg protein) % of control	Nitrite level (µg/ml protein) % of control	GSH (nmol/µg protein) % of control
Control	100 ± 7.81	100 ± 6.23	100 ± 5.23
MPTP	227 ± 6.45 *	217 ± 6.54 *	26.4 ± 4.17 *
MPTP + QC (25)	172 ± 8.27 ^b	178 ± 5.9 b	43 ± 6.41 ^b
MPTP + QC (50)	145 ± 5.76 bc	148 ± 6.7 ^{bec}	62.5 ± 5.17 he
MPTP + PP (2.5) + QC (25)	126 ± 4.38% al	124 ± 5.4 bad	81.3 ± 4.38 head

Protective effect quercetin in combination with piperine on MDA, nitrite and GSH in MPTP-treated rats: Values are given as mean \pm SEM (n = 3). Values are statistically significant at p< 0.05 according to two-way ANOVA followed by Tukey's post hoc test. *P <0.001 vs C, *P < 0.05 vs MPTP, *P < 0.05 vs QC 25, *P < 0.05 vs QC 50 respectively.

Conclusions: In conclusion the administration of combination of quercetin and piperine had significantly prevented the MPTP induced behavioral, biochemical and neurological alteration by enhancing antioxidant and anti-inflammatory properties in rats.

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Piper betle L. Attenuates 6-OHDA Induced Apoptosis in SH-SY5Y Cells and Neuronal Injury in Caenorhabditis elegans Parkinson's Model

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Objective: To explore the anti-apoptotic effects of *Piper bitle* leaf extract (PLE) on 6-OHDA induced cellular injury in human neuroblastoma cell SH-SY5Y. To analyse the neuroprotective effects of PLE in Parkinson's disease *C. elegans* model.

Background: The molecular pathogenesis leading to neurodegeneration of dopaminergic neurons in PD is largely unknown. There is a need of an effective therapy to control the progression of proteinopathies. PLE attenuates 6-OHDA induced apoptotic events by regulating various signalling cascades in SH-SY5Y cells, and PLE ameliorates the a-synuclein accumulation, DAergic neurodegeneration, restore the lipid content and increase the lifespan of *C. elegans* treated with 6-OHDA.

Methods: SH-SY5Y: Cell viability, LDH release, nuclear condensation, detection of apoptosis, mitochondrial membrane potential, cell cycle and western blot analysis. *C.elegans* : a-synuclein aggregation, lipid deposition, DAergic neurodegeneration and lifespan analysis.

Results: The results revealed that pre-treatment with PLE in SH-SY5Y cells prior to 6-OHDA exposure improves the cell viability, decrease the LDH release, reverse mitochondrial transmembrane abnormalities, restore the Bax/Bcl2 ratio, and cytochrome c release. Meanwhile, PLE inhibits the phosphorylation of MAPKs (p38, JNK and ERK) pathway and p53 activation. Moreover, PLE could increase the expression of PI3K/Akt. In addition, PLE could significantly decrease the a-synuclein aggregation; attenuates the DAergic neurodegeneration; ameliorate the lipid content in NL5901 worms; increased the lifespan and decreased the lipofuscin in 6-OHDA treated N2 wild type worms.

Conclusions: Findings demonstrated that PLE exerts its neuroprotective effect by anti-oxidative and anti-apoptotic ability. Moreover, PLE has a potent anti-parkinsonism effects and this effect was driven by the inhibition of neurotoxicity, apoptotic cascade events, and ROS-mediated activation of downstream signalling pathways, MAPKs and PI3K/Akt. Studies were strongly proves that PLE exhibits strong ameliorative futures against a-synuclein accumulation, DAergic neurodegeneration and physiological impairments induced by 6-OHDA. Taken together, we believe that PLE was a potent candidate for the prevention of neurodegeneration in the patients with PD.

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The highly-selective metabotropic glutamate receptor 2 positive allosteric modulator LY-487,379 alleviates psychosis-like behaviours and dyskinesia in the MPTP-lesioned marmoset

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Objective: To investigate the effect of metabotropic glutamate receptor 2 (mGluR2) activation on L-3,4dihydroxyphenylalanine (L-DOPA)-induced psychosis-like behaviours (PLBs) and dyskinesia in the 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset model of Parkinson's disease (PD). **Background:** Psychosis and dyskinesia undermine the quality of life of as many as 50-95% of patients with advanced PD. Available therapies are few, their efficacy is partial and they may elicit important side effects.

Serotonergic 2A receptor (5-HT2AR) blockade is a validated approach to alleviate both psychosis and dyskinesia, but the effectiveness of this approach is also limited. 5-HT2AR forms a functional hetero-complex with mGluR2 involved in psychotic symptoms of schizophrenia and hallucinogenic effects of psychotomimetic drugs. We hypothesised that mGluR2 activation is a new and effective approach to reduce both L-DOPA-induced dyskinesia and psychosis in PD.

Methods: Six common marmosets were rendered parkinsonian by MPTP administration. Dyskinesia and PLBs were induced by chronic administration of L-DOPA. The potent and highly-selective mGluR2 positive allosteric modulator (PAM) LY-487,379 (vehicle, 0.1, 1 and 10 mg/kg) was then administered in combination with L-DOPA and its effects on each of dyskinesia, PLBs and parkinsonism were assessed.

Results: LY-487,379 1 and 10 mg/kg significantly alleviated PLBs (by 35% and 42%, respectively, both P < 0.05), when compared to vehicle. LY-487,379 1 and 10 mg/kg also significantly reduced the severity of dyskinesia (by 46% and 53%, respectively, both P < 0.05). LY-487,379 also significantly improved the quality of on-time, by reducing the duration of on-time with disabling PLBs/dyskinesia. Importantly, LY-487,379 did not hinder with L-DOPA anti-parkinsonian action.

Conclusions: Selective mGluR2 activation stands as a new and promising approach to alleviate both PD psychosis and dyskinesia without negative impact on parkinsonian symptoms.

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Role of Apocyanin in modulating glial cell functions and associated inflammatory response in Lipopolysaccharide induced Parkinson's disease model.

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Objective: To explore the effect of apocyanin on glia mediated inflammatory response and a-synuclein aggregation in single intranigral LPS induced PD model.

Background: Converging lines of evidence suggest that glia associated neuroinflammatory processes may account for the progressive death of dopaminergic neurons in Parkinson's disease (PD). Also, Apocyanin, an established microglial NADPH oxidase inhibitor has been proved to have beneficial effects in modulating anti-inflammatory as well as anti-oxidative effects in case of lipopolysaccharide induced PD model.

Methods: LPS (5µg/kg b.wt) was injected intranigral stereotaxically and apocyanin (10mg/kg/ day) was given i.p. for a period of 21 days.

Results: Following LPS injection significant augmentation in the gene as well as protein expression of transcription factor NF?B as well as proinflammatory cytokines (TNF-a, IL-1a, IL-1B), NADPH oxidase subunits gp90PHOX and gp21PHOX were observed in the glial fraction thus suggesting the prevalence of inflammatory responses and activation of NADPH oxidase complex. IHC for microglial activation and a-synuclein revealed that apocyanin significantly inhibited microglial activation as well as other antioxidant enzymes (SOD,Catalase) were also observed. However, with apocyanin treatment marked improvement in NF?B activation and related parameters was observed. This was further reflected in histopathological studies showing no evidence of inflammation in case of apocyanin treated animals.

Conclusions: This can be concluded that apocyanin play an important role in modulating glial cell functions thus revealing its potential anti-inflammatory role along with its NADPH oxidase inhibiting property. Therefore, its neuroprotective role could be further evaluated in other toxicological conditions.

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MANF protects dopamine neurons and locomotion defect from Neurotoxin/Human alpha-synuclein-induced progressive Parkinson's disease models in C.elegans.

Z. Zhang (Shanghai, People's Republic of China)

Objective: To study whether Mesencephalic astrocyte-derived neurotrophic factor (MANF) has beneficial effects in Parkinson's disease and its intracellular mechanisms.

Background: The distinguishing feature of Parkinson's disease is due to the degeneration of dopaminergic(DA) neurons. Caenorhabditis elegans (*C.elegans*) has a defined neural architecture and it has been demonstrated to be a good in vivo model in the study of neurodegenerative diseases. Mesencephalic astrocyte-derived neurotrophic factor (MANF) is a novel neuron factor which exhibits a survival-promoting effect to dopaminergic neurons in vitro. However, to date, it remains unclear whether MANF can rescue DA neurons in a-synuclein (a-Syn) model of PD and the neuroprotective mechanisms of MANF on dopaminergic neurons remain unclear.

Methods: 1. We construct neurotoxin/a-synuclein induced dopamine neurodegeneration model and observe the neuronal morphology includes cell body fluorescence, cilia, dendrite, axon, nuclear morphology and the locomotory index includes bending angle, length of worms, omega bending, speed, grid counting, track length. 2. We feeded MANF/a-Syn treated worms on plates seeded with HT115 E.coli bacteria expressing dsRNA for knocking down autophagy and ER stress related genes. Then we observed the dopamine neuron survival rate of 6-OHDA induced worms treated with MANF and locomotory capacity of a-Syn induced worms treated with MANF.

Results: 1. Dopaminergic neurons show time-related degeneration in 6-OHDA and a-synuclein induced model. 2. The abnormal behavior of C. elegans occurs in both two models. Also, the neuronal morphology damaged at first, then the motor symptoms emerged. 3. MANF has protective effects in two models. At the same time, MANF rescues the function of dopamine neurons by calcium imaging (shown - [Fig1]). 4. We screening all of autophagy and ER stress related genes so far identified in C.elegans, and find that almost all genes are involved in the molecular mechanism of MANF (shown - [Fig2]).





Conclusions: MANF has protective effects in neurotoxin/Human a-Syn-induced PD models by regulating autophagy and ER stress pathway.

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Study of neuroprotective effects of Ginsenside Rg3 , the prototypal epigenetic Sirtuin-1 activator, in targeting microglia activation and neurotrophic factor (NF) neural plasticity in MPTP model of Parkinson's disease (PD)

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Objective: 1) To examine whether the phyto-neurosteroid: Ginsenoside Rg3 recently demonstrated to activate the epigenetic SIRTI signaling, will rescue the motor impairment in rodent model of PD: 2) to investigate whether Ginsensoide Rg3 neuroprotection is related to its anti-inflammatory action in antagonizing CD-11b, the inflammation biomarker of microglia activation, and its neurotrophic effect in resetting expression of NF:: Nerve Growth factor (NGF) and Neurotrophin (NF-3).

Background: Growing body of evidence supports microglia activation coupled with dysregulatino of NF-mediated neural plasticity, contributes towards loss of dopamine neurons (DA) in PD. Very few studies address the issue whether epigenetics regulation of neuroinflammation and NF signal may be neuroprotective in PD.

Methods: We evaluated the pharmacological actions of Ginsenoside Rg3 in : 1) the in vitro model of MPTP model involving exposure of rodent mesencephalic dopamine neurons to neurotoxic doses of MPTP; 2) the in vivo MPTP model in the C57/BL mice treated weekly with MPTP. We measured the motor performance with standardized behavioral paradigms of climbing pole and locomotor activity counts. DA tyrosine hydroxylase (TH+) neurons and microglia activation biomarker: CD-11b were quantified with immuno-histochemistry. NG-3 and Nerve Growth factor:NGF expression were determined with Western blot, real-time PCR assays.

Results: In the vitro model, ginsenoside Rg3 restored DA (TH+) neuronal loss . In the subchronic MPTP model, ginsensoide Rg3 administered orally at daily dosages of 5 mg/kg, 10 mg/kg and 20 mg/kg significantly blocked (p < 0.05) decline in TH(+) neurons in the striatum and substantia nigra, when compared with the placebo group. Ginsenoside Rg3 significantly improved the motor deficits and antagonized the up-regulation of CD-11b in the MPTP group. The changes in motor functions CD-11b expression were linked directly to up-regulation of mRNA levels of NF-3 and NGF .

Conclusions: Our results of Ginsenoside Rg3 in]MPTP PD model provide evidence that SIRTI epigenetic targeting rescues motor dysfunction, reduces neuroinflammation, and restores NF dysregulation in PD, Controlled trial of Ginsenoside Rg3 in PD is warranted to establish Rg3 efficacy in PD.

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Is there a significant relationship between weight loss and prevalence of side effects of Parkinsonian medication? A retrospective, single-centre analysis, South Wales, UK.

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Objective: To investigate if there is a significant relationship between weight loss in persons with Parkinson's disease and side-effect incidence, and if so to what extent this is.

Background: Parkinson's disease is a common neurodegenerative disease. Weight loss is prevalent, and its effects are poorly understood in Parkinson's disease. In particular there is very little understanding of the relationship of side effects and weight loss. Given the noted quality of life issues in Parkinson's patients these side effects are likely to contribute to worse patient outlook.

Methods: A pilot, retrospective, single-centre, analysis in Movement Disorders Clinic, Rookwood Hospital, South Wales, UK comparing varying extents of weight loss with incidents of side effects; Hoehn and Yahr scale was accounted for with additional comparison. Statistical significance was defined at p = 0.05; Mann-Whitney U test was used.

Results: 138 patients were sampled, of whom 80 were included. 53 were assigned to weight loss group (66.3% of sample) of whom 85.1% experienced side effects. 27 persons had no weight loss, of whom 59.3% experienced side effects. Weight loss was associated with a statistically significant increase in side-effect prevalence (p = 0.05). There was no statistically significant relationship between H&Y scale with side effect prevalence in weight loss (p > 0.05), or no weight-loss (p > 0.2).

Conclusions: There is a clear correlation between weight loss in Parkinson's disease and the prevalence of adverse medications effects. Clinicians should take into account body weight changes when dosing and reviewing dopaminergic medications.

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Curcumin I protect against copper induced neurobehavioral features of Parkinson's disease in rat

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Objective: evaluate the impact of acute Cu intoxication (10 mg/kg B.W. i.p) for 3 days on the dopaminergic system and locomotor performance, together with the possible restorative effect of oral administration of curcumin (30 mg/kg B.W.).

Background: Parkinson's disease is a progressive disorder of the nervous system that affects movement. The classic motor symptoms of Parkinson's disease result from progressive dopaminergic neurons death within substantia nigra. Some finding support the involvement of heavy metals, as an exogenous risk factor such as copper (Cu), excessive levels of this element are responsible for profound physiological alterations including the central nervous system. Whereas, different pharmacological trials have shown a beneficial role against Cu neurotoxicity, curcumin (*Curcuma longa*) is one of the powerful medicinal plants with an array of therapeutic effects.

Methods: Behavioral study (open field) and Immunohistochemistry.

Results: We noted, in the Cu intoxicated rats, a significant loss of TH (tyrosine hydroxylase) expression within substantia nigra compacta (SNc), ventral tegmental area (VTA) and the subsequent striatal outputs, those alterations were correlated to behavioral abnormalities such as a severe drop of locomotor performance. While curcumin administration to Cu intoxicated rats showed a noticeable beneficial effect; this potential was featured by a complete recovery of the TH expression and locomotor behavior deficiencies in the intoxicated rats.

Conclusions: The present investigation have brought, on the one hand, an experimental evidence of an altered dopaminergic innervations following Cu intoxication and on the other hand, a new pharmacological property of curcumin that may be used as a neuroprotective plant for neurodegenerative disorders touching the dopaminergic system trigged by heavy metals.

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Blink reflex recovery cycle to differentiate Progressive Supranuclear Palsy from Corticobasal Degeneration *G. Sciacca, A. Nicoletti, G. Mostile, A. Luca, L. Raciti, V. Dibilio, F. Le Pira, M. Zappia (Catania, Italy)*

Objective: To evaluate R2 Blink Reflex Recovery Cycle (BRRC) in patients with Progressive Supranuclear Palsy (PSP) and CorticoBasal Degeneration (CBD) and to determine its diagnostic sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) in differentiating PSP from CBD. **Background:** PSP and CBD are rapidly progressive neurodegenerative disorders, clinically featured by parkinsonism and additional debilitating symptoms. Phenotypic spectrum of these disorders, belonging to the group of tauopathies, is wide. The differential diagnosis between PSP and CBD is extremely difficult because of the overlap of clinical features. R2 BRRC is a neurophysiological tool used to evaluate brainstem excitability. R2 BRRC is abnormal in several movement disorders such as Parkinson's disease1 and dystonia2. **Methods:** This is a double-blind prospective case-control study. Patients affected by PSP and CBD were

Methods: This is a double-blind prospective case-control study. Patients affected by PSP and CBD were consecutively enrolled, according to the currently accepted diagnostic criteria. Patients underwent clinical (Hoehn&Yahr-stage, UPDRS-ME) and neurophysiological (R2 BRRC) assessments. R2 BRRC was performed at interstimulus intervals (ISIs) of 100-150-200-300-400-500-750 ms and it was measured as percentage of R2 amplitude ratio between conditioned and unconditioned response.

Results: Thirty subjects were enrolled: 12 PSP and 8 CBD patients and 10 healthy controls. Eleven of 12 PSP patients and one of 8 CBD patients showed an early R2 BRRC. A significantly different amplitude of R2 response was observed at ISIs of 100-150-200-300 ms between PSP and CBD patients (p=0.006, p<0.00001, p<0.00001 and p=0.02 respectively) and also between PSP and healthy controls (p<0.00001, p<0.00001 and p=0.004 respectively); no statistically significant differences were found between CBD and control subjects [figure1]. An early R2 BRRC differentiated PSP from CBD patients with a sensitivity and a specificity of 87.5% and 91.7% respectively; PPV and NPV were 91.7% and 87.5% respectively.



Conclusions: Despite both diseases belong to a common neuropathological entity, peculiar characteristics can be focused on to distinguish the two disorders. The predominant brainstem tau aggregates distribution in PSP, in contrast with the involvement of neocortex in CBD, could explain the brainstem disinhibition observed in PSP patients. R2 BRRC might be considered a useful tool in differentiating PSP from CBD.

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Voice Cepstral Analysis in Adductor-Type Spasmodic Dysphonia

L. Marsili, A. Suppa, G. Costantini, G. Saggio, D. Casali, G. Delgado, G. Ruoppolo, A. Berardelli (Rome, Italy) **Objective:** To investigate differences in voice parameters between patients affected by adductor-type spasmodic dysphonia (ASD) and Healthy subjects (HS).

Background: Adductor-type spasmodic dysphonia (ASD) is a task-specific focal dystonia manifesting with involuntary laryngeal muscle spasms leading to intermittent strained/strangled voice. ASD is often poorly recognized by clinicians not familiar with the disorder, because of the lack of diagnostic criteria and of validated severity scales. In the present study, following our recently published observations, we performed voice analysis in ASD patients by using cepstral analysis. Cepstral analysis is based on Fourier transform of the logarithm power spectrum of an acoustic signal and reflects the dominant rahmonic in the voice sample.

Methods: We investigate 20 ASD patients and 20 age and sex-matched healthy subjects (HS). Symptoms were scored using the Voice Handicap Index scale and a dysphonia clinical scale. Phoniatric evaluation included voice cepstral analysis. The crucial variable in the voice cepstral analysis is the normalized cepstral peak prominence (CPP). We collected voice samples using a high-definition audio recorder (H4n Zoom Corporation, Japan) and a

Shure WH20 Dynamic Headset Microphone. Voice samples were digitized at 44.1 kHz, 24 bit, and analysed using the Matlab software. CPP together with other cepstral and spectral features, such as CPPS (smoothed CPP), Hi/Low frequencies rate, harmonics-to-noise ratio, shimmer and jitter were extracted. Finally, we performed a classification with both neural networks and Support Vector Machine (SVM), using Weka software.

Results: Voice analysis discriminates HS from ASD, with a sensitivity of 82% by using neural networks and 87% by applying SVM; and a specificity of 90% by using neural networks and 97% by applying SVM. Positive predictive value is 87% by using neural networks and 88% by applying SVM. Negative predictive value is 85% by using neural networks and 84% by applying SVM.

Conclusions: Cepstral analysis discriminates ASD patients from HS, representing a new helpful tool to better characterize voice abnormalities in ASD. These results suggest the idea that voice features extraction and classification are important instruments to support clinicians in the correct diagnosis of ASD, among different voice disorders.

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Extended "Timed Up And Go": A Clinical Indicator Of Cognitive State In Parkinson's Disease?

T. Evans, A. Jefferson, M. Byrnes, S. Walters, S. Ghosh, F. Mastaglia, B. Power, R. Anderton (Perth, Australia) **Objective:** To evaluate an extended Timed Up and Go (extended-TUG) as a potential holistic indicator of Parkinson's disease; hypothesised to correlate closely with disease severity and cognitive impairment by a panel of clinical assessments.

Background: The disability of Parkinson's Disease (PD) is determined by variable motor and non-motor functional decline, the latter being more significant for quality of life yet under-recognised in the clinical setting. A modification to the traditional TUG, whereby total distance is increased from 6 to 14 metres, was found to be a valid treatment outcome measure, irrespective of location (home or clinic) or practitioner discipline [1]. Ostensibly a motor assessment, the extended-TUG assessment correlates closely with patient quality of life, a patient outcome derived from cognitive, motor and other aspects of the disease [2]. The value of extended-TUG in appraising cognitive status has not been probed by dedicated assessments.

Methods: 87 participants with diagnosed idiopathic PD were sequentially recruited from the Movement Disorders Clinic, Sir Charles Gairdner Hospital, Perth Australia. An Extended-TUG test was performed, and required participants to stand from a seated position, walk for 7 metres, turn 180 degrees and return. Test duration was correlated to validated assessments including the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), PD Quality of Life (PDQ-39), Scales for Outcomes in Parkinson's Disease (SCOPA-Cog), and the revised Addenbrooke's Cognitive Index (ACE-R).

Results: Time to complete extended-TUG was significantly correlated to UPDRS domains, SCOPA-Cog, ACE-R (p<0.001) and PDQ-39 score (p<0.01). Generalized linear models found the extended-TUG to be a sole variable in predicting ACE-R or SCOPA-Cog scores; where patients in the fastest extended-TUG tertile were predicted to perform 8.3 points and 13.4 points than the slowest group respectively. When stratified by known dementia cut-off scores, the dementia group exhibited significantly longer extended-TUG duration (p<0.05).

Conclusions: Extended-TUG appears to be a significant indicator of patient cognition, motor function, and quality of life in PD. Poor performance could demarcate patients for whom in-depth cognitive assessment is indicated but not self-evident; larger studies of extended-TUG as a first line tool are suggested.

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Validation of a performance-based assessment of functional ability related to cognition in Parkinson's disease S. Holden, L. Medina, B. Hoyt, S. Sillau, J. Goldman, D. Weintraub, B. Kluger (Aurora, CO, USA)

Objective: Validate the University of California San Diego Performance-Based Skills Assessment (UPSA) in Parkinson's disease (PD)

Background: Diagnostic criteria for PD dementia (PDD) require significant impairment in activities of daily living not ascribable to motor or autonomic symptoms, yet there are currently no standards for assessing such cognitive functional impairment. Questionnaire-based functional scales exist, but are open to bias by limited insight, mood or caregiver burden. A performance-based functional assessment avoids such biases, provides objective data and can be used in the validation other scales.

Methods: 52 PD participants completed the UPSA [table1], questionnaire-based cognitive functional scales (Penn Daily Assessment Questionnaire (PDAQ), PD-Cognitive Functional Rating Scale (PD-CFRS)); scales of global cognition (Montreal Cognitive Assessment (MoCA)), Dementia Rating Scale (DRS)), health-related quality of life (PDQ-39), and mood (Hospital Anxiety and Depression Scale (HADS)), Apathy Evaluation Scale (AES));

neuropsychological battery (10 tests, 2 in each of 5 domains); and motor exam (UPDRS Part III). For retest reliability, 18 participants repeated the UPSA after a mean interval of 6 weeks. Cognitive classification (PD-normal cognition (PD-NC), PD-mild cognitive impairment (PD-MCI) or PDD) was determined by consensus conference, blinded to UPSA scores.

Results: Participants included 30 PD-NC, 6 PD-MCI and 16 PDD [table2]. The UPSA demonstrated strong internal consistency (Cronbach's a=0.83) and retest reliability (r=0.9). Moderate correlations exist between UPSA and DRS (r=0.67, p<0.001), PDAQ (r=0.65, p<0.001), PD-CFRS (r=-0.55, p<0.001) and PDQ-39 (r=-0.51, p=<0.001). UPSA was strongly correlated with UPDRS Part III (r=-0.77, p<0.001); this was attenuated by adjusting for age, education and PD duration (r=-0.51, p<0.001). Correlation was weak between UPSA and HADS (Anxiety r=-0.15, p=0.28; Depression r=-0.24, p=0.09), but moderate for apathy (AES r=-0.39 p=0.004). The UPSA discriminated PDD from non-demented (PD-NC and PD-MCI) participants (AUC=0.92) [figure1]. An UPSA cut-off score of 70 detected PDD with a sensitivity of 75% and specificity of 94%.

UCSD	UCSD PERFORMANCE-BASED SKILLS ASSESSMENT				
Domain	Assessed Skill	Possible Points			
Financial	Counting change Interpreting a utility bill	20			
Communication	Calling information to request a phone number Calling the doctor to reschedule an appointment	20			
Planning/Organization	Planning a trip to a water park	20			
Travel	Reading and interpreting a bus route map and schedule	20			
Household chores	Reading a recipe Completing a shopping list	20			
	Total P	ossible Points: 100			

Table 1: UCSD Performance-Based Skills Assessme

Table 2: Participant Characteristics by Cognitive Classification

	PD-NC (n=30) Mean (SD), range	PD-MCI (n=6) Mean (SD), range	PDD (n=16) Mean (SD), range	P
Age (y)	65.1 (7.7), 53-85	74.3 (2.7), 70-78	77.3 (7.7), 63-90	< 0.001
Sex (% female)	10 (33%)	0 (0%)	1 (6%)	0.05
Education (y)	16.9 (2.6), 12-21	16.2 (3.4), 12-21	15.9 (2.9), 12-21	0.53
Disease Duration (y)	4.1 (2.5), 0.5-10.0	4.1 (2.9), 0.5-8.0	9.7 (8.1), 1-32	0.06
LEDD (mg/day)	391.7 (320.8), 0-1325	643.8 (413.9), 250-1360	693.6 (388.8), 0-1345	0.04
UPSA	84.4 (6.7), 68-96	69.3 (9.1), 51-75	56.3 (15.4), 30-87	< 0.001
MoCA	27.6 (2.2), 20-30	23.7 (3.4), 19-28	20.4 (5.0), 9-28	< 0.001
DRS	140.8 (3.1), 130-144	134.5 (8.4), 120-144	126.6 (8.7), 110-139	< 0.001
PDQ-39	22.5 (15.8), 1-62	39.0 (34.4), 12-107	48.9 (23.1), 10-102	0.005
PDAQ	51.6 (8.1), 20-60	46.0 (9.3), 28-54	37.4 (9.8), 20-50	< 0.001
PD-CFRS	2.5 (2.6), 0-11	3.3 (2.8), 0-8	8 (5.9), 1-23	0.01
UPDRS Part III	22.8 (7.4), 9-37	40.0 (7.2), 31-47	40.9 (9.7), 30-62	< 0.001
HADS Anxiety	3.3 (2.9), 0-10	3.2 (4.1), 0-11	2.9 (2.6), 0-9	0.91
HADS Depression	2.7 (2.0), 0-8	2.3 (1.5), 1-5	3.6 (2.2), 1-8	0.27
AES	24.0 (5.6), 18-37	22.5 (3.5), 18-27	29.4 (5.3), 21-40	0.004

Figure 1: ROC curve for classification of PDD by UPSA



Conclusions: The UPSA provides valid information on cognitive functional abilities in PD and reliably distinguishes demented from non-demented PD patients, though performance may be affected by motor severity and apathy.

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APOE4+ status increases rate of longitudinal cognitive decline in Parkinson's disease patients with low CSF AB42

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Objective: To determine if the presence of APOE?4 allele (APOE4+) predicts longitudinal cognitive decline in Parkinson's disease (PD) patients with low CSFAB42.

Background: Cognitive impairment in PD is common and disabling. Biomarkers that predict risk for cognitive decline are important as therapies that slow disease are likely to be more effective when implemented earlier. Studies suggest that in non-demented PD patients low CSFAβ42 increases risk for future cognitive decline. APOE4+ has also been shown to predict cognitive decline in PD. Studies from normal individuals with high CNS amyloid and APOE4+ show a higher rate of cognitive decline than either factor individually. We predicted that in non-demented PD patients with low CSF Aβ at baseline, APOE4+ will further increase risk for cognitive decline **Methods:** Using the Parkinson Progression Markers Initiative database (downloaded 6/1/2016), we included all non-demented, de novo PD patients with low CSFAβ at baseline (defined as <310 ug/mL, N=61). We then divided the cohort into APOE4+ (defined as at least one APOE?4 allele, N=22) or APOE4- (no APOE?4 allele, N=39). We considered 3 neuropsychological scores [Hopkins Verbal Learning Test-Revised (HVLT), Semantic Fluency Test (SFT), and Montreal Cognitive Assessment (MoCA)] and assessed scores at 4 timepoints (baseline, year 1, 2, and 3). In PD patients with low CSFAβ at baseline, we determined the effect of APOE4+ on baseline scores as well as the annual rate of change using a linear mixed effects model adjusted for age, gender, and education. **Results:** For the MoCA, baseline scores were similar in both groups (APOE+ and APOE-); however the rate of

decline was significantly faster in the APOE4+ group with an accelerated decline of 0.457 points annually (95%CI: 0.017-0.897, p=0.04). For the HVLT, baseline scores were similar in both groups; however, the rate of decline trended toward being faster in the APOE4+ group (p=0.13). For the SFT, baseline scores trended toward being lower in in the APOE4+ group compared to APOE4- (p=0.06); however, decline over time was similar in both groups.

Conclusions: APOE4+ accelerates rate of cognitive decline in PD patients with low CSF AB42. Additionally, baseline scores on SFT were significantly lower at baseline. These results suggest that APOE4 may represent an independent clinically significant biomarker to identify PD patients at greater risk for cognitive decline.

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Cognitive data in the Parkinson's Progression Markers Initiative: Comparison of normative data approaches *K. Wyman-Chick, M. Barrett, P. Martin, C. Manning, S. Sperling (Charlottesville, VA, USA)*

Objective: It is important to understand underlying psychometric properties of the cognitive tests included in the Parkinson's Progression Markers Initiative (PPMI) dataset to interpret the results accurately. This project examines impact of different methods of determining normative or standardized cognitive data on research outcomes in PPMI. **Background:** There are several approaches to analyzing cognitive data. The tests in PPMI are commonly used in clinical neuropsychological evaluations with age-normative data [1], as many cognitive abilities change with age. Research strategies have also included utilization of raw scores controlling for age or creation of internal standardized scores derived from PPMI control group cognitive data [2].

Methods: Data were obtained from PPMI in January 2017. Baseline data from 422 participants with Parkinson's disease (PD) were included [Age=61.7(9.7), Education=15.6(3.0)]. Tests included Hopkins Verbal Learning Test-Revised, Letter Number Sequencing (LNS), Judgment of Line Orientation (JLO), Symbol-Digit Modalities Test, and Category Fluency. Internal norms were calculated for each participant using the group mean and standard deviation of the PPMI control group. Paired-sample t-tests were conducted comparing internal norms and published agenorms for each neuropsychological test. Chi-squares were conducted to evaluate the proportion of individuals with impairment (<1 SD below the mean).

Results: Table 1 provides comparison of internal norms vs. published norms. [table1] Significant differences were found between internal and published norms for LNS, JLO, and semantic fluency. The methodologies for norming the cognitive data in PPMI result in different proportions of individuals identified with cognitive impairment at baseline. [table2]

	Raw Scores M (SD)	Test Performance Based on Internal Norms M (SD)	Test Performance Based on Published Age-Norms M(SD)	,	df	<i>p</i> -value	đ
HVLT-R Immediate Recall T-Score	24.44 (4.98)	46.43 (11.06)	46.34 (10.99)	-0.22	421	.823	-0.008
HVLT-R Delayed Recall T-Score	8.36 (2.52)	45.99 (10.85)	46.83 (11.75)	1.44	421	.152	0.074
LNS Scaled Score	10.59 (2.66)	9.67 (3.10)	11.49 (2.68)	37.79	421	<.001**	0.574
JLO Scaled Score	12.77 (2.13)	9.47 (3.23)	12.79 (2.76)	107.04	421	<.001**	0.737
Semantic Fluency T-Score	20.96 (5.34)	47.90 (9.95)	50.79 (9.84)	13.46	421	<.001**	0.293
SDMT z-score	41.18 (9.73)	-0.53 (0.92)	-0.49 (0.86)	1.35	421	.177	0.042

Table 1. Comparison between PPMI Internal Norms and Published Age-Normative Data in Participants with Parkinson Disease (n=422)

Notes: PPMI = Parkinson's Progressive Marker Initiative; HVLT-R = Hopkins Verbal Learning Test Revised Form 1; LNS = Letter Number Sequencing, JLO = Judgment of Line Orientation Odd Numbered Items; SDMT = Symbol Digit Modalities Test; Internally Normed z-scores were derived from the mean of the participant score – the group mean of the healthy control group, divided by the standard deviation of the group mean of the healthy control group for each measure. T-scores have a mean of 50 with a standard deviation of 10; Scaled Scores have a mean of 10 with a standard deviation of 3; z-scores have a mean of 0 with a standard deviation of 1.

* p≤.05 **p≤.001

	Impa	aired %	Unim	paired %			
	Internal Norms	Published Norms	Internal Norms	Published Norms	X ²	df	<i>p</i> -value
HVLT-R Immediate Recall	28.0	31.0	72.0	69.0	150.72	1	<.001*
HVLT-R Delayed Recall	15.6	32.9	84.4	67.1	69.62	1	<.001*
Letter Number Sequencing	21.1	6.4	78.9	93.6	107.93	1	<.001*
Judgement of Line Orientation	8.8	5.2	91.2	94.8	241.51	1	<.001*
Semantic Fluency	22.0	14.5	78.0	85.5	202.00	1	<.001*
Symbol Digit Modalities Test	29.4	26.4	70.6	73.6	152.16	1	<.001*

Table 2. Cognitive Impairment prevalence rates for participants with PD in PPMI at baseline using internal scores versus published norms by test

Notes: PPMI = Parkinson's Progressive Marker Initiative; HVLT-R = Hopkins Verbal Learning Test Revised Form 1; Judgment of Line Orientation Odd Numbered Items; Internally Normed z-scores were derived from the mean of the participant score – the group mean of the healthy control group, divided by the standard deviation of the group mean of the healthy control group for each measure. Impaired is defined as less than 1 standard deviation below the normative mean.

Conclusions: Among participants with PD in PPMI, there are differences in standardized cognitive scores depending upon the normative group that is used. These differences impacted impairment rates across cognitive measures and the use of internal norms resulted in lower standardized scores than age-norms with the exception of memory tests. Such findings indicate that standardization approaches are not interchangeable. Selection of appropriate normative comparison groups requires careful consideration as such decisions can impact both research and clinical interpretations of cognitive data.

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Feasibility of utilizing the NIH Toolbox in Parkinson's disease subjects with deep brain stimulation

J. Emerson, P. Dhruva, C. McLeod, R. Moses-Kessler, L. Metman, G. Pal (Chicago, IL, USA) **Objective:** To determine the feasibility of utilizing the NIH Toolbox in moderate to advanced disease Parkinson's disease (PD) subjects with bilateral subthalamic nucleus deep brain stimulation (STN-DBS).

Background: The CAPSIT-PD protocol recommends a series of neuropsychological measures which have poor tolerability in PD patients undergoing DBS [1]. A novel assessment tool, the NIH Toolbox cognition battery [2], has been developed to serve as a brief, convenient set of measures that provides a "common currency" among researchers for comparisons across a wide range of studies and populations. Though the NIH Toolbox was released in 2012 and is listed as one of the "common data elements," it's use has only been described in PD patients with mild disease and it has not been utilized in the DBS population.

Methods: We enrolled 14 PD subjects with bilateral STN-DBS who were administered the NIH Toolbox cognition battery in the ON-medication, ON-stimulation state. Additional data collected included basic demographic information, Montreal Cognitive Assessment (MoCA), and Unified Parkinson's disease Rating Scale (UPDRS). The NIH Toolbox battery fully-corrected t-scores were analyzed which have a normative mean of 50 with an SD of 10, and are corrected for age, education, sex, and race.

Results: Fourteen PD subjects were enrolled with a mean age of 63.9 ± 6.5 , mean disease duration of 12.8 ± 7.1 years, and 78.6 percent were men. All subjects had bilateral STN-DBS with a mean of 1.7 ± 1.1 years of DBS duration. Mean UPDRS-III score was 16.6 ± 8.2 years and mean MoCA score was 24.9 ± 5.1 . All but one subject (13/14) completed the full range of cognitive measures. Subjects performed in the average to above average range in nearly all measures except for processing speed where individuals performed significantly below average. Overall cognitive function was in the average to above average level based on the toolbox composite scores [table 1]. There was a moderate correlation between the NIH Toolbox global cognitive measures and MoCA scores, with the cognitive function composite score having the strongest correlation with MoCA [table 2].

Construct	Measure	Fully corrected t- score	Interpretation
Language	Picture Vocabulary Test	61.2±20.6	Above average
Executive	Flanker Inhibitory Control and Attention	51.6±16.8	Average
function and	Test		
attention			
Working Memory	List Sorting Working Memory Test	45.8±12.9	Average
Executive	Dimensional Change Card Sort Test	61.5±24.2	Above average
function			
Processing	Pattern Comparison Processing Speed	34.2±14.5	Below average
Speed	Test		
Episodic Memory	Picture Sequence Memory Test	47.4±18.2	Average
Language	Oral Reading Recognition Test	61.3±27.0	Above average
Global Cognition	Fluid Cognition Composite Score (n=13)	49.8±21.4	average
Global Cognition	Crystalized cognition composite score	62.9±27.7	Above average
Global Cognition	Cognitive function composite score (n=13)	58.7±29.3	Average

Measures of global cognition	Correlation with MoCA	p
Fluid Cognition Composite Score (n=13)	0.551	0.05
Crystalized cognition composite score	0.549	0.04
Cognitive function composite score (n=13)	0.645	0.02

Conclusions: The NIH Toolbox cognition battery is feasible to administer to moderate to advanced PD patients with bilateral STN-DBS and has modest correlation with the MoCA, a widely used assessment tool in PD. Further studies are needed to validate the NIH Toolbox in the PD population.

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Patient-reported hallucinations and the probability of progression to dementia in Parkinson's disease

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Objective: To evaluate the influence of neuropsychiatric symptoms in identifying Parkinson's disease (PD) patients who will progress to dementia (PDD) in the imminent future (~4 years).

Background: Neuropsychiatric symptoms are common in PD and may be associated with conversion to PDD. **Methods:** One hundred and twenty-three non-demented PD patients were followed over 3.5-4.5 years; 27 progressed to PDD during the study. All patients received Level II neuropsychological testing: two or more tests were assessed in each of the five cognitive domains; a global cognitive score was derived by averaging the z-scores from the attention, executive function, episodic memory, and visuospatial domains. Neuropsychiatric evaluations included the Neuropsychiatric Inventory (NPI), Geriatric Depression Scale (GDS), the hallucination and depression items from the UPDRS, and the emotional well-being, hallucination and distressing dream items from the PD Questionnaire (PDQ). ROC tests were used to analyse whether measures at study entry were associated with future progression to PDD.

Results: As expected, baseline cognition (ROC for global score, AUC = 0.87, CI = 0.79-0.94), and older age (AUC = 0.73, CI = 0.63-0.84), were useful at discriminating conversion to PDD four years later. Time since diagnosis (AUC = 0.63, CI = 0.51-0.75) and the NPI total score (AUC = 0.62, CI = 0.50-0.75) showed smaller effect sizes. The NPI sub-scale scores and GDS (AUC all < 0.62) were not significantly associated with PDD conversion. Interestingly, baseline patient-reported hallucinations, using items from the PDQ and UPDRS, were associated with conversion to PDD (AUC = 0.70, CI = 0.60-0.80; AUC = 0.69, CI = 0.57-0.80, respectively), whereas the hallucination sub-scale on the NPI (reported by the significant other) was not significant (AUC = 0.55, CI = 0.48-0.62). The AUC's of the hallucination items of the PDQ and UPDRS showed a stronger association with PDD progression compared to hallucinations reported by the NPI (p < 0.05).

Conclusions: While cognitive testing is a better predictor, patient-reported hallucinations also suggest an increased probability of conversion to PDD within 4 years. Other neuropsychiatric measures, particularly those reported by a patient's significant other, may not be as useful in this regard.

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Self-awareness of cognitive functions in Parkinson's disease patients with and without mild cognitive impairment

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Objective: To examine whether Parkinson's disease (PD) patients with or without mild cognitive impairment (MCI) show impaired self-awareness (ISA) of their cognitive abilities.

Background: PD patients may show ISA of their cognitive deficits. For disease acceptance or understanding of cognitive capabilities, self-awareness of cognitive deficits is mandatory. Hence, we examined ISA of cognitive functions in PD patients with and without MCI.

Methods: Included were 55 PD patients and 15 age-matched controls. All participants received a cognitive assessment according to the MCI MDS-guidelines. For each patient/control, a relative was included who served as informant. Self- and proxy ratings were administered applying the cognitive failures questionnaire (CFQ) and the dysexecutive questionnaire (DEX). For both questionnaires, higher scores equal more impairment. The discrepancy between less impaired self-rating and more-impaired proxy-rating was considered as ISA. All patients and controls were compared concerning cognitive tests and questionnaires. Based on the cognitive test results, patients were divided into patients with (N=11) and without MCI (N=44). These were compared using the same questionnaires applying repeated measures ANOVA for self- vs. proxy-ratings.

Results: Patients were significantly more impaired than controls in cognitive tests. CFQ-scores were significantly higher in patients/controls compared to proxy ratings, while DEX-scores where comparable. Patients and their relatives rated significantly worse on the DEX than controls and their relatives. MCI and non-MCI patients did not differ concerning sex, age and disease duration. MCI-patients were significantly more impaired in cognitive tests than non-MCI patients. When self- and proxy-ratings were compared, MCI-relatives rated patients as more impaired than MCI-patients themselves on the CFQ and the DEX, therefore implying ISA. Non-MCI patients had higher self-ratings than proxy-ratings, therefore showing the opposite result. This interaction was significant for the CFQ, and nearly for the DEX.

Conclusions: Generally, patients and controls rate themselves worse in cognitive questionnaires than their relatives, therefore showing no signs of ISA. When PD patients with MCI are analyzed the results reverse and show more impaired proxy- than self-ratings. Hence, ISA of cognitive functions should be essentially analyzed in PD patients with MCI.

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Ghrelin and the IGF-1 axis in cognitive impairment in PD

F. Johnston, M. Siervo, A. Hornsby, J. Davies, D. Burn (Newcastle upon Tyne, United Kingdom) **Objective:** To explore the association of acyl-ghrelin (AG) levels with cognitive impairment (CI) in PD. **Background:** Unintended weight loss (UWL) in PD is associated with CI. AG is produced in response to weight loss and stimulates appetite and weight gain. Levels are paradoxically low in people with PD and UWL[1]. AG can improve learning and memory in animal studies through promotion of long-term potentiation and neurogenesis. It is anti-inflammatory and stabilises mitochondria, preventing neuronal apoptosis. Thus, it has been shown to be neuroprotective in animal models of PD[2]. AG indirectly stimulates IGF-1; also proposed to be neuroprotective in PD. AG may therefore provide a mechanistic neurohumoral link between UWL and CI in PD. No studies have explored the association of ghrelin with CI in PD to date.

Methods: 55 adults aged 60-85 were recruited; healthy controls (HC) (n=20), PD without CI (PD-NC)(n=19) and PD with CI (PD-CI)(n=16). The PD-CI group included PDD and PD-MCI. All had a Montreal Cognitive Assessment of =25/30. Participants with UWL, obesity, BMI <18 or >30, diabetes, gastrointestinal disease, smoking, deep brain stimulation or non-selective anticholinergic medication were excluded. Participants were tested fasted and off PD medication. Blood was drawn at baseline, 5, 15, 30, 60, 120 and 180 minutes following a standard breakfast. AG samples were treated with 4-(2-Aminoethyl)-benzenesulfonyl fluoreide and analysed using a multiplex assay. Total ghrelin (TG), IGF-1 and GH were analysed by ELISA. At 180 minutes participants received an ad libitum meal. Area under the curve (AUC) was calculated for each analyte using the trapezoidal method and AUC compared using analysis of variance. Post-hoc comparisons were conducted by Scheffe's test. **Results:** There were no significant differences between groups for age, gender or disease duration. AUC for AG showed a trend towards lower levels in the PD-CI group (p=0.14), which had significantly lower levels compared to the PD group (p<0.05)[Figure 1], there was no significant difference between groups for TG (p=0.84)[Figure 2]or GH (p=0.76)[Figure 3]. There was a significant difference between groups for IGF-1 (p=0.02)[Figure 4], with lower

levels seen in PD-CI(p<0.05).





Conclusions: IGF-1 levels were significantly different between HC, PD and PD-CI. AG levels were significantly lower in PD-CI than PD. AG and IGF-1 should be investigated as possible biomarkers for CI in PD with longitudinal studies.

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Validation of Computerised Measures of Executive Functioning for use in Parkinson's Disease Assessments.

T. Dominey, C. Carroll, R. Noad, C. Newman, S. Hall (Plymouth, United Kingdom)

Objective: i. To validate the use of a computerised finger tapping task as a screening measure for Executive Dysfunction (EF) in Parkinson's Disease (PD), against traditional non-computerised measures. ii. To determine whether the modality of the cue stimulus (visual vs audio vs somatosensory) in the computerised finger tapping task affects performance.

Background: Previous research has demonstrated that automated tapping tasks are able to accurately predict PD symptom severity. However, the efficacy of these approaches are potentially reduced by co-morbid impairment of cognitive function such as impaired Executive Function (EF). This cohort will evaluate a novel computerised measure of EF (a paced computerised finger tapping task), against more traditional assessments.

Methods: 100 patients with a diagnosis of idiopathic PD will complete a battery of traditional EF assessments and a Computerised Finger Tapping Task (PD-TAP) on a tablet device. PD-TAP consists of a Fast Finger Tapping Task, previously shown to have high predictive value for PD symptoms, and a Paced Finger Tapping Task, which may be susceptible to EF variance. Here, we investigate the extent to which intrinsic rhythm generation is a predictor of EF. Furthermore, we compare the impact of varying the modality of the pacing cue from Auditory to Visual to Somatosensory on performance.

Results: Data from the Fast Finger Tapping Task demonstrate that tapping frequency and variance are strong predictors of motor impairment. Further analysis will determine whether the paced tapping data are predictive of EF tests, and if screening these data can improve motor symptom prediction. Furthermore, ANOVA analysis of the pacing modality data will provide insights into the role of underlying neural processing on cognitive and motor performance.

Conclusions: The sensitivity of automated assessment techniques is dependent upon the ability to control for cognitive variance. Results of this study will reveal if there are significant correlations between performance on traditional measures of EF and the computerised finger tapping task. Furthermore, differences in tapping performance across pacing modalities will offer an insight into preferential processing of cues in PD, which could inform future therapies.

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The Cats & Dogs Test: A web-based platform to detect early visual processing deficits in Parkinson's disease *R. Weil, B. Bahrami, D. Schwarzkopf, I. Pavisic, K. Pappa, R. Schade, H. Morris (London, United Kingdom)* **Objective:** To develop a sensitive web-based test to detect visuo-perceptual deficits in patients with Parkinson's disease as an early marker of dementia.

Background: Up to half of all patients with Parkinson's disease (PD) will develop dementia within ten years. Early detection of dementia will allow initiation of treatment and enrichment for clinical trials, but there are no robust clinical markers of early dementia. Converging evidence shows that patients with disease affecting visual processing brain regions are at highest risk of rapid dementia in PD. However current tests of visuo-perceptual function are poorly sensitive and non-quantitative. We present a sensitive and quantitative test of visuo-perceptual function for early detection of dementia in PD, based on identification of skewed images of cats and dogs that can be delivered via a web-based platform.

Methods: Participants accessed the online testing site that collected demographic and PD-specific information. Visual acuity was measured using an online psychometric procedure. Cat and dog stimuli were converted to grayscale, added to a proportion of visual noise and skewed along the x-axis, using an affine matrix transformation. 3 levels of skew were used, based on pilot testing. On each trial, participants indicated if the image they had seen was a cat or a dog by pressing one of two keys. Performance at each level of skew was compared using a repeated measures ANOVA. The test was validated in a face-to-face clinical cohort using approved scales (MDS-UPDRS, visual acuity, detailed neuropsychology).

Results: A total of 56 patients with PD and 283 people without PD accessed the online website. People younger than 40 were excluded, leaving a total of 247 age-matched controls. Patients with PD were worse at identifying skewed images than age-matched controls, F=3.71, p=0.025. Performance in the Cats and Dogs Test correlated with other cognitive measures in a face-to-face cohort without dementia (R2=0.33, p=0.00043) indicating that this is a robust measure.

Conclusions: Patients with PD were worse at the online Cats and Dogs test than age-matched controls. We propose that this new Cats and Dogs test may be useful to detect the earliest stages of dementia in PD. Its delivery within an online platform makes it a useful tool for collaboration.

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The Effects of Contingency-based Musical Gait Feedback on Cognition in Individuals with Parkinson's disease: An Interim Analysis

J. Burt, E. Ravid, S. Bradford, N. Fisher, Y. Zeng, B. Hu, R. Camicioli (Edmonton, AB, Canada) **Objective:** To investigate the effects of a 12-week home-based musical gait feedback program on cognition in persons with Parkinson's disease (PD).

Background: Individuals with PD can experience shortening of stride length. Previous research suggests automated feedback applications are an effective means of gait training and well-accepted by individuals with PD. In this study, we explored the effects of an iPod application that provides users with real time step-size feedback through music play. To our knowledge, this is the first time a comprehensive neuropsychological battery has been completed by PD patients completing gait training with musical cueing technology.

Methods: Twenty persons with PD (mean age 66.4 ± 8.9 , 12 males) were semi-randomized via sequential alternating enrollment into one of two training conditions. Group 1 participants (n=10, 5 males) received 12-weeks of gait training where music play was contingent on achieving a set step size. Group 2 participants received 6 weeks of passive music listening, where music played continuously regardless of step size, followed by 6 weeks of contingency-based training. Participants were instructed to use the iPod application a minimum of three times a

week for at least 15 minutes. Single-blinded assessments of global cognition (MoCA, MMSE), memory (HVLT), executive function (Stroop Color-Word Test, Trail Making Test Parts A & B), and attention and working memory (Attention Network Test, Digit Order Test) were completed at baseline, 6 weeks, and 12 weeks. **Results:** At baseline, no significant differences were present in group demographics (age, gender, education, Modified Hoehn and Yahr Stage, UPDRS Part III). Group 1 reported an average of 34 walks per participant (mean duration 26.35 minutes, mean distance 1.79 km). Group 2 participants completed 40 walks on average (20 per phase; mean duration 34.13 minutes, mean distance 2.35 km). Group 2 reported an improvement over time on the Beck Anxiety Inventory (p < 0.05). No significant changes were found in cognition, with no group differences. For walking results, see Table 1.

		Group 1			Group 2		
	All Weeks	Weeks 1-6 (Contingent)	Weeks 7-12 (Contingent)	All Weeks	Weeks 1-6 (Passive)	Weeks 7-12 (Contingent)	
Average Distance (km) 1.79		1.79	1.80	2.35	2.34	2.36	
Average Duration (min.)	26.35	26.10	26.72	34.13	35.65	32.60	
Average Speed (m/sec)	Average Speed 1.08 1.09		1.06	1.16	1.10	1.22	
Average Cadence (steps/min.)	108.2	107.7	108.8	112	110.3	113.71	
Average Step Size (m)	verage Step Size 0.60 0.60		0.59	0.63	0.60	0.65	

Table 1. Average results per walk by group and feedback phase.

Conclusions: Contingency-based musical gait enhancement is a feasible home exercise intervention for persons with PD. The optimal dose of exercise required for exercise-induced cognitive benefits in PD requires further investigation.

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Multimodal biomarkers as predictors of cognitive decline in Parkinson's disease

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Objective: To identify a set of multimodal biomarkers to predict cognitive decline in non-demented Parkinson's disease patients.

Background: People with Parkinson's disease are at high risk of developing cognitive impairment and dementia. Early identification of those at risk of developing dementia may help guide clinical decision making and inform research studies. Cross sectional studies have identified candidate biomarkers to inform predictive models of cognitive decline. Few longitudinal studies have evaluated the use of biomarkers to predict change in cognition over time, and even fewer investigate the use of biomarker panels encompassing multiple modalities.

Methods: We performed a prospective cohort study of 100 patients with a diagnosis of Parkinson's disease based on clinical examination. All participants were cognitively normal or had mild cognitive impairment (MCI) at baseline based on a consensus panel of physicians. Lumbar puncture, MRI and cognitive testing were performed at baseline and cognitive exams were performed at yearly intervals. We examined 17 biomarkers from clinical, genetic, biochemical, and MRI-based imaging modalities, investigating each marker's contribution to prediction of cognitive

decline individually, as well as developing a multimodal biomarker model to maximize predictive performance. The primary outcome was change in the Mattis Dementia Rating Scale-2 over time. The effect of APOE genotype on cognitive change over time was assessed for individual DRS subdomains.

Results: The best fit linear mixed-effects model determined the presence of *APOE* E4 allele, hallucinations and SPARE-AD score to predict longitudinal decline in dementia rating scale, with *APOE* genotype exerting the greatest effect. Indeed, in a Cox proportional hazards model, presence of the APOE E4 allele was associated with a 3.5 times higher risk of cognitive decline from normal to MCI or MCI to dementia (HR 3.53 95% CI 1.52-8.24, p<0.05) on an annual basis. This effect was not specific to any DRS subdomain.

Conclusions: These results confirm the importance of *APOE* genotype as a predictive biomarker in the development of cognitive impairment in Parkinson's disease and highlight similarities between Alzheimer's and Parkinson's disease pathogenesis.

This research has previously been presented the 18th Annual NINDS Udall Centers Meeting, 11/4/2016, Bethesda, MD.

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Predict cognitive decline with non-clinical markers in Parkinson's disease

T. Yousaf, G. Pagano, F. Niccolini, M. Politis (London, United Kingdom)

Objective: In this study, we investigated whether [123I] FP-CIT single photon emission computed tomography (SPECT) imaging measures and CSF marker profiles predict CI in PD patients and provide a simple characteristic profile of those most at risk of CI.

Background: Cognitive impairment (CI) is an increasingly recognised complication of Parkinson's disease (PD), with up to 80% of PD patients developing dementia during the course of the disease. Biomarkers provide a dynamic and powerful approach to understanding the spectrum of neurological disease with applications in observational and analytic epidemiology, randomized clinical trials, screening and diagnosis and prognosis.

Methods: 262 early-stage, *de novo* PD patients from the Parkinson's Progression Markers Initiative database were stratified into two CI groups: Level 1 diagnosis included PD patients who had a MoCA score <26; Level 2 diagnosis included PD patients with Level 1 diagnosis, who also subjectively stated having cognitive decline and at least 2 test scores (of HVLT Total Recall, HVLT Recognition Discrimination, Benton Judgement of Line Orientation, Letter Number Sequencing, Semantic Fluency Test and/or Symbol Digit Modalities; irrespective of test domain) greater than 1.5 standard deviation below the age and education-standardized mean score in healthy controls. Predictive variables of CI were divided into deciles, providing us with ideal cut-off values for each variable.

Results: At the three-year follow-up, 108/262 (41.2%) PD patients had CI as defined by Level 1, of which 40/108 (37.0%) had CI as defined by Level 2. CSF AB42 (Hazard ratio [HR]=0.996, Wald: 5.035, Confidence Interval [CI]: 0.992-0.999, P=0.025), CSF total tau ([HR]:1.023, Wald: 4.680, [CI]: 1.002-1.044, P=0.031) and caudate [1231]FP-CIT-SPECT uptake ([HR]:0.332, Wald: 4.146, [CI]: 0.115-0.960, P=0.042 were predictors of cognitive decline. Patients with reduced CSF AB42 (<384.6 pg/mL), increased CSF total tau (>45.0 pg/mL) and reduced caudate [1231]FP-CIT-SPECT uptake (<1.82) had a 65% risk of developing CI at a 3-year follow-up.

Conclusions: Here, we report a characteristic profile (reduced CSF AB42, increased CSF total tau and reduced caudate [123I]FP-CIT-SPECT uptake) that provides the ability of identifying early PD patients most at risk of developing CI, which can be used as a surrogate end-point of clinical progression, therefore aiding the efficiency of clinical trials performed in PD patients with CI.

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Sleep architecture in Parkinson's disease and Parkinson's disease associated dementia

L. Sousa, I. Laranjinha, J. Lopes, J. Ramalheira, A.M. da Silva, A.B. Lima, M. Magalhães (Porto, Portugal) **Objective:** To evaluate the differences in early sleep architecture between patients with Parkinson's disease (PD) and Parkinson's disease associated dementia (PDD).

Background: Disorders of sleep and wakefulness are a recognized manifestation of PD and are often present in a premotor phase. However, sleep architecture in PD and its relation to the development of dementia has not yet been thoroughly studied.

Methods: Patients were recruited from the movement disorders clinic of Centro Hospitalar do Porto, Portugal, as part of a longitudinal study on sleep in PD. All participants underwent baseline (drug-naïve) polysomnographic recording (PSG) and extensive clinical evaluation. The clinical diagnosis was reviewed. We then compared the

clinical and sleep data from PD versus PDD patients, using Mann-Whitney U-test or Chi-Square test when appropriate.

Results: We found 24 patients. Parkinsonism disappeared or was excluded in 3 patients. Out of the remaining 21, 8 were male and 13 were female. The final diagnosis was PD in 16 patients and PDD in 5, after a mean follow-up of 11 ± 6.45 years. The mean age of patients and mean disease duration at baseline PSG was 63.90 ± 9.02 years and 4.38 ± 8.38 years, respectively. No differences were found between baseline UPDRS, Hoehn and Yahr,

Northwestern University Disability Scale and MMS between both groups. There were no significant differences between arousals, sleep latency, REM latency and duration, duration of sleep in stages 1-2 and 3-4 and duration of NREM.

Conclusions: Our study failed to find differences in early sleep architecture between drug-naïve patients with PD versus PDD based on PSG variables analysis. The small sample size and different disease stages could account for these results.

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Quantifying reinforcement learning deficits in early stage Parkinson's patients using a strategic decisionmaking task

A. Parr, B. Coe, S. Murdison, G. Pari, D. Munoz (Kingston, ON, Canada)

Objective: 1.Characterize deficits in reinforcement learning processes in PD during a strategic game analogous to Rock-Paper-Scissors (RPS). 2.Examine the effects of dopaminergic (DA) treatment on learning rates during RPS. 3.Investigate whether dysfunction develops at the same rate across multiple motor systems.

Background: During RPS, each player's actions and associated outcomes change dynamically based on their opponent's actions. Optimizing strategies requires choosing among several actions, the likelihood of which is adjusted dynamically based on reinforcement information, a process involving corticostriatal networks. The dorsal striatum is thought to compute a reward prediction error¹, and patients with PD show decreases in prediction error signaling¹. DA medication alters learning rates in reinforcement learning tasks², potentially contributing to impulse control disorders.

Methods: PD patients (stage 1-3) and age-matched controls competed in a game of RPS against a computer opponent that exploited biases in choice patterns. Participants maximized reward by minimizing predictabilities in choice sequences (i.e., choosing stochastically). Choices were indicated with either a saccade or a button press. Both groups completed 2 sessions; patients both on- and off- medication. Reinforcement learning processes and predictabilities in choice sequences were examined using logistic regression modelling, and behavior was correlated with neurocognitive scores including the Baratt Impulsiveness Scale and MoCA.

Results: Patients were impaired in choosing optimally during the RPS, particularly in the saccade condition. Patients were more variable, exhibited more predictabilities in choice patterns, and had lower reward rates compared with controls in the saccade condition. These results were exacerbated by DA medication. Patients performed better during the button-press than saccade trials in most aspects of RPS, suggesting greater dysfunction within the oculomotor loop through the basal ganglia.

Conclusions: We propose a new tool to investigate reinforcement learning in PD, which could lead to novel insights into optimizing treatment protocols and maximizing cognitive function. Further investigation into individual differences in the PD group could provide insight into the traits that predispose certain patients to impulse control disorders.

Preliminary data presented at the 2016 MDS Congress, June, 2016

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Action Verb Generation as a marker of cognitive function in Parkinson's disease

O. Yerokhin, K. Smith (Worcester, MA, USA)

Objective: We investigated action-verb generation in relation to cognitive function and motor severity in patients with Parkinson's disease (PD).

Background: PD causes speech and language impairments, with defects in syntax, grammar and verb formulation. Action verb production may be particularly impaired and may reflect both motor and cognitive pathways. We evaluated action verb processing with a novel approach, through pauses before action verbs in semi-structured speech. We hypothesized that the duration of pauses before action verbs would be prolonged when compared with pauses before non-action verbs in PD and that action verb generation would be associated with cognitive function.

Methods: Digital recordings of non-demented PD (n=52) and healthy elderly controls (HC, n=28) participants describing the cookie theft picture or an alternative scene were analyzed with Praat software. Global cognition was assessed with MoCA. Pauses >1 second before action and non-action verbs were measured. Linguistic variables were compared in PD and HC groups with Mann-Whitney U test, then entered into a multivariate linear regression model, with dependent variable MoCA, controlling for age and motor severity.

Results: In the PD group, the mean number of action verbs used was 13.6 (SD 5.73), the number of pauses before action verbs was 0.36 (SD 0.72). There were no significant differences in pauses before action verbs or non-action verbs overall in PD compared to HC. However, PD patients generated fewer verbs relative to nouns when compared to HC (ratio of total nouns/total verbs (PD vs. HC) p=0.03). Global cognition was significantly correlated with total action verbs (r=0.40, p= 0.01), non-action verbs (r=0.46, p<0.01), and total nouns (r=0.33, p=0.02), though these associations were no longer significant in the multivariate model controlled for age and motor severity.

Conclusions: Non-demented PD patients displayed subtle deficits in verb generation in semi-structured spontaneous speech. Verb and noun generation correlated with global cognition. Our results support the further study of linguistic markers in PD, but pauses before action verbs will require further investigation to determine associations with motor and cognitive function in PD and with disease progression.

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Global inhibitory control in PD is impaired ON dopaminergic medication but not ON STN-DBS

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Objective: The aim of our study is to obtain a better understanding of how DA and STN-DBS modulate basal ganglia (BG) pathway functions.

Background: Patients with Parkinson's disease (PD) show a variety of neuropsychiatric symptoms that are relevant in terms of prognosis and quality of life. Increased impulsivity has been observed under dopamine (DA) and deep brain stimulation (DBS) of the subthalamic nucleus (STN) and can lead to serious adverse events (1). Little is known though about the effects of DA and STN-DBS on global versus specific Nogo decisions which are thought to reflect the involvement of different BG pathways (2,3).

Methods: Methods: 23 medically treated PD patients (age $62.0y \pm 10.5y$, disease duration $5.9y \pm 4.4y$) and 20 with STN-DBS (age $64.1y \pm 7.6y$, disease duration $13.6y \pm 4.9y$) underwent motor and cognitive examination ON and OFF DA or DBS respectively. We applied a novel Go-Nogo paradigm with four conditions: a global and specific Go condition as well as a global and specific Nogo condition and a specific Nogo condition. Mean reaction times and error rates were calculated for each condition and compared using Wilcoxon signed-rank tests.

Results: The DBS cohort showed more advanced disease than the medically treated cohort. Medically treated patients made more errors during ON as compared to OFF in the global Nogo (ON $3.8\% \pm 4.7\%$ and OFF $2.3\% \pm 4.9\%$; Z=-2,166, p=0.030) but not in the other conditions. Global Nogo errors during ON correlated with daily intake of DA (Spearman's rho=0.427, p=0.042). Reaction times of global Nogo errors were significantly faster ON medication (ON: $563s \pm 178s$ versus OFF: $638s \pm 215s$; t(22)=2.214, p=0.038). Patients ON STN-DBS were significantly faster compared to OFF STN-DBS in the global Go condition (ON 711msec $\pm 208msec$, OFF 778msec $\pm 243msec$; Z=-3.285, p=0.001) without making more errors in any of the conditions.

Conclusions: Better insights in non-motor side effects are crucial for the appropriate selection of individual therapeutic strategies in PD. We show that DA seems to specifically worsen global inhibition, whereas in our cohort STN-DBS had no influence on neither specific nor global inhibitory processes as measured with our new paradigm. Our data suggest a differential effect of the two therapeutic strategies DA and STN-DBS on inhibitory control.

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Variation in Longevity Gene KLOTHO Associates with Measures of Resilience against Parkinson's Disease *N. Luthra, J. Ostrem, D. Dubal (San Francisco, CA, USA)*

Objective: We investigated whether carrying one copy of the protective haplotype "KL-VS" of the longevity gene *KLOTHO* is associated with better cognitive functioning and/or attenuated CSF biomarker changes in Parkinson's disease (PD).

Background: Cognitive impairment from PD poses a major challenge for which we have no effective medical treatments. Identifying genetic variations associated with brain resilience could help elucidate mechanisms that counter PD. Klotho is a pleiotropic protein. At higher levels, klotho extends lifespan, enhances cognition, and counters neurodegenerative disease-related toxicities in model organisms. In humans, KL-VS heterozygosity associates with increased klotho levels, longevity, and better executive cognition in normal aging. In this study, we investigated whether KL-VS heterozygosity associates with resilience in PD.

Methods: The Parkinson's Progression Markers Initiative (PPMI) study is an ongoing longitudinal study in patients with newly diagnosed PD and matched healthy controls (HC). Data used in the preparation of this abstract was obtained from the PPMI database (www.ppmi-info.org/data). We evaluated KL-VS heterozygous frequencies, baseline cognitive function, and CSF biomarker levels in HC and PD subjects, based on KL-VS status.

Results: The frequency of KL-VS non-carriers and heterozygotes was similar between HC and PD subjects. In PD, KL-VS heterozygotes showed better baseline semantic and phonemic fluency compared to non-carriers, among a myriad of tests. As anticipated, CSF a-synuclein levels were lower in all PD compared to HC subjects. However, in KL-VS heterozygotes above age 50, CSF a-synuclein was unchanged between HC and PD; in contrast, non-carriers showed decreased a-synuclein levels in PD compared to HC. We are further evaluating effects of age and time on KL-VS associations.

Conclusions: We found that KL-VS heterozygosity was associated with (1) better cognitive performance in specific domains and (2) attenuation in the decrease in CSF a-synuclein in PD patients. These findings suggest a role for klotho in conferring resilience against PD and may open new therapeutic pathways.

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Implicit memory analysis in patients with Parkinson's Disease with Deep Brain Stimulation, in ON and OFF stages, using a computerized test battery

E. Barbosa, H. Charchat-Fichman, J. Santos (Rio de Janeiro, Brazil)

Objective: This study aims to analyze the DBS effects on the PD patients implicit learning.

Background: PD is considered the second more common neurodegenerative disease and initially, it was believed that cognition was preserved in PD, but current research brings data showing deficits in this aspect. Implicit learning is one of them and it refers to the casual or not, sometimes seemingly small, acquisition of a given event, but that can generate significant future consequences. In addition to the drug and therapeutics treatment, there is a subcortical structures electrical stimulation - DBS.

Methods: It was chosen 4 patients with a PD diagnosis and DBS. They were evaluated at two different times: first with the stimulation turned on (ON stage) and then turned off (OFF stage). For this analysis, it was chosen the Implicit Learning Test in CompCog: it works with the apparition of white squares on the screen and the patient is instructed to touch them, following the sequence presented - four fixed sequences and one random. We considered two variables: the difference in milliseconds between the first and fourth sequence and the difference in milliseconds between the fourth and fifth sequence for each patient.

Results: The sample had a mean of 61.75 years (\pm 6.85) and 11.33 years (\pm 1.53) of schooling. It was observed, at ON stage, that there was expected behavior of reaction time decrease between the sequence 1 and 4. Among these four patients, 3 had no time difference between the sequence 4 and 5 and, at OFF stage, that 3 patients did not present the expected behavior of reaction time decreasing between the sequence 1 and 4. Regarding the time difference between the sequence 4 and 5, 2 did not present, 1 had a decrease and 1 had an increase [figure 1] [figure 2] [figure 3] [figure 4].





Conclusions: In this small sample, the effect of implicit learning with DBS activated in the evaluated patients was observed, influencing even an improvement when the performance was expected to increase the reaction time. This effect was not observed with the DBS switched off. The next steps of the study are to assess more patients to see if this effect extends to other patients with PD and DBS, besides to evaluate, with a computerized test battery, the performance of several other cognitive functions and to establish relationships between the use of the device and cognitive functioning.

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Cognition in the PREDICT-PD Cohort

A. Nagy, E. Hardaker, J. Bestwick, G. Giovannoni, T. Warner, A. Lees, A. Schrag, A. Noyce (London, United Kingdom)

Objective: To identify whether there is evidence for cognitive dysfunction in participants identified as being at higher risk of Parkinson's disease (PD) using the PREDICT-PD algorithm.

Background: The prodromal phase of PD includes non-motor as well as motor symptoms; cognitive dysfunction is found at higher rates 2 years before diagnosis in PD cases compared to controls[1]. The PREDICT-PD study uses online assessment of multiple risk factors to estimate participants' risk of future PD and stratify into higher (highest 15%), intermediate and lower (lowest 15%) risk groups. The higher risk group show an increased rate of motor disturbance[2], increased frequency of markers associated with PD (smell loss, sleep disturbance and slowed finger tapping), and increased incidence of PD diagnosis during follow-up. Cognition in the cohort has been tested online and in-person.

Methods: Screening questions covering memory and executive function were included in the year 2 PREDICT-PD online survey; both domains were scored out of 10 giving a total score out of 20. Selected participants were additionally assessed in-person using the Montreal Cognitive Assessment (MOCA). 175 participants were included in the analysis (64 higher-risk and 111 lower or intermediate-risk). Online cognitive screening scores were validated against MOCA scores. Higher and lower-risk groups were compared using both scores. Finally, the relationship between cognitive scores and risk score was analysed with linear regression used to adjust for confounders. **Results:** Median cognitive screening score was 16 (interquartile range 15-18). Screening score significantly positively correlated with MOCA score (r = 0.25; p=0.001). The higher-risk group had slightly but significantly lower MOCA and screening scores than the lower-risk group (27 vs 28, p=0.01; 15 vs 17, p<0.0001). MOCA and screening score increased as PD risk decreased (r = 0.19, p=0.01; r = 0.23, p=0.003). After adjustment for vascular risk factors ischaemic heart disease, hypertension, hypercholesterolaemia and diabetes, risk score still significantly contributed to variation in MOCA score (p=0.004).

Conclusions: These results are suggestive of early, subtle cognitive dysfunction in the PREDICT-PD higher-risk group and show poorer cognitive function may be associated with increased risk of PD. Further work to characterise the profile of cognitive dysfunction and define sensitive measures for cognition in this group may prove useful in risk profiling for PD.

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Do Acetylcholinesterase Inhibitors (AChEI) delay institutionalisation in Parkinson's and Lewy Body Disease? L. Brown, B. Mohamed, E. Thomas (Cardiff, United Kingdom)

Objective: We explored the use of cholinesterase unhibitors in Parkinson's and Lewy body dementia through assessment of quantitative data obtained from a clinical database. We focussed on tolerability, duration of usage and standard of documentation.

Background: People with Parkinson's (PwP) have a six-fold increased likelihood of developing dementia when compared to healthy age-matched controls (Aarsland *et al.* 2001). Increased cerebral deposition of alpha synuclein has been associated with dementia with Parkinson's (Kurtz and Kaufer 2011). Cholinesterase unhibitors is the first-line treatment recommended in the UK

Methods: We audited the use of cholinesterase unhibitors via our clinical database in a University hospital Parkinson's clinic in South Wales. We assessed 163 patients for parameters including age, gender, diagnoses, date of diagnoses, initiation date of Cholinesterase unhibitors, drug dose, date of termination of cholinesterase unhibitors (where applicable), adverse effects reported and present residence.

Results: Of the 163 patients evaluated, 109 were male. Adverse effects to cholinesterase unhibitors were reported in 5.5% of patients, however the exact nature of these adverse effects was not described. At the time of audit, most patients (60.1%) were resident in their own homes. 52.1% were found to have unknown initiation dates for cholinesterase unhibitors. The average duration of use was 37.9 months

Conclusions: The retrospective nature of this review precluded further exploration of data due to incomplete documentation and is an area to focus on. There appears to be a significant proportion of people with dementia on cholinesterase unhibitors who are still resident in their own home and not reliant on institutional care. The authors conclude that AChEI may be contributing to delaying institutionalisation by positively impacting on behavioural and psychological problems associated with dementia. This aspect needs to be explored further. Cholinesterase unhibitors appears to be well tolerated in this frail cohort.

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Action Verbal Fluency is Related to the Functional Integrity of the Cognitive Cortico-Striatal Loop in Parkinson's Disease

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Objective: The objective of this study is to investigate the relationship between action verbal fluency (the capacity to name as many action words as possible in a given period of time) and executive functions using task-based fMRI. **Background:** Patients with Parkinson's disease (PD) present verbal fluency impairments even in the absence of dementia. These impairments are related to executive deficits [1]. Studies also show that PD patients present a disadvantage for the processing of words with a rich semantic motor content, such as action words, compared to other types of words. For these reasons, action verbal fluency would be particularly demanding for PD patients and would constitute a sensitive measure of cognitive deficit in PD. However, action verbal fluency's dependency on the cognitive fronto-striatal regions involved in executive processes still need to be clarified.

Methods: 15 non-demented patients with idiopathic PD and 15 controls without PD matched for age, education and global cognition were recruited for this study. They completed a full neuropsychological battery, including action verbal fluency. Participants also performed a modified version of the Wisconsin Card Sorting Task (WCST) [2] during three 8 min. task-based T2*BOLD fMRI sessions acquired on a 3T GE MRI scanner. The WCST is a card-sorting task that requires shifting between rules. It was shown to be associated with fronto-striatal activation. fMRI data pre-processing and GLM analysis was done in FSL.

Results: PD patients had a significantly lower performance than controls on the action verbal fluency task. There was a significant positive correlation between action verbal fluency and the performance on the WCST when all participants were included in the analysis. In the PD group, the performance in action verbal fluency was significantly correlated with regions usually associated with the planning of a set-shift, such as the anterior cingulate gyrus, ventrolateral pre-frontal cortex (PFC), dorsolateral PFC and caudate nucleus [2]. These correlations were not observed in the control group.

Conclusions: The results provide evidence that in PD, action verbal fluency is strongly reliant on executive processes. Furthermore, it indicates that action verbal fluency performance is dependent on the functional integrity of the cognitive cortico-striatal loop in PD.

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IGF-1 levels are associated with CSF pathology and executive dysfunction in de novo Parkinson's disease patients

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Objective: To investigate whether serum insulin-like growth factor-1 (IGF-1) is associated with clinicalneuropsychiatric, imaging and CSF markers of PD pathology in patients with early, drug-naïve Parkinson's disease (PD).

Background: IGF-1 has been shown to harbor an important role for plasticity, neuronal survival and differentiation within the nervous system. IGF-1 has been linked with an increased risk of developing dementia in middle-aged population.

Methods: Using the Parkinson's Progression Markers Initiative database, a total of 388 participants were identified and included in this study. Serum IGF-1 was measured for all participants included in the study. The relationship between serum IGF-1 levels and clinical scales, neuropsychological battery, and imaging and non-imaging markers of PD pathology was evaluated.

Results: Lower IGF-1 serum levels were correlated with older age (r=-0.20, P<0.001), higher CSF tau levels (r=-0.24, P<0.001), worse Benton Judgment of Line Orientation test scores (r=0.12, P<0.05) and worse Symbol Digit Modalities Scores (r=0.17, P<0.001). No associations were found between serum IGF-1 and other clinical (e.g. UPDRS-III) and non-clinical biomarkers (e.g. DAT uptake).

Conclusions: Our findings demonstrate that lower IGF-1 levels are associated with an increased burden of CSF tau pathology and executive dysfunction in de novo PD patients and suggest a potential pathway which may contribute to cognitive impairment early in PD.

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Prediction of cognitive progression in Parkinson's disease using three cognitive screening measures

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Objective: To assess the utility of commonly used cognitive screening tools in predicting the transition to mild cognitive impairment (MCI) and/or dementia (PDD) in Parkinson's disease (PD).

Background: Much research has been dedicated to cognitive impairment frequently associated with PD. Prior studies have compared the sensitivities of commonly used screening tools for identification of cognitive impairment in PD, but little research has been done regarding the utility of these tools in predicting cognitive progression.

Methods: We retrospectively reviewed data collected from 489 patients with UKBB-defined PD enrolled in the Pacific Udall Center. At the time of enrollment, a full neuropsychological assessment was completed, as well as three cognitive screening measures: Mini Mental Status Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Mattis Dementia Rating Scale (DRS). Diagnosis of motor and cognitive status, including PD-MCI or PDD, was made via clinical diagnostic consensus. Three-hundred eleven initially non-demented participants completed at least one follow up visit (average follow up = 2.7 years). Baseline sensitivity and specificity for the three screening measures were determined using standard cutoff scores. To assess the relationship between the cognitive screening measures and subsequent progression of cognitive symptoms, separate logistic regression models were performed for conversion from no cognitive impairment to PD-MCI, and from PD-MCI to PDD. Results: At baseline, of the three screening tests, the MoCA demonstrated the highest sensitivity for both MCI (67.3% vs. 25.9% for the DRS and 6.2% for the MMSE) and PDD (85.1% vs. 55.4% for the DRS and 20.2% for the MMSE). After controlling for demographic and clinical factors, none of the screening measures were associated with conversion from no cognitive impairment to PD-MCI. However, poorer baseline MoCA performance was significantly associated with conversion from MCI to PDD (OR = 1.23, SE = 0.11, CI 1.03-1.48, p=0.019). **Conclusions:** Of the three screening tools, the MoCA was the most sensitive for identifying baseline cognitive impairment, and lower initial performance on the MoCA was associated with subsequent conversion from PD-MCI to PDD. This study provides additional support for the use of the MoCA as a primary screening tool for cognitive impairment and prediction of conversion to dementia in patients with PD.

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Fluency boost from walking in Parkinson's disease

O. Barthelemy, R. Salazar, S. Neargarder, J. DeGutis, T. Ellis, A. Cronin-Golomb (Boston, MA, USA) **Objective:** Examine the impact of a motor task on verbal fluency in individuals with Parkinson's disease (PD). **Background:** Dual-tasking, in which individuals engage simultaneously in motor and cognitive tasks, has long been known to impair motor performance in PD; recent evidence indicates that it also impairs cognition (set-shifting). In healthy adults without PD, motor activity can *improve* performance on tasks of ideational fluency. Performance on phonemic verbal fluency (VF), an executive-function task widely used in clinical evaluation and in research studies of PD, is correlated with ideational fluency in healthy young adults and in those with focal frontal-lobe lesions. VF may likewise be enhanced by motor activity, perhaps even in PD, in which both motor and executive functions are impaired.

Methods: Non-demented individuals with mild-moderate idiopathic PD (n=18, 10 men, mean age 64 [SD=10]) performed the Timed Up and Go (TUG), a brief motor task that taxes both motor and executive function. The order was single-task TUG; cognitive/motor dual-task VF/TUG; single-task VF. VF was measured in words per second (wps), calculated for single-task VF for the time the participant needed to complete the dual-task condition. Proportionate words per second (pwps) measured dual-task impact as a percentage of single-task VF. We also examined correlations between the dual-task effect and disease severity: Hoehn & Yahr stage and United Parkinson's Disease Rating Scale (UPDRS) total score.

Results: Mean wps was higher for dual-task than single-task VF (t=3.5, p=.003). The size of this dual-task benefit inversely correlated with UPDRS total score (?=-.50, p=.03). Mean pwps also showed an advantage for dual-task VF (t=3.7, p=.002) and an inverse correlation with UPDRS total score (?=-.47, p=.05).

Conclusions: Individuals with PD may perform *better* on verbal fluency when it is performed simultaneously with a motor task. A potential explanation is the reported premotor-parietal hyperconnectivity in PD that is associated with fewer motor difficulties during dual-tasking. In mild PD, this presumably compensatory connectivity may facilitate prefrontal-parietal arousal and central executive network processing, leading to improved function or regulation of attention or fluency. In later stages of PD, this compensation may decline or be insufficient to aid fluency when basal ganglia dysfunction worsens.

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White matter microstructural damage as predictor of cognitive decline in Parkinson's disease

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Objective: To investigate patterns of cortical and white matter (WM) changes associated with progression to mild cognitive impairment (MCI) or dementia in patients with Parkinson's disease (PD).

Background: Many people with PD will eventually develop cognitive impairment as the disease progresses. Multimodal magnetic resonance imaging (MRI) might contribute predicting cognitive decline in PD. **Methods:** We enrolled 84 PD patients and 41 healthy controls. At study entry, all subjects underwent clinical and cognitive evaluations, and MRI including 3D T1-weighted and diffusion tensor imaging (DTI). Patients were followed clinically and neuropsychologically for 2 years and classified as cognitive progressors (from normal cognition to MCI, or from MCI to dementia) or non-progressors (stable cognition over two years). Measures of cortical thickness and WM tract microstructure were obtained by surface-based morphometry and probabilistic tractography, respectively.

Results: Thirty-one patients were classified as cognitive progressors. Compared with controls, both groups did not show cortical thinning, non-progressors showed microstructural changes in the cerebellar peduncles, while progressors had alterations in corpus callosum, cingulum, corticospinal and peduncolopontine tracts. Progressors did not show significant cortical thinning compared to non-progressors. Conversely, they demonstrated reduced fractional anisotropy of the body of the corpus callosum, right inferior longitudinal fasciculus (ILF), bilateral middle cerebellar and superior cerebellar peduncles (SCP) bilaterally, and right uncinate fasciculus, and increased mean diffusivity of the genu of the corpus callosum, cingulum, ILF, corticospinal tract, SCP bilaterally, as well as left superior longitudinal fasciculus and right uncinate fasciculus.

Conclusions: Our results suggest that the presence of microstructural white matter alterations at baseline may be associated with the development or worsening of cognitive deficits in PD patients over two years. DTI offers new tools to identify PD patients at-risk for cognitive impairment.

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Influences of Gender, Depression and Disease Severity on Moca Subscores in Parksinon's Disease

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Objective: We studied the causal relations between various external factors and MoCA subscores using Bayesian networks.

Background: The MoCA is a standard screening test for cognitive impairment in PD. However, MoCA scores are usually assessed in isolation, without consideration of the influences of other factors such as gender, depression and/or disease severity.

Methods: We pooled data from the Parkinson's Progression Markers Initiative (PPMI, n = 830) and the Pacific Parkinson's Research Centre (PPRC, n = 529) as the PPMI data mostly had patients with mild disease. We included all Parkinson's disease patients who were assessed with a MoCA (Montreal cognitive assessment), and depression rating scale (Beck's depression inventory or Geriatric Depression Scales). Patients who were on medications for dementia (acetylcholinesterase inhibitors or memantine) when the cognitive assessment were excluded as this may independently influence the total MoCA score. Other demographic variables (including gender, age, years of education), MoCA test subscores, and PD related features such as age of onset and LEDD were obtained. The demographic factores and MoCA subscores resulted in 16 variables and directed (causal) probabilistic relations were determined between variables using a Bayesian Network approach.

Results: A Bayesian network was obtained based on the pooled data (Fig-1). Gender, independent of other factors, had an influence on LEDD, as well as orientation and abstraction sub-scores. LEDD had independent effect on orientation, while BDI/GDS affected verbal fluency.



Conclusions: Based on > 1300 subjects, we found a significant impact of gender on orientation and abstraction, possibly due to hormonal influences. Presumably the gender influences on LEDD are a result of the reduced body mass in females. Depression, as indexed by the BDI/GDS, had the greatest impact on verbal fluency. Interestingly, depression influenced age of onset, implying that depression may represent an independent risk factor for development of PD. LEDD had a significant impact on orientation, consistent previous reports of L-dopa effects on working memory. Our results suggest that MoCA scores may need to be considered in the context of gender, depression and medication status.

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Effects of education level on motor and non-motor symptoms of Brazilian patients with Parkinson's disease

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Objective: To investigate the influence of education level (EL) on motor and non-motor aspects of Parkinson's disease (PD) in a Brazilian sample.

Background: Only 30% of older adults (above 60 years) in Brazil have secondary or higher education. EL has been suggested to influence motor symptoms and cognition in patients with PD. Those with low EL show worse symptoms and are more likely to develop mild cognitive impairment and dementia. However, this topic has been little explored in Brazilian sample.

Methods: Ninety-seven individuals with idiopathic PD were distributed into two groups according to their EL: low EL group (= 6 years of education, n = 50) and high EL group (> 6 years of education, n = 47). Participants self-reported how many years of formal education they had during life. Participants were assessed in relation to disease severity (UPDRS I, II, III and total score, and H&Y), global cognition (Mini-Mental), working memory (Weschler forward and backward Digit Span), visuospatial ability (Clox 1), attention (Weschler Symbol Search), executive function (Wisconsin Card Sorting Test and Clox 2), anxiety and depression (Hospital Anxiety and Depression Scale) and stress (Stress Symptoms Inventory- Lipp). Groups were compared using Mann Whitney-test and significance level was set as p<0.05.

Results: Groups were similar for age (p=0.295) and disease duration (p=0.084). Significant between groups differences were observed for UPDRS II (p=0.015), UPDRS III (p=0.027), UPDRS total score (p=0.022), H&Y (p=0.008), attention (p=0.004), working memory (backward digit spam, p=0.001), visuospatial ability (p=0.001) and executive function (Clox 2, p<0.001). The low EL group showed worse score than the high EL group for all these variables.

Conclusions: These results suggest that the EL has an important impact on motor and non-motor aspects of patients with PD. Since groups were paired for age and disease duration, current findings suggest that patients with low EL had a faster disease progression and a more evident decline in cognition than patients with higher EL. A possible

explanation is that higher EL may offer/build greater motor and cognitive reserves. Thus, this fact should be considered during the design of interventions to assist the Brazilian population with PD.

1011

Depression and Cognitive Performance In Patients With Parkinson's Disease

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Objective: The aim of this study was to assess the relationship between depression on cognitive performance in Parkinson's disease patients.

Background: There are very few studies in India to understand cognitive functions in Parkinson's disease (PD). This study gives an insight into the effect of Parkinson's disease on cognitive functions.

Methods: Twenty four Parkinson's patients were included in the study, and the subjects were set up by a median split of the scores obtained on the Centre for Epidemiological Studies – Depression Scale (CES-D).For high depression number of patients was 12 and for low depression it was 12. The PD subjects' age range was from 45 years to 82 years. Majority of the PD subjects were right handed. The subjects' education ranged from 4rd grade to Masters degree. Twelve subjects had high depression with a mean age of 66.17 years; 12 had low depression with a mean age of 64.23 years. The NIMHANS Neuropsychological Battery was employed. Scores were compared with age, education and gender specific norms, where scores falling below the 15th percentile of the normative data were treated as deficits. Mean, SD and t-test were used to analyse the data.

Results: The study inferred that patients on the whole did not show significant difference except for Finger Tapping Test. Individual analysis shows that cognitive impairment amongst the PD subjects is highest in Auditory Verbal Learning & Memory, the total of which is 79%, Finger tapping – Right Hand score is 75%, Left Hand score is 75%, AVLT Immediate Recall score is 67%, AVLT – DR score is 58%, ROCFT Copy score is 54%, Logical Memory IR score is 37% and ROCFT DR score is 37%. Overall, 67% of PD subjects had depressive symptoms. **Conclusions:** Parkinson's Disease subjects' cognitive impairments are observed more in motor speed, verbal & visual memory and visuo-constructive ability.

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TMEM230 mutation analysis in Parkinson's disease in a Chinese population

Z. Liu (Changsha, People's Republic of China)

Objective: To investigate the prevalence of *TMEM230* mutations in Chinese patients with familial and sporadic PD. **Background:** Recently, Hanxiang Deng and colleagues identified a missense variant (c.422G>T; p.Arg141Leu) in the *TMEM230* gene in a large North American family of northern European ancestry with PD through the use of linkage and a combination of whole-exome sequencing. Three other *TMEM230* mutations, including c.551A>G (p.*184Trpext*5), c.275A>G (p.Tyr92Cys), and c.550_552delTAGinsCCCGGG (p.*184ProGlyext*5), were identified in other PD cases. Moreover, the mutation of p.*184ProGlyext*5 was also shown to be the most common mutation of *TMEM230* in Chinese familial PD (Deng, et al., 2016). However, the association between *TMEM230* mutation and PD has not been confirmed in a larger Chinese population.

Methods: We sequenced all exons and exon-intron boundaries of TMEM230 in Chinese Han population including 192 patients with a family history of PD, 1043 cases of sporadic PD and 1252 age and sex matched healthy control subjects. The polymerase chain reaction (PCR) product was sequenced with BigDye terminator v3.1 sequencing chemistry on an ABI 3730xl DNA analyzer (Applied Biosystems) and analyzed using Sequencher software.We used SPSS 20.0 software (SPSS Inc, Armonk, NY, USA) to perform all statistical analyses. The Hardy-Weinberg equilibrium for genotype frequency in PD cases and control subjects was examined, and Fisher's exact test was used to test for association between the variants in *TMEM230* gene and PD risk.

Results: Upon sequencing the boundaries of the exon–intron and entire coding regions in *TMEM230* in 192 probands of PD families, 1043 cases of sporadic PD and 1252 healthy subjects, we did not detect any mutation in *TMEM230*. However, a synonymous variant c.357G>A p.Gly119Gly was identified in a case of familial PD exhibited autosomal-recessive inheritance, and this variant had been reported in the Exome Aggregation Consortium (ExAC, <u>http://exac.broadinstitute.org/variant/20-5086888-G-A</u>) database with a frequency of 0.002% (3/121348). Sequencing and co-segregation analysis were performed using all other samples from this family, but another affected individual from this family didn't carried the c.357G>A p.Gly119Gly variant. Moreover, we found the variant 3' UTR+3G>T in two unrelated individuals in our sporadic PD group. There were no statistically significant differences in genotypic distribution between PD (familial PD and sporadic PD) and health controls for these two variants in *TMEM230* gene (Table 2).

Table 1

Variables	PD(N = 1235)	HC(n = 1252)
Sex, male/female (%)	631/604	636/616
Family history, positive/negative	192/1043	_
Mean age at onset (y)	51.92 ± 11.41	-
Mean age at examination (y)	56.57 ± 10.23	55.8 ± 12.04
Disease duration (y)	5.08 ± 3.32	-
Average Hoen and Yahr stage at assessment	2.24 ± 1.21	<u> </u>

Key: HC, health controls; PD, Parkinson's disease.

Variants identified in TMEM230 in our study

Chromosomal position(Hg 19)	Variant		Number of carrying variants			1000 genomes	ExAC	PD versus control ^o ;
	CONA	Aminoacid	Familial PD (n = 192)	Sporadic PD (n = 1043)	Controls (n = 1252)			p-value ⁿ
Chr20:5106242	c.357G>A	p.Gly119Gly	1	0	0	ND	0.002%	0.315
Chr20:5100788	c.552+3G>T	3" UTR	0	2	0	ND	ND	0.154

Key: cDNA, complementary DNA: ExAC, The Exome Aggregation Consortium (http://exac.broadinstitute.org); ND, no data were found in database; PD, Parkinson's disease; UTR, untranslated region.

* All cases with PD (familial PD and sporadic PD) and control subjects.

^b p-value was determined using Fisher's exact test.

Conclusions: We did detect a synonymous variant c.357G>A p.Gly119Gly in a case of familial PD and the 3' UTR+3G>T variant in two sporadic PD patients. These results suggested that *TMEM230* mutation may not be a common genetic factor for Chinese familial and sporadic PD patients.

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Assessing the response to L-dopa/carbidopa intestinal gel infusion based on genetic status

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Objective: To asses genetic impact on dosage of L-dopa/carbidopa treatment

Background: L-dopa/carbidopa intestinal gel infusion (LCIG) is a method of continuous dopaminergic stimulation used in patients in advanced stages of Parkinson's disease (PD) in order to reduce dyskinesia and off phenomenon. Personalized medicine which takes into account among other things, genetic information is gaining ground. Ashkenazi Jews (AJ) constitute a unique population to start implementing such genetic based personalized approach in PD since more than one third of AJ PD patients have a known mutation in either the *GBA* (8 mutations) or the *LRRK2* (G2019S) genes. The aim of this study was to compare the response to LCIG among PD patients based on their carrier status with the hypothesis, that *LRRK2* carriers would demonstrate a milder form of disease. **Methods:** 44 PD patients underwent LCIG in the movement disorder unit of the Tel-Aviv Sourasky Medical Center since 2009. Genetic (*GBA*, *LRRK2*), demographic (age, gender) and clinical data (disease duration, list of medications, presence of hallucinations, dyskinesia, dementia, Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr, Scwab and England) was collected through medical records. Levo-dopa equivalent dosage (LEDD) was calculated as customary.

Results: The average age was 69.5, average LEDD was 1739.9, 9/29 patients were female Genetic data was available on 29/44 patients. Seventeen patients did not carry any mutation; age 69.7 (10.2) LEDD 1849 (886). 5 were *LRRK2* carriers; age 70.0 (16.1), LEDD 1382 (336), 4 were *GBA* heterozygotes; age 65.0 (7.2) LEDD 1864 (620), 2 were *GBA* homozygotes while another was a carrier of both *GBA* and *LRRK2*. No significant differences were found between the groups

Conclusions: A personalized approach to the treatment of PD is in the making; however, we currently could not detect any between group differences among these three study groups we believe that this is mainly due to the underpowered nature of this study.

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Genotype-phenotype correlations in Parkinson's disease patients who carry mutations in the GBA gene

A. Thaler, T. Gurevich, A. Ezra, M. Kestenbaum, N. Giladi, A. Mirelman (Tel Aviv, Israel) **Objective:** To assess genotype-phenotype relationship between mild and severe GBA mutation carriers among patients with Parkinson's disease **Background:** Mutations in the Glucocerebrocidase gene (GBA) are a well-established risk factor for Parkinson's disease (PD). GBA-associated PD (GBA-PD) seems to have a more severe clinical phenotype than idiopathic PD. However, differences in clinical manifestation between patients who carry severe and mild mutations in the GBA gene have yet to be reported.

Methods: We assessed motor, cognitive, olfactory and autonomic functions in a cohort of Ashkenazi Jewish PD patients who were screened for seven common mutations in the *GBA* gene. Differences in clinical manifestation were compared between patients with no known mutations (iPD), patients with mild *GBA* heterozygote PD (m*GBA*-PD), severe GBA heterozygote PD (s*GBA*-PD) and patients with PD, homozygote or compound hetrozygotes GBA carriers (GD-PD).

Results: 149 iPD, 139 m*GBA*-PD, 39 s*GBA*-PD and 25 GD-PD participated in the study. Worst motor and cognitive performance, olfaction and depression were related to GBA mutations (p<0.03). Even when adjusted to disease duration, performance deteriorated based on mutation with worst performance observed in the GD-PD group followed by the sGBA-PD and mGBA-PD. Severity of mutation was also associated with more dyskinesias (p=0.02), hallucinations (p<0.001) and higher intake of dopaminergic medications (p<0.001). When analysis was adjusted for medication intake, GD-PD and sGBA-PD patients still presented with more hallucinations (p=0.012) than mGBA-PD and iPD.

Conclusions: A "dose" like effect was observed in clinical manifestation in relation to genotype, with more severe disease manifestation in severe GBA mutation carriers and GD-PD than mild GBA-PD and iPD. These findings have important implications for patients care.

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Patient-derived GBA1-PARK2 double-mutant cellular models to study the effect of GBA1 as a modifier of familial Parkinson's disease

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Objective: In this study, we propose to decipher the role of *GBA1* as a modifier of familial Parkinson's disease (PD) using double-mutant patient-derived cellular models.

Background: Mutations in more than 20 genes have been identified as being causative for PD. Nevertheless, heterogeneity in penetrance, phenotype and age of onset of patients carrying the same mutations lead to the search of modifying factors that could influence disease onset and progression. Mutations in the *GBA1* gene, encoding the glucocerebrosidase (GCase), are an important and common risk factor for familial and sporadic PD. Indeed, 5-10% of all PD patients are carrying a *GBA1* mutation [1]. These patients are more likely to progress to dementia, develop earlier axial motor symptoms and have a slightly earlier age of onset compared to non-carrier PD patients. Consequently, mutation in *GBA1* could influence PD causal genes and modify the pathophysiology.

Methods: Fibroblasts from a PD patient harbouring homozygous mutation in the *PARK2* gene and a point mutation in the *GBA1* gene have been donated. Patient's fibroblasts have been reprogrammed into induced pluripotent stem cells (iPSC) using synthetic RNA encoding for reprogramming factors (Oct4, Nanog, Klf4, Glis1). These iPSC have been differentiated into small neuronal precursor cells to finally generate midbrain-specific dopaminergic neurons [2]. At iPSC stage, CRISPR Cas9 technology will be used to correct the *GBA1* mutation to obtain an isogenic control free from any effect caused by this mutation and only harbouring the deletion in *PARK2*.

Results: Three cellular models derived from patient's fibroblasts have been successfully generated. Enriched neuronal culture were obtained, containing more than 15% of dopaminergic neurons. The characterisation of the cellular models confirmed the quality and suitability of our cell lines to study PD relevant phenotypes. Further characterisation of the cells revealed an impairment in GCase activity and a loss of Parkin. We now aim to investigate *GBA1* mutation specific effect in the frame of the double mutation focusing on mitochondrial features, autophagy-lysosomal function and a-synuclein interplay.

Conclusions: We have established the first double-mutant *GBA1-PARK2* patient-derived cellular models. Phenotypic difference were identified and specific effect of GBA will be further studied particularly with the help of isogenic control.

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CLOCK rs1801260 polymorphism is associated with suscepibility of Parkinson's disease in Chinese population

F. Lou, X. Luo, M. Li, Y. Ren (Shenyang, People's Republic of China)

Objective: This study is aimed at evaluating the potential association between the single-nucleotide polymorphism of two functional clock genes (CLOCK gene rs1801260 and PER2 gene rs2304672) and susceptibility to Parkinson's disease in people of Northeast China.

Background: The clock genes play an important role in in the pathophysiology of aging and oxidative stress injury of neurons. Recently, the clock genes that regulate circadian rhythm arouse many researchers' interest, since a growing body of evidence suggests alterations of the circadian system may participate in the pathogenesis of PD. **Methods:** 646 cases of PD (Male 316, Female 338) from consecutive outpatient and inpatient ward of our hospital were included in this study. The technique of Kompetitive Allele Specific PCR (KASP) was applied to determine the frequency distribution of genotype and allele gene of CLOCK gene(CLOCK rs1801260,PER2 rs2304672)in both groups. After amplification, PCR plates were read with a Spectramax M5 FRET capable plate reader (Molecular Devices, Sunnyvale, CA, USA) using the recommended excitation and emission values. Data was then analyzed using SNPViewer software to identify SNP genotypes.

Results: The significant association was observed for CLOCK rs1801260 in a dominant model. The frequency of TC genotype, CC+TC genotype and C allele in PD group is significantly higher than in control group of allele gene of CLOCK rs1801260 (P<0.01, P =0.001, P =0.001, respectively). As for PER2, there was no significant difference in the distributions of genotypes and alleles of rs2304672 between PD patients and controls (P>0.05, P>0.05, respectively). The correlation still remained after adjusting for confounding risk factors of PD (P =0.034). **Conclusions:** Polymorphism of CLOCK rs1801260 may increase susceptibility to Parkinson's disease independent

Conclusions: Polymorphism of CLOCK rs1801260 may increase susceptibility to Parkinson's disease independent of other common risk factors in northeastern Chinese population. PER2 rs2304672 variants may have no association with susceptibility to Parkinson's disease in northeastern Chinese.

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CLOCK varriant correlates to motor fluctuation and sleep disorders in Chinese patients with Parkinson's disease

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Objective: This research is to explore whether there is association between Circadian locomotor output cycle kaput (CLOCK) gene polymorphism and biological rhythm disorders of Parkinson's disease.

Background: Recently, the Clock genes that regulate circadian rhythm arouse many researchers' interest. Studies on single nucleotide polymorphism of Clock genes may provide more insights about the genetic susceptibility of PD and non-motor symptoms.

Methods: The technique of Kompetitive Allele Specific PCR was applied to determine the frequency distribution of genotype and allele gene of CLOCK rs1801260. There are 124 carriers and 522 non-carriers of CLOCK rs1801260 C allele gene. The clinical information of PD group was obtained in detail, including age, gender, clinical symptom, past history, family history, education, clinical course, age of onset, medication, blood pressure and etc. Several scales for the PD group were completed face-to-face to evaluate symptoms and cognitive function, including Unified Parkinson's Disease Rating Scale (UPDRS) and Mini-Mental State Examination (MMSE). In this study, Early-onset PD (EOPD) is defined as age of onset less than 45. The evaluation of tremor and Postural instability and gait difficulty (PIGD) was completed by using items from UPDRS-?(items including 20,21,22,28,29).

Results: In PD group, there are 126 carriers and 528 non-carriers of CLOCK rs1801260 C allele gene. There is significant difference between these two group in movement symptom fluctuation (P=0.000) and subject sleep status at night (P=0.002), and there is no significant difference in age, family history, EOPD, clinical course, stage, Hoehn-Yahr scale, UPDRS?+?, MMSE scale, reaction to levodopa, depression and orthostatic hypotension. Binary logistic regression analysis showed that movement symptom fluctuation is associated with polymorphism of CLOCKrs1801260 (OR=4.500,P<0.01), UPDRS ?+? and tremor scale. There is no significant association in levodopa treatment, age, clinical course, H-Y scale, MMSE, rigidity scale, EOPD with polymorphism of CLOCKrs1801260 (P>0.05).

Conclusions: Polymorphism of CLOCK rs1801260 is associated with movement symptom fluctuation and sleep disorder in Parkinson's disease, but not associated with symptoms of biological rhythm disorders like depression, orthostatic hypotension and reaction to medication.

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Association Of Single Nucleotide Polymorphism In Maob And Risk Of Levodopa-induced Dyskinesias in Parkinson's Disease

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Objective: To identify genetic risk factors for developing levodopa-induced dyskinesias (LID) in patients with Parkinson's disease (PD).

Background: LID are common complications in PD, but there are conflicting data about genetic risk factors associated with its onset.

Methods: A cross-sectional study was conducted with epidemiological and clinical data from Brazilian PD patients enrolled from two centers as part of the Latin American Research consortium on the Genetics of PD (LARGE-PD). All PD patients were submitted to neurological examinations and semi-structured interviews performed by a neurologist with experience on Movement Disorders. Presence of LID was confirmed if UPDRS Part IV had a score = 1 on item 32. Based on previous studies, we chose eight Single Nucleotide Polymorphisms (SNP) in the following genes: *COMT, MAOB, ANKK1, DRD3, DAT1, BDNF, ADORA2A* and *NOS1*. Genotyping was performed using TaqMan SNP genotyping assays. Association between SNPs and LID was tested using multivariate logistic regression under an additive model adjusting for sex, age at onset of PD and levodopa therapy duration. **Results:** 186 Brazilian PD patients were enrolled (males - 58%; mean age 60 years). Of these patients, 91 (48.9%) presented LID. Only *MAOB* SNP rs1799836 was associated with LID, with the A allele increasing the risk of developing LIDs (OR 1.51, CI95% 1.00-2.28; p = 0.05). However, when analyzed independently in male and females (MAOB gene is located in chromosome X), these differences were not significant. **Conclusions:** *MAOB* SNP rs1799836 is a probable genetic risk factor for LID although further studies in larger

samples are required to explore the influence of *MAOB* polymorphisms on LID.

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Spiral Analysis is a Promising Biomarker in LRRK2 G2019S carriers

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Objective: To assess whether harboring a *LRRK2* G2019S mutation is associated with abnormalities in spiral drawing, including in mutation carriers with Parkinson's disease (PD) as well as those without PD (non-manifesting carriers (NMC)).

Background: Digitized spiral drawing is an objective and quantitative task that correlates with PD severity and distinguishes PD from controls. Such a motor marker may be useful in several ways: in tracking progression of disease; in detection of motor abnormalities that are a long-standing endophenotype of harboring a mutation such as G2019S; and/or as an indicator of early objective motor feature of pre-clinical disease.

Methods: Subjects: 72 G2019S mutation PD (*LRRK2* PD), 166 non-G2019S PD (IPD), 93 G2019S mutation non-PD (NMC) and 92 non-G2019S, non-PD controls (controls) from three sites completed digitized spiral drawing using methods previously described¹. Linear mixed models were applied to assess group differences in spiral indices for both the dominant and non-dominant hand, adjusting for age, sex, handedness, and site. Indices included overall degree of severity (DoS), irregularity and irregular shape (1stZC and 2ndSm), and loop-to-loop variability (SWVI). **Results:** IPD and *LRRK2* PD were older than NMC and controls, while controls were older than NMC (all p<0.01), and *LRRK2* PD had longer PD duration than IPD (p<0.01). Compared with IPD, *LRRK2* PD had less irregularity (1stZC) in both hands, but greater SWVI (all p<0.01) in the dominant hand, and lower DoS in the non-dominant hand (p<0.03). Compared to controls, NMC had higher DoS (p<0.01) and greater SWVI (p=0.012) in the dominant hand. Dominant and non-dominant DoS and

SWVI were greater in *LRRK2* PD compared to controls (both p<0.01).

Conclusions: As expected, spirals are abnormal in *LRRK2* PD compared with controls. *LRRK2* PD spirals differed from IPD in showing greater spiral width variability but less irregularity. Of interest, NMC also had greater spiral variability compared to controls, although, it was less than *LRRK2* PD. NMC also demonstrated greater overall severity compared with controls. This suggests that spiral variability may be a feature that precedes frank parkinsonism in IPD, and parallels arm swing variability during dual tasks reported in NMC². Longitudinal studies will help demonstrate whether this is a marker on the path to PD, or a compensatory endophenotype in *LRRK2* PD.

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SNCA multiplication consortium: Clinicogenetic analysis of SNCA multiplication probands and families.

A. Book, M. Farrer, T. Candido, I. Guella, D. Evans, E. Gustavsson (Vancouver, BC, Canada) Objective: Clinicogenetic analysis of 57 affected probands with SNCA multiplication, 3 unaffected carriers, and

their 60 families. To use informative pedigrees to identify penetrance modifiers within the *SNCA* locus, neighboring regions, and known variability associated with PD and cognition.
Background: *SNCA* dosage has been correlated with alpha-synuclein expression levels, age of motor onset and disease severity in PD. Patients with *SNCA* duplications present a wide range of phenotypes, while those with triplications have an earlier presentation, accompanied by psychiatric problems and cognitive decline. **Methods:** DNA samples and clinical measures of disease progression and cognitive decline were collected from 57 probands and 3 unaffected individuals carrying *SNCA* multiplication mutations. Further clinical evaluation, with analysis of intra- and inter-familial variance, and biospecimen collection is planned. To date, DNA has been genotyped with a 1.8 million SNP Multi-Ethnic Genotyping Array (MEGA). 5', 3' and intron 4 *SNCA* STR markers are assessed along with APOE, MAPT and GBA risk factors using TaqMan genotyping and Sanger sequencing. **Results:** Of the 60 individuals (30 male/30 female), 51 had three copies of *SNCA* (3C), and 9 had four copies (4C). Average age of motor symptom onset for those affected was 45.3 ± 11.1 years ($3C: 47.2\pm10.6, 4C: 34.5\pm7.9$). 25 of those affected have a secondary diagnosis of dementia, with average dementia onset at 51.1 ± 12 years ($3C: 56.5\pm9.6$, $4C: 39.6\pm5.5$) where 50% of dementia diagnoses came within 5 years of PD diagnosis (3C: 14, 4C: 1). The average length of multiplication was 2.18 ± 2.54 Mb (range: 0.16-13.83Mb) and is not correlated with age of motor onset (r=0.21).

Conclusions: With coordinating sites in Asia, Europe, and North America (lead by Nobutaka Hattori, Alexis Brice and Matt Farrer, respectively) the SNCA Multiplication Consortium uniquely serves to: 1) screen and identify new *SNCA* multiplication carriers; 2) harmonize clinical phenotyping; 3) expand pedigrees and; 4) develop biomarkers for alpha-synuclein-targeted therapies (see http://www.geopd.org/projects/6).

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eEF1A2 promotes cell survival and protects against MPP+-induced apoptotic neuronal death through the PI3K/Akt/mTOR pathway

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Objective: To assess the correlation of eEF1A2 and PI3K/Akt/mTOR expression and investigate the pro-survival role of eEF1A2 in NG108-15 rodent neuroglioma cells.

Background: Eukaryotic protein elongation factor 1 alpha 2 (eEF1A2) is one of the members of the eEF1A family, which plays a canonical role in protein synthesis during the elongation phase of protein translation. A non-canonical role in pro-survival has been shown in many cancers and neurodegenerative diseases. An increase of eEF1A2 expression causes cancer progression whereas a decrease of eEF1A2 has been linked to neuronal death in many neurodegenerative diseases. eEF1A2 is proposed to contribute protection against apoptotic cell death, likely through activation of the PI3K/Akt pathway. Akt is activated by various toxins and involved in cell survival and proliferation as well as exerting an anti-apoptotic effect. Previous evidence has also shown correlated expression of eEF1A2 with the PI3K/Akt/mTOR pathway in a cellular model of Parkinson's disease.

Methods: We studied the expression of eEF1A2 in both undifferentiated and differentiated NG108-15 after treatment with the neuronal toxin MPP+. To study the pro-survival role of eEF1A2 we also checked the expression of PI3K/Akt/mTOR both before and after RNAi knockdown of eEF1A2 by using quantitative real time PCR and western blot analysis.

Results: There was a trend towards an increase of the expression of eEF1A2 after treatment with MPP+ in both undifferentiated and differentiated cells, when compared with control. Meanwhile, the expression of PI3K/Akt/mTOR proteins were increased in both differentiated and undifferentiated NG108-15 cells treated with

MPP+, especially for the phosphorylated Akt protein. After eFE1A2 knockdown, the expression of N2K/Akt/mTOP are inside and the table and t

PI3K/Akt/mTOR was significantly increased, but the ratio of p-Akt/total Akt was lesser than that of non eEF1A2 knockdown.

Conclusions: The present findings suggested that eEF1A2 may promote survival of NG108-15 cells through the PI3K/Akt/mTOR pathway by the enhanced expression of phosphorylated Akt in order to protect MPP+ neurotoxin induced cell death. Further investigation is required to confirm our findings, such as the expression of apoptosis and oxidative stress markers.

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Association of the GBA T369M polymorphism with motor and cognitive symptoms in Parkinson's disease *A. Julius, Y.H. Lin, M. Smith, J. Leverenz, D. Weintraub, J. Trojanoswski, V. Van Deerlin, B. Ritz, R. Rausch, J. Quinn, K. Chung, S. Factor, L. Rosenthal, T. Dawson, M. Albert, A. Espay, F. Revilla, J. Devoto, J. Goldman, G. Stebbins, B. Bernard, Z. Zbigniew, O. Ross, D. Dickson, D. Yearout, S.C. Hu, C. Johnson, B. Cholerton, T. Montine, K. Edwards, C. Zabetian (Seattle, WA, USA)* **Objective:** To determine whether the GBA polymorphism T369M is associated with earlier age of onset, lower cognitive performance, and more severe motor impairment in Parkinson's disease (PD).

Background: PD is a heterogeneous disease with variable age of onset and rates of motor and cognitive progression. *GBA* mutations and the E326K polymorphism are risk factors for PD, and among PD patients those who carry these variants exhibit a more rapid decline in motor and cognitive function. A recent meta-analysis of case-control studies concluded that another *GBA* polymorphism,T369M, is a PD risk factor. However, whether T369M is associated with worse motor and cognitive function is not yet known.

Methods: In this cross-sectional study, we sequenced the entire *GBA* coding region in 1743 PD patients from 10 sites in the PD Cognitive Genetics Consortium. Patients underwent assessments of global cognitive abilities (Montreal Cognitive Assessment), language processing (semantic and phonemic verbal fluency), learning and memory (Hopkins Verbal Learning Test-Revised), working memory/executive function (Letter-Number Sequencing Test and Trail Making Test A and B), and visuospatial ability (Benton Judgment of Line Orientation). Motor function was assessed using the MDS-UPDRS III scale. We used linear regression to test for association between T369M and MDS-UPDRS III scores and cognitive performance, and logistic regression to assess the proportion of subjects with dementia. We adjusted for important covariates, including site, sex, age at testing, disease duration, education (cognitive data only) and levodopa equivalent dose (motor only). Individuals who carried a *GBA* mutation or E326K were excluded from analysis.

Results: Thirty-eight patients (2.2%) carried T369M. There was no significant association between genotype and age at onset (p=0.06), MDS-UPDRS III score (p=0.53), proportion of subjects with dementia (p=0.14), or performance on any of the cognitive tests (Table 1).

Table 1. Estimated difference in mean test score, comparing GBA T369M carriers to noncarriers.

Test	β	95% CI	Р
MoCA	-0.43	(-1.76, 0.90)	0.53
HVLT-R Total Recall	-0.65	(-2.82, 1.53)	0.56
HVLT-R Delayed Recall	0.50	(-0.58, 1.57)	0.36
HVLT-R RDI	-0.04	(-0.63, 0.54)	0.89
Semantic fluency	-0.39	(-2.02, 1.23)	0.63
Phonemic fluency	2.08	(-1.74, 5.90)	0.29
LNST	-0.82	(-1.69, 0.05)	0.07
TMT B - TMT A	-14.76	(-33.46, 3.94)	0.12
JoLO	0.18	(-1.68, 2.04)	0.85
MDS-UPDRS III	-1.54	(-6.34, 3.27)	0.53

JoLO, Benton Judgment of Line Orientation; HVLT-R, Hopkins Verbal Learning Test-Revised; LNST, Letter-Number Sequencing Test; MoCA, Montreal Cognitive Assessment; RDI,

Recognition Discrimination Index; TMT, Trail Making Test.

Conclusions: Our data suggest that unlike *GBA* mutations and E326K, the T369M polymorphism is likely not associated associated with a more severe PD phenotype. This information will be important in selecting patients for participation in future clinical trials focused on *GBA*-related Lewy body disorders.

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How common are the genomic rearrangements among possibly autosomal recessive PD cases in Turkey? *G. Yalcin Cakmakli, A. Yuzbasioglu, G. Onal, B. Peynircioglu, M. Ozguc, S. Dokmeci, B. Elibol (Ankara, Turkey)* **Objective:** In this study, we aimed to investigate the frequency and phenotypical features in a subset of early-onset Parkinson's disease (EO-PD) (age-at-onset =45 years) patients due to genomic rearrangements in *PARK2, PINK1* and *DJ-1*.

Background: EO-PD, constituting around 10% of all PD cases, is frequently associated with autosomal recessive (AR) mutations of *PARK2 (PARKN)*, *PINK1* and *DJ-1* genes. Among all different types of mutations, genomic rearrangements are common at varying degrees depending on the ethnicity of the population.

Methods: Thirty-five unrelated Turkish EOPD patients, whose clinical features are suggestive of AR-PD were recruited from our outpatient clinic. After structured clinical evaluation, the patients were screened for genomic rearrangements by using the multiplex ligation-dependent probe amplification (MLPA) method with SALSA P051

kit, before sequence analysis. The kit consists of probes for all exons of a-synuclein, PRKN, and PINK1, and specific exons of DJ-1; LRRK2; UCH-L1; ATP13A2; LPA; TNFRSF9; CAV2; CAV1 and GCH1. **Results:** We identified exonic rearrangements in 47% of 34 Turkish patients. We have identified 11 patients (32%) with homozygous whole exonic deletions in exons 2, 3, 4, and 5 of PRKN gene, 4 patients (12%) with heterozygous whole exonic deletions in exons 2, 3, 4, and 5. Exon 4 and 5 were found to be the most frequently deleted sites in PRKN gene. Clinically, the mean age at onset was found to be younger in the homozygous PRKN deletion group compared to heterozygous group (26 ± 9 vs. 35 ± 8), also with better UPDRS scores (10.5 vs 16.25) despite similar disease duration. Among motor and non-motor presenting features, sleep benefit (80%) and gait abnormality (60%) were the most common ones. Additionally, one patient was found to have homozygous whole exonic deletions in DJ-1 (in exons 1, 3, and 5). No genomic rearrangements were found in PINK-1 gene. Further genotyping continues for possible point mutations.

Conclusions: PRKN mutations are the most common cause of early onset AR-PD in Turkey. Genomic rearrangements of PRKN was found in high proportion in our study group. Therefore, we suggest that MLPA test provides a high yield for positive diagnosis of PRKN mutations as a first step of genotyping in possible AR-PD cases with early onset. In addition, we have identified DJ-1 mutation in one patient, being the first genomic rearrangement reported from Turkey.

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Physical and cognitive stimulation through environmental enrichment prevents early molecular pathology in a Parkinson's disease model

Z. Wassouf, T. Hentrich, S. Samer, O. Riess, N. Casadei, J. Schulze-Hentrich (Tübingen, Germany) **Objective:** Understand the molecular principles and identify genetic drivers underlying and mitigating the preventative effects of environmental enrichment on the unfolding of Parkinson's disease (PD) pathology. **Background:** While genomic mutations and multiplications have been linked to rare familial forms of PD, the preponderance of PD cases cannot be explained by genetics alone and seems to occur sporadically. Moreover, age as well as environmental factors correlate with onset and progression of the disease. This multi-factorial interplay suggests a highly complex pathomechanism that has remained largely enigmatic.

Methods: A transgenic mouse model over-expressing the human wildtype *SNCA* gene was generated for this study and showed early non-motor symptoms of PD. Both wildtype (WT) and transgenic (TG) animals were exposed to either a standard (SE) or enriched environment (EE), the latter modeled by enhancing social and cognitive complexity and stimulating physical activity over a period of 12 months. RNA-Seq was used to profile gene expression in hippocampal tissue of all four experimental groups in order to (i) identify genes and cellular processes disturbed through SNCA-overexpression and to (ii) reveal effects on gene activity induced through the EE. **Results:** Differentially expressed genes in transgenic animals housed in SE pointed to disturbances in synaptic processes and several other cellular pathways linked to SNCA before. Intriguingly, transgenic animals housed in EE were largely protected from these disturbances in gene activity. Bioinformatic analyses revealed specific transcription factors, kinases, and phosphatases that likely drove the observed protection by activating an array of downstream targets that counterbalanced the influence of the SNCA transgene. Together with first epigenetic data, we integrated these data to a system's view of environmental protection and its mechanisms along the geneenvironment axis in PD.

Conclusions: Our study identifies candidate genes and suggests potential cascades of activation underlying the protective effect of environmental enrichment in PD. We consider these efforts to be highly valuable in assessing whether changes in life style can delay or ameliorate PD symptoms in human, and whether these candidate genes offer opportunities to mimic the environmental influence towards much-needed novel therapies of PD.

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Parkin (PARK 2) mutations in patients with early-onset Parkinson's disease

A. Ivashynka, S. Likhachev (Minsk, Belarus)

Objective: Genetic testing Parkin (PARK 2) gene in patients with young-onset Parkinson's disease in Belarus. **Background:** The diagnosis of young-onset Parkinson's disease (PD) is the same as idiopathic, or typical, PD except for the age of the patient. Onset usually occurs between ages 20 and 40 years with an average age of onset in the early to mid-thirties. A group of patients who had onset before 40 is very likely to include people with genetic Parkinson's. PARK2, the gene encoding the protein parkin, is the only gene in which pathogenic variants are known to cause parkin type of early-onset Parkinson's disease. The diagnosis of parkin type of early-onset Parkinson's disease can only be confirmed when pathogenic variants are identified on both alleles of PARK2 (i.e., the individual is homozygous for the same pathogenic allele or compound heterozygous for two different pathogenic alleles). To date, identified 30 different mutations in this gene, and over 90% of them are located in exons 2, 3, 4 and 7 ("hot" exons), R275W mutation is one of the most frequently detected in European population, N273S mutation has been previously described in one case from France [1].

Methods: Genetic analysis of DNA samples of 22 Parkinson's disease patients with rigidity, bradykinesia, and resting tremor; 16 of them had family history of Parkinson's disease. For the study was used DNA from peripheral blood leukocytes by phenol-chloroform extraction method. To identify single-nucleotide substitutions in the gene PARK2 used the method of direct sequencing of the "hot" exons. Large exon deletions and duplications PARK2 gene was performed with the denaturing High Performance Liquid Chromatography (dHPLC). To estimate the amount of PCR product was carried out a comparative analysis of the following combinations of exons: 3/7/12, 2/7/8; 3/8/10, 6/11, 4/5, 3/9, 2/3/4.

Results: Mutations PARK2 gene was found in 4 of 22 patients: 1st patient- two heterozygous single nucleotide substitutions in R275W and N273S; 2nd patient - heterozygous R275W mutation and deletion of exons 3 and 4; 3rd patient - heterozygous deletion of exons 3 and 4; 4th patient - heterozygous deletion of exons 3 and 4.

Conclusions: Parkin type of early-onset PD is rare and clinically indistinguishable from idiopathic PD. Detected deletion of PARK2 exons 3 and 4 is possibly dominant type of mutations in Belarus and may be associated with the "founder effect".

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Screening of Gba and Lrrk2 G2019s Mutations in Egyptian Parkinson's disease patients

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Objective: We aim to estimate the frequency of mutations in the glucocerebrosidase gene (GBA) and LRRK2 G2019S in a yet unstudied Egyptian Parkinson's disease population from the region of Assiut.

Background: Mutations in GBA are the most common genetic risk factor for Parkinson's disease (PD). The G2019S mutation in leucine-repeat rich kinase (LRRK2) gene is found in 1% sporadic PD cases and 4% familial PD cases worldwide.

Methods: DNA was extracted from blood samples from 70 PD cases and 294 controls and exons 8-11 of GBA as well as exon 41 of LRRK2 were screened using Sanger sequencing. Mutations frequencies are compared using Fisher's exact test.

Results: GBA mutations were found in 5.1% (3/59) cases and 0.9% (2/217) controls; 2.9% (2/69) of cases and 0.7% (2/289) of controls carry LRRK2 G2019S. These frequencies are quite different despite not being significant (p>0.05 for both), probably due to small sample size.

Conclusions: This is the first study investigating the role of GBA and LRRK2 G2019S together in an Egyptian population. The most commonly found GBA mutation was L444P in 3 PD patients and 1 control, and has previously been characterised as a severe GBA mutation. Further analysis of the samples using NGS for screening of the common genes involved in PD risk is underway. Additional samples are being collected for a more robust estimation of the burden of these genes in PD in this population.

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Rare variant analysis of the PPMI dataset to uncover the complex genetic architecture of Parkinson's disease *D. Bobbili, P. May, R. Krueger (Esch-sur-Alzette, Luxembourg)*

Objective: To unravel the genetic factors that play a role in PD we used the whole exome sequencing data available as a part of Parkinson Progression Markers Initiative (PPMI).

Background: Parkinson's disease (PD) is a complex disease. Besides variants in high-risk genes such as LRRK2 and PARK2, multiple genes associated to sporadic PD were discovered via genome-wide association studies. Yet, there is a large number of genetic factors that need to be deciphered.

Methods: To unravel the genetic factors that play a role in PD we used the whole exome sequencing data available as a part of Parkinson Progression Markers Initiative (PPMI). The dataset comprised of 435 PD cases and 162 ethnically matched controls, respectively. We performed burden tests at single variant, gene and geneset levels on common and rare exonic and splice-variants. We also looked for severity of rare highly deleterious variants (CADD phred score > 30) using the CADD score as well as singleton (variants seen in only one individual across cases and controls) rare variants. Additionally, we performed the functional enrichment analysis with the genes harboring rare highly deleterious variants (Case_{uniq} genes) that are only present in cases.

Results: We observed an increased mutational burden of singleton variants in PD cases compared to the controls in nonsynonymous + LOF variants (empirical P-value 0.005) but not in the synonymous variants (empirical P-value 0.09). We observed a higher significant burden (P-value 0.028) as well as higher significant severity (empirical P-value 0.027) of rare, highly deleterious nonsynonymous variants, but not in the synonymous variants of the candidate genes (P-value 0.686, empirical P-value 0.556 for burden and severity respectively). The network analysis of genes having deleterious variants only present in cases (Case_{uniq}) showed a significant increase in connectivity compared to random networks (P-value 0.0002). Pathway analysis of those genes showed a significant enrichment of pathways and biological process implicated in the nervous system functioning and the etiology of PD. **Conclusions:** Our study supports the complex disease notion of PD by highlighting the convoluted architecture of PD where Case_{uniq} genes including LRRK2 are implicated in several biological processes and pathways related to PD. The main finding of this study is to discover the complex genetics of PD at an exome wide level.

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Interest in Genetic Testing in Parkinson's disease patients with DBS

A. Fraint, G. Pal, C. Timms, E. Tam, R. Bhavsar, L. Verhagen, D. Hall, K. Marder (Chicago, IL, USA) **Objective:** To determine interest in genetic testing among Parkinson's disease (PD) patients with deep brain stimulation (DBS).

Background: Nearly 27% of patients with early-onset PD carry a mutation in one of three genes: *glucocerebrosidase (GBA), leucine-rich repeat kinase 2 (LRRK2),* and *parkin (PRKN)*. Phenotypes which are unique to each mutation may inform disease progression, which patients may benefit from or develop side effects due to DBS, and which surgical targets may be optimal. As it becomes more accessible, it is important to understand whether or not patients would opt for genetic testing, and what factors may predict or influence their decisions. **Methods:** A Genetic Attitude Questionnaire (GAQ) was administered at Rush Medical Center to non-demented PD patients with DBS who were unaware of their genetic mutation status. All subjects completed the GAQ, indicating their genetic testing, and reasons why they would or would not want testing. Interest in genetic testing was dichotomized – subjects who were definitely or probably interested in testing were considered one group, and subjects who definitely or probably did not want testing were a second group. A third group of patients were undecided. Models were adjusted for age, disease duration, family history, UPDRS-III score, and mutation status.

Results: Average age of patients was 63.22 ± 8.39 and 74.1% were men. Approximately 26% reported a family history of PD. Of these, 53% believed PD is hereditary, 13% believed it is not hereditary, and 33% were unsure. At the present time, twelve subjects (20.7%) definitely wanted genetic testing, fifteen (25.9%) probably wanted genetic testing, eight (13.8%) definitely did not want genetic testing, three (5.2%) probably didn't want genetic testing, and twenty (34.5%) were undecided. Though there was a trend toward higher UPDRS-III scores and desire to obtain genetic testing, this did not reach statistical significance. Fifty-seven percent of subjects would want genetic testing to determine if they would benefit from surgical intervention.

Conclusions: PD patients are interested in genetic testing, and are more likely to obtain genetic testing if results could predict response to surgical treatment. Further studies are needed to understand the factors that influence a patient's desire for genetic testing.

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Glucocerebrosidase mutations in neurodegenerative disorders other than Parkinson's disease

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Objective: To determinate the frequencies of lysosomal glucocerebrosidase (GBA) common mutations in a large sample of neurodegenerative diseases including Alzheimer Disease (AD), Lewy Body Dementia (LBD), Amyotrophic Lateral Sclerosis (ALS) compared to Parkinson's Diseases (PD) and healthy controls.

Background: Mutations in the gene GBA increase the risk of Parkinson's Disease (PD). GBA variants predict a more rapid progression of cognitive dysfunction in parkinsonian patients. However, the precise frequencies of GBA mutations in other dementias and neurodegenerative disorders is still unclear.

Methods: We selected cohorts of unrelated consecutive patients with clinical diagnosis of neurodegenerative disorders including 139 PD, 144 AD, 48 LBD, 149 ALS and 200 healthy age- and ethnic-matched controls. The clinical diagnosi of AD was supported by the low level of beta amyloid in CSF. DNA was extracted from all patients in order to screen for selected mutations in GBA gene by specific amplification of a fragment including exons 8-11

followed by Taqman assay detecting the following variants: p.N380S, p. E326K, p. L444P and p. D409H. All samples resulted positive for these mutations were confirmed by Sanger sequencing.

Results: The preliminary screening revealed in PD patients a frequency of 2.16% for p.N370S, 1.44% for p.L444P and 2,88% for p.E326K. Among ALS, p.L444P and p.E326K where found in 0,67% of patients each, while both variants were rare among AD patients.

Conclusions: The ongoing study suggests that the most common GBA variants associated with PD are rare in patients clinically diagnosed with AD. Further analysis, including screening of N370S and D409H in all samples and screening of DLB and CTR, will reveal the possible association of these mutation with other forms of neurodegeneration.

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Genetic, epigenetic and expression profiles in alpha-synucleinopathies

E. Scott, I. Guella, A. Rajput, A. Rajput, L. Parkkinen, M. Kobor, M. Farrer (Vancouver, BC, Canada) **Objective:** To determine whether each of the alpha-synucleinopathies has distinct methylation and/or expression profiles that distinguishes them from other disorders in this class.

Background: The alpha-synucleinopathies, encompassing Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), are adult-onset neurodegenerative disorders characterized by *post-mortem* alpha-synuclein (*SNCA*) aggregate pathology. The clinical features and progression of these disorders, and the brain regions affected, are distinct. *SNCA* genetic variability has been insightful in monogenic and idiopathic PD but our understanding of gene/protein expression in disease pathogenesis remains limited. How aggregated alpha-synuclein pathology is propagated and why specific cell types are more vulnerable remains enigmatic. Nevertheless, endogenous alpha-synuclein expression modulates the induction of Lewy-like pathology. Genetic variability influences epigenetic marks and allele-specific expression in human induced pluripotent stem cells and differentiated neurons¹. Concomitantly, we have shown that an expanded *SNCA* (TTTC_n) repeat is associated with dementia in PD². Hence, we hypothesize genetic, epigenetic and expression changes in *SNCA* influence the distribution and burden of neuropathology in distinct alpha-synucleinopathies.

Methods: Using striatal (affected in PD and MSA-P), cerebellar (affected in MSA-C), entorhinal cortex (affected in DLB) and occipital cortex (unaffected) tissue from brains of clinically- and pathologically-confirmed PD, DLB and MSA along with unaffected control subjects (n=32, 8/group), we pilot genome-wide SNP, methylation and expression analyses. Brain regions are powdered for correlative DNA, RNA and protein extraction. Ampliseq Transcriptome Ion Proton sequencing enables differential gene expression analyses between tissues, patients and control subjects, adjusting for SNPs while considering the burden of inclusion pathology.

Results: We will present a comparison of gene expression profiles of the three alpha-synucleinopathies. Future studies will also assess genetic variability and methylation to determine whether there are distinct profiles for each alpha-synucleinopathy.

Conclusions: The study is to provide insight into the propagation of alpha-synucleinopathies and inform the development of novel therapeutics.

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Exome sequencing in patients with impulse control disorders in Parkinson's disease: A pilot study

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Objective: To identify genetic variants associated with impulse control disorders (ICD) in Parkinson's disease (PD) **Background:** ICD is frequently associated with dopamine agonist (DA) therapy in PD. There are growing evidence of a high heritability for ICD in general population and PD. Previous candidate gene association studies showed that variants on genes belonging to the reward pathway are involved in this genetic susceptibility.

Methods: We selected 36 PD patients on DA therapy with (n=18) and without (n=18) ICD, matched for age and gender. Whole exome sequencing was performed using MedExome SeqScape EZ kit (Roche) and NexSeq 500 sequencer (Illumina). Variants with a strong functional impact (Cadd-score=12.37) and in brain-expressed genes were selected. Allele frequencies, and their distribution in genes and pathways were analyzed respectively with single variant test and Optimized Sequence Kernel Association Test (SKAT-O). For this pilot study, pathways with p-value < 0.01 and genes and variants with p-value < 0.001 were retained for replication in the Parkinson's Progression Markers Initiative (PPMI) cohort.

Results: From the 6,953 variants selected for the analysis, we identified 5 pathways associated with ICD below the 0.01 p-value threshold: *Localization of the PINCH-ILK-PARVIN complex to focal adhesions* ($p=1.6x10^{-3}$), *adenylate*

cyclase activating pathway ($p=1.6x10^{-3}$), LRR FLII-interacting protein 1 (LRRFIP1) activates type I IFN production ($p=2.2x10^{-3}$), AMPK inhibits chREBP transcriptional activation activity ($p=2.7x10^{-3}$), and IKBKG deficiency causes anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) ($p=7.8x10^{-3}$). The association with the adenylate cyclase activating pathway was replicated in PPMI cohort ($p=2.0x10^{-2}$), resulting in a combined significant p-value taking into account multiple testing ($p=3.7x10^{-4}$, Fisher's combined test). None of the most associated genes nor variants in the discovery cohort were found associated in PPMI cohort.

Conclusions: Our results suggest that genes implicated in the signaling pathways linked to G protein-coupled receptors participate to genetic susceptibility to ICD in PD. These results are in accordance with the pharmacology of dopamine agonists, and the importance of ERK and cAMP signaling pathways in the dopamine-dependent plasticity in the striatum. Results from this pilot study need however to be replicated in independent cohorts.

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Meta-analysis of the interaction between HLA-DRB1 and smoking with Parkinson's disease

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Objective: To investigate interactions between HLA-DRB1 rs660895 polymorphisms and smoking in PD using meta-analysis to pool data from three large population-based studies.

Background: Inflammatory response plays an important role in Parkinson's disease (PD). Previous studies have reported an association between the human leukocyte antigen (HLA)-DRB1 and the risk of PD. There has also been growing interest in investigating whether inflammation-related genes interact with environmental factors such as smoking to influence PD risk.

Methods: We included 2,073 cases and 2,756 controls from PD studies in Denmark and France that obtained information on smoking through interviews. Genotyping was based on saliva or blood DNA samples. To assess interactions, we used logistic regressions with product terms of rs660895 and smoking variables. Random-effects meta-analysis of marginal associations and interactions were performed in the STATA package metan.

Results: In the meta-analysis, rs660895 variant genotypes were significantly associated with a decreased risk of PD (AG vs. AA: OR= 0.82; GG vs. AA: OR= 0.55). A sub-multiplicative interaction was found between rs660895 and smoking in both codominant and dominant genetic models (OR interaction=1.54, p=0.001), and the protective effect of the rs660895 variant on PD was lost. When separating light from heavy smokers, similar interaction effects were estimated.

Conclusions: Our study provides the first evidence that smoking modifies the previously reported protective effect of rs660895 polymorphisms on the risk of PD. The protective effect of the rs660895 G allele is only apparent in non-smokers.

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Association analyses of three susceptibility loci for Alzheimer's disease in Parkinson's disease, amyotrophic lateral sclerosis, and multiple system atrophy

Y. Chen, R. Ou, X. Chen, B. Cao, Q. Wei, B. Zhao, Y. Wu, H. Shang (Chengdu, People's Republic of China) **Objective:** Considering the overlapping of clinical manifestation and pathologic characteristics of Alzheimer's disease (AD) and Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and multiple system atrophy (MSA), we conducted a large-sample study to investigate the associations between these variants and other three common neurodegenerative diseases (PD, ALS, MSA) in a Chinese population.

Background: A number of genetic variants were identified to be associated with the risk for AD, including rs10838725 in the *CELF1*, rs28834970 in the *PTK2B*, rs17125944 in the *FERMT2* and rs1041544 in *SIRT2* based on the genome-wide association studies (GWAS) data.

Methods: A total of 2449 patients, including 1219 PD, 870 SALS, and 360 MSA patients, and 821 healthy controls (HCs) were examined in the current study. All cases were genotyped for SNPs using Sequenom iPLEX Assay technology.

Results: The genotype distributions of rs28834970 in the *PTK2B* were significant different between ALS patients and HCs, the minor allele "C" carriers have an increased risk of ALS (OR=1.26); Interestingly, the minor allele "C" of this variant increased the risk for abnormal cognitive function in PD patients(OR=1.84). In addition, the minor allele frequency of rs10838725 in *CELF1* was significant high in MSA than that in HCs, the homozygous "CC" carriers have increased the risk for MSA than the homozygous "TT" carriers(OR=1.70). However, no significant differences in the genotype distributions and minor allele frequency(MAF) of rs17125944 in the *FERMT2* and rs1041544 in *SIRT2* were found between PD, ALS, or MSA patients and HCs.

Conclusions: This study provided new clue that these four neurodegenerative diseases shared some of common pathogenesis.

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Parkinsonian Feautures in a Cohort of Gaucher's Disease (Gd) Patients and Relatives

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Objective: to investigate the prevalence and clinical features of parkinsonism in a cohort of 21 GD patients and their relatives.

Background: GD is a lysosomal storage disorder caused by *GBA1* mutations with a large range of phenotypes. Type 1 GD is the most frequent. *GBA1* mutations are by far considered the major genetic risk factor for Parkinson's disease (PD). As a matter of fact increased risk of developing PD has been observed in both GD patients and carriers.

Methods: After signed informed consent, we evaluated 21 genetically characterized GD patients under enzymatic replacement therapy and their relatives. We performed an extensive interview focused on non-motor symptoms and a neurological examination.

Results: Mean age of our cohort of GD patients was 43 y.o. The majority (16; 76%) carried at least one N370S allele: five homozygous (23%) and eleven compound heterozygous (52%). Three (14%) carried at least one L444P allele of whom one was homozygous (5%). The majority (80%) of GD patients were diagnosed during childhood after detecting hepatosplenomegaly and thrombocytopenia. Eleven patients (52%) displayed neurologic manifestations, seven (33%) of which showed parkinsonian features, especially reduced limb synkinesis and tremor (4, 19%), rigidity and bradykinesia (3; 14%). One patient (1/21, 5%) was diagnosed with PD at 52 years. Nine GD patients (42%) showed non-motor symptoms, especially RBD (6; 28%), constipation (4; 19%) and depression (3; 14%). In 15 (71%) GD families at least one relative displayed parkinsonian symptoms and in 10 (47%) cases there was a family diagnosed with PD.

Conclusions: The studied GD cohort showed an high incidence of parkinsonian non-motor symptoms (42%) which could represent prodromal markers of PD and also motor signs (33%). The incidence of PD was increased in relatives of GD patients. The characterization of GD patients and their relatives with parkinsonism may help to elucidate the mechanisms underlying this association and potential prognostic indicators for PD.

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Genetic and pharmacological rescue of DJ-1 loss-of-function caused by a c.192G>C mutation in PARK7

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Objective: In this study we investigate the cellular mechanism underlying the Parkinson's disease (PD)-associated mutation c.192G>C in PARK7 and present a compound treatment that rescues the cellular phenotype in a patient-based cell model.

Background: Homozygous loss-of-function mutations in the DJ-1 gene PARK7 cause a rare form of inherited early-onset Parkinson's disease (PD). DJ-1 covers a wide range of biological functions. It acts as sensor of oxidative stress, as chaperone, glyoxylase and as transcriptional regulator. Patient-derived cellular models harboring the homozygous c.192G>C mutation display specific cellular phenotypes due to loss of function of DJ-1. This mutation was predicted to cause an E64D amino acid change, however, using patient-based material we show a different mechanism leading to loss of DJ-1.

Methods: Patient's fibroblasts were obtained from skin biopsy and reprogrammed into induced pluripotent stem cells (iPSCs). Fibroblasts and iPSC-derived neurons, were used to study the effect of the mutation and to identify compounds that rescue cellular phenotypes.

Results: We identified the c.192G>C mutation to cause mis-splicing of DJ-1 pre-mRNA instead of an amino acid change. We identified impaired U1 mediated recognition of the splice-donor site at exon 3 of PARK7 leading to skipping of exon 3 (?Ex3). Although the levels of ?Ex3 mRNA in patient cells are comparable to wild-type DJ-1 mRNA in control cells, DJ-1 protein levels in patient cells are dramatically reduced. Genetic intervention restored DJ-1 protein levels only when cells were transduced with full-length DJ-1 vectors. Translation of full-length mutant DJ-1 could be rescued when patient cells were transduced with genetically engineered U1 snRNA in patient cells. Moreover, we identified a combination of two compounds that rescues mis-splicing of DJ-1 mRNA and cellular function in patient-derived cell models.

Conclusions: In contrast to current notion we have discovered that the c.192G>C mutation in PARK7 does not cause an E>D missense mutation but a loss of protein due to exon skipping and provide strategies for genetic and pharmacological rescue. Treatment with a combination of two compounds rescues correct splicing of mutant DJ-1 mRNA as well as cellular function in patient cells.

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Genetic variants influencing dyskinesia; potential consequences for treatment in Parkinson's disease

C. Kusters, K. Paul, I. Guella, J. Bronstein, J. Sinsheimer, M. Farrer, B. Ritz (Los Angeles, CA, USA) **Objective:** To examine the association between dyskinesia and haplotypes in the genes of three dopamine receptors (*DRD1, DRD2* and *DRD3*) and of the Brain Derived Neurotrophic Factor (*BDNF*).

Background: Dyskinesia is a known side-effect of levodopa treatment of Parkinson's Disease (PD). While some patients develop dyskinesia early in their disease, there are exceptions of patients who never develop dyskinesia even when treated with high doses of levodopa. The *DRD* and *BDNF* loci have been hypothesized to influence the development of dyskinesia.

Methods: Patient data was drawn from a population-based case-control study, the Parkinson's Environment and Gene study. We included 418 patients with: a confirmed diagnosis by a movement disorder specialist, levodopa treatment, and a minimum three years disease duration at the time of assessment. Applying Haploview and Phase, we created a single haploblock for *DRD1* and *BDNF*, and three haploblocks for *DRD2* and *DRD3*. We generated risk scores for *DRD2* and *DRD3*, and used Poisson regression with robust error variance to estimate risk ratios **Results:** There was no difference in dyskinesia prevalence among carriers of haplotypes in *DRD1* nor *BDNF*. In each of the *DRD2* haploblocks, there was one haplotype that was associated with a 29% to 50% increase in the risk of developing dyskinesia compared to the reference haplotype. Each unit increase in our *DRD2* risk score was associated with a 16% increase in dyskinesia risk (95%CI: 1.05-1.29). For the *DRD3* haploblocks, there might be an association between some haplotypes and dyskinesia although the confidence intervals included the null. Each unit increase in our *DRD3* risk score was associated with a 17% increase in dyskinesia risk (95%CI: 0.99-1.40). While the *BDNF* haploblock was not associated, the minor allele of the rs6265 SNP was associated with dyskinesia (adjusted RR 1.31 (95%CI: 1.01-1.70)).

Conclusions: Carriers of *DRD2*, and potentially *DRD3*, risk haplotypes had an increased risk of developing dyskinesia. Thus, the *DRD2* gene appears to be involved in pathomechanisms leading to the development of dyskinesia. Furthermore, the *DRD3* and *BDNF* gene might also influence dyskinesia prevalence. PD patients with these *DRD2* risk haplotypes would be prime candidates for treatments that aim to prevent or delay the onset of dyskinesia.

* This abstract has been presented as a poster during the World Parkinson Congress on September 23, 2016.

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Data driven analysis for exploring phenotypic differences in patients with Parkinson's disease with or without genetic mutations

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Background: Recent studies investigated genotype-phenotype relation in PD patients carriers of genetic mutations in the *LRRK2* and *GBA* genes. These studies explored specific features in relation to genetic status. Data driven analysis utilizes methods of big-data analytics to explore the relation of multiple features across domains while accounting for multiple comparisons to provide a more accurate and unbiased presentation of the findings. **Methods:** Data was collected from 1,724 participants diagnosed with PD; 163 *G2019S-LRRK2* carriers, 201 *GBA* carriers and 1360 Idiopathic PD. Data included 778 measures; demographic information questionnaires, cognitive assessments, physical and neurological examination, performance based measures and non-motor symptoms questionnaires. Statistical analysis was conducted by testing each of the measures and its association with genotype accounting for age, gender and disease duration resulting in more than 3000 tested comparisons. P-values were corrected for hierarchical multiple comparisons.

Results: 49 (out of 778) measures passed the significance threshold. Differences were found between groups in presenting motor symptoms, existence of psychiatric manifestations and response to dopaminergic treatment. PD

carriers of the *G2019S-LRRK2* mutation were more likely to present with gait difficulty as first motor symptom (adjusted p-value <0.0001), had more severe gait involvement and were more likely to experience freezing of gait within 3 years from diagnosis (p=0.004), compared to the 2 other groups. PD GBA mutation carriers had more cognitive involvement (p<0.0001), more autonomic dysfunction and hyposmia (p=0.0013), higher risk for psychiatric involvement (p=0.002) and for developing hallucination related to pharmacological treatment (p<0.0001).

Conclusions: The findings support a characteristic phenotypic disease based on genotype. Using a robust analytical approach strengthens earlier studies and extends them to portray a possible unique disease progression based on genotype. Such findings could help direct a more personalized therapeutic approach.

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A member of the HSP40/DNAJ family is a novel gene for early-onset parkinsonism

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Objective: We aim to implicate novel genes/mutations using whole-exome sequencing (WES) in selected pedigrees. **Background:** Mutations have been identified in only 30% of familial parkinsonism.

Methods: DNA from affected probands with a family history of early-onset (<45 ys at onset) recessive Parkinson's disease (PD) were selected for WES. Mutational screening was performed in multiethnic familial probands with early-onset PD. Functional studies included gene and protein expression. When possible, brain imaging was reviewed and neuropathology performed.

Results: Null homozygous mutations in a HSP40/DNAJ gene were identified in 2 unrelated families: i) a nonsense mutation (c.187A>T, p.K63X) in a Saskatchewan family (famA); ii) a splicing mutation (c.79-2A>G, S26fs13X) in an Italian family (famB). Both mutations segregate with disease, and are absent in ethnically-matched controls and public databases. Initial clinical findings in famA were reported (Mov Disord1997,12:453-6) and the proband (onset at 13) has since come to autopsy (at 74). FamB proband (onset at 32) has a similar negligible progression of motor symptoms over 30 ys (H&Y stage 1/5 nowadays), with mild executive (FAB 12.1/18) and visuo-spatial dysfunction. Her brother (onset at 51) had early and prominent psychiatric features (hallucinations, delusions) with mild nonprogressive parkinsonism. FamA and B probands had similar sustained symptomatic benefit on small dose of levodopa, showing intermittent mild dyskinesia. Dopaminergic dysfunction was subtle and non-progressive in both families. Neuropathology (famA) revealed no alpha-synuclein pathology and only some age-related Alzheimer's disease changes. Considering the mild nonprogressive course of motor symptoms, clinical diagnosis of PD was challenged in both families: however, levodopa discontinuation led invariably to substantial worsening of symptoms. Functional analyses showed that both mutations ablate the protein expression and might interfere with alpha-synuclein processing.

Conclusions: Loss of the HSP40/DNAJ protein, a Hsc70 interactor, is a rare cause of parkinsonism and the 3rd DNAJ protein genetically linked to parkinsonism. Notably, it seems to be related to a very slow neurodegenerative process. Little is known on the protein function, but it is abundant in the *substantia nigra pars compacta* and plays a critical role in its function.

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Gene associated differences in pre-diagnostic symptoms of Parkinson's disease: A retrospective study

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Objective: To investigate whether glucocerebrosidase (*GBA*) L444P and leucine-rich repeat kinase 2 (*LRRK2*) G2385R and R1628P mutations are associated with different symptoms and manifesting patterns in the prediagnostic stage of PD.

Background: Previous studies suggested that *GBA* L444P mutation was associated with postural instability and gait disorders, motor complications, cognitive decline and constipation in manifesting PD; whereas the motor and nonmotor symptoms of PD patients with *LRRK2* G2385R or R1628P mutations were similar to that of idiopathic PD. The features and manifesting patterns in the pre-diagnostic stage of PD patients with or without these mutations have not been examined.

Methods: PD patients were recruited from the PD cohort of the Chinese National Consortium on Neurodegenerative Diseases established by the Chinese Parkinson Study Group [1]. The occurrence and onset time of pre-diagnostic symptoms and history of environmental exposures were collected and compared between groups. Individual

likelihood ratios (LR) before diagnosis were calculated according the MDS research criteria for prodromal PD [2], which were modified based on the evidence from Chinese population and were compared as indicators for PD manifestation.

Results: 1796 PD patients entered the study, including 226 patients with *LRRK2* G2385R (9.89%) or R1628P (2.84%) mutation, 44 patients with *GBA* L444P (2.45%) mutation and 1526 patients (87.28%) without mutations. *GBA*-subjects had nearly 4 times higher LR at -3 years before diagnosis (P = 0.006), and more than 2 times higher LR at -2 years (P = 0.024; Table 1) than idiopathic subjects. The increase patterns of LR differed between groups: LR of *LRRK2*-subjects increased from 19.73 at -3 years to 80.95 at diagnosis and the value almost doubled within the last year; whereas *GBA*-subjects had high LR of 80.82 at -3 years which increased steadily to 137.43 at diagnosis (Table 1). Micrographia and "mask face" were the only symptoms that differed in cumulative percentage between groups before diagnosis and no significant difference in environmental exposure was found.

Time	LRRK2 +	GBA +	LRRK2- GBA-	Р	LRRK2 + vs LRRK- GBA-	GBA + vs LRRK2- GBA-
At diagnosis	80.95 <u>+</u> 15.80	137.43 <u>+</u> 56.11	88.70 <u>+</u> 6.81	0.517	0.723	0.178
1 year before diagnosis	47.56 <u>+</u> 9.32	108.25 <u>+</u> 54.75	59.13 <u>+</u> 5.67	0.322	0.500	0.099
2 years before diagnosis	30.68 <u>+</u> 6.68	89.11 <u>+</u> 54.68	36.21 <u>+</u> 4.10	0.137	0.663	0.024*
3 years before diagnosis	19.73 <u>+</u> 5.13	80.82 <u>+</u> 54.77	23.38 <u>+</u> 3.59	0.050	0.762	0.006*

Table 1 Likelihood ratio of LRRK-subjects, GBA-subjects and idiopathic subjects before diagnosis

Data are given as mean \pm standard deviation.

* P-value < 0.05.

Conclusions: The PD manifestation of *GBA* L444P mutation carriers is early and gradual in the pre-diagnostic stage; while the manifestation of *LRRK2* G2385R or R1628P mutation carriers tends to be radical within the last year before diagnosis, possibly representing the breakdown of compensation.

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First Reported Case of Parkinsonism in a Patient with Argininosuccinate Lyase Deficiency

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Objective: The purpose of this case report is to detail the phenotype of parkinsonism encountered in a patient with Argininosuccinate Lyase Deficiency (ASLD) that has never been previously reported.

Background: ASLD is a rare metabolic disorder of the urea cycle, resulting in decreased conversion of argininosuccinate into fumarate and arginine, causing argininosuccinic aciduria and low arginine levels. Movement disorders, mostly dystonia, have been previously reported in ASLD, but parkinsonism has not been reported. Methods: Case report: pubmed literature search for argininosuccinate lyase deficiency, ASLD, urea cycle disorder, parkinsons, parkinsonism, movement disorder, dystonia, microdeletion, PRODH, DGCR2, 22q11.2 Results: A 61-year-old female with no significant family history and previously unknown cause of moderate intellectual disability was evaluated for tremors and falls and diagnosed with new onset parkinsonism. On examination dysmorphic facial features were appreciated with high forehead, dolichocephaly, high arched palate and short 5th metacarpals. Neurological examination showed mild symmetric mixed rest and action tremor present in all four extremities, rigidity, mild bradykinesia and postural instability. Also noticeable were cerebellar ataxia signs, upper motor neuron signs, frontal release signs and severe oculomotor impersistence with apraxia. Brain MRI revealed mild volume loss and mild chronic small vessel disease. Workup revealed markedly elevated urine argininosuccinic acid levels with normal ammonia level. Serum and urine proline levels were normal. Microarray showed an incidental finding of heterozygous 108 kb deletion at chromosome 22q11.21 involving PRODH (Proline dehydrogenase) and DGCR2 (DiGeorge syndrome critical region 2). No association with parkinsonism has been reported with these genes. A diagnosis of ASLD was made after complete work up by the metabolic expert and was started on treatment.

Conclusions: Urea cycle disorders (UCDs) such as ASLD can have prominent neurocognitive manifestations. Symptoms appear to be unrelated to the severity or duration of hyperammonemia episodes, unlike other UCDs, suggesting an alternative mechanism of neuronal insult. This patient's symptoms appear to be unrelated to her incidental microdeletions in *PRODH* and *DGCR2*. Our case is the first reported phenotype of Parkinsonism in patient with ASLD and hopefully will be useful to future studies in this area

Capgras syndrome in advanced Parkinson's disease

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Objective: The aims of this study were to investigate the frequency of Capgras syndrome in Parkinson's disease patients who have undergone Deep Brain Stimulation (DBS) surgery and to report the characteristics of Parkinson's disease patients with Capgras syndrome following DBS surgery.

Background: Psychosis is common in Parkinson's disease, especially in advanced disease. Though visual hallucinations are the most common manifestation, other psychotic symptoms can occur, including delusions. One type of delusion that may occur is Capgras syndrome (1). In Capgras syndrome, the affected individual believes that a closely related person (or sometimes inanimate object) has been replaced by an impostor or duplicate. Capgras syndrome has been reported in a small number of Parkinson's patients with advanced disease (1). A recent report of Capgras syndrome occurring in a Parkinson's disease patient following DBS targeting the subthalamic nucleus raised the possibility that DBS may be involved in the development of Capgras syndrome (2).

Methods: Using a clinical database, we identified 115 Parkinson's disease patients who underwent unilateral or bilateral DBS targeting either the subthalamic nucleus (STN) or globus pallidus interna (GPi) over a 6 year period. We performed a retrospective review of the electronic medical record to collect clinical information from the presurgical, surgical, and post-operative follow-up notes. To identify those with Capgras syndrome, we searched each subject's record at least 6 months after DBS surgery using search terms specific to Capgras syndrome. When search terms were present in a subject's record, clinical notes was reviewed to verify the diagnosis.

Results: Of the 115 PD patients in this cohort, three developed Capgras syndrome. Surgical targets in these three patients were the STN in two patients and GPI in one patient. The length of time between surgery and development of Capgras syndrome varied, and all three had evidence of worsening cognition prior to development of Capgras syndrome.

	All (n=115)	Case 1	Case 2	Case 3	Previously Reported Patient
Sex	38 F/ 77 M	F	F	M	M
Age at PD symptom onset, y (I.Q. range)	53.7 (47.9, 58.1)	50.6	58.4	61.7	71
Age at DBS surgery, y (I.Q. range)	63.5 (58.8, 68.1)	63.2	63.4	71.8	76
Duration of disease at time of surgery, y (SD)	10.3 (4.7)	12.6	4.9	10.1	5
Time between surgery and Capgras syndrome, y		~6 months	~4.5 years	~8 months	3 weeks
Surgical Indication	85 Motor Fluctuations/ 18 Tremor/ 7 Tremor & Motor Fluctuations/ 5 Medication Intolerance	Motor Fluctuations	Motor Fluctuations	Motor Fluctuations	Tremor
Neurosurgical Target	62 STN/ 53 GPi	GPi	STN	STN	STN
Side of Surgery	95 Bilateral/ 20 Unilateral	Bilateral	Bilateral	Bilateral	Bilateral

Table 1. Characteristics of Parkinson disease patients who underwent deep brain stimulation surgery

*Abbreviations: F=female; M=male; y=years; I.Q.=interquartile; SD=standard deviation; GPi=globus

pallidus interna; STN=subthalamic nucleus.

Conclusions: Even in advanced Parkinson's disease patients who underwent DBS, Capgras syndrome is an uncommon occurrence. Capgras syndrome is likely a manifestation of psychosis in a subset of patients and DBS may not alter its onset. Given the distressing nature of the condition, patients with advanced Parkinson's disease who

undergo DBS should be regularly screened for Capgras syndrome in addition to other more common symptoms of psychosis.

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Systematic Evaluation of Major and Minor Psychotic Symptoms in Parkinson's Disease

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Objective: To evaluate a structured clinical interview (SCI) based on the Parkinson's disease-specific Scale for the Assessment of Positive Symptoms (SAPS-PD) in the identification of delusions and olfactory, tactile, gustatory, and minor hallucinations in PD psychosis (PD-P).

Background: Most PD-P rating scales focus on visual hallucinations (VHs), auditory hallucinations, and specific delusions, but not other psychotic symptoms.

Methods: Cross-sectional analysis of 150 outpatients with PD (40% female; ages 67.0+9.7 years). Median disease duration was 81 months (range 3-301), modified Hoehn and Yahr was 2 (range 1-5), UPDRS motor score was 22 (range 3-73), and MoCA was 26 (range 16-30). Subjects participated in an SCI that included the SAPS-PD with additional prompts for delusions and olfactory, tactile, gustatory, and minor hallucinations. Symptoms detected by this SCI were compared with those identified by standard clinical assessments.

Results: Our SCI detected psychotic symptoms in 45 subjects (30%). Hallucinations were present in 43 subjects (29%); most commonly VHs (n=37, 25%), followed by olfactory (n=8, 5%), auditory (n=3, 2%), tactile (n=3, 2%), and gustatory hallucinations (n=1, 1%). Well-formed major VHs were reported by 7 (5%), and minor VHs by 36 (24%); these included passage hallucinations (n=29), illusions (n=17), and presence hallucinations (n=10). Delusions were endorsed by 12 subjects (8%), and were mostly persecutory (n=8). Overall, our SCI had much greater sensitivity for detection of psychotic symptoms than the SAPS-PD alone (42%), clinic visit (36%), Non-Motor Symptoms Questionnaire (27%), or UPDRS part 1 (20%). While the clinic visit identified 86% of major visual hallucinations, it missed 100% of tactile and gustatory hallucinations, 92% of delusions, 75% of olfactory hallucinations, and 72% of minor VHs.

Conclusions: The prevalence of delusions and olfactory, tactile, gustatory, and minor hallucinations is markedly underestimated by standard measures. Our SCI more than doubled the number of identified psychotic symptoms compared with other clinical assessments.

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Perceptions of Fluctuation Treatment in Parkinson's Disease Impact Suicidality

J. Hinkle, K. Perepezko, Z. Mari, L. Marsh, G. Pontone (Baltimore, MD, USA)

Objective: Our goal was to examine the relationship between suicidality and motor fluctuations in Parkinson's disease (PD) patients.

Background: On/off motor fluctuations in PD are an inevitable consequence of dopaminergic therapy and can be associated with mood fluctuations, including severe dysphoria. These affective symptoms may be overlooked in the treatment of motor fluctuations.

Methods: We analyzed data from the Methods of Optimal Depression Detection in Parkinson's Disease (MOOD-PD) study of 223 individuals with PD recruited from three community-based movement disorder clinics. Subjects were asked to report if they experienced motor fluctuations and, if yes, if they had received treatment for these motor fluctuations. Suicidality was measured using items from three clinician-rated depression scales: the Hamilton Depression Rating Scale (HAM-D-17); the Montgomery-Åsberg Depression Rating Scale (MADRS); and the Inventory for Depressive Symptomatology (IDS-C). Multivariate Poisson regression analyses tested whether self-reported motor fluctuations and their treatment status were associated with suicidality while controlling for recognized risk factors.

Results: Thirty-one patients (13.9%) reported suicidal thoughts and 89 (39.5%) self-reported motor fluctuations, of whom 21 (23.6%) perceived their fluctuations as untreated. Patients with untreated motor fluctuations more frequently had a current depressive disorder (p < 0.001) and endorsed suicidality (p = 0.006) than patients with treated or no motor fluctuations. They also had significantly higher total scores on the HAM-D-17, MADRS, and IDS-C depression scales (p < 0.001 for each). Regression analyses showed significant associations between untreated motor fluctuations and higher scores on each suicide question extracted from the HAM-D-17, MADRS, and IDS-C (p < 0.05 for each).

Variable	NF (n=134)	TF (n=68)	UF (n=21)	р
	Demographic	Information		
Age, years?	69.0 (67.3-70.7)	62.0 (59.8-64.1)	66.4 (63.0-69.9)	< 0.001***
Age at PD onset, years [†]	62.8 (60.9-64.7)	49.0 (46.3-51.7)	57.8 (53.3-62.3)	< 0.001***
Sex, male ¹	94 (70.1%)	47 (69.1%)	12 (57.1%)	0.499
Mini-Mental State Exam!	28.4 (28.1-28.6)	28.1 (27.7-28.6)	28.4 (27.7 (29.1)	0.895
Family history of PD [‡]	33 (24.6%)	17 (25.0%)	7 (35.0%)2	0.656
	Parkinson's diseas	e characteristics		
Disease duration	4.5 (3.9-5.1)	11.0 (9.4-12.6)	7.0 (4.8-9.1)	< 0.001***
Hoehn & Yahr Stage [†]	2.1 (2.0-2.2)	2.4 (2.3-2.6)	2.3 (2.0-2.6)	0.007**
UPDRS-III Motor Examination Score [†]	16.8 (15.2-18.4)	19.6 (16.4-22.8)	22.0 (17.7-26.4)	0.069
Levodopa Usage (yes/no)	118 (88.1%)	68 (100%)	20 (95.2%)	0.003**
LEDD (mg/day) [†]	510 (457-564)	897 (775-1018)	721 (596-846)	< 0.001***
# with Bilateral DBS (n,%)	7 (5.2%)	19 (27.9%)	0	
	Fluctua	ations		
UPDRS-II ADL "on" vs. "off" score difference [†]	1.24 (0.94-1.54)	4.50 (3.47-5.53)	3.38 (1.19-5.57)	< 0.001***
Mood Fluctuations (non-UPDRS) [‡]	2 (1.5%)	10 (14.7%)	4 (19.0%)	< 0.001***
	Psychiatric	Measures		
Quality of Life (PDQ-8) [†]	4.9 (4.1-5.6) ¹	8.0 (6.9-9.1)	9.2 (6.9-11.4)	< 0.001***
HAM-D-17 total score [†]	6.0 (5.3-6.8)	7.7 (6.5-8.8)	13.0 (10.1-15.9)	< 0.001***
MADRS total score [†]	6.5 (5.4-7.7)	8.3 (6.6-10.0)	16.0 (11.5-20.6)	< 0.001***
IDS-C total score	10.9 (9.4-12.3)	12.8 (10.7-14.8)	22.8 (17.0-28.6)	< 0.001***
Any current depressive disorder (DSM-IV TR diagnosis) [‡]	64 (47.8%)	47 (69.1%)	18 (85.7%)	< 0.001***
Suicidality Present [‡] (yes/no)	14 (10.4)	9 (13.2%)	8 (38.1%)	0.006**

Table 2: Subject Characteristics, Grouped by Presence of Self-Reported On/Off Symptoms (n=223)

 $^{2}n=20.$

[†]p-values derived from Kruskal-Wallis tests

¹p-value derived from Fisher's exact tests.

*p<0.05, **p<0.01, ***p<0.001.

Patients with a score of 1 or greater on any of the three depression scale suicide items were counted as having suicidality present.

Suicide Scale Question (Outcome)	Independent	Odds ratio	95% CI	р
2	UPDRS-II: On vs. off total score difference	1.04	0.94 to 1.16	0.417
	UPDRS-III: Motor examination total score	1.03	1.01 to 1.06	0.011*
HAM D.17	Endorsed Mood Fluctuations (non-UPDRS)	3.34	1.47 to 7.60	0.004**
HAM-D-1/	Self-reported no on/off symptoms (reference)		•	
	Self-reported treated on/off symptoms	0.99	0.32 to 3.03	0.987
1	Self-reported untreated on/off symptoms	2.74	1.10 to 6.86	0.031*
2	UPDRS-II: On vs. off total score difference	1.03	0.95 to 1.13	0.465
	UPDRS-III: Motor examination total score	1.03	1.01 to 1.05	0.009**
MADDE	Endorsed Mood Fluctuations (non-UPDRS)	2.85	1.36 to 5.99	0.006**
MADRS	Self-reported no on/off symptoms (reference)			
	Self-reported treated on/off symptoms	0.94	0.34 to 2.60	0.908
	Self-reported untreated on/off symptoms	2.74	1.15 to 6.55	0.023*
	UPDRS-II: On vs. off total score difference	1.07	0.98 to 1.17	0.117
	UPDRS-III: Motor examination total score	1.03	1.01 to 1.06	0.002**
IDC C	Endorsed Mood Fluctuations (non-UPDRS)	3.36	1.57 to 7.21	0.002**
IDS-C	Self-reported no on/off symptoms (reference)			
	Self-reported treated on/off symptoms	1.06	0.37 to 3.05	0.909
	Self-reported untreated on/off symptoms	2.81	1.17 to 6.75	0.020*

Table 3: Poisson Regression: Suicidality and UPDRS, Self-Report, or Mood Fluctuation Data (n=223)

Each model includes the following additional covariates: current depressive disorder (DSM-IV TR diagnosis), history of alcohol dependence, LEDD, disease duration, and sex. *p<0.05, **p<0.01.

Conclusions: Suicidal thoughts may be more likely in PD patients who recognize motor fluctuations but have not received treatment for them. Our findings underscore the importance of inquiring about mood changes once a patient begins to experience motor fluctuations.

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Domain-Specific Cognitive Impairment in Non-Demented Parkinson's Disease Psychosis

J. Hinkle, K. Perepezko, C. Bakker, T. Dawson, V. Johnson, Z. Mari, C. Marvel, K. Mills, A. Pantelyat, O. Pletnikova, L. Rosenthal, M. Shepard, D. Stevens, J. Troncoso, J. Wang, G. Pontone (Baltimore, MD, USA) **Objective:** Our objective was to determine whether psychosis in non-demented Parkinson's disease (PD) patients is associated with domain-specific cognitive impairment on the Mini-Mental State Exam (MMSE).

Background: Cognitive impairment, an important and common complication of PD, has been associated with the presence of psychosis. Identifying the cognitive domains impaired among PD patients with psychosis is critical for understanding the pathophysiology of psychosis and may help guide treatment strategies.

Methods: We analyzed data from 137 patients enrolled in the Morris K. Udall Parkinson's Disease Research Center of Excellence Longitudinal Study at Johns Hopkins University.Psychosis diagnoses were established by psychiatrist interview per DSM-IV criteria. Visits where patients were diagnosed with dementia were excluded from analysis. We used generalized estimated equations (GEE) to model the relationship between MMSE subscale scores and psychosis, adjusting for potential confounding variables identified through univariate analysis.

Results: Nineteen patients in our non-demented sample (13.9%) were diagnosed with psychosis at baseline and the cumulative prevalence of psychosis among non-demented patients in the study was 22.6% (31 patients). In univariate analyses of patients at baseline, disease duration (p = 0.042) and scores on the language (p < 0.001) and intersecting pentagon (p = 0.006) MMSE subscales were significantly associated with psychosis. In multivariate GEE analyses, psychosis was significantly associated with lower scores on the orientation (odds ratio: 0.73; 95% CI: 0.58-0.93; p = 0.011), language (odds ratio: 0.64; 95% CI: 0.48-0.86; p = 0.003), and intersecting pentagon (odds ratio: 0.43; 95% CI: 0.20-0.92 p = 0.030) subscales of the MMSE.

Table 3: Clinical and	l demographic	characteristics (of sample	at baseline	(n=137)
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Characteristic	Median or n (%)	Standard deviation	Range
Age at enrollment, years	67.0	10.1	42.1 to 90.4
Age at diagnosis, years	59.7	10.8	36.0 to 86.4
Disease duration, years	5.0	5.1	0.0 to 31.0
Education, years	9	4.5	2 to 27
MMSE	28	2.7	17 to 30
Hoehn & Yahr, n (%) (1) (1.5) (2) (2.5) (3) (4) (5)	11 (8.0%) 6 (4.4%) 51 (37.2%) 32 (23.4%) 25 (18.2%) 11 (8.0%) 1 (0.7%)	_	_
Sex, male	80 (58.4%)	_	_

Table 4: Overview of patient participation in longitudinal follow-up evaluations (n=137)

Variable	Statistic
Length of follow-up, years, median (IQR) (range)	3.8 (2.0-6.9) (1.4-15.8)
Time between serial evaluations, years, median (IQR) (range)	2.1 (1.9-2.3) (0.9-4.7)
No. serial evaluations (1/2/3/4/5/6/7/8)	40/47/14/19/5/6/3/3
Total evaluations included in analysis (psychosis diagnoses)	358 (50)
Period prevalence of psychosis, n (%)	31 (22.6%)

IQR = interquartile range. Length of follow-up and average time between evaluations only calculated for patients with at least two serial observations (n=97). "Psychosis diagnoses" indicates the number of evaluations where a patient was diagnosed with psychosis, whereas total incidence of psychosis indicates the total number of patients who were diagnosed with psychosis at least once during the study.

Table 5: Univariate and multivariate regression analyses with GEE evaluating factors associated with psychosis.

	Univariate regr	ession	Multivariate regression		
Independent Variable	Odds Ratio (95% CI)	р	Odds Ratio (95% CI)	р	
Age	1.02 (0.98-1.06)	0.276		2 - 2	
Disease duration	1.06 (0.99-1.13)	0.110	-	-	
Hoehn & Yahr Stage	1.72 (1.00-2.94)	0.048*			
LEDD (mg/day/500)	1.47 (1.08-2.01)	0.015*		-	
Education	0.90 (0.83-0.98)	0.017*		-	
Female sex	0.48 (0.20-1.18)	0.110		-	
Anticholinergic medication usage	2.00 (0.83-4.82)	0.120		1	
MMSE: Registration	0.54 (0.26-1.14)	0.100	—	_	
MMSE: Attention and calculation	0.82 (0.62-1.07)	0.140	_	_	
MMSE: Recall	0.83 (0.64-1.09)	0.180	—	_	
† MMSE: Orientation	0.68 (0.53-0.87)	0.002**	0.73 (0.58-0.93)	0.011*	
† MMSE: Language	0.62 (0.46-0.83)	0.001**	0.64 (0.48-0.86)	0.003**	
† MMSE: Intersecting pentagons	0.36 (0.18-0.72)	0.004**	0.43 (0.20-0.92)	0.030*	

LEDD, Levodopa Equivalent Daily Dosage. *p < 0.05; **p < 0.01.

A univariate logistic regression model with GEE was created for each of the independent variables listed, with the corresponding odds ratios, 95% confidence intervals, and p-values. LEDD values were divided by 500 to facilitate odds ratio interpretation.

[†]Three multivariate logistic regression models with GEE were created for the three MMSE subscales that were significantly associated with psychosis in univariate. Each multivariate model included Hoehn & Yahr stage, LEDD, and years of education as covariates.

Conclusions: In PD, executive dysfunction, disorientation, and impaired language comprehension are associated with increased odds of psychosis, which could suggest cortical co-localization of these symptoms. Domain specific cognitive deficits assessed using the MMSE may be clinically useful for identifying PD patients at elevated risk for psychosis.

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Suicidality in Parkinson's Disease: A Case Control Study M. Akbostanci, E. Bayram, D. Sayar, T. Ayidaga (Ankara, Turkey) Objective: To investigate suicidality in Parkinson's disease (PD) by a case control study **Background:** Depression, a risk factor for suicidality, is rather common in PD patients. Nevertheless, a small number of clinical studies report conflicting data on suicidality in Parkinson's disease (PD). In addition, to the best of our knowledge, this is the first study to investigate suicidal ideation in a case control manner.

Methods: One hundred PD patients, and 100 age-, sex-, years of education-, and marital status- matched healthy controls (HCs) were included. Cognitive impairment was assessed by Mini Mental State Examination (MMSE) and participants with a score <24 were excluded. Beck Depression Inventory (BDI) and Suicide Probability Scale (SPS) were filled by each participant. For PD group, data on disease duration, Hoehn-Yahr stages (HYS), levodopa equivalent daily doses (LEDD), and whether they had subthalamic deep brain stimulation (DBS) or not were obtained. As data were not normally distributed, nonparametric analyses were used.

Results: All data are reported as mean (standard deviation) or number (percentage). Suicide Probability Scale score was significantly lower in PD group (56,6 (+-12,9) vs 63,9 (+-13,5) U=3367.5, p<.01), lower score meaning lower suicidality. Demographics and scale scores of each study group are summarized in Table 1. Disease features of PD group are summarized in Table 2. Healthy controls had a significantly higher MMSE score. Although SPS scores were significantly lower in PD patients both groups had similar BDI scores. Suicide Probability Scale had a moderate positive relationship with BDI and a very weak negative relationship with MMSE (rs=.515 p<.01; rs=. .142, p=.045). For PD group, SPS had weak positive relationships with disease duration and LEDD (rs=.219 p=.037; rs=-.213, p=.033). Although MMSE and BDI scores were significantly different HYS (X2 (5) = 8.787, p=.118; X2 (5) = 3.569, p=.613), SPS scores were significantly different (X2 (5) =11 .983, p=.035) (Figure 1). Nevertheless; MMSE, BDI and SPS were not affected by DBS (U=708, p=.784; U=735, p=.978; U=544.5, p=.082). **Table 1.** Means (standard deviations) and comparisons of demographic features and scale

results of two groups

	Parkinson's disease patients	Healthy controls	Statistical analysis
Age	59,4 (10)	57,1 (10,8)	U=4211, p=.054
Sex	60 (60%) male 40 (40%) female	54 (54%) male 46 (46%) female	X ² (1) = .734, p=.391
Years of education	9,6 (5)	10,1 (4)	U=4643.5, p=.373
Marital status	91 (91%) married 1 (1%) single 8 (8%) divorced/widow	86 (86%) married 8 (8%) single 6 (6%) divorced/widow	X ² (2) = 5.871, p=.053
Mini Mental State Examination score	27,8 (1,7)	28,4 (1,5)	U=3972, p=.01
Beck Depression Inventory	10,7 (9,1)	10,3 (7,5)	U=4945.5, p=.894
Suicide Probability Scale	56,6 (12,9)	63,9 (13,5)	U=3367.5, p<.01

Table L. Discuse reduces of rankinson's discuse patient	Table	2.	Disease	features	of	Parkinson	's	disease patients	s
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Disease duration	6,8 (6,1)	
Hoehn-Yahr stages	Stage 1- 15 (15%) Stage 1,5- 2 (2%) Stage 2- 46 (46%) Stage 2,5- 12 (12%) Stage 3- 24 (24%) Stage 4- 1 (1%)	
Levodopa equivalent daily dose	747,3 (501,1)	
Number of patients with Deep Brain Stimulation	18 (18%)	





Statistical significance is marked with * for p<.05

Conclusions: Suicidality is lower in PD compared to healthy controls. Depression is a risk factor and disease severity increases suicidality in PD.

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Absence of depression in de novo Parkinson's disease: A benign motor phenotype?

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Objective: This study aimed to assess the impact of early depression on motor deficits relative to the level of striatal dopaminergic depletion in patients with *de novo* Parkinson's disease.

Background: Depression frequently accompanies Parkinson's disease and often precedes the onset of motor symptoms.

Methods: We analyzed the data of 474 non-demented patients with *de novo* Parkinson's disease (mean age, 64.6 ± 9.8 years; 242 men) who underwent both dopamine transporter scan and depression assessment using the Beck Depression Inventory.

Results: Patients were classified into tertile groups by Beck Depression Inventory score. The high tertile group (Beck Depression Inventory score =15, n = 157) showed more severe motor deficits and lower cognitive function than the low tertile group (Beck Depression Inventory score =7, n = 158; p = 0.025 and p = 0.008, respectively). Parkinson's disease motor subtypes differed among the three tertile groups (p = 0.007); more patients with the

postural instability/ gait difficulty subtype (49.7%) were included in the high tertile group than in the low tertile group (32.3%). However, dopamine transporter bindings in striatal subregions were similar among the three groups. After controlling for dopamine transporter binding in the posterior putamen as well as age, sex, symptom duration, Parkinson's disease motor subtype, and Mini-Mental State Examination score, the lowtertile group exhibited fewer motor deficits thanthe other groups.

Conclusions: These results demonstrate that depression level influences motor deficit severity relative to the striatal dopamine depletion level in early Parkinson's disease and suggest that the absence of depression in *de novo* Parkinson's disease is a benign motor phenotype.

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Improving Diagnosis and Treatment of Anxiety in Parkinson's Disease: Idata-Pd Study

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Objective: We investigated PD-specific features of anxiety for clear conceptualisation, and assessed targeted psychotherapy for anxiety in Parkinson's disease (PD).

Background: Anxiety is poorly diagnosed in PD and there is no evidence-based treatment for anxiety in PD. **Methods:** PD patients were recruited from neurology outpatient clinics and the Queensland Parkinson's Project database. Patients with dementia or prior neurosurgery were excluded. Eligible participants completed self-report questionnaires and a diagnostic interview. A subset with anxiety were offered 6 weeks Cognitive Behavioural Therapy (CBT) for anxiety. Carers were included in CBT sessions.

Results: Of 90 patients, 52% met diagnostic criteria for a DSM-IV anxiety disorder. We profiled 30 PD-specific anxiety symptoms in all patients. Frequent (>25%) PD-specific anxiety symptoms included distress, worry, fear, agitation, embarrassment and social withdrawal due to motor symptoms and PD medication complications1. A new inventory was developed based on these results (PD-specific Anxiety Inventory, PD-SAI). CBT phase 1 feasibility study2: Twelve out of 17 PD patients with DSM-IV anxiety disorders completed the intervention. This uncontrolled sample showed a significant reduction in Hamilton Anxiety Rating Scale scores in PD immediately post CBT [t(11)=3.59, p<0.01], maintained at 3-month [t(8)=2.83, p=0.02] and 6-month [t(7)=2.07, p=0.04] follow-up. Improvements in the UPDRS motor scores [t(11)=2.41, p=0.04] and PD Cognitive Rating Scale Scores [t(11)=-2.92, p=0.01] were observed post intervention and at followup. A reduction in carer burden assessed using the Zarit Burden Inventory [t(11)=2.68, p=0.03] was seen at post-CBT, but was not maintained at followup. CBT phase 2 RCT: Inclusion was commenced in Aug 2016 for a controlled CBT trial for anxiety in PD (ACTRN12616000764437). To date, 3 patients in the CBT intervention group and 2 in the control group have completed the trial. Reduced Parkinson's Anxiety Scale (PAS) scores were evident in the intervention group (mean difference between pre and post CBT= 4.33; SD=7.02) compared to controls (mean difference= 1.00; SD=4.24). Conclusions: This study demonstrates preliminary evidence for effectiveness of CBT for anxiety in PD. Furthermore identifying PD-specific symptoms of anxiety should help the diagnosis and selection of PD patients with anxiety for treatment such as CBT.

(parts were presented at ANZAN 2016)

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Electrophysiological markers for emotional and cognitive impairment in Parkinson's disease

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Objective: This study aims to identify markers for emotional and cognitive dysfunctions in Parkinson's disease (PD) using non-invasive electroencephalography (EEG). This study investigates event related potential (ERPs) elicited when evaluating for valence judgements on negative and neutral target words in an automatic affective priming paradigm, and examines correlates with depression and cognitive impairment scores.

Background: Neural mechanisms underlying common neuropsychiatric deficits such as depression and cognitive impairment are poorly understood in PD. EEGs are better tolerated by patients with PD, allows recordings of neural events as they unfold at a millisecond time frame, and may serve as potential markers for improving diagnostic accuracy and monitoring disease progression.

Methods: Fifty non-demented PD patients unmedicated for depression or anxiety completed an affective priming task while EEG was simultaneously recorded. The paradigm presented prime and target word pairs of negative or neutral valence at a 250ms interval. Participants were asked to evaluate the valence of the target word by button

press. Depression, anxiety, and cognitive impairment were measured using rating scales. Repeated measures ANCOVA and correlational analyses were performed and examined whether ERPs varied as a function of depression, anxiety and cognitive impairment.

Results: Key findings were, reduced central parietal Pz-P300 and LPP difference waves between congruent and incongruent neutral targets in patients with higher depression scores, reduced Pz- N400 difference waves between incongruent and congruent neutral targets in patients with higher depression scores and cognitive impairment scores, and a loss of left central Slow Negative Wave (SNW) in patients with higher cognitive impairment scores. **Conclusions:** The present study identifies ERP markers relating to emotional and cognitive dysfunction in PD, and advances knowledge in the neural underpinning of these common neuropsychiatric deficits in PD.

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Compulsive sexual behaviour in Parkinson's disease is associated with higher doses of levodopa

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Objective: To assess whether compulsive sexual behaviour in individuals with PD is associated with higher doses of levodopa.

Background: The lifetime prevalence of compulsive sexual behaviour in PD is estimated to be 2.7%. In patients using dopamine agonists (DA) this number rises to 7.4%. Male gender, earlier PD onset, younger age and higher doses of DA are recognised risk factors. (1)

Methods: Patients with ICBs were seen at the National Hospital for Neurology and Neurosurgery, London, UK during 2005-2016. All patients were screened for the presence of impulsive compulsive behaviours and the hospital notes were reviewed by a movement disorder specialist for clinical, demographic and treatment data when ICBs were most active.

Results: 128 PD patients with ICBs were identified. Seventeen cases were excluded because the data on dopaminergic treatment was incomplete. The remaining 111 patients were divided in two groups based on the presence or absence of hypersexuality: HS+ (N = 55) and HS- (N = 56). Age at PD onset and PD duration until development of ICBs did not differ between groups. There was a male predominance in the hypersexuality group (HS- 60.7%; HS+ 94.5%; p < 0.001). Patients with hypersexuality were younger when ICBs emerged (HS- 59.16 years; HS+ 54.62; p = 0.02). More than one ICB was present in 48.2% of individuals without and 76.36% of individuals with compulsive sexual behaviour (p = 0.002). A similar number of individuals in both groups were using levodopa (HS- 91%; HS+ 98.18%; p = 0.206), dopamine agonists (HS- 89.2%; HS+ 94.54%; p = 0.48) and MAO inhibitors (HS- 26.7%; HS+ 36.3%; p = 0.312). Levodopa equivalent daily dose (LEDD) was calculated as previously described. (2) Total LEDD (HS- 1163.6; HS+ 1400.15; p = 0.014) and levodopa daily dose (HS- 704.93; HS+ 994.51; p = 0.043) were significantly higher in the HS+ group, whereas DA LEDD did not differ between groups (HS- 357.86; HS+ 385; p = 0.802).

Conclusions: Our study confirms that compulsive sexual behaviour is more frequently seen in male PD patients. Furthermore, compulsive sexual behaviour emerged earlier and was associated with higher doses of levodopa compared to other ICBs. Finally, multiple ICBs are frequently seen in all patients with behavioural addictions but seem to be particularly common in PD patients with compulsive sexual disorder suggesting that treatment strategies may be even more challenging in this subgroup of patients.

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Changes in motor subtype designation of early Parkinson's disease patients

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Objective: To examine changes in the designation of motor subtypes in Parkinson's disease (PD) patients within five years of diagnosis.

Background: Distinct motor subtypes of PD have been identified through both clinical observation and data-driven approaches. However, the extent to which motor subtypes are mutable during disease progression is not fully known.

Methods: We used the Parkinson's Progression Markers Initiative database of 423 newly diagnosed PD patients to identify unique motor subtypes. Specifically, we found distinct 1) Tremor Dominant (TD), 2) Axial-dominant (AxD), 3) Appendicular-dominant (ApD), 4) Rigidity-dominant (RD), and 5) Postural Instability and Gait Disorder (PIGD) groups. We converted these categories to an ordinal scale by assigning the subtypes numerical values 1 through 5, as they progressed on the spectrum between TD to PIGD respectively. Next, for each off-medication motor assessment time point, we assigned patients to one of these five subtypes. Patients with consistent subtypes

and patients with inconsistent subtypes were analyzed separately. For patients with inconsistent subtypes, we computed relative subtype frequencies over time using a bin width of 6 months to produce sample-level averages. **Results:** The number of motor assessment time points for each patient ranged from 2 to 14 (M= 6.81, SD = 2.40). Subtypes for 54.8% of patients were consistent at every time point while 45.2% of patients fit criteria for at least two different subtypes across time points. A chi-square test suggests that subtype frequencies change over time, X2(25) = 42.01, p < 0.05. Using the numerical scale described above, a linear regression showed that average subtype increased with disease duration, R2 = 0.61, p < 0.05 [figure1]. In other words, on the spectrum from TD to PIGD, the cohort as a whole progressed away from a TD phenotype with disease progression. These results suggest that at least in early PD, motor subtypes may change or progress over time.



Conclusions: Early PD subtypes are stable for some patients and unstable for others. By frequency, more patients are classified as TD soon after diagnosis. There is an overall shift away from TD within the first five years of diagnosis. These results suggest that motor subtype designation may be influenced by disease duration.

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Freezing of gait in Parkinson's disease: Clinical features and possible predictors

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Objective: To compare clinical features of patients with Freezing of gait (FOG+) and without FOG (FOG-), and explore probable predictors of early onset freezing.

Background: FOG is a motor phenomenon observed in patients with Parkinson's disease (PD). The pathogenesis and natural course of FOG in PD has not been fully understood.

Methods: A retrospective chart review of 100 patients with PD (FOG+:50,FOG-:50) was performed at the Department of Neurology, National Institute of Mental Health and Neurosciences, Bangalore, India. FOG+ patients were subdivided by a median split of time from motor onset to development of FOG (median:6yrs) into early onset FOG [EOFOG(n=24)] and late onset FOG [LOFOG(n=26)].

Results: The mean age at onset (AAO) of PD was 50.24 ± 8.22 yrs in FOG+ and 56.71 ± 7.60 yrs in FOG-. Latency from the onset of motor symptoms to the development of FOG was 6.47 ± 3.97 yrs. In both groups, men outnumbered women (FOG+:men 70%, FOG-:men 74%). FOG+ patients were older than FOG- patients

 $(58.58\pm7.75\text{yrs},54.18\pm8.23\text{yrs},p<0.01)$ and had longer duration of symptoms $(8.16\pm9.86\text{yrs},3.90\pm3.22\text{yrs},p<0.01)$. Off-state freezing was reported in 88%, with freezing occurring on a daily basis in 88%. The mean Freezing of Gait Questionnaire score was 11.88 ± 1.85 . Prevalence of several non-motor symptoms (NMS) were higher in the FOG+ compared to the FOG- patients; these included constipation (56% vs24%, p<0.01), psychosis (50% vs10%, p<0.01), weight loss (46% vs10%, p<0.01) fatigue (48% vs16%, p<0.01) and drooling (36% vs2%, p<0.01). Freezers more frequently reported dyskinesia (64% vs10%, p<0.01) and wearing off (84% vs24%, p<0.01). UPDRS-III off-state scores were significantly higher in freezers $(44.59\pm13.97, 30.51\pm12.09, p<0.01)$.

Comparison of demographic and clinical characteristics did not reveal any significant differences between EOFOG and LOFOG groups. Correlation analysis was performed between the AAO of motor symptoms and the latency of onset of FOG. There was a significant negative correlation between the AAO of motor symptoms and the latency of

FOG, suggesting a later age at onset of motor symptoms to be a predictor of FOG during the course of PD (r - 0.392,p<0.01).

Conclusions: Significant differences exist between FOG+ and FOG-, especially a higher burden of non-motor symptoms in the former group. Older age at onset of motor symptoms of PD may be a predictor of early onset of FOG during the course of illness.

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Serum uric acid levels and freezing of gait in Parkinson's disease

R. Ou, B. Cao, Q. Wei, Y. Hou, Y. Xu, W. Song, B. Zhao (Chengdu, People's Republic of China) **Objective:** To investigate the relationship between serum Uric acid (UA) levels and freezing of gait (FOG) in Parkinson's disease (PD).

Background: UA is a natural antioxidant and iron scavenger in the human body, which has been hypothesized to exert an anti-oxidative effect in PD.

Methods: A total of 321 Chinese PD patients with fasting serum UA evaluated were included in the cross-sectional study. Demographics, clinical features, and therapeutic regimen were collected. The Unified PD Rating Scale (UPDRS) III and Hoehn and Yahr (H&Y) stage were used to evaluate the severity of disease, and the Frontal Assessment Battery (FAB) and Montreal Cognitive Assessment (MoCA) scales were used to assess cognitive function.

Results: PD patients with FOG showed lower proportion of male, longer disease duration, lower body mass index score, lower concentrations of serum UA, higher total levodopa equivalent daily dosage, higher UPDRS III score, greater median H&Y stage, lower scores of FAB and MoCA, and higher frequencies of motor fluctuation, dyskinesia, falls, and festination than patients without FOG (P < 0.05). The binary logistic regression model indicated that high UPDRS III score (OR = 1.049, P < 0.001), fluctuation (OR = 2.677, P = 0.035), dyskinesia (OR = 6.294, P = 0.003), festination (OR = 3.948, P < 0.001), falls (OR = 7.528, P < 0.001), and low serum UA levels (OR = 0.990, P < 0.001) were associated with FOG.

Conclusions: Our study suggests that low serum UA concentration is associated with the occurrence of FOG in PD.

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Accuracy measures of imbalance bedside examination

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Objective: This study explores the accuracy of bedside examinations used to screen for imbalance, using the Berg Balance Scale (BBS) as gold standard (cut-off point:45).

Background: Balance and gait disorders are prevalent in general population, and increase fall risk. The accuracy and reliability (test characteristics) of bedside examination of balance is largely unknown, making it difficult to differentiate in the clinic between patients versus those not prone to falling. Although the BBS is a well-validated and popular tool among physical therapists, it is lengthy and not commonly used in general practice. Therefore, a fast, accurate bedside test for imbalance could be useful.

Methods: 65 subjects (47 females, 72.3%), 44 with balance complains, and 21 controls participated in the study. The average age was 69.37 years old (±9.508). Subjects were evaluated using multiple bedside balance examination tests (truncal sway, UPDRS-raising (from the Unified Parkinson's Disease Rating Scale, UPDRS part 3), stance base, standing with feet close or separated, with eyes open or closed, line of ambulation, tip-toe walking, tandem walking, UPDRS-pull test (multiple cut-off), 3-, 5- and 10-hop unipodal jumping, BARS-gait (from Brief Ataxia Rating Scale, 0=normal), and others.) Then the BBS was administered by blinded physical therapists. The screening ability of each bedside tests (alone or in combinations) was measured using the BBS as gold standard.

Results: 46 participants had a normal balance performance by BBS, while 19 had balance impairment. Highsensitivity tests (over 90%) included: stance base, standing with feet apart eyes closed, standing with feet close eyes open, standing with feet close eyes closed, general gait, pull test(0=normal), 10-hop unipodal jump. High-specificity tests (over 90%): truncal sway, UPDRS-raising, and the pull test(0,1=normal). The combined procedure of 3-hop unipodal jumping and pull test(0,1=normal; failed in either one counted as balance impairment) showed 89% sensitivity and 83% specificity.

Conclusions: The best imbalance screening tests were the UPDRS-pull test(0=normal), the BARS-gait, standing with feet apart-eyes closed, and the 10-hop unipodal jump (each with a sensitivity over 95%). Those with decent specificities, such as truncal sway, raising and UPDRS-pull test (0,1=normal), could rule in people with balance impairment.

Mirror Movements in extrapiramidal diseases

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Objective: To analyze the presence of mirror movements (MM) in different extrapiramidal diseases.

Background: MM are involuntary movements that appear during voluntary activity in contralateral homologous body regions emulating the same motor task. It has been postulated that alteration or functional deficiency of motor programs and neural circuits responsible for unilateral voluntary movements, may result in motor overflow across the midline. Even though, it is known that MM could be present in neurodegenerative diseases but there are few reports of their frequency and characteristics in extrapyramidal diseases.

Methods: We conducted a descriptive transversal study in four groups of patients with different movement disorders: Parkinson's disease (PD), Ataxias, Huntington disease (HD) and Essential Tremor (ET). The assessment included a video tape of five tasks performed: finger-tapping, hand-movements, prono-supination, toe-tapping and the three-step Luria test. MM were evaluated by a movement disorders specialist using a scale previously described (Lang, 2005).

Results: Thirty three of 98 patients presented MM (34%): 16/48 of PD patients, 8/15 of HD patients, 3/8 of subjects with ET and in 6/29 of ataxic patients.PD patients with MM had a shorter time of progression of the disease compared to the patients without MM (2.3 years vs. 12 years). MM were observed in upper limbs in 82% and in lower limbs in 29,4%. In PD patients MM were predominant unilateral and in 81% they were present in the less affected side. Conversely, in patients with ataxia, HD and ET, MM were bilateral (100%, 71,4%, 100% respectively). With the three-step Luria test, MM were present in 25% of PD patients, 67% in ataxic patients, and 14% in HD patients.

Conclusions: In a previous report, our group described that MM were frequent in PD patients. This study shows similar results and reveals that MM would also be present in others movement disorders. The presence of unilateral MM could be a semiological finding to distinguish between PD and other movement disorders. Regarding the pathophysiology underlying MM, it was observed that the basal ganglia are reciprocally and directly connected to the contralateral motor cortex. According to this, it would be possible that modifications of these circuits are implicated.

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Assessing Bone Health in Parkinson's - When and how?

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Objective: To assess the impact of, and practicality of, assessing bone health routinely in people newly diagnosed with Parkinson's disease in a South Wales University Hospital Parkinson's service

Background: People with Parkinson's (PWP) are at an increased risk of fracture through their increased risk of both osteoporosis and falls. It follows that after a fracture, the risk of further falls and the need for institutional care are increased. This negatively impacts on quality of life, morbidity and has significant economic burden. In recent years new tools have emerged for risk-stratification of osteoporosis in Parkinson's along with recommendations for management of bone health.

Methods: Using our clinical patient record and database, we compared two sample cohorts of PWP – those diagnosed in 2010 (n=30) and those diagnosed in 2016 (n=20). We examined whether bone health had been assessed and recorded any subsequent fracture incidences. We applied risk stratification to the 2016 cohort to assess for "gold standard" treatment using the available tools (Qfracture, FRAX). In a separate study, we examined the practicality of using these tools within the framework of the busy Parkinson's clinic setting

Results: None of the 2010 cohort had any documentation of specific screening or risk stratification of bone health. In the 2016 cohort, all patients were eligible for further investigation (DEXA) or treatment (vitamin D or anti-resorptives) on the basis of their QFracture or FRAX scores. PWP found the questionnaires in clinic quick and acceptable, and the time taken to complete the scores ranged from 1-3 minutes which the authors did not feel would add any significant burden to clinical time.

Conclusions: Bone health screening historically has been poor, and newer tools are now available for clinicians. Further study is needed to determine whether the FRAX and QFracture may be too sensitive as all patients diagnosed with PD were deemed eligible for bone health intervention – negating the need for the tools to be used. However, the tools are acceptable and do not significantly prolong clinical consultations.

Beyond shuffling: Gait phenotypes in Parkinson's disease

L. Solis-Cohen, C. Ashton, D. Simon, M. Fox, D. Tarsy, R. Alterman, V. Vanderhorst, L. Shih (Boston, MA, USA) **Objective:** To describe commonly observed gait phenotypes in a cohort of advanced Parkinson's disease (PD) patients.

Background: Gait disorders in PD are varied and complex. Even the most experienced movement disorders neurologists have difficulty characterizing PD-related gait phenotypes because current rating scales lack the necessary qualitative details. Here we propose categorizing Parkinsonian gait in relation to specific gait characteristics such as stride length, base width and regularity of the movements and whether movement is affected by dyskinesia and/or dystonia.

Methods: We studied 18 advanced PD patients who were evaluated at our Parkinson's disease and Movement Disorder Center and subsequently underwent deep brain stimulation between January and October 2016. Patient performance on standardized assessments of gait and motor function was captured including the freezing of gait questionnaire (FOGQ) and UPDRS motor score and gait item 3.10.

Results: Our cohort included 13 men and 5 women (mean age 62.2 +/- 8.1; mean disease duration in years 8.1 +/- 4.0), 14 of whom had gait disturbance. We identified four distinct gait phenotypes in these patients during their most representative on-state: 1) Small, symmetric, shuffling steps (5 patients); 2) Asymmetric hypokinetic stride (2 patients); 3) Asymmetric dyskinetic/dystonic stride (6 patients); 4) Lurching with postural instability (1 patient). The median off-medication UPDRS motor scores for each group were as follows: 51.0 +/- 11.1; 30.0 +/- 1.4; 50.5 +/- 17.4; 40 (single value), respectively. The median FOGQ score for each group were as follows: 5.0+/-3.8; 8.5 +/- 3.5; 5.0 +/- 5.0; 17, respectively. The mean UPDRS gait scores were similar among the four groups (1.0 +/- 0.9; 1.5 +/- 0.7; 2.0 +/- 0.5; 3, respectively).

Conclusions: Our exploratory study of gait disorders in a cohort of advanced Parkinson's disease patients reveals 4 gait impairment categories that are not easily discerned with current gait questionnaires or metrics. Our study highlights the need for further study of Parkinsonian gait phenotypes in PD and their differential responses to deep brain stimulation.

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Distinguishing Subclinical Postural Instability in Early-stage Parkinson's disease and postural instability of normal elderly using Sensory Organization Test and Limit of Stability

S.-K. Lee, J.-H. Park (Bucheon, Korea)

Objective: To distinguish postural instability differences in Parkinson's disease patients and normal elderly patients with computerized dynamic posturography

Background: Postural instability is a core symptom of Parkinson's disease. However, it is uneasy to clinically distinguish mild postural instability of early-stage PD patients from that of normal elderly. Using computerized dynamic posturography, we investigated diagnostic performance of sensory organization test(SOT) and limit of stability(LOS) for detecting subclinical postural instability of early stage PD patients

Methods: Patients with a diagnosis of idiopathic Parkinson's disease, Hoehn-Yahr(H&Y) stage score less than 3, and non-faller were recruited consecutively from the outpatient neurologic clinic of Soonchunhyang University Bucheon Hospital. Total of 38patients (14 females and 24 males) in the age range 46-78 years (mean age: 64 years) and 29 age-matched controls participated in this study;mean duration of disease was 18.7 months (range 6-80 months). The targeted clinical measures included BMI, disease duration, H&Y staging, Schwab-England Activities of Daily Living scale, Unified Parkinson's Disease Rating Scale motor subscore, gait and posture subscore, levodopa-equivalent daily doses, Beck anxiety inventory, and fear of fall. Sensory organization test and LOS were performed using computerized dynamic posturography (Smart Equi-test, Neurocom®, Clakoma, USA).All subjects were tested on their usual drug regimen 2 hours after taking medication. Diagnostic performance of SOT and LOS parameters for distinguishing patients from control in term of postural stability were evaluated by odds ratio obtained from the multiple logistic regression analysis, sensitivity, specificity, accuracy, and AUC. **Results:** Most of the equilibrium scores and composite score of SOT were similar between patients and controls (p>0.05), while LOS variables showed significant differences between both groups (AUC 0.75-0.81,p<0.001).

Among the LOS parameters, mean velocity revealed significant diagnostic performance in all directions. **Conclusions:** Limit of stability is more powerful than sensory organization test in distinguishing subclinical postural instability of early-stage PD patient

Can glabellar and palmomental reflexes differentiate neurodegenerative from non-neurodegenerative parkinsonism?

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Objective: To evaluate if the presence of glabellar and palmomental reflexes in patients with parkinsonism is significantly more common in neurodegenerative etiology compared with non-neurodegenerative etiologies. **Background:** The clinical distinction between neurodegenerative and non-neurodegenerative parkinsonism can be difficult. Misdiagnosis of PD or other neurodegenerative parkinsonian conditions is not uncommon. Diagnostic tests have been developed to increase the accuracy in the diagnosis of parkinsonism. The dopamine transporter scan (DATscan) has become a useful tool in the evaluation of dopaminergic neurodegeneration. Unfortunately, due to limited availability and substantial cost, its use in daily clinical practice is restricted. Other tools have been evaluated to make the distinction between neurodegenerative and non-neurodegenerative parkinsonism. Primitive reflexes are a group of motor-behavioral evoked responses, physiologically present in childhood and suppressed during normal development. The reappearance of these reflexes in adulthood may occur in different neurological conditions including neurodegenerative disorders. To the best of our knowledge, glabellar and palmomental reflexes have not been studied as clinical tools to make the distinction between degenerative and non- neurodegenerative parkinsonism.

Methods: This is a case control prospective study. Patients with neurodegenerative parkinsonism with at least grade 2 loss on a DATscan and patients with non-neurodegenerative parkinsonism confirmed by a normal DATscan were recruited. Patients with significant cognitive impairment were excluded. In each subject, glabellar and palmomental reflexes were elicited and recorded.

Results: Recruitment was completed as of 1/6/2017. Total of 100 patients were recruited, 54 with neurodegenerative parkinsonism, 46 patients with non-neurodegenerative parkinsonism. Two blinded raters will be asked to indicate absence or presence of the reflexes based on the video clip. Presence or absence of the glabellar and palmomental reflexes will be analyzed as categorical variables. Statistical tests will be applied.

Conclusions: Available upon data analysis and completion of study.

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Fatigue in Functional Motor Disorders

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Objective: To investigate fatigue severity and the nature of fatigue in functional motor disorders (FMD). Secondarily, to determine the relationship between fatigue, quality of life, depression and sleep. **Background:** In clinical practice, fatigue seems to be a major problem for patients with FMD. In chronic neurological disorders like Multiple Sclerosis and Parkinson's disease fatigue has been found highly impairing, but studies on this topic in FMD are scarce.

Methods: Baseline data of the ongoing SHIFT-study (Self-Help on the Internet for FMD, a randomised trial), was used. Patients with FMD who were 18 years and older, able to read Dutch and provide informed consent, were recruited by neurologists from all over the Netherlands. Patients filled out an online questionnaires including several validated scales, before randomisation for the trial.

Results: 106 FMD patients were included, with a mean age of 48 years (SD 14). Functional motor symptoms consisted of gait disorder (30%), tremor/jerky movements (35%), dystonia (16%) and paresis (18%). Mean CIS fatigue total score was 89 (SD26), scores on the subscales were fatigue severity 41 (SD12) (max 56), concentration 20 (SD9) (max 35), motivation 14 (7)(max 28) and physical activity 13 (SD5)(max 21). Severe fatigue, (> 35 on the fatigue severity subscale) was present in 72% of patients. Fatigue severity was a significant factor contributing to dichotomised QoL (poor/very poor/neutral (67% of cases) versus good/very good (33% of cases)) in a binary logistic model (p=0,006, odds ratio 0,948 (0,914-0,985)), corrected for depression on the PHQ-9, the SF36 subscale for physical functioning and sleep disturbance. Depression was correlated to fatigue severity (Spearman p<0,001). **Conclusions:** Fatigue is highly prevalent among patients with FMD and is significantly correlated to impaired quality of life. A preliminary comparison with data from Kalkman et al. (2005) in fatigue in neuromuscular disorders, showed a similar percentage of patients (69%) had severe fatigue (chi square, p=0,564). Compared to the largest studied neuromuscular group, myotonic dyostrophia (n=322), Fatigue severity and physical activity were the same, while concentration was more severely impaired (p=0,013) and motivation was less impaired (p=0,0001).

Parkinson's disease subtypes correlate with clinical severity: a Brazilian population study

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Objective: To correlate Parkinson's disease (PD) subtypes with a clinical severity in a Brazilian population sample. **Background:** Current studies have shown that PD may comprise different clinical subtypes. Systematic review has failed to demonstrate a single subgroup classification which may be applied across different populations (1). Therefore, the characterization of local populations help clinicians to provide better management to different patients.

Methods: Patients (N=201) from a reference center in the Southern region of Brazil (Porto Alegre) were evaluated between 2006 and 2014. After signing consent forms, all participants underwent MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Schwab & England (SE) and Hoehn & Yahr (HY) testing. A k-means CA of UPDRS motor scores, age of onset, SE, and HY was performed. A subsequent post hoc testing (chi-square, Kruskal-Wallis, and One-Way ANOVA) was undertaken to compare the patient subgroups. Statistical analysis was conducted using IBM SPSS v.18.

Results: Hierarchical analysis identified three clusters (Table 1). The first group (N=78; 38%) was characterized by early age of onset (56 ± 11), less severe progression (median HY = 2), and less impact on daily life activities (SE = 87 ± 13). The second group (N = 70; 34.8%) was found to have later age of onset (60 ± 11), tremor dominant, and moderate progression and impact on daily life activities (median HY = 2; SE = 75 ± 17). The third group (N = 53; 26.4%), age of onset similar to the second (58 ± 11), more prevalent akinetic-rigid symptoms, and the most severe progression and impact on daily life activities (median HY = 3; SE = 46 ± 24). All motor symptoms were statistically different among the groups (p < 0,01). The SE and HY scales were also statistically different (p < 0,001). The difference of age of onset among subgroups was not significant (p = 0,11).

Subgroups	Early onset	Tremor dominant	Akinetic-rigid dominant	<i>p</i> -value
Sample size	N=78(38%)	N=70(37,8%)	N=53(26,4%)	
Gender	Fem=43 Male=35	Fem=30 Male=40	Fem=21 Male=32	0,16
Age of onset	56 ± 11	60 ± 11	58 ± 11	0,11
Hoehn & Yahr	Mediana 2 [1-4]	Mediana 2 [2-4]	Mediana 3 [2-5]	< 0,001
Schwab & England (Média <u>+</u> DP)	87±13	75±17	46±24	< 0,001
Pull test +	N=28(36%)	N=39(56%)	N=45(85%)	< 0,001

Table 1

Conclusions: Our findings highlight that PD does not comprise a single clinical entity. Identifying subgroups helps predict progression and determine those patients who are likely to have more debilitating symptoms. It may also help personalize treatments to each particular set of patients.

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Is there a correlation between functional capacity upper limbs and falls risk and postural instability in Parkinson's disease?

T. Capato, R. Rodrigues, E. Barbosa, M.E. Piemonte (SAO PAULO, Brazil)

Objective: The goal of this study was to verify by a Brief Battery Functional Assessment (BBFA) the correlation between upper limb function skills with falls and balance

Background: A current clinical bradykinesia assessment tools do not aim to help clinicians identify the underlying movement control systems responsible for poor functional of upper limbs activity in people with Parkinson's disease

(pwp). The ability to modulate posture is poor when the patients performing complex multi tasks and these individuals adopt an even more rigid posture when performing a precision manual task. Although gait and balance have been researched before, few studies were target to this subject to identify the influence of a lack of upper limbs movement in falls and balance.

Methods: 80 subjects with idiopathic PD H&Y 1 to 4 and 20 normal subjects ranging in age from 55 to 88 years old, were recruited from the Movement Disorders Ambulatory Clinic of the University of São Paulo Faculty of Medicine Clinics Hospital. They were rated concurrently on the BBFA by 04 therapists, 04 students, and Parkinson's disease researchers. Balance was assessed by MiniBest and Falls Efficacy Scale-International. The number of falls were registered by a questionarie. Concurrent validity was measured by correlation between the BBFA and balance confidence, as assessed with the ABC scale. Each participant performed 3 trials with each upper limb (right and left) of BBFA.

Results: Consistent with our theoretical framework, pwp scored poorly on different sections of the BBFA. In comparison with normal subjects these results of this subjects were worse and the accuracy was significantly difference between gropus (p=0.020). There were a strong intraclass correlation (p=0,01) and variability (p=0,01). In a Post-hoc comparisons showed that there was a strong correlation with balance and falls with the decrease in range of motion, dexterity and bradykinesia. BBFA allows clinicians to identify the type of motor control problems to direct specific treatments for patients is useful correlate balance and poor upper limb function skills. **Conclusions:** There is a strong correlation between upper limb function skills with falls and balance. The BBFA is easy to learnt and to be managed, with excellent reliability and very good validity. It is a good clinical tool to

evaluate motor control of upper limbs in all stages of H&Y.

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Diplopia: An interesting complication of dropped head syndrome

W. Deeb, I. Malaty (Gainesville, FL, USA)

Objective: To describe an interesting case of new-onset diplopia due to loss of compensation for trochlear nerve palsy as a result of dropped head in the setting of Parkinson's disease (PD).

Background: Dropped head syndrome can emerge within a diverse range of neuromuscular conditions including myopathies, motor neuron disease, and parkinsonism, most commonly multiple system atrophy (1). Incidence of dropped head syndrome in idiopathic PD is less than 6% in patients with H&Y 3, based on available data (2), and increases in risk with disease progression. Dropped head may cause pain, impaired balance, but to our knowledge has not been reported to provoke diplopia in a vulnerable patient.

Methods: Case Report

Results: A 71-year-old man with congenital well-compensated left trochlear nerve palsy developed idiopathic PD that presented with stooped posture and right-sided rigidity and rest tremor, and had a good and enduring levodopa response. Around 5 years into the course, he started developing subacute progression of forward flexion of the neck and later, double vision. His postural change was severe, and ultimately his chin touched his chest at rest (Figure 1). The dropped head was refractory to his dopaminergic therapy and had only partial response to physical therapy and botulinum toxin injections to bilateral sternocleidomastoid muscles. MRI neck demonstrated 2mm anterolisthesis at C6-7 but no other contributory findings. He reported that double vision would occur with two images in a V-shaped configuration. He relayed that he had been told he previously "shifted his horizon" to compensate, and his driver's license demonstrated the prior right head tilt. Recently, he discovered that he could improve his double vision by slouching down in his chair and tilting his body to the right. Ophthalmologic evaluation revealed a left superior oblique palsy with 2-5 degrees of incyclotorsion on the right on double Maddox rod testing and left hypertropia (Figure 2). A Fresnel prism was prescribed to correct for his left hypertropia with only partial benefit.



Conclusions: This case highlights an interesting and unexpected consequence of dropped head syndrome in a man with formerly well-compensated congenital trochlear nerve palsy.

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Antiphospholipid syndrome presenting with craniocervical dystonia: A case study

C. Dietiker, C. Clelland, S. Gupta, M. Richie, M. Shah, I. Bledsoe (San Francisco, CA, USA) **Objective:** Antiphospholipid Syndrome (APLS) is a hypercoagulable state characterized by arterial or venous thrombosis and/or pregnancy morbidity with laboratory evidence of antiphospholipid antibodies. Movement disorders occur in a minority of patients with APLS, most commonly chorea. Parkinsonism, hemidystonia, and hemiballism have been reported more rarely. Here, we report a case of APLS presenting with craniocervical dystonia, aphasia, encephalopathy, and psychotic symptoms. **Background:** A 76 year old woman with a history of coronary artery disease and basal cell carcinoma was admitted to the neurology service after four months of progressive cognitive decline, insomnia, gait dysfunction, auditory/visual hallucinations, and hyperkinetic movements described as "restless" by her family. At onset, she was diagnosed with a pulmonary embolus secondary to deep venous thrombosis and began anticoagulation. She subsequently started antipsychotics for hallucinations and agitation. Diagnoses of conversion disorder, dementia, and tardive dyskinesia had been considered.

Methods: She was evaluated with neurological examination, laboratory studies, lumbar puncture, EEG, brain CT and MRI/MRA, abdominal, pelvis, and chest CT, pelvic ultrasound, and whole body PET.

Results: On exam, she was nonverbal and unable to follow commands. She exhibited orofacial dystonic movements including jaw opening, lip pursing, and blepharospasm. She had left torticollis and phasic shoulder elevation bilaterally, as well as continual agitated and semi-purposeful movements in her limbs that did not appear choreiform. Abnormal movements did not improve with discontinuation of antipsychotic medications. MRI brain at admission showed subacute strokes in the left caudate and bilateral centrum semiovale. LP and EEG were unremarkable. She was diagnosed with APLS after laboratory studies revealed positive cardiolipin and beta-2-glycoprotein antibodies as well as positive lupus anticoagulant. She began IV solumedrol and transitioned to prednisone and mycophenolate mofetil, with gradual improvement in cognition, aphasia, and marked improvement of her dystonia. At a follow-up appointment three months later, her movement disorder had completely resolved. **Conclusions:** APLS should be considered in a patient with progressive cognitive decline and hyperkinetic movements, even in the absence of definite chorea.

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Expanding the spectrum of Faciobrachial Dystonic Seizures

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Objective: A 71 year old Italian man presented progressive dysarthria and involuntary movements.

Background: Within two months he developed dysarthria, progressive homolateral oromandibular and arm dystonic posture, knee buckling and retropulsion. Movements were sudden, increased by action and sustained posture, lasting <5 seconds. Two years prior he was diagnosed with idiopathic CD4+ lymphocytopenia (ICL) and CMV infection. HIV and hematological/oncological disorders were excluded. The patient progressively developed parkinsonism and cognitive decline, with memory and visuospatial impairment. One year later, kidney tumor was suspected and after two months he died.

Methods: Brain MRI and EEG were performed and were unremarkable, whereas PET study showed significant hypermetabolic alterations in basal ganglia. Laboratory tests (blood ASLO, TSH, ANA, anti-phospholipid antibodies, ceruloplasmin and urinary copper) were normal. Positivity for HHV6, JCV e BK viruses was treated with no significant improvement. CSF showed oligoclonal bands (pattern type 4).

Results: Based of clinical manifestations, progression and imaging results, the diagnosis of faciobrachial dystonic seizures (FBDS) was formulated. Anti-VGKC and -LGI1 antibodies were negative, as well as anti-CASPR2, AMPA1/2, GABA-B1, NMDA, GQ1b, GAD, DPPX and Ho-Yu-Ri-Ma1/2-amphiphysin antibodies. Histoblot analysis with patient's serum showed positive staining on rat brain sections, strengthening the hypothesis of autoimmune disorder. He was treated with IVIG and PEX with partial improvement.

Conclusions: Although ICL has been associated with autoimmune diseases in 14-23% of cases¹, this is the first report of autoimmune encephalopathy in this context. Moreover, our patient presented typical FBDS features, except for dysarthria and absence of hyponatremia, but classical anti-VGKC and anti-LGI1 antibodies were negative. LGI1-negative FBDS has been reported also in the context of insular seizures, characterized by prolonged dystonic episodes and hypersalivation². These reports support the hypothesis that FBDS associated with atypical features can be due to specific etiologies different from VGKC-complex antibodies. The identification of patient's antibody target antigen(s) will be important to expand the spectrum of this progressive but curable condition, to shed light in the intricate landscape of autoimmune movement disorders, and to allow correlations between new antibodies and specific FBDS phenotypes.

1137

Comorbid normal pressure hydrocephalus with Parkinson's disease: A call for clinical awareness

A. Cucca, M. Biagioni, J. Golomb, J. Fleisher (New York, NY, USA)

Objective: To examine a case of comorbid normal pressure hydrocephalus (NPH) with Parkinson's disease (PD).

Background: PD and NPH are the most common high level gait disorders in the elderly. The pathophysiology of parkinsonian symptoms in NPH has not been identified. Odagiri retrospectively analyzed the findings on iodine-123-meta-iodobenzylguanidine SPECT in 21 patients with definite diagnosis of NPH. One third showed signs of sympathetic cardiac denervation, indicating a potentially associated alpha-synucleinopathy [1]. Importantly, NPH is a treatable neurological disorder.

Methods: A 79 year-old woman presented with a 2 years history of mild left-hand tremor, asymmetric bradykinesia, rigidity and mild freezing of gait (FoG). Her UPDRS Motor Score was 34. Carbidopa/Levodopa was initiated without subjective benefits despite objective improvement of appendicular bradykinesia. In the following months she showed a significant gait impairment with unsteadiness, frequent falls, severe FoG out of proportion to her mild parkinsonism. She also reported occasional urge incontinence. Neuropsychiatric evaluation showed moderate executive impairment. A brain MRI showed ventriculomegaly disproportionate to sulcal enlargement, callosal angle of 63°, flow-void at the aqueduct and confluent T2-hyperintense changes in the periventricular white matter (fig.1).





cortical atrophy with associated





Results: A large volume tap provided a significant improvement in gait and balance, leading to a ventricularperitoneal shunt. Video gait analysis was performed on a distance of 60 feet with post-processing of gait parameters; six months post-shunt assessment showed significant improvement in all parameters (fig. 2). The UPDRS-II FoG item improved from 2 to 0, UPDRS-III from 34 to 13. Montreal Cognitive Assessment improved by 3 points. FoG, falls and urinary disturbances resolved. She has persistent, mild, asymmetric bradykinesia and rigidity. **Conclusions:** We report a case of levodopa-responsive parkinsonism with overlapping NPH. While appendicular bradykinesia mildly improved with dopaminergic therapy, axial symptoms and locomotion dramatically responded to shunt placement. The time lapse between clinical onset and shunting is a critical prognostic factor. Clinicians

should be aware of the potential coexistence of these two pathologies to promptly provide the most effective treatment.

1140

Comparative age-relatedness of dyskinesia, dystonia and ataxia rating scales in healthy children

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Objective: In healthy children (4-16 years of age), we aimed to associate DIS scores with age, and compare agerelated influences on dyskinesia (DIS), dystonia (BFMDRS) and ataxia (SARA) rating scales

Background: Reliable movement disorder rating scales are important instruments for accurate interpretation of disease progression from childhood to adulthood. We have previously shown that physiologic movements of healthy children reveal dystonic and ataxic features, resulting in age-related scores of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS; movement(BFMMS) and disability(BFMDS) subscales) and Scale for the Assessment and Rating of Ataxia (SARA). The Dyskinesia Impairment Scale (DIS, consisting of dystonia (DIS-D) and choreoathetosis (DIS-C) subscales) was recently launched for the quantification of dyskinetic movements in children with cerebral palsy. Until now, it is unclear whether DIS (DIS-D and DIS-C) scores are also influenced by age. **Methods:** Three independent movement disorders specialists scored DIS in 52 healthy children (4-16 years, 4

children/year of age; male/female=1), according to previously published methods.(1,2) By regression analysis we determined the association between median DIS scores and age. We compared age-related factors (regression coefficients of z-scores) between DIS, BFMDRS(1) and SARA(2).

Results: DIS total and DIS-D outcomes revealed a significant association with age (β =-0.56; p=0.003 and β =-0.53; p=0.006, respectively), in contrast with DIS-C outcomes (β =-0.18; p=0.381). Comparing age-related factors between DIS-D (B=-0.138), dystonia (BFMMS: B=-0.191 and BFMDS: B=-0.179) and ataxia scales (SARA: B=-0.182) revealed similar regression coefficients (p>0.05), with the strongest association between DIS-D and BFMMS outcomes (r=0.544; p=0.004).

Conclusions: In healthy children (4-16 years), age influenced dyskinesia, dystonia and ataxia rating scale scores in a similar way. In contrast to the age-*dependent* DIS-D subscale, DIS-C appeared age-*independent*, implicating that chorea is not a physiologic feature of neuro-development in children between 4-16 years. DIS-D showed the strongest association with the BFMMS scores, reflecting the same objective (i.e. quantification of dystonic motor output by developing basal ganglia networks). For accurate interpretation of quantitative movement disorder rating scale scores in children, consideration of the age-related effect is advisory.

1156

Genotype-Phenotype correlations and expansion of the molecular spectrum of AP4M1-related Hereditary Spastic Paraplegia

S. Efthymiou, C. Bettencourt, V. Salpietro Damiano, H. Houlden (London, United Kingdom) **Objective:** To identify possible novel variants in a HSP family from Greece.

Background: Autosomal recessive hereditary spastic paraplegia (HSP) due to *AP4M1* mutations is a very rare neurodevelopmental disorder with a few reported patients presenting the combination of infantile hypotonia, severe intellectual disability, progressive hypertonia and spasticity, coupled with variable cerebellar involvement and white matter loss on brain magnetic resonance imaging (MRI).

Methods: We investigated a Greek family with three siblings affected with a phenotype characterized by the combination of: (a) febrile seizures with onset in the first year of life (followed by epileptic non-febrile seizures); (b) distinctive facial appearance (e.g., coarse features, bulbous nose and hypomimia); (c) developmental delay and intellectual disability; (d) early-onset spastic weakness of the lower limbs; (e) cerebellar hypoplasia/atrophy on brain MRI.

Results: Genetic analysis of the family using whole exome sequencing (WES) identified a novel compound heterozygous mutation of the *AP4M1*A gene segregating with the phenotype in all the three probands (c.521dupT, p.V174fs and c.T955C, p.C319R). The mutation was confirmed by sanger sequencing and the unaffected parents were found to be carriers of the variants.

Conclusions: We reported on a Greek family with a phenotype of early-onset epilepsy, developmental delay and progressive spastic paraplegia, due to a previously unreported *AP4M1* mutation. The *AP4M1* gene encodes a subunit of the heterotetrameric adaptor protein (AP) complex that mediates vesicle trafficking of glutamate receptors between the trans-Golgi network (TGN) to the synaptic membrane, and thereby contribute to regulate brain development and neurotransmission.

Tics exacerbations in adults with tic disorders: A case series

S. Schaefer, C. Chow, E. Louis, D. Robakis (New Haven, CT, USA)

Objective: To identify patterns of tic re-emergence in adult patients with a history of childhood tics.

Background: Tics and Tourette syndrome (TS) have been described as peaking in childhood and early adolescence with regression as patients enter adulthood. In this series, we report patients who belong to a little-described subset of TS patients: those who were diagnosed with TS during childhood who then experienced a period of relief from or absence of symptoms followed by tic re-emergence in adulthood.

Methods: We performed a retrospective chart review of outpatients over age 21 seen at the Yale Medical Group neurology clinic between January 2012 and July 2016 who were diagnosed by a movement disorders neurologist with childhood onset tics or TS, and who experienced a latent period of relative tic abatement (defined as a significant reduction in or absence of tics) followed by exacerbation.

Results: Sixteen patients were identified. The mean latent period of tic abatement was 16 years, range 3-35 years. Ten patients (62.5%) identified a trigger for their exacerbation; common triggers were work-related, interpersonal, or involved changes in substance use. Three patients (18.8%) reported that the phenomenology of their tics during the exacerbation had evolved since childhood, and seven patients (43.8%) reported that their tics were now worse. Six patients (37.5%) had received medications for tics as children, and 15 patients (93.8%) received

pharmacological intervention for their tics during the adulthood exacerbation. Six of fifteen patients (40.0%) had a documented effective response from those pharmacological intervention(s).

Conclusions: 1) Our study, which represents the largest single series to date of adults with tic recurrences, raises the possibility that the steady decline in symptoms many patients experience as they enter their early 20s may in fact represent temporary improvement. 2) The period of tic abatement lasted years in our patients, different from the more rapid fluctuations in children. 3) As in children, psychosocial and vocational stressors were common triggers in this study, but substance-related issues may also be an important trigger in adults. 3) Patient desire for pharmacological intervention was not necessarily correlated with worsening tic severity. Treatment is challenging, and multiple medications may need to be trialed for optimal efficacy.

1161

The study of deep brain stimulation of globus pallidus internus for refractory Tourette syndrome

M. Zhao, Y. Guan, J. Zhou (Beijing, People's Republic of China)

Objective: Investigate the antineural antibodies (ANAb) level in the individuals with Tourette syndrome (TS) and the relationship with clinical characteristics. Analyze the clinical results and safety of globus pallidus internus (GPi) deep brain stimulation (DBS) in refractory TS patients and the comparison of ANAb level of preoperation and postoperation.

Background: Autoimmune etiology associated with TS. DBS is an effective and safe treatment.

Methods: The level of serum ANAb was detected in 15 refractory TS patients and 4 of them were treated with GPi DBS. The patients were interviewed to evaluate the severity of their tics and others by YGTSS, YALE-BROWN and SDS at preoperative and 1 month, 6months, 1 year and subsequent follow-up after the surgery. Side effects were documented. Comorbid neuropsychiatric disorders were also identified based on the information from the interviews with the patients.

Results: In the group of 15 TS patients the course of disease, YGTSS Motor scores and YGTSS total scores are positively associated with the age (P<0.05), YGTSS Motor scores and YGTSS total scores are positively associated with the course of disease (P<0.05). There is a lack of correlation between the ANAb level and the course of disease, gender and YGTSS scores (P>0.05).4 refractory TS patients was performed GPi-DBS procedure. The time of follow-up is 60.00 ± 21.91 months. Compare with the preoperation, there is a significant difference in YGTSS score from 6 months after Gpi-DBS. There is a lack of correlation between the ANAb level and DBS treatment. None of the 4 patients showed serious permanent side effects.



Conclusions: This study indicates patients' symptoms are more severe, the patients are older and the courses of disease are longer. There is no significant correlation between the ANAb level and the course of disease, gender and YGTSS scores which showed that autoimmune has no effect on the development of the disease. The results suggest GPi DBS is an effective and safe treatment for refractory TS patients. There is a reduction of ANAb level compared with preoperation and postoperation which indicated the mechanism of DBS may involve autoimmune reaction. But there is no significant difference because of the small sample size (only 2 cases). So this study needs to expand the sample size to further clarify the relationship.

1163

Apathy in adolescents with Tourette syndrome (TS), more than a teenager attitude

W. Deeb, M. Hensley, A. Bernier, I. Malaty (Gainesville, FL, USA)

Objective: To explore the presence of apathy in teenagers with TS.

Background: TS is a complex neuropsychiatric disorder generally classified as a hyperkinetic disorder. Apathy has not been studied in TS as it is usually associated with hypokinetic movement disorders. In our clinic, adolescents with TS at times seem disengaged from health care. We explored whether this is characteristic of adolescents with health conditions, or is specific to TS.

Methods: 12 to 16-year-old TS subjects were recruited during routine clinic visits. Age, age at onset, sex, co-morbid diagnoses, medications, and Yale Global Tic Severity Scale severity score (YGTSS) were collected. TS subjects and their parents filled the Gilles de la Tourette syndrome quality of life scale (GTS-QOL) and the center for epidemiological studies depression scale for children (CES-DC). The parents completed the children's motivation scale (CMS), higher scores indicate lower apathy. To explore whether any findings were attributable to a state of disease affliction in general, or to TS specifically, age-matched type 1 diabetics (DM) were recruited as controls. **Results:** 14 TS subjects and 5 DM controls have been recruited (recruitment ongoing). The mean YGTSS is 25.2. The TS group included more males (86% vs. 60%). Independent samples t-test was used to compare the means. The mean ages were not statistically different ($\mu_{DM} = 14.2$, $\mu_{TS} = 13.4$, ? $\mu=0.8$ with 95% confidence interval -1.1 to 2.6). There was no difference in the CES-DC score ($\mu_{DM} = 14.6$, $\mu_{TS} = 17.1$, ? $\mu=-2.5$ with 95% confidence interval -9.2 to 4.1). There was a statistically significant difference in CMS ($\mu_{DM} = 44.6$, $\mu_{TS} = 34$, ? $\mu=10.6$ with 95% confidence interval -9.2 to 4.1). A significant linear regression equation was found (F(1,12)=5.123, p=0.043), R-squared = 0.299. TS subjects predicted CMS is equal to 19.548 + 0.206 (GTS-QOL visual scale). TS subjects mean CMS scores increased by 2 for every 10 points increase in the GTS-QOL visual scale. Similar analyses on other variables did not identify significant regression equations.

Conclusions: In this small study, adolescent TS subjects are more apathetic than controls, independent of depression. The predictive value of the GTS-QOL visual scale on CMS highlights the need for a larger study to confirm and elaborate these findings.

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Effect of personal characteristics on semiology of the first tic episode in children with Tourette syndrome *J. Oražem Mrak, J. Kodric, D. Osredkar, D. Neubauer (Ljubljana, Slovenia)*

Objective: to determine the correlation between personal characteristics and semiology of the first tic episode in children with Tourette syndrome.

Background: there is a lack of information in literature regarding the effect of personal characteristics on tic semiology at the onset of the chronic tic disorder.

Methods: we abstracted the data from electronic medical records of children seen in our outpatient clinic between 1.1.2014 and 31.12.2016 fulfilling the diagnostic criteria for Tourette syndrome. We grouped them in 5 groups according to the semiology of their first tic episode $(1 - \text{single motor}, 2 - \text{multiple motor}, 3 - \text{single phonic}, 4 - \text{multiple phonic}, 5 multiple motor and phonic}). We determined the age at the onset of the disorder (age), sex and family history for tic disorders of children in each group and analyzed the differences between groups. We merged groups together to acquire additional information (in example groups 3 and 4 - only phonic tics at the onset).$ **Results:**60 patients fulfilled the inclusion criteria. 36 (60%) were included in group 1 (single motor), age 5.28 years <math>(2 - 10), 10 (27%) were female, 18 (50%) had positive family history. 12 (20%) children were included in group 2 (multiple motor), age 5.67 years (3 - 13), 5 (42%) were female, 6 (50%) had positive family history. 6 (10%) children were included in group 3 (single phonic), age 5.83 (3 - 7), none were female, 1 (17% had positive family history). 1 child was included in group 5 (multiple motor and phonic), age 5.80 (3 - 9), 2 (40%) were female, 3 (60%) had positive family history.

Conclusions: additionally to the results that we expected (majority of children presented with motor tics, children that presented with phonic tics were older), our analysis showed some data, that was not previously reported. None of the female patients had isolated (single or multiple) phonic tics as their presenting semiology. Percentage of females in groups with multiple (motor, phonic or both) tics at the onset was larger than in groups with single one (39 vs 24%). Family history was less likely to be reported as positive in patients that presented with isolated phonic tics compared to patients that presented with at least one motor tic (14 vs 51%).

1166

Joint pain as premonitory urge in patient with Ehlers Danlos Syndrome and Tourette Syndrome *A. Fraint, G. Pal (Chicago, IL, USA)*

Objective: We report the case of a 21 year old male with Ehlers-Danlos syndrome (EDS) and Attention Deficit Hyperactivity Disorder (ADHD) who presented with joint discomfort and was found to meet clinical diagnostic criteria for Tourette syndrome (TS). We present this case to report an atypical pre-monitory urge which was attributed by the patient to an underlying mixed connective tissue disorder but was related to a co-morbid tic disorder.

Background: EDS includes a group of heritable connective tissue disorders mainly characterized by joint hypermobility. There are many neurologic complications of EDS including headache, muscle weakness, paresthesia, intracranial aneurysms, subarachnoid hemorrhage, spontaneous arterial dissection, cavernous sinus fistula, seizures, and neuropathy.

Methods: A 21 year-old right handed male with EDS and ADHD presented to the Movement Disorders Center at Rush Medical Center in Chicago with joint discomfort. He was not aware of any tics, but described a painful sensation in his hips, right shoulder, and neck which was followed by movement in these joints. He could briefly suppress the movements and described a sense of relief with their performance. He had a history of throat clearing when he was previously taking lisdexamphetamine for ADHD and his brother has motor tics. His neurologic exam was notable for multiple tics including eye rolling, alternating eye blinking, mouth puckering, mouth twitching, right shoulder jerking, and right hip jerking.

Results: Basic lab-work including complete blood count, complete metabolic profile, electrolytes, thyroid, and parathyroid studies was normal. MRI was obtained of both hips and both shoulders. These tests were notable only for mild tendinosis of the supraspinatus and infraspinatus muscles in the left shoulder.

Conclusions: This patient showed evidence of motor tics on physical exam and provided a history of prior vocal tics when treated for ADHD. He thus met the diagnostic criteria for TS. Though the movements did not bother him, he was started on guanfacine given his increased risk for joint dislocation. This case describes an atypical pre-monitory urge of joint pain which preceded motor tics, and which was attributed a known diagnosis of EDS. We present this case to increase awareness of abnormal urges that can precede tics and which patients may attribute to a seemingly un-related co-morbid disease.

1167

Tourettism associated with the Xq25 Microduplication Syndrome

C. Spears, I. Malaty (Gainesville, FL, USA)

Objective: To present a novel case of Tourettism emerging within the Xq25 microduplication syndrome. **Background:** Tourette syndrome (TS) is a childhood-onset neurobehavioral disorder hallmarked by the presence of motor and vocal tics and often accompanied by comorbid psychiatric and behavioral symptoms. The etiology is complex and posited to be multifactorial, with a clear role of genetics. Many genetic loci have been implicated but to our knowledge there has not been an association with Xq25 microduplication, which itself has previously been typified by neurodevelopmental delay, speech deficits, a specific facial phenotype and widespread hypotonia. Behavioral abnormalities have been described including hyperactivity, autistic behavior, and opposition, but never tics or tremors. We present a case of an adolescent with Xq25 microduplication and significant Tourettism. **Methods:** Case report.

Results: A 16-year-old male presented to our movement disorders clinic for further evaluation and treatment of motor and vocal tics presenting over the last year. Motor tics included blinking, nodding, pulling back lips, clonic truncal contractions, and arm movements like conducting an orchestra. Vocalizations included grunting, whispering, and more complex phrases and sentences, all starting at 16 years old[IM1] . He manifested anxiety and aggressive behavior. Birth history had been relatively uncomplicated except for mild jaundice, but he had early global neurodevelopmental delay and significant regression of prior milestones starting at 10 years old. He was known to have seizures, self-injurious behavior and mild low amplitude tremor prior to onset of tics. Exam demonstrated a tall, thin male for age with retrognathism and a supernumerary nipple. Multiple simple motor and vocal tics were recorded. Prior to our visit a genetic microarray proved to be remarkable for a 3.7Mb interstitial duplication of the Xq24-25 gene locus which included the genes GRIA3, XIAP and STAG2 which have been previously associated with intellectual disability and other symptoms, but not reported to be associated with tics or Tourettism. **Conclusions:** We report the first case of Tourettism associating with the Xq25 microduplication syndrome. This, along with limited scattered reports, serve to continue to expand the understanding of Xq24-25 microduplication syndrome.

1190

Parkinsonics – A Prospective, Randomized, Blinded, Cross-Over Trial of Group Singing for Motor and Non-Motor Symptoms in Idiopathic Parkinson's disease (PD)

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Objective: To assess the effects of weekly group singing on PD patients' objective vocal and motoric function, cognition, mood, self-efficacy and quality of life.

Background: PD frequently causes communication difficulties due to several voice impairments. There are few treatment options for vocal/communication complaints. Accessible rehabilitative therapies that encourage active participation and promote socialization may be self-reinforcing, potentially improving voice volume and quality of life.

Methods: In a randomized controlled comparative effectiveness study, 32 participants were assigned to either a singing group or facilitated discussion weekly over 12 weeks. After 12 weeks, participants crossed over for an additional 12 weeks. Evaluations were performed at baseline and every 6 weeks for 30 weeks. Objective voice measures included loudness (decibels), held vowel duration, jitter, shimmer, and harmonic-to-noise ratio. Additional outcome measures included patient-centered quality of life, voice-related quality of life, MDS-UPDRS scores, Montreal Cognitive Assessment, and subjective scales of depression, self-efficacy and overall well-being. Group means were compared using repeated measures ANOVA, and linear mixed models were used to assess changes in variables over time controlling for age, gender and PD stage.

Results: Twenty-six patients (16M/10F; Hoehn&Yahr stage 2.3(2-3); Age 68.6(55-89)) completed the study. There was significant improvement from baseline in average loudness on the Cookie theft picture description(2.06 dB) at 24 weeks as well as decreased volume range at 30 weeks(7.7 dB), corresponding with improved minimal reading volumes at 24 weeks (4.4 dB) and 30 weeks (8.1dB). Similarly, there were significant decreases in the volume range (4.9dB at 24 weeks, 8.8dB at 30 weeks) and improvements in minimal loudness on Rainbow passage reading at 24 (4.3dB) and 30 weeks (7.2dB) for both). Participants also improved on the MDS-UPDRS Motor scale between baseline and 24 (5.9 points) and 30-week visits(8.4), regardless of intervention order.

Conclusions: Weekly group singing is a feasible intervention that may improve some aspects of conversational voice volume in PD. Some improvements were sustained at least 6 weeks after interventions ended. Further investigations of the mechanism of benefit and longitudinal effects of singing in PD are necessary.

1193

Noninvasive cerebellar stimulation for adults with cervical dystonia

A. McCambridge (Sydney, NSW, Australia)
Objective: To examine whether a 5 day treatment period of anodal transcranial direct current stimulation (a-tDCS) over the cerebellum would improve patients' symptoms and alter their neurophysiology.

Background: Cervical dystonia (CD) is the most pervasive form of dystonia and is characterized by painful, involuntary twisting of the neck, and sometimes tremor. Unfortunately, treatment options for CD are limited. There is emerging evidence implicating cerebellar dysfunction in the pathophysiology of CD. A-tDCS) is a non-invasive brain stimulation technique that can up-regulate cortical excitability.

Methods: Patients received 5 sessions of a-tDCS and sham tDCS in a randomised, cross-over design that was double-blinded. Clinical features were examined using the TWSTRS2, CDQ-24, cervical range of motion, and visual analogue scales of pain. Neurophysiological assessments were performed using eye-blink conditioning to examine cerebellar excitability and transcranial magnetic stimulation (TMS) over the motor cortex to examine corticomotor excitability and intracortical inhibition. Motor evoked potentials (MEP) and cortical silent periods (cSP) were recorded from the left and right upper trapezius (UT) and first dorsal interosseous (FDI). All dependent measures were assessed on the first and last day of treatment, and follow up questionnaires were completed at 1 and 4 weeks post treatment. There was a minimum washout period of 5 weeks between real and sham treatment blocks, and patients undergoing botox were tested 4 weeks post injections.

Results: The study is at the late stages of data collection therefore treatment type is currently concealed. Repeated measures ANOVAs will compare pre/post differences between real and sham. Post hoc paired t-tests and corrections for multiple comparisons will be performed if necessary.

Conclusions: The outcome of this research may lead to the development of an effective and noninvasive intervention for the management of cervical dystonia and improve understanding of the dysfunctional neurophysiology.

1197

A Pilot Multiparametric MEG Study of coherence in generalized and cervical dystonia

A. Mahajan, S. Bowyer, A. Zillgitt, P. LeWitt, P. Kaminski, C. Sidiropoulos (Detroit, MI, USA) **Objective:** To explore functional connectivity at network level with MEG, pre and post-administration of medications, in generalized and cervical dystonia.

Background: The underlying mechanisms of dystonia remain poorly understood. Mechanisms thought to play a critical role include reduced intracortical inhibition and distorted somatotopic cortical representation. Prior studies showed altered functional connectivity within the sensorimotor, the executive control and the primary visual network.

Methods: MEG Data on 5 patients, 3 with cervical and 2 with generalized dystonia (age: 16-70 years) were matched to 4 healthy controls. All patients (3 on Diazepam and baclofen, 1 on Sinemet, 1 on Botulinum toxin) showed clinical benefit with medications. Two 15-minute MEG scans spaced one hour apart in each treatment condition (pre- medication and 1 hour after ingested medication) were obtained. Synchronization of neuronal activity was quantified by calculating coherence source imaging (CSI) between cortical sites from MEG imaged brain activations. A region-of-interest (ROI) tool was used to identify 54 regions in the brain (27 in each hemisphere). Within the frequency band 3-50Hz, a t-test was conducted to assess group difference in average CSI values for each pair of brain regions (N= 1,431). A P value was produced for each region pair. The false discovery rate (FDR) was used to adjust for multiple testing. Only statistically significant coherence values (p<0.05) with a large effect size were considered.

Results: In both pre-treatment and post-treatment groups, the biggest difference in coherence between patients and controls was seen in the occipito-striatal and occipito-parietal regions, with some differences in the fronto-striatal and fronto-occipital regions. On comparing pre- and post-treatment dystonia patients, a decrease in coherence was observed in these regions post treatment.

COHERENCE IMAGES for 2967Dys_EpiCont15_2_DATA1_FILT3_50_Hz





Conclusions: Our exploratory study using MEG, while limited by a small sample size, showed increased coherence in regions associated with visuospatial and executive function, with a decrease post medication in patients with cervical and generalized dystonia. The latter may be a biomarker for normalization of aberrant connectivity and merits further exploration.

1204

Motor stress elicits dystonia-like movements in a pharmacological mouse model for Rapid-Onset Dystonia-Parkinsonism (DYT12)

L. Rauschenberger, J. Volkmann, C.W. Ip (Wüerzburg, Germany)

Objective: To study if a mild stressful trigger by motor activity leads to development of dystonia-like movements in a pharmacological mouse model for DYT12.

Background: DYT12 dystonia, linked to loss-of-function of the ATP1a3 gene, is characterized by generalized dystonic postures and parkinsonian symptoms that abruptly develop after a stressful event. Previous publications reported the development of a pharmacological DYT12 model by perfusion of ouabain, a selective ATP1a3-blocker, into basal ganglia and cerebellum of wt mice via osmotic pumps that lead to dystonia-like postures and parkinsonian symptoms if mice were subjected to severe stress by electric foot shocks.

Methods: Ouabain concentrations between 9 - 36 ng/h in cerebellum and basal ganglia were tested with a final concentration of 11.2 ng/h being used. As motor stressors, ouabain-perfused mice were repeatedly subjected to the Rotarod Performance test and Pole test. The exhibited phenotype was longitudinally assessed through Open Field analysis, video recordings of spontaneous movements and tail suspension test over 72 h. Motor symptoms were evaluated by an adapted Motor Behavioral Scale with 0-2 points per category to assess general activity, postural instability, hind limb dystonia and truncal dystonia. A new 8-point scoring system to assess dystonia-like movements was applied for the tail suspension test: crossing of hyperextended forelimbs as well as tonic flexion, scored from 0-4 points depending on severity and duration; hyperextension of hindlimbs and clasping behavior was scored from 0-3 points; 1 point was given for truncal distortion.

Results: Abnormal motor behavior observed in ouabain-perfused mice were hyperextensions of limbs, kyphosis, reduced locomotion and postural instability. The Motor Behavioral Scale in stressed mice was significantly higher than in unstressed mice $(5.06 \pm 0.22 \text{ vs} 3.19 \pm 0.36$, respectively; P<0.0001). Open Field analysis showed reduced locomotion in stressed mice with 16.7 % less distance moved than unstressed animals. Scoring of the mice in tail suspension placed the stressed group at 5.50 ± 0.32 compared to 3.77 ± 0.53 in the unstressed group (P<0,005). **Conclusions:** This modified pharmacologic mouse model for DYT12 with reduced ouabain-dosage exhibits dystonia-like movements and a parkinsonian phenotype with significant increase of symptoms when subjected to motor stress.

1213

Brainstem connection of Writer's cramp: Electrophysiological correlates

S. Choudhury, P. Chatterjee, R. Singh, S. Shubham, S. Trivedi, M. Baker, S. Baker, H. Kumar (Kolkata, India) **Objective:** In this study, we explored the involvement of brainstem in Writer's cramp (WC) patients through prepulse inhibition of blink reflex and Start-React paradigm.

Background: WC might result due to reduced inhibition of motor output and sensory motor disintegration at various anatomical levels. Pre-pulse inhibition of blink reflex is a physiological phenomenon where the blink reflex (R2 component) is inhibited by preceding sensory stimulation. Start-React is an experimental technique which evaluates brainstem function through quantification of reaction latency to startling acoustic stimulation. Methods: Eight patients of WC and eight healthy participants were evaluated for pre-pulse inhibition of blink reflex. Extent of blinks was measured through surface EMG placed on Orbicularis oculi muscles of both eyes. Half of the Supraorbital nerve stimulation was randomly conditioned with preceding low intensity median nerve stimulation. The extent of inhibition was estimated through an Index (R2 area at conditioned stimuli/ R2 area at test stimulus). 17 patients with WC were compared with 12 healthy participants through Start-React paradigm. The participants were asked to perform a task of pinching on a force transducer immediately on illumination of a LED light. On some trials, the visual stimulus was co-presented with either a quiet acoustic stimulus or a startling acoustic stimulus. The reaction latency was quantified through EMG placed on first dorsal interosseous muscle. **Results:** Median nerve stimulus inhibited the blink reflex in healthy as well as WC patients. However, the extent of inhibition was significantly less in WC patients (average pre-pulse index in WC 0.44, healthy participants -0.10, p 0.01). The onset of ipsilateral R2 component of blink reflex was 46.3 s for WC patients and 38.2 s for healthy participants (p 0.02). The attenuation of reaction latency to acoustic stimulus was consistently present in both the groups. Nevertheless, in WC patients the attenuation of latency was higher than healthy participants (41.6 s, 28.6, p 0.03).

Conclusions: The sensory inhibition of motor volley was inadequate at brain stem level in WC patients, as reflected through deranged pre-pulse inhibition of blink reflex. Whereas, increased startling reaction to acoustic stimulus was possibly related to the reduced inhibitory influence at the level of brainstem in WC patients.

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Non motor symptoms in patients with Writer's cramp

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Objective: We aim to explore the non-motor features of WC patients and correlate those with motor symptoms. **Background:** Writer's cramp (WC) is essentially a motor disorder, involving the basal ganglia and its connections. It is well known that Non-motor symptoms (NMS) are coexisting features in a number of movement disorders involving basal ganglia. But NMS are not well documented in cases of WC.

Methods: Patients attending the outpatient department of a tertiary care neurology referral centre in the eastern part of India were recruited, who presented with writing difficulty and diagnosed as writer's cramp by neurologist. Individual patients were thoroughly assessed through various motor (DASH, WCRS, ADDS) and non motor (MINI, MOCA, GAD7, PHQ9, OCI, SF36) scales. Audio visual recording of uniform writing tasks were performed for all patients.

Results: 30 consecutive patients with WC were recruited. Interestingly, all of them were male. The mean age of the patients was 54.83 years (SD 10.77). Mean disease duration for this cohort was 72.36 months. The average motor disability of the patients was 18.4% of maximum possible disability (DASH score). 70% and 60% patients reported Generalized Anxiety Disorder (GAD) and Major Depressive Episodes (MDE) respectively in recent past. 50% had Obsessive Compulsive Disorder (OCD) with a mean OCI score of 2.22 (maximum mean score 4). Panic disorder and social phobia were present among 26.7% and 60% respectively. Out of 18 patients suffering from social phobia, 12 were phobic specific to writing tasks in public.95.2% patients with GAD and MDE had moderate to severe grade of anxiety and depression respectively. Cognitive impairment was present in 25 (83.3%) WC patients. DASH score is negatively correlated with total MOCA score and attention score.

Conclusions: Anxiety, depression, social phobia and OCD are four most frequent non motor symptoms present in WC patients. Functional disability in WC is proportional to the cognitive impairment and attention tasks.

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Dystonia-like phenotype in a DYT1 rat model after peripheral trauma

S. Knorr, K. Grundmann-Hauser, J. Volkmann, C.W. Ip (Würzburg, Germany) **Objective:** Establishment and characterization of a DYT1 rat model with dystonia-like movements after sciatic nerve crush injury.

Background: Penetrance of DYT1 dystonia is markedly reduced with 30-40%. To verify if environmental factors can trigger dystonia in genetically predisposed DYT1 gene carrier (second hit hypothesis), we aimed to induce dystonia in a transgenic DYT1 rat model (?ETorA), that harbors the full human mutant *Tor1A* gene and is asymptomatic per se, by a peripheral nerve injury.

Methods: Dystonia-like movements of the hindlimbs during tail suspension were scored before and after unilateral sciatic nerve crush injury with a new scoring system at week 2, 5, 9 and 12. Nerve conduction velocity (NCV) and compound muscle action potentials (CMAP) of wildtype (wt) and ?ETorA rat sciatic nerves were evaluated by in vivo electroneurographic recordings (ENG) 12 weeks after nerve injury.

Results: Both wt and ?ETorA rats developed dystonia-like movements after nerve injury with a maximum score at week 2. In wt rats, the score then continuously decreased to a minimum at week 9 (0.4 ± 0.3) and stayed at this low level, that was comparable to naïve rats, until week 12 (0.6 ± 0.3). However, compared to this group a significantly higher dystonia-like movement score was observed in nerve injured ?ETorA rats at week 9 (1.9 ± 0.4) (p< 0.01) and at week 12 (1.9 ± 0.4) (p< 0.05). Moreover, after nerve injury a higher penetrance of dystonia-like movements was found in ?ETorA rats (70%) compared to wt rats (30%). Additionally, a spreading of dystonia-like movements to the contralateral hindlimb was seen in 35% of nerve injured ?ETorA rats but not in nerve injured wt rats. ENG recordings didn't show any significant differences in NCV or CMAP comparing wt rats with ?ETorA rats, 12 weeks after nerve injury, although both genotypes demonstrated slower NCV and reduced CMAP amplitudes after nerve crush compared to naïve controls of both genotypes.

Conclusions: Our data indicate that a peripheral nerve trauma can trigger dystonia-like movements in genetically predisposed ?ETorA rats, which supports the "second hit" hypothesis. Functional assessment by ENG excluded impaired nerve regeneration after injury as a reason for a higher dystonia-like movement score in ?ETorA rats.

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Striatal cholinergic neurons in cervical dystonia

K. Mente, N. Edwards, D. Pratt, D. Iacono, D. Urbano, A. Ray-Chaudhury, M. Hallett (Bethesda, MD, USA) **Objective:** To determine if there is cholinergic neuronal loss in the putamen in cervical dystonia.

Background: The etiology of cervical dystonia is unknown. Striatal cholinergic abnormalities have been implicated in the pathogenesis of dystonia in animal models, human imaging, and other studies. In dystonia animal models, there are decreased numbers of striatal cholinergic interneurons.

Methods: Formalin-fixed posterior putamen samples from 8 cervical dystonia (73.7 ± 11.1 years; 7 females, 1 male) and 7 neurologically healthy control (72.9 ± 12.2 years; 6 females, 1 male) brain donors were obtained from the University of Maryland Brain and Tissue Bank after review of medical records. Samples were embedded in paraffin and 5-mm thick slides were cut. Hematoxylin and eosin (H&E) and Bielschowsky silver stain were used. Immunohistochemistry was performed with beta-amyloid, phospho-tau, and choline acetyltransferase (ChAT) antibodies. The ChAT antibody was used to identify cholinergic neurons. ChAT-stained slides were scanned with a whole slide imager. ChAT-positive neurons in the putamen on each slide were manually enumerated in ImageScope software.

Results: There were no significant pathologic changes, including neurodegeneration, in cervical dystonia. The numbers of ChAT-positive neurons appeared similar in both groups by visual inspection. There were no statistically significant differences in the density of ChAT-positive neurons: 2.35 ± 0.80 cells/mm² in the cervical dystonia group and 1.81 ± 0.58 cells/mm² in controls (p=0.17). There was no gliosis.

Conclusions: The results of this study do not support a finding of cholinergic neuronal loss in the posterior putamen in cervical dystonia.

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A kinematic analysis of finger tapping in dystonia

R. Newby, S. Muhamed, S. Smith, J. Alty, S. Jamieson, P. Kempster (Melbourne, NSW, Australia) **Objective:** To perform a computerised analysis of finger tapping in patients with dystonia and healthy controls in order to develop a better understanding of the dynamics of repetitive actions in dystonia.

Background: The electromyographic features of dystonia—abnormally long EMG bursts, agonist-antagonist cocontraction, overflow activity in remote muscles—are well recognised. Kinematic studies reveal slower, less precise and more variable movements.(1) Analysis of bradykinesia in dystonia has revealed no decremental tendency.(2) However, a detailed exploration of its characteristics has not yet been performed.

Methods: 30 patients with cervical and/or limb dystonia and 23 healthy controls were compared. A simple task involving repetitive finger tapping was assessed while subjects wore electromagnetic sensors secured to index finger and thumb. Subjects were advised to tap "as fast and as big as possible" for two trials, each 15 seconds long. Precise position and orientation data, in six degrees of freedom, were recorded from each sensor. A high sampling rate permitted 'real time' analysis of movement. Separable components (such as rhythm, speed and amplitude) were derived from a comparison of the *x*, *y* and *z* coordinates of each sensor. These components were extracted from the data using a custom script written in MATLAB (The MathWorks Inc., Natick, Massachusetts, USA). Data was then analysed for statistical significance by Mann-Whitney *U* test using Matlab statistical toolbox software. **Results:** The following parameters were significantly different between the groups: in the dystonia group frequency

(p = 0.001), maximum opening deceleration (p = 0.0004) and maximum closing acceleration (p = 0.04) were reduced, halt duration was increased (p = 0.01) and the product of amplitude and frequency (a marker of superior overall performance) was lower (p = 0.001).

Conclusions: There is a loss of efficiency of repetitive actions in dystonia. Extrapyramidal disturbance in dystonia generates slowness of voluntary movement, in addition to the involuntary movement disorder. Improved knowledge of the specific components of bradykinesia in dystonia will aid diagnosis and enhance understanding of its underlying mechanisms.

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Combined effects of rTMS and botulinum toxin therapy in benign essential blepharospasm

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Objective: To determine whether repetitive transcranial magnetic stimulation (rTMS) of anterior cingulate cortex (ACC) when added to botulinum toxin (BoNT) therapy improves benign essential blepharospasm (BEB) symptoms. **Background:** BEB is a disabling focal dystonia commonly treated with BoNT therapy. However BoNT outcomes are suboptimal in many patients and may wear off earlier than the expected time frame of 12 weeks. Previous research found modulation of ACC excitability with rTMS therapy alleviated BEB symptoms.

Methods: Twelve patients with BEB participated in a randomized, sham-controlled study with blinded clinical assessments (six in each arm). These patients received 0.2 Hz rTMS over the ACC using a double cone TMS coil. rTMS was initiated about four to six weeks-after BoNT injections (BoNT_{peak} benefits) and delivered for two weeks.

The primary outcome was physician-rated videos and patient-rated BEB frequency and severity score on Jankovic rating scale (JRS) and craniocervical dystonia quality-of-life (QOL) questionnaire. The secondary outcome was the change in blink reflex recovery (BRR) curve. These were measured before rTMS therapy (T0), two weeks-after (T1) and prior to the next BoNT injections (T2, BoNT_{trough}). Age and gender matched healthy controls were enrolled for normative BRR data.

Results: All patients tolerated the therapy well. There were three males and nine females in the study (mean age \pm standard deviation 69.1 \pm 7.1; age range 57-79 years). In the patient-rated outcomes, there were significant improvements in the real arm at T1 when compared to T0. The JRS frequency improved by 48% (p = 0.04), BEB severity by 46% (p = 0.02) and QOL by 46% (p = 0.002). In the physician-rated videos, only the forced blinks improved by 56% (p = 0.04) at T1. However none of the rTMS related benefits remained sustained at T2. The BRR revealed an increased excitability in the BEB group compared to healthy controls. rTMS therapy did not induce any significant change in the BRR curve.

Conclusions: rTMS has a potential to be used as an add-on treatment in BEB to enhance benefits related to BoNT therapy. A larger follow-up study is required for further confirmation.

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A Comparison of Temporal Discrimination Thresholds in Musicians with and without Dystonia

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Objective: To compare the Temporal Discrimination Thresholds (TDT) of Musician's Dystonia (MD) patients with those of healthy control musicians.

Background: The TDT is a measure of the shortest time interval at which two stimuli are perceived as different and is abnormal in several movement disorders including Adult-Onset Isolated Focal Dystonias (AOIFD). The reported frequency of abnormal TDTs in MD subjects is considerably lower than that found in other forms of AOIFD. Previous studies found intact timing abilities in MD patients when compared with control musicians but did not use TDT as a metric.

Methods: Participants were recruited from two centres in New York and Dublin with retrospective inclusion of results from previous TDT studies and prospective testing of additional subjects. Three cohorts were recruited: subjects with clinically diagnosed MD, healthy professional musicians without a family history of movement disorders and healthy Non-musician Controls. TDT testing was conducted using a visual TDT paradigm consisting of a pair of flashing lights, which began synchronously and became asynchronous in 5 ms increments. Z-scores were calculated in order to compare the performance of individual subjects to the control groups' means.

Results: Data were collected from 20 MD subjects, 20 Musician Controls and 94 Non-musician Controls. Age and gender were balanced across groups. Comparison of MD subjects to non-musician controls resulted in 4 (20%) MD subjects being identified as abnormal (statistically insignificant using Fisher's Exact Test; p = 0.09), in line with previous studies. However, use of a Z-score, derived from Musician Controls, resulted in the detection of 9 (45%) abnormal MD subjects and 21 (22%) abnormal Non-musician controls. Both these results were statistically significant when applying Fisher's Exact Test (p<0.001 and p=0.02, respectively).

Conclusions: Healthy musicians have faster temporal discrimination than non-musicians. These results further support the model of abnormal temporal discrimination in AOIFD suggesting similar pathophysiological mechanisms between MD and other Focal Dystonias. They also challenge previous findings of normal or intact timing abilities in MD.

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Prevelance, clinical pathology and Treatment of Dystonia in Pakistani Population

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Objective: Evaluate the gender, mean age, clinical spectrum and non-motor symptoms of the disease in Pakistan, a developing country of South East Asia.

Background: Dystonia, a neurological syndrome, is characterized by stereotypic, abnormal muscle contractions and disabling movements. Developed countries have enough data for its incidence and prevalence, often relating it to severe morbidity and mortality, but for developing countries like Pakistan scarce data is available.

Methods: This one year study (May 2015 to October 2016), was conducted in local neurology clinic visited by many referred patients from adjacent cities and provinces because of better health care facilities. Informed written consent was obtained from all patient or their guardians for the documentation and evaluation of clinical features

including motor and non-motor symptoms along with demographic distribution, laboratory, radiological investigation, medication and response towards medication.

Results: Excluding secondary cases, 52 patients were observed with 41 male and 11 female. Mean age of onset of disease was 42. Primary distribution varies from 45% cervical dystonia, 19% Blepharospasm, 12% Oromandibular dystonia, 5% Writer's cramp to 2% Lower limb dystonia. Four patients(5.7%) have positive family history with one parental consanguineous marriage. Among 52 patients, 36(69%) belong to rural area and 16(30.7%) have urban residence. Magnetic resonance imaging and computed tomography revealed no significant Basal ganglia calcifications and in 5 cases aging was a major contributor for age related cerebral atrophy leading to Dystonia. Red blood cell morphology was normal for 86%. Bone profile (75%) exhibited below average serum calcium level (< 2.3mmol/l.) and those patients upon the administration of Vitamin D felt improvement in non-motor symptoms like depression and fatigue. Most effective treatment were Levodopa, Tetrabenazine and Botax (Botulinum toxin A). Among those 09 persons have dopa-responsive dystonia and 21 were given Botax. Depression(71%),lack of self-confidence(81%),insomnia(58%),fatigue(33%) and dizziness(39%) are some common non-motor symptoms observed by the patients from the time of onset of disease.

Conclusions: Our study adds valuable data to existing literature for better diagnosis and treatment. Dystonia,more prevalent among males and cervical dystonia is most common type of dystonia. Dominating factors of rural area,leading to Dystonia needs further investigation.

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The Volatility of Local Field Potential Oscillations in Dystonia and Parkinson's disease

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Objective: To assess the volatility of low frequency (4-12Hz) and beta-band (13-30Hz) oscillations in local field potentials (LFPs) in dystonia and compare this to LFPs volatility in Parkinson's disease (PD)

Background: Adaptive deep brain stimulation (aDBS) has been successfully applied in PD using 'bursts' of beta oscillations as biomarker to titrate stimulation.(Little & Beudel et al., 2016) Likewise, bursts in the low frequency band might be used as biomarker for aDBS in dystonia.(Huebl et al., 2014) However, the volatility of LFPs oscillations in dystonia has not yet been established.

Methods: Bipolar LFPs were obtained from four dystonia patients (23 LFPs) and five PD patients (30 LFPs) during one-minute rest directly after the implantation of bilateral DBS leads in the GPi (dystonia) or the STN (PD). Time-frequency analyses were performed using a convolution method with a moving Hanning window of 1-sec length and a temporal resolution of 25ms. For every LFP recording, the median and 75th percentile of beta and low-frequency power were obtained. This was used to calculate the average time that beta and low-frequency power spectral density exceeded these thresholds [figure1].

Results: Dystonia patients showed significantly more low-frequency oscillations than PD patients (p=0.005). Nevertheless, the median burst duration above the median (p=0.762) and the 75th percentile (p=0.965) were similar [figure2]. The same held for the beta oscillations (p=0.696 and p=0.696 resp.).



Conclusions: In this pilot study, the volatility of LFP low-frequency and beta oscillations appears to be similar in dystonia and PD. This might implicate that aDBS based on low-frequency oscillations is possible in dystonia.

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Substantial psychiatric symptoms, sleep disturbances and reduced quality of life in well-treated adult patients with GTP-cyclohydrolase deficient dopa-responsive dystonia

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Objective: The aim of this study was to systematically investigate the prevalence of psychiatric disorders, sleep problems and health-related quality of life (HRQoL) in patients with GTP-cyclohydrolase deficient dopa-responsive dystonia (DRD).

Background: It is hypothesized that non-motor symptoms are an important part of the DRD phenotype. **Methods:** We assessed the type and severity of psychiatric co-morbidity, sleep problems, fatigue and HR-QoL in 12 adult DRD patients with a confirmed CGH1 mutation and 24 matched healthy controls. Psychiatric assessment included the Mini International Neuropsychiatric Interview - PLUS (MINI-PLUS) and quantitative questionnaires for depression and anxiety (BDI and BAI). Sleep problems, fatigue and HR-QoL were assessed with validated questionnaires (ESS, FSS, PSQI and RAND-36 Health Survey).

Results: In all patients dystonia symptoms were well-controlled (mean BFM score 7.4). A high percentage of patients had a history of mental health care consultation; 66.7% vs. 33.3% of the controls (p=0.08). The MINI-PLUS interview also revealed a higher life-time prevalence of psychiatric disorders in patients; in particular more anxiety was found (41.7% vs. 0%, p<0.01). The scores on the quantitative depression and anxiety rating scales did not significantly differ, although the BDI score was on average almost 3 points higher in the DRD group than in the control group (7.8 vs 4.6, p=0.10). Significantly more sleep disturbances and fatigue were reported in the patient group. Even when corrected for anxiety and depression, daytime sleepiness remained significantly more frequent than in controls (p=0.02). DRD patients also had significantly lower HR-QoL scores than the control group and a decreased physical QoL was associated with fatigue, daytime sleepiness and quality of sleep.

Conclusions: Non-motor symptoms were highly prevalent in our cohort of DRD patients despite good dystonia control. Our findings support accumulating evidence of an important non-motor phenotype in DRD. This highlights the need for systematic research into these symptoms and the underlying neurobiology. Adequate treatment of their non-motor symptoms could significantly contribute to a better quality of life in patients with DRD.

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Associations between functional networks and temporal discrimination thresholds in cervical dystonia patients and their unaffected relatives

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Objective: To investigate resting state functional networks across cervical dystonia patients and their unaffected relatives with and without abnormal temporal discrimination thresholds (TDTs) based on independent component analysis and graph theoretical analysis of resting state functional magnetic resonance imaging data.

Background: Cervical Dystonia is hypothesised to be a functional network disorder associated with aberrant gamma-amino-butyric acid levels in the mid-brain. While an abnormal TDT is an endophenotype for cervical dystonia, the functional networks involved in temporal discrimination and their links to the pathomechanism of cervical dystonia remain unexplored. Resting state functional studies may elucidate the mechanisms of abnormal TDTs in unaffected relatives; we postulate functional connectivity aberrations will be similar in patients and unaffected relatives with abnormal TDT.

Methods: We employed independent component analysis followed by dual regression and graph theory analysis to examine and compare large-scale topology of functional brain networks using resting state functional magnetic resonance imaging data acquired from 64 age and sex matched participants (16 in each group - cervical dystonia patients, unaffected first degree relatives with normal temporal discrimination, unaffected first degree relatives with normal temporal discrimination, unaffected first degree relatives with normal temporal discrimination.

Results: On comparison of the functional connectivity and network architecture across the four cohorts, first degree unaffected relatives and patients showed similar (i) widespread functional network reorganization and significant differences in connectivity (p<0.05) in the Visual, Basal Ganglia (BGN), Cerebellum, Mid-Brain and Sensorimotor (SMN) resting state networks (ii) significant abnormalities in the inter-connectivity between the BGN and SMN (iii) SMN connectivity correlated significantly with TDT values (iv) significant differences in network properties at the nodal level compared to healthy controls (reduced clustering coefficient and increased number of shortest paths). **Conclusions:** Our results suggest that first degree unaffected relatives with abnormal TDT manifest some common functional network aberrations as observed in cervical dystonia patients, shedding new light on the pathomechanisms of this disorder.

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Determinants of health-related quality of life in children and young adults with dystonia

H. Eggink, M. Coenen, A. Elema, W. Veenstra, K. Peall, D. Sival, M. Tijssen (Groningen, Netherlands) **Objective:** To systematically investigate to what extent motor and non-motor symptoms were related to healthrelated quality of life (HR-QoL) in children and young adults with dystonia. Secondly, we assessed whether the importance of these symptoms differed between primary (non-lesional) and secondary dystonia patients. **Background:** In addition to motor symptoms, there is an increasing interest in the presence and importance of nonmotor symptoms in dystonia. However, information on the significance of motor and non-motor symptoms in children and young adults dystonia is still lacking. **Methods:** We studied 60 patients aged between 6 and 25 with childhood-onset dystonia. Patients underwent a multidisciplinary assessment of dystonia severity (BFMDRS-M, global clinical impression), motor function (Gross motor function measure, Melbourne assessment of unilateral upper limb function), pain (visual analogue scale), intelligence (Wechsler Intelligence Scale), anxiety and depression (Child/Adult Behavior Checklist) and executive functioning (Behavior Rating Inventory of Executive Function). Measures were analyzed with a principal component analysis and subsequent multiple regression to evaluate which components were associated with HR-QoL (Pediatric Quality of life Inventory).

Results: Patients (29 primary, 31 secondary) had a mean age of 13.6 ± 5.9 years and a mean disease duration of 9.6 ± 5.1 years. The principal component analysis revealed three components: 1) motor symptoms; 2) anxiety, depression and executive functioning; and 3) pain. A lower HR-QoL was associated with more impairments in motor symptoms and problems in anxiety, depression and executive functioning (R²=0.75). Within the secondary dystonia subgroup similar results were found (R²=0.84). In primary dystonia patients, only problems in anxiety, depression and executive functioning were significantly correlated with a lower HR-QoL.

Conclusions: Non-motor symptoms are at least as important as motor symptoms for the HR-QoL in young patients with dystonia. We plead for a multidisciplinary assessment of motor and non-motor symptoms to optimize management and improve the HR-QoL.

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Cognitive function is preserved 10 years following DBS in people with dystonia

E. Hogg, J. Eskenazi, E. During, J. Wertheimer, R. Alterman, M. Tagliati (Los Angeles, CA, USA) **Objective:** To study cognitive function in people with dystonia chronically treated with Deep Brain Stimulation (DBS).

Background: The impact of DBS on cognition is a matter of debate. While short follow-up studies have found no significant cognitive changes following DBS for dystonia, the effects of longer stimulation periods remain unknown. **Methods:** A telephone survey based on the Montreal Cognitive Assessment (the T-MoCA) was administered to people with dystonia who underwent DBS surgery at least 5 years before study onset. In addition, we analyzed scores from a self-administered survey comparing current day and pre-surgical cognitive function, the 39-item Measurement of Every Day Cognition (Ecog-39). Results were analyzed using a Pearson's correlation. **Results:** 19 people with dystonia treated with DBS (18 GPi, 1 STN) for an average of 10 years (range 5-15 years) completed both T-MoCA and Ecog-39. Average age was 37.5±17.6 years, 9 were female, 14 were DYT1, 1 DYT6, 3 other primary dystonias and 1 secondary dystonia. Average T-MoCA was 20.1±1.9 out of a maximum score of 22 (range 15-22). Only 3 subjects (15.7%) had scores in the impaired range (18 or less), none of which were younger than 30. There was no statistical correlation between age and T-MoCA (r=-0.33, p=0.17). Average overall Ecog-39 score was 1.23±0.32 (range 1.0-2.07). Two subjects (10.5%) scored in the range of concern for impaired cognition (<1.81). There was no statistical correlation between age and Ecog-39 (r=0.05, p=0.87) and between years since DBS surgery and T-MoCA or Ecog score (r=0.08 and r=0.09).

Conclusions: Our results show that cognitive function is preserved in subjects with dystonia treated with DBS for an average of 10 years. Very few subjects reported cognitive concerns. The study was underpowered to show a correlation between age or time from DBS and cognitive scores. Further limitations were the small sample size, self-reporting methodology, and lack of pre-surgical comparison data.

Acknowledgments: this study was funded by a DMRF clinical fellowship.

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Self-assessed psychological symptoms, fatigue and depersonalization in dystonia

R. Newby, J. Alty, S. Jamieson, S. Smith, P. Kempster (Melbourne, NSW, Australia)

Objective: To assess depressive, anxiety, fatigue and dissociative symptoms in patients with dystonia. **Background:** The basal ganglia, once considered exclusively concerned with motor control, are now recognized to have a role in psychiatric disorder as well as sensory perception, cognition and sleep regulation. An excess of psychopathology in inherited dystonia—depression in DYT1 and anxiety spectrum disorders in DYT11 (myoclonus dystonia)—has been reported, with a pattern of expression that suggests that they are part of dystonia's endophenotype.(1) Case-controlled research also shows an increased prevalence of depression, anxiety and obsessive-compulsive traits in most of the adult-onset idiopathic focal dystonia.(2) **Methods:** 36 patients with cervical and/or limb dystonia and 26 control subjects were asked to complete a hospital anxiety and depression scale (HADS), fatigue severity scale and the Cambridge depersonalization scale. Data was analysed for statistical significance by Mann-Whitney *U* test using SPSS software.

Results: Scores for HADS-anxiety (p < 0.01), HADS-depression (p < 0.005), the fatigue severity scale (p < 0.01) and the Cambridge depersonalization scale (p < 0.05) were all significantly higher in the dystonia group. **Conclusions:** Patients with dystonia in this study had higher levels of fatigue, anxiety and depressive and dissociative symptomatology than healthy controls. Altered cortico-striatal connectivity may explain the increased incidence of psychomorbidity and dissociation in dystonic disorders.

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Mirror dysonia in writer's aramp: a study with advanced multi-channel micro-electrode recording EMG system

V. Rama Raju, R. Borgohain, R. Kandadai (Hderabad, India)

Objective: To differentiate between those with concordant(C) and discordant (D) MMs in WC, in order to establish that there is a quantifiable difference between these two groups and to design/fabricate a sophisticated multichannel microelectrode-recording EMG system.

Background: The main hypothesis is that when a Writer's cramp(WC) patient inscribes with an abnormal posture, it is difficult to determine if that posture is because of the primary dystonic-force or if a compensatory-force applied by the WC-patient has overcome the primary dystonic-force and has resulted in that posture. One way to differentiate those two would be is to look at the mirror-movements (MMs).

Methods: Multivariate statistical analysis for 12 patients in their means, differences in means, standard deviations, variances, t, F and p-values between RHWS and LHWS were compared using student *t*, χ^2 (*Chi-square*) and Fisher's tests. RootMeanSquare(RMS) measured the amplitudes of WC signals and its complexity. decomposition,latent variate factorial analysis principal component analysis, clustering, Canonical correlation/multidimensional scaling,entropy.

Results: 12 patients with writer's cramp (8 with concordant and 4 with discordant MMs) were assessed. On comparison of the measures of dispersion; D group had statistically significant difference between LHWS and RHWS (variance, standard deviation and F ratio) with a larger variance in RHWS, as compared to C group where variances and SD were equal or smaller in the RHWS compared to LHWS. Mean amplitudes for RHWS and LHWS for the same muscles though differ significantly in statistical terms, showed a consistent pattern only in the fifth muscle with a larger mean-amplitude on left-side in all patients and were not of value in differentiating between concordant (C) and discordant (D) groups of patients.



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1	able	Squared	Squared canonical correlations			
Patient	t λ ₁	λ_2	λ3	λ4	λ5	
Al	0.6527	0.3015	0.0006	0.0003	0.0000	D
A2	0.1566	0.0023	0.0004	0.0001	0.0000	
A3	0.0021	0.0015	0.0002	0.0002	0.0000	
A4	0.1734	0.0018	0.0004	0.0000	0.0000	
A5	0.0383	0.0018	0.0015	0.0001	0.0000	
A6	0.0509	0.0033	0.0011	0.0004	0.0001	
A7	0.0022	0.0014	0.0009	0.0008	0.0000	D
A8	0.0799	0.0018	0.0004	0.0002	0.0000	
A9	0.2615	0.0707	0.0030	0.0002	0.0000	
A10	0.0502	0.0069	0.0009	0.0004	0.0001	
A11	0.0034	0.0021	0.0006	0.0002	0.0000	D
A12	0.0013	0.0006	0.0002	0.0002	0.0000	D

Table Squared canonical correlations

Patient	(1,3)	(1,4)	(1,5)	(2,3)	(2,4)	(2,5)	(3,4)	(3,5)	(4,5)
A1	* *	* *	+ *	+ +	* *		* -	- *	* *
A2	* *	* *	+ *	+ +	* _	* *	* -	* *	* *
A3	* *	* *	+ +	* *	* *	* *		* *	* *
A4 🚽				N	Ι	L			→
A5 <				Ν	Ι	L			
A6	* *	* *	+ +	* *	* *	* *		* *	* *
A7 .				N	Ι	_L			
A8	+ *		* +	+ *	* *	* *		* *	* -
A9	* *	* *	+ +	* *	* *	* *	* *	* *	* *
A10	* *	* *	+ *	* *	* _	* *	* *	* -	* *
A11	* *	* *	+ +	* *	- *	* *	* *	* *	* *
A12	* *	* *	+ +	* +	-	* *	- *	* -	* *

Patient	Nearest two	Farthest two
	Patients	Patients
1	5, 2	3,11
2	1,10	3,11
3	7, 4	2,10
4	6, 7	2,11
5	1,10	11,3
6	4, 9	2,11
7	6,4	2,10
8	4,12	11,10
9	6,4	2,8
10	1,2	3,4
11	12,7	2, 8
12	11,7	2,10





Conclusions: This study showed significant quantifiable EMG differences in the signals seen while inscribing with the right and left hands between those writer's cramp patients with concordant mirror movements (C group) versus those with discordant mirror movements (D group). This was mainly seen in the measures of dispersion of the signal i.e., standard dispersion, variances and their ratio (F-ratio). These were statistically significantly different between the two groups, C and D, and the pattern of differences were consistent with the hypothesis that the discordant group had a compensatory force which overcame the dystonic force resulting in the final abnormal posture. These analyses could possibly be applied to longitudinal follow-ups and correlations with a normal control population in future to better comprehend the WC phenomenon.

1244

Sensory trick in a dystonic patient: insights from Magnetoencephalogram

A. Mahajan, A. Zillgitt, S. Bowyer, C. Sidiropoulos (Detroit, MI, USA)

Objective: To explore the mechanism of action of a sensory trick by comparing cerebral oscillations at network level, with a sensory trick and administration of botulinum toxin, using MEG in a patient with cervical dystonia. **Background:** Up to 83% of cervical dystonia patients note partial to complete benefit with a sensory trick. Parietal cortex, a region associated with multimodal sensory integration, has been reported to be hyperactive during execution of the sensory trick.

Methods: MEG data was collected on a patient with cervical dystonia with a definite and effective sensory trick, in the form of a yawn. Patient was scheduled for a MEG scan, pre and post Botulinum toxin injection and pre and post yawn. For each cortical model site, coherence is defined as the oscillations of neural activity and their synchronization with all other active network sources, and further averaged over frequencies. Coherence imaging was performed to quantify default mode network connectivity of subjects.

Results: Pre and post Yawn, pre and post injection. Beta levels decreased and gamma increased after yawn. Left cerebellar activity is seen pre yawn followed by activity in the Right cerebellar region post yawn. Differences with yawn, pre injection. Maximal changes were see in the following locations for pre yawn: Left Medial Occipital Gyrus, lingual and cerebellar regions. Post yawn changes were seen in the Left lingual, parahippocampus regions. Differences with yawn, post injection: Maximal changes were see in the following locations for pre yawn: Left

Cerebellum and middle occipital areas. Post yawn changes were seen in the Left Superior Marginal and angular gyri. Pre and Post injection, no sensory trick: Beta levels increased and gamma levels stayed the same after injection. Left cerebellar activity stays unchanged post injection but activity in the Right cerebellar region increases.



Right <----> Left

pre yawn (GREEN) vs post yawn (RED)

Mean Coherence Parameters

Image: Coherence Parame

Right <----> Left

Conclusions: Prior hypothesis suggests that sensory tricks act via faulty proprioception by enhancing pathways between the occipital and parietal lobes. Our study shows hyper excitability in the parietal cortex with sensory trick. An increase in gamma levels perhaps indicate increasing GABAergic activity. Moreover, we note an increase in activity in the Right cerebellar region post sensory trick and post injection, perhaps even indicating a common sensory pathway for neuronal activation.

1247

Effect of Valproic Acid on Dystonia in a patient with Traumatic Brain Injury: A case report *N. Fatima (Lahore, Pakistan)*

Objective: Valproic Acid, a branched short chain fatty acid, is widely used as an epileptic drug and mood stabilizer [1]. Its mechanism of action is related primarily to neurotransmission and modulation of intracellular pathway. In particular, Valproic acid affects neuronal survival/apoptosis and proliferation /differentiation balance, as well as synaptic plasticity, by acting both directly on neurons and indirectly through glial cells [2]. Dystonia occurs when subtle changes in neuronal function corrupt normal co-ordination and lead to disabling motor disorder [3]. Axonal stretch injury not only damages cytoskeleton but also disrupts membrane permeability thus causes reversal of Na+/Ca2+ antiporter in the axolemma leading to increase in Ca2+ within the cell which causes mitochondrial damage [4].

Background: Dystonia comprise a group of movement disorders that is characterized by involuntary movements and postures [3]. It may be associated with pain and disability. Clinical Electrophysiological studies show that CNS exhibit aberrant plasticity-perhaps related to deficient inhibitory neurotransmission [5]. It can be focal, segmental, axial or generalized. Dystonias are classified according to cause into primary which is idiopathic and secondary which include drug induced dystonia, post traumatic, brain tumors, post anoxic, psychogenic, infectious, pseudodystonia [6]. Traumatic Brain Injury lead to dynamic stretch injury of axons which causes proteolytic disruption of the cytoskeleton ultimately leading to influx of calcium through Voltage Gated Calcium Channels modulated by mechanically sensitive Sodium Channels [7] and reversal of Na+-Ca2+ exchangers. Calcium flows into the cell and activates phospholipases and other proteolytic enzymes ultimately leading to mitochondrial dysfunction [8]. Rigidity and decerbrate posturing occurs with lesion in the midbrain blocking normal inhibitory signals to pontine and vestibular nuclei. Thus, nuclei become active and spinal reflexes become hyper excitable [9] and decreases threshold for excitation of a motor response. Valproic acid is widely used as an anti epileptic and mood stabilizer. Anti epileptic properties have been attributed to inhibition of GABA Transaminobutyrate and ion

channels. Besides the elevation of GABA levels, Valproic acid reduces the high frequency firing of neurons by blocking Voltage gated Na+channels, K+ and Ca2+ channels [2]. In my patient, generalized dystonic posturing hypothesized to be dramatically reduced by the administration of Valproic acid in addition to Midazolam. The idea behind this is that Valproic acid in addition to inhibiting the excitatory signals also minimizes the entry of Calcium within the axons and inhibits the excitatory signals thus minimizing the decerbrate rigidity.

Methods: Written informed consent was obtained from the patient for publication of this case report. **Results:** A 24-year-old man of Asian origin presented with 3-day history of fall from an electric pole (20 foot) and 2-day history of altered sensorium. This was followed by intermittent moderate to high-grade fever, tachypnea (33 Respiratory Rate), tachycardia (115/min Heart Rate), excessive sweating and extensor posturing. Examination revealed consciousness of 3/15 on Glasgow Coma Scale, pupils bilaterally equally reactive to light, increased tone of all limbs of the body and decerebrate posturing. CT Scan Brain showed Brain stem 2*2 cm hyper density. Patient was intubated and ventilator support was adjusted. Conservative Management was started, in addition to continual infusion of Midazolam administered at10 microdrops/min, Valproic Acid was also administered at 500mg Intravenously B.D. Patient showed dramatic improvement in a period of 3 weeks.

Conclusions: Besides the role of valproic acid as anti epileptic, it can also be used to reduce the dystonic posturing in a patient with traumatic brain injury. Valproic acid antagonizes the transmitters both at cellular and molecular level involved in causing dystonia. Thus, its role in treatment and management of abnormal posturing and movements should further be assessed

1248

NUBPL mutations cause combined dystonia with bilateral striatal necrosis and cerebellar atrophy *B. Balint, G. Charlesworth, M. Stamelou, L. Carr, N. Wood, K. Bhatia (London, United Kingdom)* **Objective:** To elucidate the genetic cause of a distinct combined dystonia syndrome, inherited in an autosomal recessive fashion in a small UK kindred [Figure1A].



Background: With the increasing number of genetically defined dystonia syndromes, distinct clinico-radiological phenotypes are a welcome handle to guide the diagnostic work up.

Methods: Exome sequencing of both affected individuals and their mother was followed by variant filtration to look for rare or novel compound heterozygous or homozygous candidate mutations. Information from homozygosity mapping and linkage analysis was used in a supportive role. Other genetic causes known to be associated with the clinical or radiological phenotype were excluded by use of exome data or Sanger sequencing.

Results: Using whole exome sequencing, linkage analysis and homozygosity mapping, we identified compound heterozygous mutations in the *NUBPL* gene as the cause of autosomal-recessive combined dystonia. The gene lay in a region of positive linkage and segregated with disease in the family. The phenotype is characterized by early-onset generalized dystonia, cerebellar ataxia and pyramidal signs, which gradually progressed and led to loss of independent ambulation in adolescence, whereas cognition remained preserved. The brain MRI featured bilateral striatal necrosis and cerebellar atrophy [Figure1B].



Conclusions: We identified NUBPL mutations as the cause of autosomal-recessive dystonia combined with cerebellar ataxia and pyramidal involvement, with bilateral striatal necrosis and cerebellar atrophy on MRI. The here reported cases expand the clinical and radiological spectrum of NUBPL mutations. Bilateral striatal necrosis and cerebellar atrophy might be a useful handle in the differential diagnosis of the long list of early-onset combined dystonias.

1249

Trisomy 8 Mosaicism and dystonia: a THAP1 overdose?

A. Fois, M. Tchan, V. Fung (Westmead, NSW, Australia)

Objective: We report a case of Trisomy 8 Mosaicism (T8M, Warkany Syndrome) with craniocervical and hand dystonia, an hitherto unreported disease association.

Background: T8M is a rare genetic condition (1/25000 to 1/50000 live births) with a protean clinical phenotype including facial dysmorphism, deep palmar and plantar creases, camptodactyly, agenesis of the corpus callosum and a variable degree of intellectual disability. An expressive speech disorder has been described in this condition but not extensively characterised.(1) Movement disorders are not a reported feature.

Methods: Case: A 17-year-old male student was referred to adult neurology services with dysarthria. He was the product of a normal pregnancy with normal early motor milestones but delayed speech until age 3, at which time poor tongue control was noted on speech therapy. Since age 5 he had a stable speech impediment with impaired volitional tongue movements, smiling, and whistling, but normal comprehension, lip function, and swallowing. Handwriting was impaired with both hands when he first started to learn at age 8 and dystonic posturing of his hands was observed on writing. His gait was remarkable for involuntary neck flexion and Fogs' test revealed mild symmetrical posturing of the upper limbs. Deep plantar creases and camptodactyly were also noted. There was a family history of late-onset cervical dystonia in his paternal grandmother. Skin biopsy confirmed T8M. Genetic testing for hereditary dystonias revealed no mutation of TOR1A (DYT1) and a mutation of THAP1 (DYT6) of uncertain pathogenicity (c.530T>C, p.Leu177Pro) not listed in the ExAC or ClinVar databases. His father, who had no dystonia, had the same THAP1 mutation. Our patient subsequently developed a severe cervical dystonia at age 19 which progressed rapidly to peak severity over one month and responded well to botulinum toxin therapy. Results: In our case T8M presented with a young-onset, predominantly craniocervical dystonia with prominent speech involvement, reminiscent of the clinical phenotype of DYT6. We hypothesise that overexpression of THAP1, which may be due to an extra copy of chromosome 8 on which it is located or due to failure of autoregulation from a DYT6-causative THAP1 mutation (2), may represent a common mechanistic pathway to explain the presence of a DYT6-like dystonia in T8M.

Conclusions: Dystonia can occur in T8M and may be a mechanism for the well-reported phenomenon of impaired speech in this condition.

1250

Dystonia Gravidarum Improved After Joint Position Error Training

T. Pham, A. Elder, A. Wu (Los Angeles, CA, USA)

Objective: Describe a case of new dystonia gravidarum improving with joint position error training **Background:** KB is a previously healthy 34-year-old primiparous female without previous exposure to neuroleptics who developed new onset cervical dystonia (CD) within the first month of her pregnancy. Her symptoms began within a week of conception, and developed into CD with severe anterocollis and right rotation with a dystonic head tremor. Her symptoms were severe enough to cause her to completely stop working and take disability leave.

Initially a sensory trick would temporarily improve her symptoms, but this stopped being effective. Of note, the patient did recall having a severe case of varicella zoster as a child requiring hospitalization but denied any neurologic sequelae. She has a twin sister (presumed identical) that did not experience CD during her own pregnancies. She has a remote history of mild neck injury, but denies any previous dystonia or movement disorders, rheumatic fever, or family history of movement disorders. Basic laboratory testing was within normal limits. The patient deferred MRI brain. A presumptive diagnosis of dystonia gravidarum was made based on two previous case reports described in two primiparous women in China and Italy (1, 2). Due to her pregnancy, traditional treatments for CD including botulinum toxin were considered too risky for the unborn fetus. She was referred to a Neurological Clinical Specialist (NCS) physical therapist (PT) for treatment. Treatment focused on using joint position error (JPE) training, which is a method that aims to assess the patient's ability to return their head back to neutral position using a laser centered on her forehead and a target 90 cm in front of the patient. The patient was assessed with 10 trials on each side at every session and instructed to perform the exercises at home. **Methods:** Case Report

Results: [Table 1]



clate	LEFT	RIGHT	TWSTRS
10/10/16	11 out of 30	7 out of 30	
10/17/16			62
10/26/16	14 out of 30	11 out of 30	
11/2/16	19 out of 30	15 out of 30	
11/10/16	12 out of 30	23 out of 30	
11/15/16	17 out of 30	15 out of 30	
12/7/16	28 out of 30	23 out of 30	
12/21/16	17 out of 30	20 out of 30	36

Conclusions: Conclusions: Dystonia gravidarum is a very rare clinical syndrome that has only been described in 2 previous case reports. Pregnancy limits the treatment options for dystonia, but in this case the patient is improving subjectively as well as objectively (TWSTRS and JPE scores) after undergoing treatment with JPE. JPE should be considered as a treatment for future cases of dystonia gravidarum.

1251

Marc Chagall's L'homme À La Tète Renversée (Man With His Head Thrown Back) – An Artistic Depiction Of Severe Retrocollis In Neurodegeneration With Brain Iron Accumulation

L. Oliveira, M. Caeira, F. Germiniani, H. Teive, T. Roza, C.H. Camargo (Curitiba, Brazil)

Objective: To propose that Marc Chagall's L'Homme À La Tète Renversée (Man With His Head Thrown Back) could be a depiction of severe retrocollis due to Neurodegeneration with Brain Iron Accumulation.



Background: Artistic representations of medical conditions, particularly those that cause severe deformity, have been a constant in the history of art. Marc Chagall paintings depicted the everyday lives of Russians, especially the Jewish community. Among his paintings, L'Homme À La Tète Renversée (Man With His Head Thrown Back), is a 1919 oil painting that depicts a man with a strikingly exaggerated backward bending of his head and neck. **Methods:** We present Marc Chagall's original depiction of L'Homme À La Tète Renversée (Man With His Head Thrown Back).

Thrown Back), as well as an edited view with red lines corresponding to the accentuaded backwards arches of both the upper torso and the neck, leading to a posterior head-drop. We also comment on the likely diagnosis related to the possible ethnicity of the painting's subject.

Results: Neurodegeneration with Brain Iron Accumulation syndromes (NBIAs) are a group of varied geneticallyinduced diseases that can affect different ethnical groups, with a worldwide distribution. Among their clinical features, one may find akinetic parkinsonism and severe forms of axial dystonia, sometimes leading to exacerbated retrocollis. By carefully analyzing Marc Chagall's L'Homme À La Tète Renversée (Man With His Head Thrown Back) we propose that he might have involuntarily depicted a case of NBIA with severe retrocollis and bent spine. This could have been a Russian-Jewish subject that lived in a Russian village and suffered from one of the many NBIAs, possibly Panthotenate Kinase Associated Neurodegeneration (PKAN).

Conclusions: Marc Chagall's L'Homme À La Tète Renversée (Man With His Head Thrown Back) is a possible depiction of severe retrocollis with bent spine syndrome, likely due to any of the diseases of the NBIA group, including PKAN.

1252

Treatment of back pain in patient with extensor truncal dystonia with lumbar radiofrequency ablation (RFA) S. Giles, N. Shneyder, J. Cupido, C. Brock, E. Gaitour (Jacksonville, FL, USA)

Objective: Extensor truncal dystonia in majority of cases leads to significant low, mid back pain and discomfort secondary to muscle spasms and early degenerative spinal involvement that is refractory to treatment **Background:** Benefit of muscle chemodenervation with botulinum toxin is well established in different types of focal and segmental dystonia, including truncal dystonia. Symptomatic management with trigger point injections, botulinum toxin in lumbar paraspinal muscles gives temporal relief of abnormal posture and pain. Here we present a patient with facetogenic back pain secondary to sustained lumbar paraspinal muscle spasms in the setting of primary idiopathic truncal dystonia non responsive to standard conservative treatment. Lumbar facet medial branch radiofrequency ablation gave the patient longstanding back pain relief and significantly improved muscles spasms for the same period of time.

Methods: Case report of 42 y/o man with PMH of primary idiopathic extensor truncal dystonia, presents to interventional pain clinic secondary to left sided chronic low back pain. He had trialed multiple medications, trigger point injections for his back pain without success. Pain is a sharp, localized to left low back that is a constant 10/10. Movement increases pain. MRI lumbar spine revealed moderate – severe facet arthropathy most significant at L4 & L5. Left Lumbar Medial Branch Blocks (MBB) at L3/4 & L4/5 was performed with dramatic temporary pain reduction and subsequent lumbar RFA decreased the patient pain for about 6 months.

Results: Patient had repeated left lumbar RFA two times per year for the past 3 years for his chronic left low back pain secondary to truncal dystonia. He reports ongoing pain reduction by greater than 90% and increase in function. **Conclusions:** RFA is an effective procedure in management of patients with back pain. The benefits of the procedure are related to denervation of facet joints. In patients with truncal dystonia, where spine degenerative processes are accelerated the procedure may be introduced to these patients in early stages of the disease since RFA may not only decrease the pain secondary to facet denervation but also slow down degenerative cascade by eliminating muscle spasm in multifidus muscles.

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1256

Oculogyric Crisis Due To Treatment with Flunarizine

M. Kurtz, D. Ballesteros, J. Crespo, J. Perez Garcia, J. Lopez, I. Lagger, F. Knorre (CF, Argentina) **Objective:** To report the first case of oculogyric crisis (OC) secondary to flunarizine.

Background: Oculogyric crisis (OC) are an infrequent neurologic complication of dopamine antagonists treatment. They commonly present as an acute disorder, but they can also occur after weeks of starting treatment or following dose increment. They are usually a cause of disturbance and because of their variable clinical severity and infrequency may be misinterpreted. Flunarizine, a selective calcium channel antagonist, is frequently used in the treatment of episodic migraine. It is associated with aggravation or even induction of movement disorders, usually parkinsonism and very infrequently acute dystonia, but there is not in our knowledge, previous reports of (OC) due to flunarizine.

Methods: Case report.

Results: A-18- year-old female patient with a history of anorexia and episodic migraine with visual aura and frequent episodes was treated with 10 mg of FL during two weeks at another institution. Because of lack of response, the dose was increased to 15 mg of flunarizine with the development of multiple episodes of sustained conjugated upward dystonic deviation of eyes of seconds of duration without impairment of consciousness. Brain MRI, blood and urine copper levels were normal. After the withdrawal of flunarizine, the symptoms completely remitted in less than 24 hours.

Conclusions: In our case, the presentation of the symptoms after the increase of the dose of flunarizine, the improvement following the suspension of the drug and the normal results of the complementary studies suggest that the cause of the OC was related to the use of flunarizine. It was probably caused by a dopamine receptor blocking effect. Although there are reports of OCs produced by drugs with the same mechanism of action, this is the first case secondary to flunarizine. Due the potencial side effects, treatment with flunarizine should be carefully indicated and doses higher than 10 mg must be avoided.

1257

Focal dystonia as an early symptom of CACNA1A mutation: case report and literature review.

Y. Gu, K. Kumar, C. Sue (Sydney, NSW, Australia)

Objective: We describe two cases, a father-daughter pair, of *CACNA1A* mutation with task specific dystonia as an early feature. The father otherwise had a phenotype of adult-onset pure cerebellar ataxia.

Background: Mutations in *CACNA1A*, even in pedigrees demonstrating the same mutation, are understood to present with a heterogeneous spectrum of phenotypes including familial hemiplegic migraine, episodic ataxia type 2 and spinocerebellar ataxia type 6.

Methods: Case 1: A 39-year-old male, referred for assessment of progressive cerebellar ataxia, first noted poor balance as a teenager. In his 20s he experienced a decline in handwriting with features of tremor, cramping, pain and abnormal posturing when writing. Symptoms were alleviated by touching the wrist with the left hand. MRI brain revealed cerebellar atrophy. Testing for vitamin E, frataxin, fragile X-associated tremor/ataxia syndrome, DYT1, SPG3A, SPG4, SPG6 were negative. Triplet repeat testing for SCA 1, 2, 3, 6, 7 was negative. Case 2: 6 years later his 8-year-old daughter was assessed due to concerns regarding balance. She had difficulty riding a bike, climbing stairs, mild bilateral past pointing and hypometric saccades. She experienced in-turning of one foot when descending down stairs and required an orthotic. Genetic testing in the proband and his daughter for *CACNA1A* revealed a c.1748G>A missense mutation in chromosome 19, resulting in an arginine583 to glycine substitution in both individuals.

Results: Dystonia is not typically associated with CACNAIA mutation but there are several reports in the literature. CACNA1A null mouse models exhibited dystonia early in addition to absence seizures and ataxia. Dystonia has been described both ictally and inter-ictally in cases with the episodic ataxia phenotype. It has also been observed in spinocerebellar ataxia type 6 resulting from CAG expansion in exon 47. In the pediatric population cases of dystonia are also reported in association with the episodic ataxia phenotype. Furthermore, studies in benign paroxysmal torticollis of infancy have also revealed mutations in the CACNA1A.

Conclusions: Thus dystonia can be an early aspect of the clinical phenotype of CACNA1A. This clinical observation also indicates a relationship between dystonia and abnormal calcium signaling and further studies may elucidate additional insights.

1258

Improvement in hand tremor following carpal tunnel release surgery

A. Hollingsworth, S. Wijemanne (San Antonio, TX, USA)

Objective: To describe a case of a dystonic tremor improvement following treatment of a peripheral nerve lesion, in this case carpal tunnel release surgery.

Background: The pathophysiology of dystonia and dystonic tremors is complex and includes loss of surrounding inhibition in the cerebral cortex and reduced reciprocal inhibition at many levels of the motor system. Previous cases of peripherally induced dystonic tremors exist in the literature, but there are no previous reports of improvement of the tremor following carpal tunnel release surgery.

Methods: The patient is a 66 year old right handed Caucasian male who was referred for evaluation of a new onset tremor. The tremor symptoms began 3 months prior to the initial visit and were localized to the left hand. Upon physical examination, he did not have a rest tremor but was found to have a 5 cm large amplitude, 5-6Hz tremor that appeared when the arm was held flexed at the wrist and at the elbow which was consistent with a dystonic tremor. Brain MRI and workup for Wilson's disease was negative. Patient reported symptoms of carpal tunnel syndrome (CTS) and underwent electromyography (EMG) testing, which showed findings consistent with severe CTS in his left wrist with denervation occurring. The patient underwent carpal tunnel release surgery.

Results: One week after the surgery patient started to notice improvement in tremor which continued to improve over the next few weeks. There was marked improvement in the frequency and the amplitude of the tremor. Conclusions: The patient's clinical improvement of the dystonic tremor suggests that his tremor had a peripheral cause secondary to his carpal tunnel syndrome. This finding suggests the importance of consideration of peripheral causes of focal dystonic tremors if central causes have been ruled out. Furthermore, this case suggests that treatment of the peripheral lesion in these cases can lead to improvement of their dystonic tremor.

1260

Physical Activity in Early Parkinson's disease

S. Mantri, M. Fullard, J. Duda, J. Morley (Philadelphia, PA, USA) Objective: To characterize physical activity habits in patients with early Parkinson's disease (PD). Background: Physical activity is an important therapy for PD as it may affect both symptoms and disease progression. The American Heart Association (AHA) recommends at least 150 minutes of moderate or 75 minutes of vigorous activity weekly for all adults[1]; however, little is known about activity levels in early PD. Methods: We queried the Parkinson Progression Markers Initiative (PPMI) database for responses to the Physical Activity Scale in the Elderly (PASE)[2], a well-validated assessment in subjects older than 65. Because PASE scores were higher than published norms, we audited the data where possible to ensure proper scoring. Twenty percent of records were recoded due to incorrect assignment of activities but recoded scores did not differ significantly from non-recoded scores. For subjects over 65, we compared raw scores and percentage of individuals meeting AHA activity guidelines in PD patients and age- and gender-matched controls and examined associations between PASE score and clinical characteristics.

Results: Initial PASE score was lower for PD patients (N=161) than healthy controls (N=73) (161.8±83.6 vs 183.7±68.5, p=0.036), driven by females aged 70 and above [table 1]. Less than half of PD patients met AHA activity guidelines [table 2], and adherence declined with age, especially among women. After controlling for age and gender, there were no significant associations between PASE score and baseline clinical characteristics [table 3].

Group		oup PD patients (n) Healthy Com		l p
All	95	161.8 ± 83.6 (387)	183.7 ± 68.5 (175)	0.036
Men	65-69	181.3 +/- 94.9 (55)	206.98 +/- 72.6 (21)	0.212
70+		155.8 +/- 72.2 (62)	161.0 +/- 57.0 (26)	0.747
Women	65-69	166.3 +/- 89.5 (21)	170.7 +/- 56.4 (14)	0.859
	70+	127.0 +/- 69.0 (23)	207.1 +/- 83.1 (12)	0.005

Table 1: Mean PASE scores

Group		PD patients (n)	Healthy Controls (n)	p	
All		47.0 (387)	44.6 (175)	0.588	
Men	65-69	43.6 (55)	47.6 (21)	0.755	
March 1	70+	40.3 (62)	42.3 (26)	0.863	
Women	65-69	52.4 (21)	64.3 (14)	0.440	
19910-022	70+	30.4 (23)	50.0 (12)	0.061	

Table 2: Percentage meeting AHA guidelines

Variable	0.	P
SIMI	0.390	0.811
Years of education	-0.210	0.924
MDS-UPDRS III	-0.063	0.915
MOGA	-0.696	0.795
SCOPA-Autonomic	-1.411	0.154
Schwan/England	1.076	0.319
Epworth Sleepiness Scale	-1.170	0.533
Geriatric Depression Scale	-0.470	0.914
REM behavior disorder	-1.807	0.460

Table 3: Linear regression analysis for PASE score and clinical characteristics for patients with PD, controlling for age and gender.

BMI + body mass index; MDS-UPDRSIII + Movement Oborders Society Unified Parkinson Disease Rating Scale, motor subscale*;

MoCA + Montreal Cognitive Assessment: SCOPA + Scale for Outcomes of Parkinson Disease

*We used existing epidemiologic MDS-UPDRS scores from RPMI; we did not administer MDS-UPDRS independently

Conclusions: Most early PD patients, like healthy controls, are not compliant with AHA activity guidelines, highlighting the need to encourage exercise even in early PD patients. In particular, older women with PD may benefit from targeted interventions to increase physical activity. Although physical activity was not associated with baseline clinical characteristics, the longitudinal design of PPMI will allow future studies to examine the relationship between baseline physical activity and progression of PD.

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Validation of the MDS Research Criteria for Prodromal Parkinson's Disease: Longitudinal assessment in a REM sleep behavior disorder (RBD) cohort

S.M. Fereshtehnejad, J. Montplaisir, A. Pelletier, J.F. Gagnon, D. Berg, R. Postuma (Montreal, QC, Canada) **Objective:** 1) To calculate diagnostic accuracy of the International Parkinson and Movement Disorder Society (MDS) prodromal criteria to predict conversion to Parkinson's disease (PD) or dementia with Lewy bodies (DLB); 2) to evaluate the association between prodromal PD likelihood ratios and the time to conversion and 3) to investigate the independency of prodromal markers.

Background: Recently, the MDS introduced the prodromal criteria for PD. Accuracy of the MDS criteria for prodromal PD needs to be validated, particularly in different cohorts in which the markers are combined. **Methods:** This prospective cohort study was performed on 121 individuals with REM sleep behaviour disorder (RBD) who were followed annually for an average of 3.6 years. Using data from a comprehensive panel of prodromal markers, likelihood ratio (LR) and post-test probability of the criteria were calculated at baseline and during each follow-up visit.

Results: Forty-eight (39.7%) individuals with RBD converted to PD/DLB. The MDS prodromal criteria had 81.3% sensitivity and 67.9% specificity for conversion to PD/DLB at 4-years follow-up. One year before conversion, sensitivity was 100%. The criteria predicted DLB with even higher accuracy than PD without dementia at onset. Those who met the threshold of prodromal criteria at baseline had significantly more rapid conversion into a neurodegenerative state (4.8 vs. 9.1 years, p<0.001). Furthermore, there was a stepwise increase in conversion rates according to the quartiles of the baseline post-test probability of prodromal PD calculated by from the MDS criteria (*Figure 1*). Pairwise combinations of different prodromal markers showed that markers were independent of each other except for a significant interaction between hyposmia and quantitative motor testing.



1. Kaplan-Meier survival curve for the conversion time to neurodegenerative disease in different quartiles of posttest probability

Conclusions: The MDS prodromal criteria are a promising tool for predicting incidence of PD/DLB and conversion time in an RBD cohort. In RBD, they have high sensitivity and negative predictive value (NPV). Prodromal markers influence the overall LR independently, allowing them to be reliably multiplied. Increasing the number of markers, further longitudinal assessment and testing of different thresholds in different target populations will continue to improve the criteria.

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Clinical Criteria for Subtyping Parkinson's Disease: Differences in imaging and CSF biomarkers and longitudinal progression

S.M. Fereshtehnejad, Y. Zeighami, A. Dagher, R. Postuma (Montreal, QC, Canada)

Objective: To introduce a new practical classification method to assign individuals with Parkinson's disease (PD) into distinct subtypes using baseline dataset, then to compare neuroimaging, biospecimen markers and disease progression between the subtypes.

Background: PD varies widely in clinical manifestations and prognosis from person to person. Identification of distinct PD subtypes is of great priority to predict progression and develop more efficient personalized care approaches.

Methods: We recruited 421 individuals with de novo early PD from the Parkinson's Progression Markers Initiative (PPMI). Cluster analysis was performed using a comprehensive dataset at baseline consisting of demographic and genetic information, motor, neuropsychological and other non-motor manifestations. For analysis of longitudinal progression, we created a global composite outcome (GCO) by combining standardized scores of non-motor symptoms, motor symptoms and signs, activities of daily living and global cognition at baseline and the latest follow-up visit.

Results: The key classifiers in cluster analysis were motor summary score and three non-motor features (cognitive impairment, RBD and dysautonomia). Based upon this, we assigned individuals into 3 specific subtypes: "mild motor-predominant" (composite motor and all 3 non-motor scores<75th percentile), "diffuse malignant" (composite motor score >75th percentile, or all three non-motor scores>75th percentile) and "intermediate". People with "diffuse malignant" PD had the lowest level of CSF amyloid-beta and amyloid-beta/t-tau ratio. A PD-specific brain network in MRI had more atrophy in the "diffuse malignant" subtype, with the "mild motor-predominant" subtype having the least atrophy. Although disease duration and follow-up time were similar, people with "diffuse malignant" PD progressed faster in GCO with greater decline in SPECT measure of dopamine innervation after 2.7 years.

Table 1. Post hoc comparison of the baseline demography and clinical features, brain imaging and CSF biomarkers between the three phenotypes of
Parkinson's disease population in the PPMI based on the recommended clinical definition (N=421)

	Phenotype I Mild	Phenotype II	Phenotype III	ANOVA/Chi ²	Post hoc
Characteristic	Motor-Predominant	Intermediate (n=146)	Diffuse Malignant (n=52)	p-value	p-value
	(n=223)	Raseline			
Age at onset (year)	60.0 (9.7)	62.2 (9.6)	62.8 (9.6)	0.038	None
Male sex (%)	140 (62.8%)	98 (67.1%)	38 (73.1%)	0.329	
White race (%)	215 (96.4%)	135 (92.5%)	49 (94.2%)	0.331	-
Education history (year)	15.7 (3.0)	15.4 (2.9)	15.4 (3.2)	0.514	
Symptoms duration (month)	6.6 (6.7)	6.2 (6.2)	7.4 (7.0)	0.531	
Positive family history (%)	29 (13.1%)	18 (12.5%)	8 (15.4%)	0.869	
Genetic Risk Score (GRS)	-0.015 (0.008)	-0.17 (0.010)	-0.018 (0.009)	0.170	
UPDRS-total score	26.4 (9.4)	35.2 (11.8)	51.7 (11.3)	<0.001	All comparisons
	Moto	or Symptoms and Signs	11.0.(1.2)		
UPDRS-Part II	4.0 (2.7)	6.9 (3.9)	11.8 (4.3)	<0.001	All comparisons
UPDRS-Part III	18.3 (7.5)	21.9 (8.9)	30.0 (9.2)	<0.001	All comparisons
Tremor score	94.7 (5.0)	92.2 (0.2)	0.58 (0.38)	0.085	All comparisons
PIGD score	0.15 (0.16)	0.26 (0.23)	0.46 (0.28)	<0.003	All comparisons
FIGUISCOTE	Non-Me	ator Symptoms and Sig	16	40.001	An comparisons
UPDRS-Part I	4.0 (3.0)	6.5 (3.6)	9.9 (5.3)	<0.001	All comparisons
Epworth sleepiness score	5.1 (3.0)	6.1 (3.5)	7.6 (4.1)	<0.001	All comparisons
Geriatric depression scale (GDS)	1.9 (2.2)	2.4 (2.3)	4.1 (3.0)	< 0.001	III vs. I, III vs. II
State-trait anxiety inventory (STAI) score	62.2 (16.0)	65.9 (18.1)	78.7 (22.7)	< 0.001	III vs. I, III vs. II
(QUIP sum score)	0.22 (0.55)	0.28 (0.56)	0.40 (0.77)	0.111	-
REM sleep behavior disorder (RBD) score	2.1 (1.5)	4.6 (2.9)	6.6 (3.0)	<0.001	All comparisons
Olfaction UPSIT percentile	23.0 (8.0)	22.1 (8.1)	19.8 (9.3)	0.040	I vs. III
Drop in systolic blood pressure (mmHg)	3.3 (12.0)	5.1 (11.3)	8.3 (17.4)	0.030	I vs. III
SCOPA autonomic questionnaire					
Orofacial symptoms	0.6 (0.9)	1.3 (1.3)	2.5 (1.6)	<0.001	All comparisons
Constipation	0.6 (0.9)	1.5 (1.5)	2.0 (1.5)	<0.001	All comparisons
Urinary	3.2 (2.0)	5.0 (3.2)	7.9 (9.9)	<0.001	All comparisons
Cardiovascular	0.3 (0.5)	0.6 (0.9)	0.9 (1.1)	<0.001	All comparisons
Thermoregulatory	0.8 (1.1)	1.4 (1.4)	2.0 (1.8)	<0.001	All comparisons
Pupillomotor	0.3 (0.6)	0.5 (0.6)	0.8 (0.8)	<0.001	III vs. I, III vs. II
Total score	0.8 (1.2)	1.3 (1.7)	1.7 (2.0)	<0.001	All comparisons
Coonitive function	0.0 (3.4)	11.7 (0.5)	10.5 (0.0)	~0.001	An comparisons
MOCA (adjusted score)	27.5 (2.1)	26.8 (2.5)	26.7 (2.5)	0.005	1 vs. II, 1 vs. III
Benton judgment of line orientation (adjusted score)	12.6 (2.6)	11.7 (3.2)	10.5 (2.9)	<0.001	All comparisons
HVLT-total recall (T score)	48.0 (11.0)	45.4 (11.1)	42.9 (10.2)	0.004	I vs. III
HVLT-delayed recall	48.3 (11.4)	46.4 (12.1)	42.3 (11.1)	0.003	I vs. III
(T score)					
HVLT-retention (T score)	50.9 (11.6)	49.0 (11.2)	48.1 (13.3)	0.093	-
HVLI-recognition discrimination index	50.4 (11.3)	47.1 (11.8)	50.2 (16.3)	0.039	I vs. II
Letter number sequencing (LNS) scaled	12 0 (2 7)	110/26	10.8 (2.6)	0.001	
score	12.0 (2.7)	11.0 (2.6)	10.5 (2.0)	0.001	1 45. 11, 1 45. 11
Semantic fluency (T score)	52.1 (9.6)	49.9 (9.6)	47.6 (10.8)	0.004	I vs. III
Symbol digit test (T score)	46.9 (7.6)	43.8 (9.0)	41.2 (9.7)	<0.001	l vs. II, I vs. III
		Brain Imaging			
SPECT Striatal binding ratios (SBR)					
Caudate	2 10 (0 52)	1 00 (0 52)	1 72 (0 71)	0.001	
Ridamon	0.23 (0.81)	0.18(0.91)	0.14 (1.40)	0.001	Lys. II, TVS. III
MPI	0.23 (0.81)	-0.19 (0.31)	-0.14 (1.40)	0.005	1 43. 11
Deformation-based morphometry (DBM)					
PD-related ICA network	0.17 (1.04)	-0.13 (0.94)	-0.33 (0.90)	0.018	Lvs. III
Substantia nigra score	0.10 (1.09)	-0.13 (0.91)	-0.03 (0.86)	0.269	-
		CSF Biomarkers			
CSF biomarkers					
a-synuclein	1823.3 (756.7)	1890.0 (863.4)	1829.7 (741.3)	0.727	-
Αβ42	378.3 (97.7)	373.3 (101.8)	329.0 (96.7)	0.006	III vs. I, III vs. II
P-tau	16.2 (11.3)	15.5 (9.3)	14.3 (6.6)	0.458	-
T-tau	43.7 (16.7)	46.2 (20.0)	46.6 (21.6)	0.385	-
Aβ42/T-tau ratio	9.5 (3.1)	9.1 (3.2)	8.2 (3.0)	0.032	I vs. III
Aβ42/α-synuclein ratio	0.24 (0.10)	0.23 (0.09)	0.21 (0.10)	0.223	-
P-tau/α-synuclein ratio	0.010 (0.009)	0.009 (0.006)	0.010 (0.008)	0.583	-



Figure 1. A) DBM maps within PD-specific network have been compared between each subtype and healthy controls, corrected for multiple comparison using FDR. There is higher atrophy in "diffuse malignant" phenotype compared to "intermediate" phenotype and in "intermediate" phenotype compared to "mild motor-predominant" phenotype. B-C) whole brain atrophy pattern within each group compared to controls (uncorrected) shows consistent pattern to Braak PD stages (last schematic row from: Jucker M, Walker LC. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature. 2013;501(7465):45-51) (The last column is showing the overlapped pattern of atrophy in all phenotypes merged together.)

Conclusions: We introduce new clinical criteria for subtyping PD which can be applied in clinical practice using baseline information. Even in the early-stage, patients with "diffuse malignant" subtype demonstrated more profound dopaminergic deficit, increased atrophy in brain network, a more Alzheimer's disease-like CSF profile and more rapid progression of motor and cognitive deficits.

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Movement Disorders in Demyelinating Diseases: a retrospective review from a tertiary academic center.

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Objective: To review the prevalence of movement disorders (MD) in patients with demyelinating diseases (DD) treated at a tertiary academic center and to characterize their therapeutic response and imaging features. **Background:** MD have been reported in DD[1] but, while adding to the disability and disease burden are frequently overlooked or undertreated. Data on efficacious treatment of these MD is also sparse.

Methods: We reviewed the chart of patients seen at our academic center between 1/1/2009 and 6/1/2016 with ICD 9 or ICD 10 codes for MD and DD or patients who were seen by both a movement disorder and a white matter disease specialist. 209 patients were identified. We reviewed the clinical characteristics, brain and spine MRIs, medications and therapeutic responses to both MD and DD treatments. Spasticity was not included in the list of MD reviewed. **Results:** Of the 209 patients reviewed, 123 patients (75% female, age 48.8 +/- 12.8 years) had one or more MD. The most common MD were ataxia, followed by isolated tremor, then ataxia and tremor in combination. Other MD reported in these patients were parkinsonism, dystonia, myoclonus, paroxysmal kinesegenic dyskinesia, restless legs syndrome and tics. The average age at diagnosis of MD was 41 years. MD were related to an acute onset in 31% of patients, and 11.3% responded to DD therapy. Only 42 patients (34%) had any treatment for MD. Of those, 29 (69%) responded at least partially to a first MD agent and 7 patients (16.6%) responded at least partially to a 2nd, 3rd or 4th agent. There was signal abnormality in the basal ganglia (BG) or the cerebellum in 58 (47%) of the patients. Patients with Parkinsonism, tics-tourettism, and myoclonus did not have any imaging involvement of the BG or cerebellum.

Conclusions: MD are commonly untreated in DD patients, but have a 69% therapeutic response to a first therapeutic trial. Greater awareness of potential therapeutic options is needed to decrease disability in these patients.

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Cinnamomum verum on Learning and Memory in Wistar Albino Rats

N. Ahmed, D. Agrawal, A. Chughtai (Aligarh, India)

Objective: Several studies have been performed on Cinnamomum verum, but not much is known about the activity of Cinnamomum verum on Memory Enhancing. Therefore Cinnamomum verum is selected for this study to understand its efficacy on Learning and Memory.

Background: Learning and Memory are the basic need through which we try to interact with surrounding, but with stress, depression in our socio-economical and sedentary lifestyle which affects our mind and behaviour and in turn they also alter our thinking process and dampens our learning and memory. In Unani medicine, many drugs are described to be effective in enhancing the memory but only very few of them have been scientifically evaluated. So, one of the single drug is, Cinnamomum verum. In the present study it was evaluated for its learning & memory enhancing effect in experimentally induced stress in Male wistar albino rats.

Methods: Animals were divided into 4 groups with 6 animals in each group, Group I Control, Group II Acute Noise Stress alone, Group III treated with C. verum and Group IV Stress and Drug Treated. Group I and II received equal amount of saline, whereas Group III and IV was administered with C. verum powder in a dose of 100 mg/Kg/body weight dissolved in distilled water (1ml) and administrated orally for 22 consecutive days. Reference Memory Error, Working Memory Error, Triad Error and Total Time Taken were noted using 8-Arm and Y-Maze were evaluated and statistically compared with the similar values obtained in all the groups for same duration respectively. Phytochemical studies were also done to know the active compound & constituent of C. verum.

Results: Oral administration of C. verum in the treated group exhibit high percentage of correct responses when compared to the control rats, C. verum treated group also exhibit decreased Reference Memory Error, Working Memory Error, Total Time Taken and Latency period compared to control and stress rats. Both 8 Arm and Y Maze showed the memory enhancing property of C. verum. After withdrawal from the drug for 10 days, the test rats showed an improved performance compared to the control rats, which can be interpreted as good retention performance.

Kingdom:	Plantae
Division:	Magnoliophyta
Class:	Magnoliopsida
Order:	Laurales
Family:	Lauraceae
Genus:	Cinnamomum
Species:	Cinnamomum verum
Common names:	Darchini, Laungpattai, Cinnomon

Figure: 1. Cinnamomum verum, as illustrated by Franz Eugen Köhler, in his Medicinal- Plants in Natural Garden Abbildungen and kurzerläuterndem Text, published in 1887.



Cinnamomum verum is a very common traditional Indian Spice known as Darchini in Hindi/Urdu and Lavangapatta, Karuvapattai in Tamil & Telugu. The word cinnamon comes from the Greek word "kinnamomon".



Fig: 2. CINNAMOMUM VERUM PLANT



Fig: 3. CINNAMOMUM BARK

Fig: 4. EIGHT ARM RADIAL MAZE



Fig: 5. Y-MAZE



Table 1: 8-ARM RADIAL MAZE- REFERENCE MEMORY ERROR

S No	CROUPS	REFERENCE MEMORRY ERROR						
3.110	GROUPS	DAY 1	DAY 8	DAY 15	DAY 22			
1	CONTROL	1.33 ± 0.21	1.33 ± 0.21	2.17 ± 0.31	2.33 ± 0.21			
2	STRESS	2.66 ± 0.21	2.83 ± 0.17	2.83 ± 0.17	2.67 ± 0.21			
3	CONTROL + DRUG TREATED	1.17 ± 0.17	1.50 ± 0.22	2.50 ± 0.22	0.50 ± 0.22			
4	STRESS + DRUG TREATED	2.50 ± 0.22	2.67 ± 0.21	2.67 ± 0.21	1.67±0.17			

Figure 8: REFERENCE MEMORY ERROR-8 ARM RADIAL MAZE



The data are expressed as mean \pm SEM. *a compared to control, *b compared to acute noise stress group, *c compared to drug treated group and *d has compared to the stress with drug treated group.

Table 2:8-ARM RADIAL MAZE- WORKING MEMORY ERROR

S. No	GROUPS	WORKING MEMORY ERROR				
		DAY 1	DAY 8	DAY 15	DAY 22	
1	CONTROL	0.50 ± 0.22	0.50 ± 0.22	1.33 ± 0.21	2.83 ± 0.17	
2	STRESS	1.33 ± 0.21	1.50 ± 0.22	2 ± 0.26	3±0.26	
3	CONTROL + DRUG TREATED	0.33 ± 0.21	0.50 ± 0.22	1.17±0.17	1.33±0.21	
4	STRESS + DRUG TREATED	1.17±0.17	1.33±0.21	1.50 ± 0.22	0.50 ± 0.22	

Figure 9: WORKING MEMORY ERROR-8 ARM RADIAL MAZE



The data are expressed as mean \pm SEM. *a compared to control, *b compared to acute noise stress group, *c compared to drug treated group and *d has compared to the stress with drug treated group.

S. No	GROUPS	TOTAL TIME TAKEN				
		DAY 1	DAY 8	DAY 15	DAY 22	
1	CONTROL	45.17 ± 5.19	48 ± 5.13	67.50 ± 3.82	90.83 ± 5.83	
2	STRESS	93.33 ± 8.82	106.67 ± 7.49	115 ± 7.64	131.67 ± 9.46	
3	CONTROL+ DRUG TREATED	46.67 ± 4.41	45.83 ± 5.69	66.67 ± 4.41	40.83 ± 5.83	
4	STRESS+ DRUG TREATED	92.50±6.42	73.33 ± 8.82	115±6.19	75 ± 7.64	

Table 3: 8-ARM RADIAL MAZE - TOTAL TIME TAKEN

Figure 10: TOTAL TIME TAKEN-8 ARM RADIAL MAZE



The data are expressed as mean \pm SEM. *a compared to control, *b compared to acute noise stress group, *c compared to drug treated group and *d has compared to the stress with drug treated group.

Table 4: Y MAZE- TRIAD ERROR

S. No	GROUPS	TRIAD ERROR				
		DAY 1	DAY 8	DAY 15	DAY 22	
1	CONTROL	0.66 ± 0.21	0.83 ± 0.17	1.17 ± 0.17	1.50 ± 0.22	
2	STRESS	0.83 ± 0.17	1.17 ± 1.67	1.67 ± 0.21	1.83 ± 0.17	
3	CONTROL + DRUG TREATED	0.67 ± 0.21	0.67±0.21	0.50 ± 0.22	0.33±0.21	
4	STRESS + DRUG TREATED	0.83 ± 0.17	0.83 ± 0.17	1.17 ± 0.17	0.33 ± 0.21	
Figure 11: TRIAD ERROR-Y MAZE



The data are expressed as mean \pm SEM. *a compared to control, *b compared to acute noise stress group, *c compared to drug treated group and *d has compared to the stress with drug treated group.

S. No	CROUPS	TOTAL TIME TAKEN						
	GROUPS	DAY 1	DAY 8	DAY 15	DAY 22			
1	CONTROL	33.33 ± 4.41	45.83 ± 4.72	52.50 ± 3.82	56.67 ± 4.41			
2	STRESS	39.17±5.39	52.50 ± 3.82	53.33 ± 4.41	66.67 ± 4.41			
3	CONTROL + DRUG TREATED	37.50 ± 4.23	42.50 ± 3.82	37.50 ± 3.81	33.33 ± 4.41			
4	STRESS + DRUG TREATED	40.83 ± 5.07	50.83 ± 3.00	43.33 ± 4.41	30.82 ± 5.83			

Table 5: Y MAZE- TOTAL TIME TAKEN

Figure 12: TOTAL TIME TAKEN-Y MAZE



The data are expressed as mean \pm SEM. *a compared to control, *b compared to acute noise stress group, *c compared to drug treated group and *d has compared to the stress with drug treated group.

Table 6: Y MAZE- LATENCY PERIOD

C 11	CROURS	LATENCY PERIOD					
5. NO	GROUPS	DAY 1	DAY 8	DAY 15	DAY 22		
1	CONTROL	1.62 ± 0.23	2.03 ± 0.22	2.17 ± 0.25	2.40 ± 0.30		
2	STRESS	2.35 ± 0.23	2.55 ± 0.23	3.48 ± 0.28	5.28 ± 0.39		
3	CONTROL + DRUG TREATED	1.67±0.22	1.77 ± 0.14	1.08 ± 0.18	0.78±0.15		
4	STRESS + DRUG TREATED	1.60±0.18	1.22 ± 0.19	0.88 ± 0.14	2.10±0.30		

Figure 13: LATENCY PERIOD -Y MAZE



The data are expressed as mean ± SEM. *a compared to control, *b compared to acute noise stress group, *c compared to drug treated group and *d has compared to the stress with drug treated group.

Conclusions: Present study shows that Cinnamomum verum improves learning and memory it may be due to the presence of Cinnamon being an exceptional source of anti-oxidant; it also contains phyto-chemicals that assist the brain in metabolizing glucose, an essential form of energy for mental function.

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The Use of Atypical Antipsychotics in Depression and Anxiety may Unmask Parkinson's Disease: A Retrospective Chart Review

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Objective: Characterize the population with parkinsonism and exposure to antipsychotics who underwent dopamine transporter single-photon emission computed tomography (DATSPECT).

Background: Atypical antipsychotics are used in refractory depression and anxiety, which are highly prevalent in Parkinson's disease (PD) and can present in the prodromal period. While less commonly associated with atypical antipsychotics than typical antipsychotics, drug induced parkinsonism (DIP) remains a concern and in susceptible individuals, these drugs may unmask subclinical PD^{1,2}.

Methods: We identified individuals with parkinsonism, exposure to antipsychotics, and DATSPECT imaging who were evaluated by a neurologist between March 2011 and February 2016. We abstracted information regarding demographics, psychiatric history, clinical characteristics of parkinsonism, and DATSPECT imaging. We used descriptive statistics to characterize the population and either the chi-square test or Student's *t* test as appropriate to compare the abnormal and normal DATSPECT groups.

Results: We identified sixteen individuals; eleven with abnormal DATSPECTs, indicative of neurodegenerative parkinsonism, and five with normal DATSPECTs, consistent with DIP. The abnormal DATSPECT group was 45% male with a mean age of 57.7. The normal DATSPECT group was 60% male with a mean age of 59.4. All 16 individuals had been exposed to an atypical antipsychotic, with 15 of the 16 having been exposed to only atypical

antipsychotics. The indication for antipsychotics was depression and/or anxiety in 73% of the abnormal and 60% of the normal DATSPECT group. Of the examined clinical characteristics of parkinsonism, the only statistically significant difference observed was that there was no progression of symptoms among 80% in the normal DATSPECT group versus 18% in the abnormal DATSPECT (p=0.017). Interestingly, equal proportions in each group presented with asymmetric parkinsonism.

Conclusions: While this study was limited by a small sample size, our findings suggest that there are minimal clinical differences between DIP and PD. The most common indication for atypical antipsychotic use was depression and/or anxiety. It is possible that motor features of PD may be unmasked by atypical antipsychotic use in certain patients with early disease, manifesting only premotor symptoms.

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Pregnancy and Parkinson's disease: A review and update

M. Seier, A. Hiller (Portland, OR, USA)

Objective: To investigate the literature on pregnancy in the setting of Parkinson's disease (PD) in order to better understand and treat women who become pregnant.

Background: PD only presents before the age of 40 in about 5% of cases and it is estimated that only about 400 women less than 50 years old are diagnosed with PD each year in the United States. Additionally, epidemiologic studies have shown that men are more than 1.5-2 times as likely to develop PD than women. As a result, the incidence of pregnancy in the setting of PD is relatively low and our knowledge is largely limited to cases reported in the literature. There has not been a systematic update to the literature in nearly 20 years. As a result, knowledge in treating and counseling women of childbearing age with PD is lacking.

Methods: We collected reports in the English literature from 1985 to 2016 to find cases of pregnancy and PD. Analysis of the papers included patient characteristics, birth outcomes, PD symptom control, use and dosages of anti-parkinsonian medications during pregnancy.

Results: There are 79 cases of pregnancy and PD reported in the literature from 28 separate articles. Of those, 75 resulted in live births. Regarding motor symptom outcomes, 41% of women were found to have worsening of their PD symptoms while 44% were found to have no change or improvement in PD symptoms. PD symptom control was not mentioned in 14% of cases. Regarding medication use in the setting of PD and pregnancy, levodopa was by far the most common medication used, with 47 pregnancies discussed. The dose of levodopa used ranged from 100 to 2500mg/day. No major abnormality (other than one case of osteomalacia) or birth complications were directly related to levodopa use. In cases where both medication status and symptoms were reported, 64% of women who were treated with anti-PD medications had improvement or stability during pregnancy, compared to only 33% of women who were not treated with anti-PD medication. Limited cases of dopamine agonists, anticholinergics, MAO-B and COMT inhibitors were also found. There is strong evidence of poor fetal outcomes associated with amantadine use.

Conclusions: Women with PD should be counselled that pregnancy has variable effects on PD symptoms and that levodopa has been used safely in many patients. Amantadine use should be avoided if possible and there is insufficient data to make recommendations on the use of other PD medications.

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Neural correlates of movement sequence kinematics in substantia nigra dopaminergic cells

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Objective: To develop a new behavioral task for assessment of mice forelimb movements, and evaluate the substantia nigra *pars compacta* dopaminergic cells' (SNpc) correlates of movement kinematics.

Background: Models of basal ganglia function frequently focus on initiation deficits. This contrasts with what is observed in Parkinson's Disease (PD) where chronic dopamine depletion is associated not only with "slowness of initiation" but also with "progressive reduction in speed and amplitude of repetitive actions" (Bradykinesia). The role of basal ganglia on movement speed and amplitude remains unclarified, but it seems reasonable to hypothesize that dopamine has a pivotal role.

Methods: Repetitive finger tapping is commonly used to assess movement speed and amplitude in PD. Using this as an inspiration we developed a novel self-paced operant task, in which mice learn to perform a particular sequence of actions, using only one forelimb. The task was designed to collect data regarding the spatial position, speed and acceleration of the forelimb of the mouse. A miniature epifluorescence microscope (~1.9g) was used to image GCaMP6f fluorescence (a calcium indicator) in dopaminergic SNpc cells while TH-cre mice performed the task.

After animals learned the task we induced partial dopamine depletion by unilateral intrastriatal 6-Hydroxydopamine injection.

Results: Preliminary results showed that after depletion there is a redistribution of movement speed with an increase in slower movements and with longer within-sequence inter-press intervals. We also found changes in the sequence microstructure, including the number of lever presses/sequence. Using in vivo calcium imaging we identified phasic activity of SNpc dopaminergic accompanying the start of a learned lever-press sequence both in healthy and partially dopamine depleted animals.

Conclusions: We developed a clinically-relevant task for movement sequence kinematics assessment in mice, and identified SNpc correlates of movement. Ongoing analysis using the combination of these 2 tools will allow us to clarify the role of SNpc dopaminergic neurons in different type of movements (slow vs. fast movements), in healthy and chronic dopamine depleted mice. This will have impact in our comprehension on the role of basal ganglia dysfunction in PD symptoms.

1274

Patients affected by functional motor symptoms are not liars: an experimental deception study with the Guilty Knowledge Task

B. Demartini, R. Ferrucci, D. Goeta, F. Ruggiero, A. Priori, O. Gambini (Milano, Italy) **Objective:** To assess deception in patients affected by functional motor symptoms.

Background: The relationship between functional neurological symptoms (FNS) and feigning is not an easy one for many clinicians. Most neurologists do not see the two as entirely distinct and would rather not get involved in the uncomfortable business of distinguishing them. Research conducted in the past decades has tried to challenge a common clinicians' view according to which patients affected by FNS are liars. Nevertheless, no study has systematically investigated deception in these patients.

Methods: Thirteen patients affected by functional motor symptoms and 14 healthy controls, matched for age and gender, underwent a modified version of the Guilty Knowledge Task (GKT), a computer-controlled procedure used to detect truthful and deceptive responses. All participants were also screened for depression (HAM-D), anxiety (HAM-A) and alexithymia (TAS-20).

Results: No significant difference was found between the two groups either in terms of reaction time (for true responses p=0.865, for false responses p=0.765), or in terms of accuracy (for true responses p=0.654, for false responses p=0.643). No significant correlation was found between responses at the GKT and HAM-D, HAM-A and TAS-20 score.

Conclusions: Our data showed that patients affected by functional motor symptoms have the same capacity to lie than healthy controls. These results are reinforced by the fact that depression, anxiety and alexithymia did not correlate with the GKT responses, excluding they might represent confounding factors.Patients affected by functional motor symptoms are not liars. Clinicians should start considering these patients as genuine as patients with multiple sclerosis or Parkinson's disease.

1277

Falls in Parkinson's disease are related to delayed recovery time after unexpected external perturbations *V. Beretta, F. Barbieri, D. Orcioli-Silva, P. Santos, M. Pereira, R. Vitório, L. Gobbi (Rio Claro, Brazil)* **Objective:** The aim of this study was to analyze the postural adjustments in fallers and non-fallers Parkinson's disease (PD) patients.

Background: Adequate reactive postural response as sure a successful recovery from unexpected perturbations. The ability to successfully recover from external perturbations can be accessed through the center of pressure (CoP) behavior analyses. Although PD patients have an impaired postural control (usually linked to higher number of falls) the CoP reactive adjustment differences between PD fallers and non-fallers were not deeply investigated. **Methods:** Forty patients with PD (21 fallers and 19 non fallers) and nineteen neurologically healthy people (CG) participated in this study. Fall status was determined considering the occurrence of at least one fall inthe previous 12 months. For the postural control assessment, a custom-made equipment was used in order to provoke an unexpected posterior surface translation (50 mm; 15 cm/s). A force plate (positioned above this equipment) allowed the achievement of the following CoP parameters: total displacement, range displacement after perturbation and recovery, response time to perturbation and time to recovery, mean velocity response to perturbation and mean velocity to recovery, and the root mean square of the displacement. An ANOVA one-way was used to compare all

groups.

Results: The statistical analyses showed a group difference in recovery time (p<0.001). The post-hoc test showed that PD fallers take a longer time to recover than non fallers (p=0.004) and CG (p<0.001). No other variables showed statistical differences between groups. Additionally, a Spearman test showed a good correlation between falls occurrence and time to recovery (r=0.651; p=0.001).

Conclusions: It can be concluded that fallers seem to have more difficulties to recover from unexpected perturbation remaining for a longer time in an unstable situation. Our results also show that this difficulty to fast recover from external perturbation is highly correlated to falls occurrence. Finally, our results suggest that the inability to recovery from external perturbations is not determined by the presence of PD, since non-fallers showed very similar results than CG. Since fallers show a higher time to recover the stable position because they have several impairments as the decrease of lower limb strength's and as the sensory-motor integration impairments.

1278

Motor Heterogeneity in Parkinson's Disease: A Bayesian Perspective

A. Johnson, A. Loftus, N. Gasson, B. Lawrence, M. Thomas, R. Bucks (Perth, NSW, Australia) **Objective:** To identify motor symptom subtypes in idiopathic Parkinson's disease (PD) using a Bayesian analytic approach to latent profile analysis.

Background: Several subtypes of Parkinson's disease (PD) have been proposed to account for the considerable heterogeneity in symptom presentation. However, current analytic approaches assume that motor symptom scores are perfect measures of a given symptom, and that there are no correlations between motor symptom scores within each subtype: given that all individuals share a diagnosis, there are likely to be facets of the disease common to all that cannot be explained by subtype membership, leading to correlations within subtypes. A Bayesian statistical framework deals with measurement error, allows correlations within subtypes (does not assume local independence), and is suitable for smaller samples.

Methods: 249 individuals with idiopathic PD completed the revised Unified Parkinson's Disease Rating Scale. Using Bayesian estimation, a factor analysis (with informative priors for cross-loadings) was conducted. A mixturemodel of these (error-free) factors was then estimated, using informative priors to relax the assumption of local independence within subtypes. This allows for subtyping based not only on differences in symptom severity, but also on differences in the relationships between symptoms.

Results: Significant cross-loadings and subtype-specific symptom correlations support the need for a Bayesian approach. The 3-class solution showed the best fit and clear separation of individuals. A group with significantly increased postural, rigid, and akinetic severity was identified. A group with reduced overall symptom severity and greatly reduced rest tremor severity was also identified. The third class was an intermediary, sharing a mixture of the other two classes' symptoms.

Conclusions: Previous studies have proposed postural instability and gait difficulty, and akinetic-rigid subtypes. However, these results indicate that both are part of the same subtype, and that assessing postural or akinetic symptoms in isolation would not accurately capture an individual's motor subtype. This may be largely responsible for inconsistent subtyping results to date. This robust approach to subtyping in PD reveals three novel classes of motor symptoms in PD, and demonstrates a framework for exploring heterogeneity in PD. Longitudinal studies are required to explore the prognostic value of subtypes.

1279

Oscillatory Activity in the Nucleus Basalis of Meynert

M. Nazmuddin, D. Oterdoom, J. van Zijl, A. Kampman, J. van Dijk, G. Drost, T. van Laar, M. Beudel (Groningen, Netherlands)

Objective: Characterize oscillatory activity in and around the nucleus basalis of Meynert (NBM).

Background: The NBM is the major source of cholinergic innervation to the neocortex. It is a new potential target of deep brain stimulation (DBS) for cognitive sequelae in Parkinson's disease (PD) dementia and Lewy Body dementia (1, 2). In order to effectively stimulate the NBM, more knowledge about its anatomical delineation and local neurophysiological activity is needed. PD patients with implanted globus pallidus interna (GPi) electrodes often have their most distal contact points in the vicinity of the NBM. This enables the recording of neural activity in this area.

Methods: Bipolar LFPs from adjacent DBS contact pairs (bottom to top: 0-1, 1-2, 2-3) were recorded in two patients during the replacement surgery of an implanted pulse generator. For each bipolar derivation (n=12), frequency spectra were calculated over 15-sec epochs of resting state. Stereotactic coordinates of each contact and

their distance to the NBM were calculated based on CT-MRI fusion images and correlated with spectral power in different frequency bands.

Results: Normalized peak power in delta band (1-4 Hz) was significantly higher in the 0-1 contact compared to the 2-3 contact pair (p=0.02, Fig. 1). The distance of the middle of the bipolar contact pairs to the NBM correlated negatively with delta peak power (cc=-0.72, p=0.007, Fig. 2) and positively with gamma (30-100 Hz) peak power (cc=0.6, p=0.03).



Conclusions: The increased delta and decreased gamma activity might help to functionally delineate the NBM and might be applied for directing stimulation of the NBM and the development of biomarkers for adaptive algorithms.

1280

New method to evaluate new motor skill learning

A.P. Quixadá, V. Sotero, J.F. Daneault, G. Diaz, Â. Torres, J.P. Vieira, M. Fonseca, P. Bonato, N. Peña, J.G. Miranda (Salvador, Brazil)

Objective: To present a novel approach to assessing improvements in new motor skill learning.

Background: Several methods have been employed over the years to try to understand how the central nervous system plans and controls voluntary movements. Despite the work that has been done over the last decades, studies have provided conflicting results and have continued to focus on simple reaching tasks. In the current study, we propose a novel method (movement elements decomposition - MED) that enables the analysis of simple and complex motor tasks to further understand how the brain manages the computational load associated with motor planning and control. We present an experiment that suggest that we can measure movement complexity and smoothness from the elements decomposition point of view.

Methods: 29 Participants positioned themselves on the Wii Balance board® in order to catch the arrows in a game specifically developed for the purpose of this experiment. Participants were asked to control an on-screen target through lateral weight transfer on the Wii Balance Board® (Figure 1). Each participant performed seven trials; Participants had never used a Wii Balance board® prior to this study and no information about the game was previously provided to them. A GoPro camera was positioned in front of the participants in order to track the anatomical landmarks using the CvMob Software. In order to follow the optimization rule, all human movements have to begin and end with zero velocity. This is the basis of the hypothesis suggesting that complex movements need to be segmented by the CNS during motor planning and performance. To segment movement elements were considered the complexity of movement and the natural response to motor learning is decrease complexity. To evaluate the smoothness we proposed a model as a neutral model of the intended movement and measured the irregularity *W*.

Results: Our results shows that the number of elements segmented in the horizontal axis and the W were significantly different between the first and last trial of the game (p<0.01), demonstrating a tendency to simplify and smooth the movement with practice (Figures 2, 3, 4 and 5).





Conclusions: The number of elements and the irregularity W are good measures to identify improvement on new motor skills acquisition.

1282

The combination of clinical scales and walking measures to predict falls in Parkinson's disease: Does the length of the prospective follow-up period matter?

R. Vitório, R. Moraes, A. Baptista, E. Lirani-Silva, L. Simieli, D. Orcioli-Silva, F. Barbieri, L. Gobbi (Rio Claro, Brazil)

Objective: This study aimed: (i) to identify the best combination of clinical scales and walking measures to predict falls in people with Parkinson's disease (PD) after a four-, six-, and 12-month prospective follow-up period; (ii) and to identify the circumstances of falls reported.

Background: Fall occurrence is a major problem for people with PD. Exploring the length of the prospective follow-up period in order to optimize the prediction of falls in PD is particularly important because it has potential to guide the frequency for fall risk assessment that patients should be submitted to.

Methods: Fifty-eight patients with idiopathic PD completed the baseline clinical (rating scales for PD) and walking assessments (spatiotemporal parameters of gait and obstacle avoidance) and reported falls for 12 months. Falls were classified according to the circumstances they occurred. The participants were classified as a 'faller' if they suffered at least two falls during the periods of interest. The ability of each outcome measure and combinations to predict falls at four, six, and 12 months was assessed using receiver operating characteristic curve analyses. Top predictors were combined and for each hit cutoff value one point was added at the final score of each combination.

Results: Thirty-one individuals (53.4%) felt at least once during the 12-month fall assessment (fallers: 7 individuals at four months, 12 individuals at six months, and 17 individuals at 12 months). The area under the curve, sensitivity, and specificity scores were highest at four months [table1]. Three combinations of predictors were able to identify 100% of fallers patients at four months, with false positive rates between 11.8% and 17.6% [table2]. The best combination included the UPDRS section II, the Mini-Mental State Examination and stride length [figure1]. Most falls occurred in the morning (57%), under good effect of medication (82%), in a domestic indoor environment (56%). The major causes of falls were loss of balance with no apparent cause (42%) and tripping (39%). Table I. Receiver operating characteristic analyses for clinical scales and walking measures.

	134 4														
Dependent variable	4 Months						6 Month	8				12 Months	1		
Dependent variable	P	Cutoff	Sensitivity	Specificity	AUC	P	Cutoff	Sensitivity	Specificity	AUC	P	Cutoff	Sensitivity	Specificity	AUC
UPDRS-I (score)	0.009	3.5	0.857	0.686	0.805	0.017	3.5	0.667	0.696	0.725	ns	-	5	15	-
UPDRS-II (score)	0.002	14.5	0.857	0.784	0.861	0.042	12.5	0.667	0.674	0.692	ns	-	2	-	2
UPDRS-III (score)	0.045	20.5	0.714	0.549	0.735	ns	-	-	-	0.70	ns	-		17	-
UPDRS total (score)	0.007	39.5	0.714	0.647	0.815	0.047	39.5	0.583	0.652	0.688	ns	2	2	12	2
MMSE (score)	0.025	27.5	0.857	0.706	0.763	ns	-	-	-		ns	-			-
Stride length (cm)	0.002	96.9	0.857	0.824	0.866	0.014	105.1	0.75	0.674	0.732	0.001	106.4	0.765	0.707	0.77
Stride velocity (cm/s)	0.013	96.2	0.714	0.686	0.793	0.036	98.3	0.667	0.674	0.697	0.003	98.3	0.706	0.732	0.749
Leading foot placement before the obstacle (cm)	0.008	61.3	0.857	0.824	0.812	0.011	75.6	0.667	0.652	0.741	0.006	75.6	0.647	0.683	0.732
Leading horizontal mean velocity (crossing, cm/s)	0.012	102.1	0.714	0.863	0.796	0.05	130.9	0.667	0.652	0.681	0.02	130.9	0.647	0.683	0.696
Trailing foot placement before the obstacle (cm)	ns	D.	-			0.05	19.9	0.583	0.761	0.681	0.028	19.9	0.588	0.805	0.684
Trailing foot placement after the obstacle (cm)	0.019	63	0.714	0.686	0.776	ns	ā.	57		101	0.035	63.8	0.647	0.659	0.677
Trailing toe clearance (cm)	ns	-	-	-	-	ns	-	-		-	0.012	21.6	0.765	0.683	0.711
Trailing horizontal mean velocity (crossing, cm/s)	0.01	149.5	0.714	0.725	0.801	ns	2	2	0	-	0.008	163.9	0.765	0.683	0.723
Crossing step length (cm)	0.039	56.6	0.714	0.686	0.742	ns	0	2		12	0.027	57.1	0.706	0.732	0.686
Recovery step length (cm)	0.006	44.2	0.857	0.765	0.735	0.035	47.9	0.75	0.63	0.699	0.013	47.9	0.706	0.659	0.709

Notes: AUC- area under the curve; ns- non significant; UPDRS- Unified Parkinson's Disease Rating Scale; MMSE- Mini-Mental State Examination.

Table 2. Receiver operating characteristic analyses for combinations (at 4 months).

a 11 4	a		4 N	fonths			
Combinations	P-value	Cutoff	Sensitivity	Specificity	AUC	LR-	LR+
Combination 12	0.003	1.5 score	0.857	0.863	0.854	0.17	6.26
Combination 13	0.001	1.5 score	0.714	0.961	0.93	0.3	18.31
Combination 14	0.003	1.5 score	0.857	0.863	0.95	0.17	6.26
Combination 15	0.001	1.5 score	0.714	0.941	0.912	0.3	12.1
Combination 23	0.001	1.5 score	0.714	0.941	0.923	0.3	12.1
Combination 24	0.003	1.5 score	0.857	0.863	0.85	0.17	6.26
Combination 25	0.001	1.5 score	0.714	0.941	0.912	0.3	12.1
Combination 34	0.001	1.5 score	0.714	0.961	0.922	0.3	18.31
Combination 35	0.001	1.5 score	0.714	0.941	0.906	0.3	12.1
Combination 45	0.001	1.5 score	0.714	0.922	0.896	0.31	9.15
Combination 123	0.001	1.5 score	0.857	0.843	0.934	0.17	5.46
Combination 124	0.002	2.5 score	0.857	0.882	0.857	0.16	7.26
Combination 125	0.001	1.5 score	0.857	0.824	0.927	0.17	4.87
Combination 134	0.001	1.5 score	0.857	0.824	0.936	0.17	4.87
Combination 135	0.001	1.5 score	1	0.882	0.965	0	8.47
Combination 145	0.001	1.5 score	0.857	0.765	0.926	0.19	3.65
Combination 234	0.001	1.5 score	0.857	0.843	0.93	0.17	5.46
Combination 235	0.001	1.5 score	1	0.863	0.961	0	7.3
Combination 245	0.001	1.5 score	0.857	0.765	0.926	0.19	3.65
Combination 345	0.001	1.5 score	1	0.824	0.962	0	5.68
Combination 1234	0.001	2.5 score	0.857	0.843	0.936	0.17	5.46
Combination 1235	0.001	2.5 score	0.857	0.941	0.962	0.15	14.53
Combination 1245	0.001	2.5 score	0.857	0.863	0.93	0.17	6.26
Combination 1345	0.001	2.5 score	0.857	0.941	0.966	0.15	14.53
Combination 2345	0.001	2.5 score	0.857	0.922	0.964	0.16	10.99
Combination 12345	0.001	3.5 score	0.857	0.941	0.958	0.15	14.53

Notes: AUC (area under the curve); LR- (negative likelihood ratio); LR+ (positive likelihood ratio); 1 (stride length); 2 (leading foot placement before the obstacle); 3 (Unified Parkinson's Disease Rating Scale section-II); 4 (recovery step length); 5 (Mini-Mental State Examination).

Figure 1. ROC curves for the top three combinations at four months. 1 (stride length); 2 (leading foot placement before the obstacle); 3 (Unified Parkinson's Disease Rating Scale section-II); 4 (recovery step length); 5 (Mini-Mental State Examination).



Conclusions: These findings suggest that the combination of clinical scales and walking measures should be used in clinical practice to assess the possibility of people with PD become fallers in the next four months. Fall phenotype observed support preventive actions to reduce fall occurrence in PD.

1286

Neuroprotective propensity of PTUPB, a dual inhibitor of sEH and COX-2 against rotenone induced neurotoxicity in cell line and Drosophila model of Parkinson's disease

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Objective: To evaluate the potential anti-parkinson activity of PTUPB (4-(5-phenyl-3-{3-[3-(4-trifluoromethyl-phenyl)-ureido]-propyl}-pyrazol-1-yl)-benzenesulfonamide) a dual inhibitor of soluble Epoxide hydrolase (sEH) and cyclooxygenase-2 (COX-2) against rotenone induced mitochondrial dysfunction, oxidative stress and neuroinflammation in N27 dopaminergic cell lines and *Drosophila melanogaster*.

Background: The metabolites of arachidonic acid cascade such as epoxyeicosatrienoic acids (EETs), is reported to play a crucial role in cytoprotection, due to their ability to attenuate oxidative stress, in ammation, and apoptosis. However EETs are subjected to rapid *in vivo* metabolism by sEH. The progressive neuroinflammation induces the release of COX-2 which is rapidly expressed in several cell types in response to cytokines, and pro-inflammatory mediators. The potential downstream toxic effects of COX-2 are further increase in progression of inflammation and oxidative stress via production of oxidizing reactive species during the peroxidase activity. Therefore, one of the novel strategy is inhibition of both sEH and COX-2 (Fig 1).



Methods: Cytoprotective role of PTUPB was confirmed in N27 cells against rotenone (400nM) treatment by MTT and LDH release assays. Further, total intracellular ROS, protein oxidation, lipid peroxidation, mitochondrial membrane potential, antioxidant, anti-inflammatory, and anti-apoptotic status was evaluated as per the standard protocols. Further, *in vivo* neuroprotective ability of PTUPB was confirmed against rotenone induced toxicity in *Drosophila*. Survival rate, negative geotaxis, antioxidant status, dopamine level was evaluated as per the standard protocols.

Results: Our results indicated that PTUPB pre-treatment significantly improved cell viability as confirmed by cytotoxicity assays. Further, neuroprotective role of PTUPB was associated with amelioration of ROS production, proteins oxidation and lipids peroxidation against rotenone induced toxicity. PTUPB also significantly protect the mitochondrial damage and improved the enzymatic antioxidant, anti-inflammatory, anti-apoptotic status which was declined with rotenone treatment in both N27 cell line and *Drosophila model of PD*.

Conclusions: These results substantiate the neuroprotective effect of PTUPB indicating its potential therapeutic benefits in the treatment of PD.

1292

Immunomodulatory therapy in stiff-person syndrome (SPS): a controlled Rituximab-randomised study *M. Amarandei (Bucharest, Romania)*

Objective: The efficacy of the anti-CD20 antibody, Rituximab, in the treatment of patients with stiff-person syndrome.

Background: SPS is a rare autoimmune progressive disorder of the central nervous system(CNS). Symptoms are stifness and painful extensor spasms. Stiffness affects the thoracolumbar paraspinal muscles, arms and legs, it has insidious onset; it appears in 3rd decade of life, without trigger infections. The diagnostic is based on clinical signs and sustained by electromyography (EMG) and high serum and cerebrospinal fluid titres of antibodies against acid decarboxylase (GAD).EMG shows the muscle stiffness is produced by involuntary co-contraction of motor units, resembling a normal voluntary contraction in needle EMG-recordings [figure 1].Rituximab has recently been proposed to modulate B-cells activity in CNS in SPS.

Methods: Twenty anti-GAD antibody positive patients were randomised to receive Rituximab or placebo for 4 months. Ten patients received rituximab intravenously(375mg/^{m2}) and ten received placebo (saline solution and human albumin-Flexbumin 0,4 mg/ml). After the washout, the patients crossed the alternative therapy for another 4 months.Efficiency was sustained by the titer of anti-GAD antibodies and clinical signs. Direct therapy effect was compared for both groups. The patients didn't smoke or drink alcohol.

Results: In the group with rituximab-randomised patients, the anti-GAD antibodies decreased significantly from month one through four:7 patients (70%) had a low titer of antibodies. The scores in placebo-randomised group were the same from month 1 to 4 and declined when they crossed to rituximab therapy.



Conclusions: The anti-GAD antibodies declined after rituximab, but not after placebo. Our clinical succesful utilisation of a monoconal anti-B cell antibody treatments leads to the conclusion that SPS is a B cell mediated autoimmune disease.

1293

Characterization of Pisa syndrome in Parkinson's disease.

T. Clark, J. Nutt, F. Horak, M. Mancini, M. Jurado, T. Hullar (Portland, OR, USA)

Objective: This study has two main objectives. The first objective is to elucidate the effects of distraction and alteration of sensorimotor inputs (visual and proprioceptive clues) on the development of lateral truncal flexion in patients with Pisa Syndrome (PS) and Parkinson's disease (PD). The second objective is to examine the contribution of vestibular system dysfunction on the development of lateral truncal flexion in patients with PS and PD. **Background:** PS is defined as lateral truncal flexion of greater than or equal to 10 degrees, which is not due to an underlying mechanical restriction and is almost completely alleviated by passive mobilization or supine positioning. PS has been seen to develop after exposure to various medications and also in the context of certain neurodegenerative conditions, including PD. There is currently no consensus on the pathophysiologic mechanisms driving the development of PS in PD; however, both central and peripheral generators have been implicated. The development of PS in PD can cause a significant increase in disability and there are currently no effective evidence-based therapies that significantly rectify lateral postural deviation in this syndrome.

Methods: This is an observational study. Our goal is to recruit 20 subjects with the diagnosis of PD and PS and 20 patients with PD without PS who will act as controls. Inclusion criteria include having the diagnosis of idiopathic PD, having objective findings consistent with PS which developed during the course of the patient's PD and requiring the patient to be able to ambulate unassisted for 1 minute. Our outcome measures include degree of trunk lateral inclination (measured objectively with motion analysis) while standing quietly under different sensorimotor manipulation (foam/eyes closed) and with a concurrent dual-task as well as vestibular function measures (head thrust, Vestibular Evoked Myogenic Potentials (VEMPs) and calorics).

Results: This study is currently ongoing. We have recruited and completed 4 study visits at this time (all patients who have been seen have PD and PS). We plan on having half of our study visits (10 patients with PD and PS and 10 control patients) completed and data analyzed by the time we present our data at MDS. **Conclusions:** Study is currently ongoing.

1297

Evaluating the experience of diagnosis in Parkinson's disease

A. Robinson, E. Pearson, F. Murphy, J. Davis, C. Carroll (Plymouth, United Kingdom) Objective: To evaluate a newly-designed diagnosis patient pathway for Parkinson's disease, in terms of quality measures and patient satisfaction.

Background: Receiving a diagnosis of Parkinson's disease can result in patients feeling vulnerable and alone. We have previously conducted a patient-led project to evaluate patient experience of diagnosis: a regional baseline evaluation identified areas of deficiency, based upon best practice as outlined in a Parkinson's UK guide.1 A new nurse-led patient pathway covering the first year post-diagnosis has been developed by the new patient pathway group (which includes patients) and implemented in Plymouth, UK, to address the key issues identified by the baseline audit. In this project we aimed to evaluate patient experience of the new patient pathway.

Methods: An 8 item questionnaire was designed by clinicians and Parkinson's Disease Nurse Specialists (PDNS) to evaluate whether the new patient pathway was meeting objectives derived from the results of the baseline audit and the patient pathway group. The questionnaire was delivered to 40 patients diagnosed within the new pathway at Plymouth Hospitals NHS Trust from March 2016 to September 2016.

Results: 19 responses were received from patients, giving a response rate of 38.7%. The main findings included: 100% of patients felt they were fully involved in their treatment decisions; 95% felt that treatment was tailored to their needs; 89% of patients had access to information pre-appointment and knew to bring a partner; 100% of patients were given written information during the appointment; 100% of patients felt supported in their diagnosis; 100% said they were given a point of contact and 88% of patients eligible for clinical research were offered the opportunity.

Conclusions: In comparison to the evaluation prior to the new pathway, there is a dramatic increase in patient satisfaction. However improvement still needs to be made to the information given to patients prior to their first PDNS appointment and the opportunity for research. Further improvements are planned within the pathway to address these areas.

1298

Developing a guide to facilitate involving people with Parkinson's disease and their careers in service improvement

N. Shaw, V. Evans, J. Rideout, C. Carroll (Plymouth, United Kingdom)

Objective: To develop an easy-to-use guide for service development project leads and patients/carers to facilitate the involvement of the latter in the development and implementation of Parkinson's disease (PD) service improvement projects.

Background: Involving patients and carers in service improvement projects is an essential aspect of patient-centred care, but happens only rarely. It can bring new perspectives to discussions and improve knowledge, health care engagement, and health outcomes. While guidelines are available supporting patient and carer involvement in service improvement these do not address the specific needs of patients with PD.

Methods: We used a semi-structured interview based around the Plan-Do-Study-Act model of improvement to ensure we captured good practice and barriers to service user involvement at each stage of service development. Local clinicians with experience of leading service improvement projects in PD, and patients and carers who have been involved in service improvement projects have been invited to be interviewed over the telephone.

Results: Data collection for this project is still ongoing. Pragmatic grounded analysis of the data generated from the interviews will be used to identify concepts and build common themes. These will describe how patients have been

involved in projects and how this could be done better from the perspectives of patients, carers and clinicians. These themes will then inform further discussion by a focus group to define and develop the guide.

Conclusions: Currently most PD services are designed without patient/carer input. Current guidelines for involving patients and carers in service improvement projects do not specifically consider the needs of patients with PD and their carers. Involving this group of service users in improvement projects is essential for facilitating patient-centred care. We will develop a specific, practical guide to help both clinicians and service users ensure the latter are able to actively participate in improving the services they use. The guide will be disseminated via the Parkinson's Excellence Network.

1305

Inpatient care for stiff person syndrome in the United States: A nationwide readmission study

J. Crispo, D. Thibault, Y. Fortin, A. Willis (Sudbury, ON, Canada)

Objective: To describe national inpatient care for stiff person syndrome (SPS) in the United States and characterize all-cause 30-day readmission.

Background: SPS is a rare and progressive autoimmune disorder that is characterized by axial muscle rigidity and involuntary spasms, which may lead to significant patient disability. To date, many case reports have described SPS onset, progression, and treatment; however, there is a paucity of population-based data on SPS hospitalizations. Methods: The 2013 Nationwide Readmission Database was queried for SPS index events, which were defined as inpatient encounters where an ICD-9 diagnosis of SPS (333.91) was documented, length of stay was recorded, and the patient was discharged alive. December discharges were excluded to ensure that sufficient follow-up was available for readmission analyses. Survey weighting methods were used to generate nationally representative estimates of SPS index events, all-cause readmission within 30 days of inpatient discharge, and principal reasons for readmission. Secondary analyses examined whether readmissions were to the same index event hospital. Results: A total of 1,094 SPS index events were identified, with an all-cause 30-day readmission rate of 19.4%. SPS was the principal diagnosis for 27.4% of index events, but only 14.0% of readmissions. Readmissions were primarily for neurological conditions (22.9%), epilepsy/convulsions (5.9%), septicemia (5.2%), pneumonia (4.7%), diabetes mellitus with complications (4.0%), and respiratory failure (3.8%). Length of stay was comparable between index events (7.0 days) and readmissions (6.4 days). Among readmissions, 27.4% presented to a different hospital. Conclusions: Hospital readmissions among individuals with SPS are relatively common, and include potential disease complications or medical conditions associated with SPS. Our finding of readmission to a different hospital may reflect specialty care patterns or gaps in discharge planning. Future studies are needed to determine the extent to which readmissions in SPS patients are avoidable.

1306

Gait and balance impairment after methanol intoxication

K. Peterová, H. Brožová, J. Klempír, I. Lišková, S. Zakharov, O. Bezdícek, M. Vanecková, Z. Seidl, E. Ružicka (Prague, Czech Republic)

Objective: We analyzed gait and postural instability in patients after methanol intoxication, with the aim to verify prevailing parkinsonian gait pattern.

Background: Methanol is a highly toxic substance, resembling ethanol in smell and taste. Besides acute symptoms, parkinsonism and gait disturbances were reported as late-term neurological sequelae after intoxication. 137 patients were intoxicated by methanol in the Czech Republic since 2012, during mass outbreak due to unintentional ingestion of adulterated spirits, mortality was high with 83 survivors.

Methods: 43 patients (9 females; mean age 46, range 24-73 years) were seen 2 to 8 months after proven acute methanol intoxication. Examination included the Natural History and Neuroprotection in Parkinson Plus Syndromes - Parkinson Plus Scale (NNIPPS-PPS), the shortened version of Falls Efficacy Scale-International (FES-I), Pull-test, and Timed Up and Go test (TUG). Gait cycle was evaluated using the GaitRite system, at comfortable and fast speed, and with eyes closed. Neuropsychological assessment included Digit Span Backwards, Controlled Oral Word Association Test, Trail Making Test and Stroop Interference. Findings were statistically processed and compared with age and sex-matched healthy controls.

Results: Total NNIPPS-PPS score was low $(9.8\pm$ SD10.7), signs of parkinsonism were present in only 7 patients, 6 had positive pull test. 19 patients admitted balance and gait difficulties with fear of falling according to FES $(9.9\pm$ SD4.4). In comparison with controls, patients were slower in the TUG test (p<0.001), produced shorter steps with prolonged step time, had lower velocity, longer duration of double support phase (all p<0.001) and wider base of support (p=0.006). Executive deficit was proven in 11 patients, who had higher cadence in comfortable gait

compared to patients with normal cognition. MRI of brain revealed lesions in basal ganglia in 16 patients and hemorrhagic necrosis was rarely seen in brainstem, cerebellum and subcortical white matter, however no significant correlation with gait parameters was observed.

Conclusions: Patients after methanol intoxication did not show parkinsonian gait, Instead, they presented slower wide-based gait with shortened steps and fear of falling, what corresponds with frontal gait disorder. Frontal type of impairment is also supported by proven executive deficit.

1310

Optimization and evaluation of whole body MRI sequences for patients with deep brain stimulators *C. Drews, S. Wolff, L. Lunden, O. Jansen (Kiel, Germany)*

Objective: The aim of the study was to optimize MRI sequences in order to make possible a safe MRI examination for DBS patients. The optimized MRI sequences should be comparable with the sequences used in everyday clinical practice with regard to image quality and scan time.

Background: Magnetic resonance imaging (MRI) of patients with implanted deep brain stimulation (DBS) devices is a challenge for healthcare providers. Due to the safety concerns about the magnetic field interaction with the device, e.g. thermal damage due to the radiofrequency heating, the device manufacturer admitted stringent guidelines. New stimulators allow whole-body measurements with 1.5T MRI, provided that a high-frequency transmission field (B1rms) of a maximum of $2.0 \ \mu T$ is maintained.

Methods: We optimized MRI protocols from the following body parts (brain, spine, heart, liver, knee) according to the requirements of the manufacturer. The protocols are based on sequences used in everyday clinical practice. The MRI protocols were optimized for two MRI scanners. The standard protocols and the optimized protocols were measured for each body region in 5 subjects each. The images were compared and evaluated by 3 blinded radiologists with regard to image quality. This was done by means of a standardized questionnaire.

Results: Results showed that the energy-optimized sequences have a similar image quality compared to the standard sequences. The measurement times of the optimized protocols did not differ significantly from the protocols used in everyday clinical practice.

Conclusions: The optimized MRI sequences showed a good image quality at acceptable scan time and make whole body MRI measurements in standard body regions possible. When MRI sequences are adapted to required energy conditions, MRI examination of DBS patients is no longer a contraindication.

1312

Gait asymmetry and asymmetry index in a sample of patients with PD and control group in Cali Colombia. B. Munoz, A. Enriquez-Marulanda, J. Orozco (Cali, Colombia)

Objective: To objectively evaluate gait asymmetry and asymmetry index as a measure of gait in a sample of patients with PD compared to a control group.

Background: Gait asymmetry is a crucial feature for patients with Parkinson's disease (PD) because it is related to a loss of functional independence that is one of the most important indicators of quality of life. Gait speed, stance time and postural instability are associated with falls. Gait impairments in PD affect functional mobility that requires changes in balance and gait strategies.

Methods: Fifteen PD patients and 15 age and sex matched healthy subjects were recruited (Table 1.). Lower limbs spatiotemporal parameters were acquired by using eMotion capture system (that uses a motion sensing camera). Descriptive analysis was performed for gait variables. Parametric and non-parametric analysis of Gait Asymmetry (GA) and Asymmetry Index (AI) between PD patients and control group was performed. The following are the equations required for the calculation of GA and AI: GA= {100 X [ln(Vmin/Vmax)]}, AI= Standard deviation left & right / Mean left & right

Table 1.

Age	59.5 (IQR 56 - 67)
Sex	
Female	14 (46.67%)
Male	16 (53.33%)
PD* subtypes	n=15
PIGD**	9 (60%)
TD***	4 (26.67%)
Indeterminate	2(13.33%)

*Parkinson's Disease

**Postural instability/gait difficulty

***Tremor Dominant

Results: Analysis of GA and AI were similar in the distribution and the two measures did not appear to distinguish patients with PD. For GA only stance time was significantly different between patients and the control group (Table 2.)

Table 2.

		Cases	Controls	p-valu
Culturentes	Asymmetry index**	10.15 (±19.34)	9.42 (±19.51)	0.459
cycle number	Gait asymmetry**	6.46 (±12.35)	6.02 (±12.46)	0.461
	Asymmetry index**	24.66 (±32.14)	30.30 (±16.40)	0.725
Stancetime	Gait asymmetry*	8.89 (IQR 2.56 - 19.44)	21.69 (IQR 10.60 - 27.64)	0.048
6. June 199	Asymmetry index**	9.39 (±5.79)	13.54 (±25.75)	0.726
Swingtime	Gait asymmetry**	2.21e+07 (±6.09e+07)	4.20e+07 (±6.30e+07)	0.807
Cariful Lawrence	Asymmetry index**	30.03 (±32.39)	31.39 (±37.60)	0.542
Stridelength	Gait asymmetry**	21.30 (±27.74)	24.20 (±36.55)	0.595
	Asymmetry index**	25.29 (±24.78)	32.64 (±38.02)	0.732
Cycletime	Gait asymmetry**	16.37 (±16.67)	25.40 (±37.68)	0.798
	Asymmetry index*	7.84 (IQR 1.81 - 15.09)	14.32 (IQR 5.81 - 20.06)	0.140
Stance percent	Gait asymmetry*	4.82 (IQR 1.11 - 9.30)	8.82 (IQR 3.57 - 12.40)	0.140
	Asymmetry index*	9.54 (IQR 3.03-19.53)	17.05 (IQR 8.75-23.88)	0.237
Swingpercent	Gait asymmetry*	5.87 (IQR 1.86-12.07)	10.52 (IQR 5.38-14.81)	0.237
2 0.000	Asymmetry index**	11.82 (±9.94)	18.11 (±11.13)	0.943
Duration time	Gait asymmetry**	7.31 (±6.19)	11.24 (±6.94)	0.943
FIG	Asymmetry index**	1.64 (±2.72)	4.50 (±6.43)	0.938
Distine	Gait asymmetry**	1.00 (±1.67)	2.77 (±3.97)	0.938
SW/ST 1	Asymmetry index*	17.14 (IQR 4.84 - 37.19)	30.99 (IQR 14.79 - 42.51)	0.350
		1		24

*Median (Interquartile range), p: p-Value Mann-Whitney test

**Mean (Standard deviation), p: p-Valuetwo samplet-test

¶Swingtime/Stancetime

Boldvalues p<0.05

Conclusions: Gait asymmetry has been considered previously as a characteristic of PD gait and now its presence has been associated to enhanced risk of falls. Objective evaluation of gait continues to be a challenge in the daily clinic neurological examination. Portable motion sensing devices may be an alternative for objectively analyzing gait parameters in clinic. We found a significant difference in stance time between PD patients and controls using the GA equation (p=0.0488). Differences in stance time indicate temporal dysregulation of gait, that include compensatory responses for regulating step length, and it is considered a risk factor for falls. We didn't find other significant differences for the rest of the variables.

1313

Availability of anti-Parkinsonian drugs in Thailand

K. Sakdisornchai, R. Bhidayasiri, O. Jitkritsadakul, P. Panyakaew, J. Sringean (Bangkok, Thailand) **Objective:** To determine the availability of two categories of anti-PD drugs in each level of healthcare facilities and region in Thailand.

Background: Anti-Parkinsonian (PD) drugs in Thailand are classified into 2 categories; (1) National drug lists (levodopa, anticholinergics, bromocriptine) and (2) Special drugs used under evaluations (other dopamine agonists, COMT inhibitors and MAO-B inhibitors). Drugs in the category (1) are prescribed by general physicians while drugs in the category (2) are only be prescribed by specialists.

Methods: Validated questionnaires for determining the anti-PD drugs availability were sent to a total of 1299 hospitals in 77 provinces of Thailand. The questionnaires were consisted of drug availability in each hospital, cost of anti-PD drugs and hospital details [details are in figure1].

Results: A total of 791(61%) hospitals including 28 (3.5%) referral hospitals, 654 (82.7%) community hospitals and 109 (13.8%) private hospitals responded to our questionnaires. The top three most common anti-PD drugs availability among Thai hospitals were anticholinergic agents (85.1%), followed by levodopa (69.3%) and dopamine agonists (16.6%). Anticholinergics was the only drug available in every province[figure2]. Levodopa was available in almost provinces[figure2]. Other drugs in the category (2) were available less than 75% of provinces[figure3]. Both categories of drugs were mainly available in the referral and private hospitals as well as hospitals in the central region of Thailand.



MAP I demonstrates diversity in the distribution of national drug lists (levodopa, anticholinergics and bromocriptine) across Thailand



MAP II demonstrates diversity in the distribution of special drugs used under evaluations (other dopamine agonists, COMT inhibitors and MAO-B inhibitors) across Thailand **Conclusions:** The basic anti-PD drugs which can be prescribed by general physicians are available in every province in Thailand whereas the drugs which can be prescribed only by specialists are still limited. Advanced PD patients who need more options of anti-PD drugs should have an opportunity to be referred to high level hospitals for best treatment

1315

Vascular hemiballismus due to a lentiform nucleus infarct

D. Gams Massi, J. Nyassinde, K. Toure, N.S. Diagne, M. Ndiaye, A.G. Diop, M.M. Ndiaye (Dakar, Senegal) **Objective:** The aim of this study is to present a case of right hemiballism due to an ischemia located in the left lentiform nucleus.

Background: Hemiballism is a rare clinical manifestation of ischemic stroke located in basal ganglia. Many studies have been done on post-stroke movement disorders worldwide but few of them have been conducted in sub-Saharan area particularly in Senegal [1].

Methods: It is a case report of a patient admitted in the neurology department of Fann national teaching hospital in Dakar, Senegal. He was received in out-patient department on May 9th, 2016 and A Brain CT-scan and others exams were done to find an etiology. The patient was informed and gave his consent for this presentation. Results: We therefore present a man of 71 year's old living in Dakar with past history of high blood pressure known since three years. He has presented one week prior to consultation a brutal onset of abnormal right side movements especially of the arm which disappeared when the patient was sleeping. Clinical exam revealed involuntary, repetitive and non-stereotyped rapid movements with a large amplitude of the proximal part of right limbs considered as right side hemiballism associated to a right Babinsky's sign. The blood pressure was 160/110 mmHg. The brain CT scan shown lacunar infarcts of left lentiform nucleus and internal capsule associated to cerebral cortical and subcortical atrophy with leukoaraiosis. Biological exams revealed high LDL cholesterol (1.80 g/l) and high total cholesterol (2.60 g/l). Cervical arteries Doppler ultrasound done showed bilateral carotid atheromatous plaque with left predominance. EKG and Trans-thoracic cardiac ultrasound revealed left ventricular hypertrophy. The other exams done were non-contributive. The patient received Haloperidol, low dose Aspirine, Captopril and lipid lowering therapy (Statin and diet). The evolution was is slightly favorable by the decreasing of these movements, blood pressure control and lowering of LDL cholesterol (last control = 1.10 g/l). The patients is actually followed up in the post-stroke consultation and we had low dose of trihexyphenidyl in the treatment to prevent some side effects of Haloperidol.



Conclusions: Hemiballismus is a severe type of movement disorders which is difficult to manage by current medication [2]. It is therefore important for neuroscientist to consider combination of therapy such as drugs and neurostimulation to improve to quality of life of patients.

1317

Ocular motor disorders among Filipino "LUBAG" or x-linked dystonia parkinsonism (XDP) patients

M. Macas, E.C. Rossi, S. Abantas-Diamla, A. Punzalan-Sotelo, E. Palisoc, C. Go (Manila, Philippines) **Objective:** To determine the prevalence of ocular motor disorders among x-linked dystonia parkinsonism (XDP) patients seen in Jose R Reyes Memorial Medical Center, and at a collaborative movement disorders clinic in Roxas City, Philippines.

Background: For most people with x-linked dystonia parkinsonism, the most obvious concern is the involuntary movement: dystonia, poor mobility and impaired balance. The study of eye movement abnormalities as well as the possible neurophysiologic correlates using the blink reflex studies will pave the way to interaction of basic science and clinical studies to this rather, under-recognized, solely Filipino movement disorder. No report on ocular abnormalities in XDP patients has been made as of the time of this writing. Knowing how prevalent the eye movement abnormalities are in this cohort of patients will increase our understanding of the pathophysiology of the disease and perhaps will eventually lead to the discovery of future diagnostic/prognostic markers in this extremely disabling neurodegenerative condition.

Methods: Twenty-three XDP patients from our IRB-approved registries were evaluated of eye movement abnormalities. Demographic data such as age, sex, place of origin, onset and duration of illness were obtained. Staging of XDP was also assessed.

Results: The mean age of patients was 45 years. All were male, about 90% came from the Island of Panay, mostly married with children, and with a duration of illness ranging from 8 months to 20 years. All patients were noted to have ocular motor abnormalities with 95% (n=22) having impaired convergence movements, regardless of the stage of XDP. This was followed by reduced range of saccadic movement particularly on horizontal plane in 35% (n=8) of patients. Additionally, blink reflex studies were done on four patients which all revealed normal results.

TABLE 1. PROPOSED SIMPLIFIED STAGING OF XDP

Stage	Clinical features	Functional impairment
Stage I	D - focal dystonia	No impairment
	or P - One parkinsonian trait	Independent
Stage II	D - Segmental dystonia or P - Two parkinsonian traits	Minimal impairment of function
Stage III	 D – Multifocal dystonia or/and P – More than two parkinsonian traits 	Some impaired function but still independent
Stage IV	D - Generalized dystonia or/and	Moderate to severely impaired function
	P - Moderate to severe parkinsonian trait	Needs help in many acti- vities of daily living
Stage V	D + P - Any combination of dystonia and	Bedridden or wheelchair bound
	parkinsonism	Requiring help or totally dependent for activi- ties of daily living

Note: D, dystonic features; P, parkinsonian features. In case any of the three components is of a more advanced stage, the final overall stage of the illness will be that stage wherein the severest component belongs.

Adapted from International Journal of Neuroscience, 121, 3-11 (2011) by Lee et al.

TABLE 2. CHARACTERISTICS OF OCULAR MOTOR ABNORMALITIES IN PATIENTS WITH XDP

EYE MOVEMENT	NATURE OF ABNORMALITY	NO. (%) OF PATIENTS AFFECTED
FIXATION	Steady fixation disrupted by inappropriate saccades	0 %
SACCADES	Impaired initiation reflected by: Increased latency	0%
	Obligatory head movement	0%
	in vertical plane	0%
	Obligatory blink	0%
	Slow saccades	0%
	in horizontal plane	0%
	Hypometria and reduced range of saccadic movement	
	-in vertical plane	17.4%
	in horizontal plane	34.8%
SMOOTH PURSUIT	Disrupted by inappropriate saccades; reduced gain in more advanced cases	
	in vertical plane	4.3%
	in horizontal plane	30.4%
VERGENCE	Convergence movements usually impaired because of extraneous saccades that took the eye off target	95%
ECCENTRIC GAZE HOLDING	Eyes brought back to primary position by inappropriate saccades	8.7%
VESTIBULO-OCULAR REFLEX	Decreased gain (eye velocity/head velocity)	0%

TABLE 3. BLINK REFLEX VALUES

		R1 latency (ms)	R2 latency (ms) Ipsilateral	R2 latency (ms) Contralateral
Patient 1	Left	10.2 ms	29.1 ms	22.2 ms
	Right	11.2 <u>ms</u>	28.0 ms	32.8 <u>ms</u>
Patient 2	Left	10.8 ms	34.3 ms	32.7 ms
	Right	10.6 ms	39.9 <u>ms</u>	27.5 ms
Patient 3	Left	10.8 ms	34.3 ms	32.7 ms
	Right	10.6 ms	39.9 <u>ms</u>	27.5 ms
Patient 4	Left	11.5 <u>ms</u>	25.9 <u>ms</u>	30.9 <u>ms</u>
	Right	10.0 <u>ms</u>	27.8 ms	29.7 <u>ms</u>

TABLE 4. CHARACTERISTICS OF DIFFERENT OCULAR MOTOR DISORDER ACCORDING TO THE STAGE OF XDP DISEASE

OCULAR MOTOR DISORDER					STAC	GE OF XDP	(n=23)	
				Stage I (n=4)	Stage II (n=8)	Stage III (n=6)	Stage IV (n=4)	Stage V (n=1)
Fixation				0	0	0	0	0
Saccades Slow (vertical)		ical)	saccades	1	0	1	0	0
	Нуро	ometria Vertical		1	0	2	1	0
		Horizontal		1	2	2	2	1
Smooth pu	rsuit	Vertica	ĺ	0	0	1	1	0
2	2212200.002	Horizon	ntal	1	2	1	2	1
Vergence		50. 2000-000		3	8	6	4	1
Eccentric g	jaze h	olding		0	0	0	2	0
Vestibulo-ocular reflex		0	0	0	0	0		
Optokineti	C	Vert	ical	1	5	1	2	0
nystagmus Horizont		zontal	1	4	1	2	0	

Conclusions: In our XDP patients, like the other progressive, neurodegenerative disorders such as Parkinon's disease, Progressive Supranuclear Palsy and Huntington's disease, we have observed similar ocular movement abnormalities, particularly abnormal convergence, slow smooth pursuit, and hypometric saccades. However, due to small data, we could not establish correlation between the stage of illness and type of ocular movement abnormality.

1323

Antiparkinson and antioxidant effect of n-methanesulfonylpyrazolinyl substituted heterosteroids in lps induced neuroinflammation model of rats

R. Singh (Chandigarh, India)

Objective: This present study is mainly focused at design and synthesis of new therapeutically useful steroidal neuroprotective agents against neuroinflammation which involved in the progression of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. The new androstane derivative has been synthesized by fusing *N*-methylsulfonyl substituted pyridylpyrazoline moieties at [17,16-*c*] position of the steroid. These D ring modified heterosteroids were then explored for their antiparkinson and antioxidant effect. **Background:** Parkinson's disease (PD) is a progressive, disabling neurodegenerative disorder characterized by an insidious onset with variable expression of motor, vegetative, sensory and psychopathological symptoms. Recent literature reports indicated that neuroinflammation cause dopaminergic neuron death that involved in progression of PD.

Methods: Aldol condensation of dehydroepiandrosterone with requisite pyridine carboxaldehyde in basic medium gave corresponding 16-arylidene steroidal derivatives, treatment of which with hydrazine hydrate in refluxing methanol afforded pyrazoline substituted steroids. Pyrazoline intermediates were further treated with mesyl chloride at 0° C to afford target *N*-methyl sulfonyl substituted pyrazoline steroids **1a-c**. Rats (male wistar) were anesthetized with thiopental sodium (45 mg/kg, i.p.), stereotaxic surgery has been done and intranigral injection of LPS (10µg in 2µl) was infused into left substantia nigra using the Hamilton microsyringe.³ Heterosteroids were evaluated against behavioral alternations using actophotometer, elevated plus maze at dose 2mg/kg after 7th, 14th and 21st day of LPS administration. Biochemical estimation of different makers for neuroinflammation, cholinergic activity and oxidative stress has also been carried out.

Results: The synthetic heterosteroids were characterized using IR, ¹H NMR. All heterosteroids **1a-c** exhibited potent activity against PD. The pyridin-4-yl group substituted steroid **1c** displayed activity comparable to that of standards dexamethasone and celecoxib.



Conclusions: The findings suggests that *N*-methanesulfonylpyrazolinyl substituted exhibit potent antineuroinflammatory activity and could be useful for the prevention of PD and oxidative stress.

1338

Does the side of onset affect motor and non-motor symptoms in Parkinson's disease?

J. Silva, A. D'Abreu (Campinas, Brazil)

Objective: To assess the association between motor and non-motor symptoms of Parkinson's disease (PD) and side of onset considering hand dominance.

Background: PD motor symptoms are asymmetric at onset, and some level of asymmetry persists throughout the disease. There are few studies exploring the relationship between symptoms and side of onset, and even fewer considering hand dominance.

Methods: This was a cross sectional study. We included 80 PD patients and classified them into two groups according to side of onset. All patients underwent a standardized questionnaire including information about: sex, PD clinical information and familiar and medical historic. Patients were also assessed by Scales for Outcomes in Parkinson's Disease-Cognition (SCOPA-COG), non-motor symptoms scale (NMSS) and Unified Parkinson's Disease Rating Scale (UPDRS). A general linear model (GLM) was applied to assess the relation between scales scores from SCOPA, UPDRS and NMSS and side of onset as the independent controlling for age, sex, time of disease and hand dominance (p<0.05). However, since there were only 7 left-handed subjects, we performed a second GLM only including the right-handed ones (table 1).

Scale	Side of Onset	Mean	S.E.	Confidence Interval
SCODA	Right	18.8461	1.145	16.5635 - 21.1287
SCOPA	Left	18.0882	1.1816	15.7325 - 20.4438
LIDDDC	Right	33.5897	3.2975	27.0161 - 40.1633
UPDRS	Left	33.8529	3.1687	27.5360 - 40.1698
NMSS	Right	64.0769	7.9138	48.3009 - 79.8529
	Left	62.7941	6.489	49.8583 - 75.7298

Table 1: Scales of the all patients and side of onset (right-handed subjects)



Results: Sixty-seven percent (67.6%) of patients were men. Mean age was 62.7 ± 9.4 years and mean time of disease was 10.48 ± 7.41 years. Forty patients presented the first symptom at right, and 40 at left. Among the right-handed (N=73), 39 (53,4%) patients had the first symptoms in the right side, while only one (14,3%) of the left-handed had the first symptom on the right side.

Conclusions: The side-of-onset did not seem to influence PD symptoms, motor, cognitive and non-motor, in righthanded subjects. This lack of association is unclear in left-handed ones. Future studies, should strive to include more left-handed subjects and to perform a longitudinal evaluation taking in account side of onset and hand dominance.

1345

Wearing off frequency in different hoehn-yahr stages in Parkinson's disease

H. Cotur Levent, E. Bayram, M. Akbostanci (Ankara, Turkey)

Objective: To determine wearing off frequency in different stages of Parkinson's disease (PD).

Background: Levodopa is the gold standard in the symptomatic treatment of PD. The most frequent motor complication in patients treated with levodopa is wearing off (WO) (patient suffering from predictable "off" states due to levodopa having a short term clinical effect). Different WO rates have been reported in early stage (ranging between 0%-42%).

Methods: One hundred seventy-five patients were included in the study. Staging of PD was determined using "Hoehn-Yahr Staging" (HYS). Wearing Off Questionnaire (WOQ), consisting of 19 items, was used to evaluate wearing off.

Results: The number of patients in each HYS are given in Table 1. Overall, WO frequency was 67,43% (118/175 patients). Mean WOQ scores for each HYS are summarized in Table 2. According to WOQ, WO frequency was 81,82% (63/77 patients) in HYS 2; 77,36 (41/53 patients) in HYS 2,5; 80,95 % (4/21 patients) in HYS 3; 58,33% (7/12 patients) in HYS 4 and 25% (3/12) in HYS 5 (Figure 1).

Table 1. The number (percentage) of patients in different Hoehn-Yahr stages

HYS 2	HYS 2,5	HYS 3	HYS 4	HYS 5
77 (44%)	53 (30,29%)	21 (12%)	12 (6,86%)	12 (6,86%)

 Table 2. The mean (standard deviation) Wearing Off Questionnaire scores for each

 Hoehn-Yahr stage

HYS 2	HYS 2,5	HYS 3	HYS 4	HYS 5
4,09 (3,71)	4,74 (4,42)	5,48 (4,57)	5,08 (5,38)	5,17 (4,99)



Figure 1. Wearing off frequency in each Hoehn-Yahr stage

Conclusions: We report a WO frequency over 50% even in early stages of the disease.

1346

Ambulatory movement measurement in evaluating deep brain stimulation effect in patients with advanced Parkinson's disease

M. Koivu, F. Scheperjans, E. Pekkonen (Helsinki, Finland)

Objective: To assess the use of the Parkinson's KinetigraphTM (PKGTM) in evaluating the effect of Deep Brain Stimulation (DBS) in patients with advanced Parkinson's disease (PD).

Background: Assessment of the effect of DBS on bradykinesia and fluctuations is often based on the patients' own report or diary. The PKGTM allows an objective measurement of PD motor symptoms providing a Bradykinesia Score (BKS), a Dyskinesia Score (DKS), and a Fluctuation Dyskinesia Score (FDS). These scores have been validated using UPDRS and modified Abnormal Involuntary Movement Scale (mAIMS). In our study the aim was to assess DBS effects with PKGTM.

Methods: We performed six days PKGTM measurements in three patients before DBS operation and 3 months after DBS operation. Patients filled out simultaneously paper diaries of their motor fluctuations. The diary data was compared with PKGTM measurements. DBS was programmed 1 and 3 months after operation.

Results: Paper diaries were sparsely filled out and no comprehensive data of motor fluctuations could be obtained. PKGTM measurements revealed clear changes of daily fluctuations. Median scores with standard deviations (SDs) before DBS were: FDS 13.8±5.4, BKS 22.7 ± 10.2 and DKS 3.0 ± 10.3 (Fig 1.). After DBS stimulation median scores with SDs were FDS 8.1±2.7, BKS score 26.4.4±6.3 and DKS 0.7±0.4 (Fig 2).





Figure 2. The six-day recording of the same patient after 3 months' DBS.



Conclusions: PKGTM measurements revealed reduction of daily fluctuation and dyskinesia after DBS more reliable than diaries. Bradykinesia score was increased which could be due to decreased dyskinesia and postoperative levodopa reduction. PKGTM seems to offer an objective method to assess DBS effect on motor symptoms in PD. Further studies on the eligibility of PKGTM measurement in analyzing the DBS effect are warranted.

1349

Transcranial direct current stimulation enhances consolidation of learning in Parkinson's disease

S. Broeder, E. Nackaerts, E. Heremans, K. Cuypers, R. Meesen, G. Verheyden, A. Nieuwboer (Leuven, Belgium) **Objective:** To examine the effects of training combined with transcranial direct current stimulation (tDCS) on writing performance and consolidation of learning in Parkinson's disease (PD).

Background: Rehabilitation can improve motor impairments in PD patients, albeit for a limited period. Compared with healthy controls, learning efficiency of sequential motor learning and consolidation is reduced in PD. Recent

research has highlighted the potential of tDCS to complement and enhance neuroplasticity and learning in patients with neurological diseases, including PD patients.

Methods: Ten PD patients (ON medication state) and 10 age-matched controls received 2 sessions of writing training on a digital writing tablet combined with 20 minutes of 1 mA anodal tDCS or sham on the left primary motor cortex in a randomized cross-over design with a 3-week washout period. Writing skills on the tablet and paper were assessed at baseline, after training and after a 1-week retention period. Tests on the tablet included writing of trained and untrained sequences to assess transfer (figure 1). Writing on paper included the 'Systematic Screening of Handwriting Difficulties' (SOS-test).

Results: No tDCS effects were found for the amplitude (% of target size) of the trained task. For the amplitude of the untrained task significant Time x Stimulation interactions were found for both the cued and the non-cued condition (resp. p=0.009 and p=0.019) showing an increased writing size after tDCS, regardless of group. Sub-analysis per group revealed for the PD patients a significant Time x Stimulation interaction for the amplitude of the non-cued condition of the untrained task (p=0.038), which was not found in controls. Post-hoc analysis showed for PD a significant improvement after tDCS during the post and retention measurements compared to baseline (resp. p=0.041 and p=0.003) (figure 2). No improvements were found after sham stimulation. TDCS effects were also not apparent during transfer measured with the paper test.



Figure 1: Writing tasks on the digital tablet (A) Trained sequences in 2 sizes and 4 patterns (B) Untrained sequences in a cued and non-cued condition.



Figure 2: Mean \pm standard error of the mean of the amplitude (% of target size) in PD patients (N=10) for the untrained writing task (non-cued) after anodal tDCS and sham stimulation of M1 (20 minutes, 1 mA). Patients showed a significant increase in writing amplitude after tDCS during post and retention measurements compared with baseline (resp. p=0.041 and p=0.003).

Conclusions: These results suggest that tDCS combined with training improves the transfer of a learned writing task to a novel one, specifically for PD patients performing in a non-cued setting. However, transfer to real life writing

did not occur. These findings warrant further study during prolonged training to investigate the potential of tDCS to enhance consolidation in PD.

1353

Effect of non-invasive vagus nerve stimulation in freezing and oxidative stress in Parkinson's disease patients *B. Mondal, S. Choudhury, G. Paul, M. Mondal, M. Baker, K. Chatterjee, P. Chatterjee, R. Banerjee, R. Singh, H. Kumar (Kolkata, India)*

Objective: In this observational pilot study we explored the long term effect of Non-Invasive VNS to improve the FOG and reduce oxidative stress in PD patients.

Background: Freezing of gait (FOG) is a unique and disabling clinical phenomenon in Parkinson's disease (PD). Vagus nerve stimulation (VNS) is a galvanic stimulation to Vagus nerve possibly modifying the cortical excitability. We hypothesize that VNS could improve FOG and reduce oxidative stress in PD patients with FOG.

Methods: Ten patients of PD with freezing recruited from the Movement Disorders Clinic of Institute of Neurosciences, Kolkata. Their motor function, gait parameters and anti-oxidant enzymes (CAT, SOD, MDA) were assessed pre and post VNS. VNS (GammaCore) was applied to them for one month time and thrice a day. Differences between the parameters before and after VNS were assessed using Wilcoxon Sign Rank test with significance level of P < 0.05.

Results: The mean age of the patients were 62.8. The mean pre and post UPDRS (III) score were 42.5 and 33.8. UPDRS(III) which significantly improved after VNS application. Statistical results suggested significant improvements in gait parameters including velocity (Pre VNS 62.80, Post VNS 79.5, p value 0.006), stride velocity (L) (Pre VNS 65.348, Post VNS 79.878, p value .002) and stride length (L) (Pre VNS 37.554, Post VNS 40.974, p value .048). The risk of fall, RBD and freezing components were assessed using FES, RBD screening questionnaire and FOGQ which showed significant improvement after VNS application. The freezing parameters were video recorded and it revealed significant improvement in time taken for start hesitation (P 0.012), steps taken for start hesitation(P 0.011) and total freezing episode(P 0.015). The level of MDA(Pre VNS 5.269, Post VNS 4.690) was reduced which indicates that lipid peroxidation decreases and level of catalase (Pre VNS 183.30, Post VNS 195.57) and superoxide dismutase (Pre VNS 7.24, Post VNS 9.54) was increased after one month VNS compared to baseline showing that VNS reduces oxidative stress level in these patients.

Conclusions: The study showed VNS significantly improves gait parameters in FOG in patients. It also improves the motor functions and fear of falling in these patients. Beside this VNS also plays a crucial role in reduction of oxidative stress. This could provide way for non invasive therapeutic alternative for freezing.

1355

Acquisition, validation and preprocessing of wrist-worn sensor data in patients with Parkinson's disease and healthy controls

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Objective: We describe relevant aspects and data processing steps for accelerometry and gyroscopy recordings made with a wrist-worn low-cost sensor device. In order to generalize and compare results between subjects, we propose the use of a body-centered frame of reference for motion data.

Background: Body-worn sensor data can assess physiological motion as well as Movement Disorders, e.g. Parkinson's disease (PD) with high temporal resolution in free-living situations. Appropriate evaluation of this data opens opportunities for objective symptom measurement. The collection of large amounts of data by use of commercially available sensors poses hitherto unknown challenges to data validity.

Methods: Ethical approval was obtained from Technical Uni. of Munich. For this principal of proof study, we included 27 PD patients and 8 healthy controls. Raw data was recorded at a rate of 62.5 Hz using the MS band 2 (Microsoft). We applied low-pass filters to reduce accel. noise, and high-pass filters to reduce impact of gyro. integration drift. Data was normalized by rotating it from the sensor coordinate system to the reference coordinate system. Sensor pose was estimated using quaternion based complementary filters. Ground truth data was created to validate such pose estimation (PE). Movements reflecting gradings of severity of MDS-UPDRS items, e.g. bradykinesia, were recorded using the MS band 2 and synchronized to data captured by a motion capture system (Qualisys Track Manager, QTM). The QTM pose was compared to the PE from the wristband data. The data was used to train neural networks (NN) as described in Pfister et al.

Results: Specific steps of data processing were required to reduce inter-subject variability caused by differences in sensor orientation and placement. The PE obtained by integration from the sensor signals accurately reflects the

motion patterns, visible in the corresponding QTM recordings, and approves our steps of processing. Preprocessing increased the precision of NN to correctly classify short data segments as clinical meaningful data by 55.5%. **Conclusions:** Wrist-worn sensors can be used to describe spontaneous movement with unprecedented reliability. However, a high degree of sophistication and preprocessing is necessary to overcome problems inherent to this data type. The normalization of the coordinate system can be used to improve inter-subject recognition of NN.

1358

Automated dosing schemes for administration of microtablets of levodopa for Parkinson's disease, using wearable sensors

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Objective: The aim of this study is to investigate the feasibility of using a dose optimization algorithm for dose individualization of microtables of levodopa.

Background: Motor complications in PD are managed by individualizing oral levodopa treatment. An algorithm that uses sensor ratings (Memedi et al., 2016) to produce individualized dosing schemes was developed. Dosing schemes with specific intervals and dose sizes can be programmed into the device that contains microtables of levodopa-carbidopa.

Methods: A clinical trial was conducted in Gothenburg, Sweden. For a two week period before a test day the patients used the device with a dosing schedule equivalent to their regular doses and wore the Parkinson's kinetigraph (PKG) to monitor motor states in the last six days. Neurologist FB reprogrammed the device based on the PKG data and the clinical impression during the test day. The patients performed alternating hand movements at a pre-determined time schedule, before and following a single dose of levodopa (120% of the normal morning dose), while wearing one sensor on each wrist (Shimmer3 sensor). The signals from the sensors were mapped to a dose-effect scale, providing an effect value for each test. An individual dose-effect model was fitted to the values (Figure 1) and the fitted model was used as input to a dose optimizing algorithm. The algorithm produced optimized dosing suggestions for multiple dosing intervals, a different suggestion for each one. The predicted outcome of each interval was visualized to facilitate the identification of the optimal interval. The dosing suggestions of the algorithm were compared to the experts' prescriptions for the interval that the neurologist chose. The algorithm derived optimal interval was compared to the neurologist's therapeutic decision.



Individual model

Figure 1: Individual model fit for a patient in the study. The first point on the time axis represents the effect value before the dose administration (baseline), the second point the effect at the time of the dose administration and the following points the effect values after the dose administration. The straight line is the individual fitted model.

Results: Preliminary results from 14 patients have been obtained. In 10 cases the dosing suggestions are within 20% of the actual doses and the interval suggestions within 20 minutes of the neurologist choice. In 3 cases the dosing suggestions deviate more than 20% but the suggested intervals are within 20 minutes of the neurologist choice in 2 of those cases. In 1 case an individual model could not be fitted.

Conclusions: The preliminary results suggest that the described system can suggest appropriate dosing schedules for a majority of the patients.

1360

Levodopa effect and motor function in late stage Parkinson's disease

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Objective: To assess responsiveness to Levodopa (L-dopa) in patients with late stage Parkinson's disease (PD). Moreover, to investigate if the L-dopa effect is stable or whether motor fluctuations and dyskinesias are present. **Background:** A majority of PD patients treated with L-dopa develop motor complications, in many cases within a few years of treatment. It is unclear to which degree L-dopa remains effective also in the last stages and whether motor fluctuations and dyskinesias remain a problem.

Methods: The study included 30 patients with PD in Hoehn and Yahr (HY) stages IV and V in "on" and/or having a substantial need of help with ADL (<50% Schwab and England Scale) and having been diagnosed with PD for =7 years. Nineteen were men, median age 83 and median PD duration 12 years. Nineteen were in HY stage IV and 11 in V. L-dopa responsiveness was assessed with an L-dopa test and motor evaluation according to a standardized protocol in the defined "off" and defined "on" state. Motor performance was assessed by the Unified PD Rating Scale (UPDRS) III and timed tests for gait and hand-arm. The participants were further evaluated with a mobile movement-analyses-system, the Parkinson's Kinetigraph (PKG) for 10 days.

Results: The number of participants with an improvement in UPDRS III during L-dopa test of =15% were 15 (50%) and of =30% were 6 (20%). The median UPDRS III score in "off" was 46 (q1-q3, 37-53) and in "on" 36 (28-46), with a median improvement of 15.5% (8-27%), p<0.001. There was a statistically significant effect in almost all variables; UPDRS III total score; speech (item 18); resting tremor (item 20); tremor (items 20, 21); rigidity (item 22); bradykinesia (items 23-26, 31); gait (item 29); axial signs (items 18, 19, 22, 27-30); dyskinesias (Clinical Dyskinesia Rating Scale); hand-arm movement; gait test and blood pressure. According to the UPDRS IV, 67% experienced predictable off-fluctuations, while 30% had unpredictable off-fluctuations. The prevalence of dyskinesias according to item 32 (duration of dyskinesias =1) of the UPDRS IV was 47%. According to the PKG registrations, some patients were experiencing significant motor fluctuations, though very few had significant dyskinesias.

Conclusions: Half of a group of patients with late stage PD (HY IV-V in "on") had a significant L-dopa response (=15% on the UPDRS III). According to the UPDRS IV, a majority of the patients still had motor fluctuations and about half had dyskinesias.

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Intensive short term dance intervention in Parkinson's disease

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Objective: To evaluate changes in motor symptoms and quality of life for people with Parkinson's disease (PD) as a result of an intensive short-term dance intervention.

Background: Physical activity and exercise based rehabilitation programs, which aim at improving motor symptoms such as balance, strength and range of motion as well as non-motor symptoms, are commonly recommended to people with PD. Studies consisting of weekly and biweekly intervention propose that dance can be a feasible form of rehabilitation with the additional benefit of a reduced dropout rate due to its highly enjoyable and social nature. However, few of the aforementioned studies have examined the relationship between benefits and dosage. In order to attain the largest effect from dance on patients affected by PD, daily intervention may be crucial. Consequently, our aim was to examine the effect of daily participation of this population in Argentine tango classes. **Methods:** Eight people with mild and moderate severity (Hoehn & Yahr scale I-II) idiopathic Parkinson's disease participated in a study consisting of ten 90' dance classes within a period of 2 weeks. Two tango instructors taught the classes. Participants were partnered with volunteers who had previous experience in tango dancing. Motor symptoms were evaluated using the MDS-UPDRS part III before and after the training session. A 12 question Likert scale and personal interviews with PD patients were used to evaluate the effects on quality of life following the training session.

Results: Our study found improvements in motor behaviour as measured by the UPDRS (p < 0.05, n=8), as well as positive outcomes in Likert scales showing improvements in perceived managing of activities of daily living (ADL), quality of sleep, and psychological basic needs such as relatedness, autonomy and competence. An augmented sense of vitality was also reported by participants.[Table 1] [Table 2].

Table 1. UPDRS (part III)

	Pre-intervention	Post-intervention
S1	31	28
S2	16	6
\$3	33	32
\$4	30	25
\$5	12	8
\$6	14	15
\$ 7	28	21
\$8	5	3

Table 2 Likert Scale

ltem	%
I feel I can walk faster	90.00
I feel I can walk with more confidence	93.70
I can perform ADL easier	87.50
I can dress myself easier	78.10
I can take a shower with more security	84.30
I feel happier	92.50
I feel more integrated with the people surrounding me	97.50
I sleep better	85.00
I feel less lonely	91.20
I feel more physically active	93.70
I feel with more energy and vitality	91.40
I feel more willing to take care of myself	90.00
I feel more enthusiastic	91.40
I feel fewer tremors	83.30
I have more confidence in my capabilities	92.80

Conclusions: Participation in a two week daily dance classes intervention shows significant improvements in motor symptoms and quality of life of people with PD. The dosage of dance intervention needs further study and consideration in order to help participants obtain the best possible results from this form of rehabilitation.

1363

The landscape of interventional trials in Parkinson's disease: A 10-year review of ClinicalTrials.gov between 2006 and 2016

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Objective: To review the scope of interventional trials for Parkinson's disease registered on clinicaltrials.gov in the past 10 years.

Background: Parkinson's disease (PD) is a broad chronic condition with variable manifestations and different paths to clinically meaningful disability. In general, clinical trials in PD aim to advance novel therapeutics through a wide variety of approaches. In an environment with a limited number of eligible PD trial participants however, it may be reasonable to consider whether clinical trials can and should confirm to the ordinal research priorities of the PD community, including patients, caregivers, and researchers. Since 2007, the Federal Drug administration (FDA) has required interventional clinical trials occurring in the US to be registered on the website clinicaltrials.gov.

Methods: Using the search term "Parkinson's disease" and the trial subtype "interventional trials", we reviewed all resultant studies catalogued on clinicaltrials.gov between 1/1/2006 and 8/1/2016. Our initial search retrieved 1226 studies, 1157 of which were determined to be relevant to Parkinson's disease. Using descriptive statistics, we reviewed these trials and categorized their characteristics.

Results: Trials studying drugs 59.12% (n=681) were the most common, followed by trials for devices 19.97% (n=231), behavioral modifications 8.21% (n=95), physical activity 10.71% (n=124), and access to care 1.30% (n=15). Of the funding sources, industry and single medical center or universities were the most common comprising 42.44% (n=491) and 42.18% (n=488) of the funding respectively. Other sources included federal (8.47%, n=98), foundations (8.30%, n=96), nonprofit organizations (2.33%, n=27), and research institutes (1.77%, n=21). The majority of PD trials were randomized (68.71%). Less than half were placebo controlled (44.86%). Blinding/Masking was performed in 60.85% of studies; of these, 21.86% were single blind and 78.13% were double blind.

Conclusions: Less than 20% of PD trials receive federal/foundation funding—raising the possibility that the vast majority of all PD trials and per-person-effort by PD trial participants are not on protocols subject to pre-funding peer review. We aim to use this dataset to further explore other properties of PD trials to better understand concordance and mismatches between PD trial designs and published PD community research priorities.

1364

How will new technology change deep brain stimulation programming?

G. Duffley, A. Schiewe, B. Lutz, J. Krüger, M. Okun (Salt Lake City, UT, USA)

Objective: Assess the ways in which decision support tools and directional leads are affecting DBS programming. **Background:** The typical approach to DBS programming has changed little since this therapy was introduced: a monopolar review followed by exploration of bipolar settings if needed. This approach is limiting for several reasons. First, the amount of time required to perform a monopolar review increases with the number of electrode contacts, and this problem is compounded by the large number of possible bipolar or multipolar settings available on directional leads. Hence, it is worthwhile to explore new approaches to DBS programming that reduce the amount of time and complexity, and could be used by non-experts. We are currently conducting a two-phase clinical trial to evaluate a mobile decision support for DBS programming that is being used by experts as well as home health nurses.

Methods: Patient specific models of DBS were generated using previously published methods [1] to predict the volume of tissue activated for a wide range of settings. Computational models are delivered to the DBS programming nurse via on a tablet decision support system; these models are reviewed before each patient's initial programming visit in lieu of doing a monopolar review. The DBS programming nurse determines four electrode configurations from the model and starts the programming process from those settings rather than the thresholds determined by the monopolar review. This is an ongoing study and clinical outcomes are not yet available. Here we report our preliminary observations on the use of our programming platform for four Parkinson's disease subjects who were followed for 6 months post-operatively [figure1].



Figure 1: Analysis of the programming of a single patient in the experimental arm. (A-D) The four stimulation settings chosen using our mobile decision tool before the patient arrived at the clinic (volume of tissue activated—orange, pallidum—blue, DBS lead—gray and black). (E) Optimized DBS setting at 6 months (volume of tissue activated—green). (F) Axial, (G) coronal, and (H) sagittal preoperative FGATIR MRI slices with the optimized DBS setting at 6 months (green), the closest initial setting (orange) and pallidum segmentation (blue) overlaid.

Results: For each of the four patients, the electrode configuration chosen after 6 months used either the same contact chosen during their initial visit or an adjacent contact, signifying at least a 25% reduction in the parameter

space of possible contacts. Two of the four patients had their optimal electrode configuration as a setting determined from the tablet model during initial programming.

Conclusions: The current paradigm for DBS programming is likely to be untenable given the increasing complexity of the implanted systems and diminishing time available for DBS programming. Our preliminary results suggest that effective settings can be chosen using decision support tools that, at the very least, obviate the need for a monopolar review.

1371

Deep brain stimulation in Parkinson's disease: Outcome after more than nine years

B. Thomsen, S. Jensen, A. Clausen, B. Jespersen, M. Karlsborg, A. Løkkegaard (Copenhagen, Denmark) **Objective:** The aim of this study is to examine the long-term effects of deep brain stimulation of the subthalamic nucleus (STN DBS) in Parkinson's disease (PD).

Background: STN DBS has become a well-established, symptomatic treatment for advanced PD and is the most effective therapy for fluctuating PD. As the surgical procedure is still quite new, only little is known of the long-term effects.

Methods: 82 patients underwent surgery in Copenhagen between 2001 and 2008 and are potential candidates for this follow-up study more than nine years after surgery. The follow-up proceeds like the pre-surgical examination. Patients are shortly hospitalized, and rated by the UPDRS with and without stimulation and medicine.

Neuropsychological testing is performed. In addition, data from patients' medical records are collected. 43 patients are still alive and possible candidates for long-term follow-up. This study is ongoing. 16 patients have finished the long-term follow-up and 69 patients are included so far. The mean [SD] (range) age at surgery was 60.4 [15.3] (41.9-77.6) years and the duration of disease was 13 [10] (5-25) years. 59 % of the patients are men and 41 % are women.

Results: Data from the first 16 patients included for follow-up show that the effect of medication on the motor UPDRS 3 before surgery was an improvement of 55.8 [36.0] %. The OFF UPDRS 3 score (with neither stimulation nor medicine) was 50.0 [24.8] before surgery, 54.3 [24.5] after one year and 59.5 [27.9] at the 9-15 (mean 12.1) years follow-up. This corresponds to a progression of 18.9 [56.3] % after 12 years. The improvement of UPDRS 3 with stimulation alone compared to the OFF UPDRS 3 was 67.4 [13.3] % after one year and 39.9 [27.3] % at follow-up 9-15 years after surgery. Data from the medical records for the 69 included patients show that compared to before surgery, medication was reduced by 52.6 [77.4] % after one year, and 44.4 [100] % after 9-15 years; 53.4 % of these patients developed dementia and 37.7 % moved to a nursing home.

Conclusions: STN DBS is an efficient and safe treatment in advanced PD. It remains effective after more than 9 years, however, the effect seems to decrease through the years. Disease progression evaluated by motor symptoms OFF treatment is modest and the number of patients who developed dementia is not higher than would be expected from a PD population.

1374

Factors associated with perceived walking difficulties in people with Parkinson's disease

M. Kader, S. Ullén, S. Iwarsson, P. Odin, M. Nilsson (Lund, Sweden)

Objective: To investigate factors that independently contribute to perceived walking difficulties in people with Parkinson's disease (PD).

Background: Despite that walking difficulties are common in people with PD, there is limited knowledge regarding factors that independently contribute to their perceived walking difficulties in daily life.

Methods: The study included 243 persons (62% men) with PD; mean (min-max) age and PD duration were 70 (45-93) and 8 (1-43) years, respectively. A postal survey with self-administered questionnaires preceded a home visit which included observations, clinical tests and interviews. The dependent variable was perceived walking difficulties assessed with the self-administered generic Walk-12 (Walk-12G, scored 0-42; higher=worse). The independent variables included personal (e.g., age, general self-efficacy) and socio-environmental factors (e.g., social support, living situation) as well as disease-related factors including motor (e.g., freezing of gait (FOG), lower extremity functions) and non-motor symptoms (e.g., orthostatic hypotension, cognitive function). Each independent variable was examined with simple linear regression analyses, and variables with p-values <0.3 were then entered into a multivariable linear regression analysis model.

Results: The multivariable model identified eight (out of 15) significant independent variables, explaining 56.3% of the variance in perceived walking difficulties. The strongest contributing factor was FOG (25% of the variance),
followed by general self-efficacy, fatigue, PD duration, lower extremity function, orthostatic hypotension, bradykinesia and postural instability.

Conclusions: Personal factors (i.e., general self-efficacy) as well as motor and non-motor symptoms (e.g. FOG, PD duration and fatigue) seem to be of importance when addressing perceived walking difficulties in people with PD. With such knowledge at hand, interventions addressing modifiable factors could be developed, ultimately enhancing walking ability in people with PD.

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A prospective randomized cross-over study of telemedicine system in Parkinson's disease

S. Sekimoto, G. Oyama, T. Hatano, F. Sasaki, R. Nakamura, T. Jo, Y. Shimo, N. Hattori (Tokyo, Japan) **Objective:** To investigate the validity of telemedicine system in Parkinson's disease (PD).

Background: PD patients may be difficult to visit the hospitals because of decline of activity of daily living (ADL) levels. Furthermore, there are few neurologists who is specialized in PD. Access to neurologists is considered an important factor that ameliorates management of the symptoms in PD. In this study, we investigated the efficacy and safety of a video-based telemedicine system utilizing tablet device in PD.

Methods: We conducted a randomized cross-over trial comparing telemedicine period (regular bimonthly visits with intermediate video calls utilizing iPad mini®) to control period (regular bimonthly visits). Patients were randomized to receive either telemedicine period followed by control period, or control period followed by telemedicine period. Both periods were 6 months. The primary outcome measure was the Parkinson's Disease Questionnaire (PDQ-39) summary index, which was measured at baseline, 6 months and 12 months. The secondary outcomes included the Unified Parkinoson's Disease Rating Scale (UPDRS) part I-IV, Hoehn and Yahr Stage, Beck Depression Inventory (BDI). The visual analog questionnaires for satisfaction of the telemedicine system was also evaluated at 12 months.

Results: Ten patients were recruited and nine patients with PD completed the study periods. Average age at onset, average disease duration (year) and average Hoehn and Yahr stage were 53.7 ± 5.9 , 7.0 ± 6.3 , and 2.0 ± 0.5 ,

respectively. There were no significant differences between the two periods in PDQ-39 SI, as well as UPDRS part I, II, IV, Modified Hoehn and Yahr Stage, and BDI (P > .05). The participants rated the telemedicine system high scores. The number of extra hospital visit and phone call did not differ between two periods.

Conclusions: This study revealed that telemedicine system was well accepted. As this study did not show inferiority of telemedicine system for care of relatively mild PD, this system may be able to apply to care of advanced PD. Further studies are needed to reveal the validity of telemedicine system in advanced PD.

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Virtual research visits in individuals with Parkinson's disease enrolled in a clinical trial: REACT-PD Study interim analysis

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Objective: To demonstrate the feasibility, reliability, and value of conducting web-based clinical trial assessments in individuals with Parkinson's disease (PD).

Background: Increasing interest has been focused on the use of web-based clinical trial assessments (virtual research visits) given the rising cost and difficulties with recruitment and retention in clinical trials. Virtual research visits have the potential to reduce infrastructure costs, expedite recruitment, and improve participant retention through improved accessibility and convenience of trial participation.

Methods: We are conducting an add-on study of 40 individuals with PD enrolled in the phase 3, double-blind, placebo-controlled trial STEADY-PD III (Safety, Tolerability, and Efficacy Assessment of Isradipine for Parkinson's disease). Enrolled participants complete virtual research visits using a smart phone device equipped with telehealth software from AMC Health. Each participant will complete two to four virtual visits over 12 months, occurring within four weeks of their scheduled in-person research visits. All clinical trial assessments performed at the preceding in-person visit are performed remotely during the virtual research visit. Study outcomes include (1) feasibility determined by the ability to conduct remote assessments; (2) reliability of remote assessments compared to in-person assessments; (3) value of virtual visits measured by patient and provider preference of remote versus in-person visits.

Results: To date, 40 participants have been enrolled and consented. 33 participants have successfully completed their first visit and all participants are scheduled to complete at least one visit by March, 2017. 88% (28/33) of

virtual research visits have been completed as scheduled, and all virtual research visits have been completed. The study will be completed in March, 2018.

Conclusions: This study assesses the feasibility and comparability of remote assessments to in-person assessments in an ongoing PD clinical trial. Preliminary results suggest the intervention is feasible. Further results will determine if virtual research visits are a reliable and valuable method of conducting clinical trials, and may serve as a model for increasing access, recruitment, and retention in PD clinical trials.

1380

Gait asymmetry and Parkinson's disease

C. Ashton, L. Solis-Cohen, L. Wagenaar, R. Laracuente, E. Sorberg, V. Vanderhorst, L. Shih (Boston, MA, USA) **Objective:** To evaluate gait asymmetry using velocity-dependent gait analysis and compare to UPDRS asymmetries.

Background: Motor impairment, including gait impairment, in patients with Parkinson's disease (PD) frequently manifests asymmetrically. Previous studies have suggested that gait asymmetry may be a contributing factor to freezing of gait (FOG) and falls. It is unclear whether asymmetry found in the cardinal signs of PD (tremor, rigidity, bradykinesia) is a major determinant of asymmetry represented in gait. We sought to use velocity-dependent gait analysis using a pressure-sensitive gait walkway to analyze relationships between gait asymmetry and asymmetry in PD motor signs and to relate them to clinically relevant gait-related disability.

Methods: Using a 16 x 2 foot walkway, we collected gait metrics [step-by-step stride length, step length, swing time, stance time, stride velocity and cadence] in 19 PD patients and 11 healthy control (HC) subjects across multiple walking speeds. In PD patients, we also collected MDS-UPDRS, PDQ-39, FOG-Q, and frequency of falls. We analyzed step by step metrics, preserving left-right steps separately, as a function of velocity and generated regression curves (gait curves). Asymmetry of bradykinesia (A_B) and rigidity (A_R) was calculated as a difference in right/left sums of MDS-UPDRS III items 4-8 or item 3 respectively. Severity of gait curve asymmetry was binarized as either mild or moderate based upon area calculated between left and right gait curves in all parameters.

Results: In four HC subjects, we found minor asymmetry in step length; otherwise no gait curves were asymmetric. By contrast, in eleven PD subjects we found left/right asymmetries across all gait curves, with unique configurations in many subjects. Global gait curve asymmetry was ranked across subjects according to laterality and severity. Global gait curve asymmetry was uncorrelated with A_B or with A_R . Global gait curve asymmetry was correlated strongly with falls but only weakly with FOG-Q scores.

Conclusions: Our data suggests that global gait asymmetry in PD subjects is uncorrelated with bradykinesia asymmetry and may not be a strong predictor of FOG. The correlation between self-reported fall frequency and gait asymmetry further suggests that asymmetry in itself is an important clinical metric that justifies further studies.

1385

Five-year results from the NSTAPS trial: Comparing bilateral deep brain stimulation of the globus pallidus pars interna versus the subthalamic nucleus for advanced Parkinson's disease

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Objective: Comparing motor, cognitive, and psychiatric outcome 5 years after bilateral deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) and the subthalamic nucleus (STN) for advanced Parkinson's disease (PD).

Background: Previous results from our clinical trial indicated better off-drug phase motor improvement after STN DBS 1 and 3 years after surgery (Odekerken et al., 2016). Additionally, we reported no relevant between-group differences on measures of cognitive and psychiatric functioning 3 years after surgery (Boel et al., 2016).

Methods: Patients were randomized to GPi DBS (n=65) or STN DBS (n=63). Standardized test assessment was performed at baseline, 1 year, 3 years, and 5 years. GPi and STN DBS were compared on UPDRS motor scores, MMSE, and HADS (Hospital Anxiety and Depression Scale) scores 5 years after surgery.

Results: A total of 71 patients completed (at least a part of) the 5-year follow-up, GPi DBS=33 and STN DBS=38. Drop-out rate was not significantly different between the groups (X2; p=0.28). The analyses on UPDRS, MMSE, and HADS scores are currently being performed.

Conclusions: The results of 5-year follow-up data will be presented at the congress.

Sentence comprehension in Slovak speaking patients with Parkinson's disease - preliminary results *A. Kušnírová, J. Marková, Z. Košutzká, M. Egryová, M. Pápayová, P. Valkovic, Z. Cséfalvay (Bratislava, Slovakia)* **Objective:** The aim of our research was to analyze comprehension of various syntactic constructions in Slovakspeaking PD-ND patients. We were particularly interested in exploring the influence of length, order of thematic roles, and presence of a morphological cue placed on the first noun.

Background: According to some studies sentence comprehension in patients with different neurodegenerative disorders is preserved, at least in the early stages of the disease. By contrast, other researchers suggest that this level of language information processing is already compromised in non-demented patients with Parkinson's disease (PD-ND).

Methods: We used our Slovak battery of sentence comprehension that required matching pictures to spoken sentences. The test consists of 48 semantically reversible sentences. These sentences contain transitive verbs and two nouns (person/animal), one functioning as a subject and the other as an object that can both perform the action expressed by the verb. We evaluated 20 Slovak speaking PD-ND participants.

Results: We descriptively assessed 20 PD-ND patients (11 men and 9 women) with the duration of disease 8, 58 (\pm 4, 92) years. The mean age of patients was 61, 65 (\pm 9, 69). UPDRS III score of clinician-assessed motor function was 33, 85 (\pm 8, 99) and the average of H&Y stage was 2,45 (\pm 0, 46). Statistical analyses indicated mild impairments affecting the comprehension of some complex sentences in PD-ND patients (i.e. embedded object clause). There was no significant correlation between results in the sentence comprehension test and UPDRS III score (-0, 397) or Hoehn & Yahr stage (-0, 176).

Conclusions: Comprehensive assessment of language comprehension in patient with neurodegenerative disorders can reveal impairments at the sentence level even in the early stages of the disease. These results have implications not only for early diagnosis but also for communication with patients with PD.

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Programming of deep brain stimulators in Parkinson's disease with early motor complications (EARLYSTIM-study)

K. Knudsen, J.L. Houeto, P. Krack, J. Rau, C. Schade-Brittinger, A. Schnitzler, W.M.M. Schuepbach, L. Timmermann, L. Tonder, G. Deuschl (Kiel, Germany)

Objective: Recently the EARLYSTIM study showed the superior effect of subthalamic stimulation to best medical treatment in Parkinson's disease with early motor complications.

Background: EARLYSTIM patients were implanted and programmed in highly specialized DBS centers in Germany and France according to current and common guidelines for all the centers but customized for each patient. **Methods:** Statistical analysis of DBS-programming was performed in the cohort of 114 patients with bilateral programming at the 12 and 24 month visits. We investigated the influence of atypical programming (non-unipolar, frequency other than 130 Hz and impulse-width other than 60μ s), change of contact and energy changes in the course of stimulation in relation to clinical outcome. The influence of baseline characteristics was also assessed. **Results:** The mean stimulation energy (TEED, total electrical energy delivered) increased on both sides over time. The second highest contact was used mostly. Unipolar programming (using one single contact) was sufficient in more than 80% of leads. TEED was significantly higher on the initially affected side. There was no statistically significance between the patient group needing contact changes (n=32, 28.1%) or not regarding outcomes (UPDRS II worst-mobility and total, PDQ-39 mobility and ADL subscores). Additionally, we did not find a significant influence of typical (n=83; 72.8%) versus non-typical programming. Interestingly there was no significant difference in TEED for the first implanted versus second implanted side. We found higher TEED in the patient group with less improvement of the PDQ-39 (=20%).

Conclusions: Monopolar stimulation using one single contact was found sufficient for optimal treatment for the majority of EARLYSTIM patients. The more affected side and patients with lower improvement of life quality were associated with higher stimulation energy. Although the study was not designed to compare different stimulation regimens, these results emphasize that experienced programming can provide homogeneous results.

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The occurrence of dopamine-responsive and dopamine-resistant resting tremor in Parkinson's disease *H. Zach, M. Dirkx, D. Roth, J. Pasman, B. Bloem, R. Helmich (Nijmegen, Netherlands)* **Objective:** To investigate dopamine-responsiveness of resting tremor in Parkinson's disease **Background:** Unlike the core Parkinson motor symptom, bradykinesia, resting tremor has a variable response to levodopa. It appears that levodopa alleviates tremor approximately in only half of all patients. However, it is unclear whether there are two distinct tremor phenotypes (dopamine-responsive and dopamine-resistant) or whether these groups are two ends of a spectrum. Furthermore, it is unclear to what extent the dopamine response of resting tremor is different from that of bradykinesia.

Methods: We performed a standardized L-Dopa challenge in 76 tremulous Parkinson patients. Clinical scores (MDS-UPDRS part III) were collected OFF and ON dopamine (200/50 mg levodopa-benserazide). In both sessions, resting tremor intensity was quantified during REST and during cognitive co-activation (COCO), using accelerometry of both arms. We calculated the distribution of dopamine-responsiveness for resting tremor and for bradykinesia.

Results: Using clinical scores, the dopamine-response of bradykinesia showed a clear normal distribution. For resting tremor, the findings were more complex: the accelerometry findings showed a normal distribution of the dopamine-response at rest, but not during cognitive co-activation. The clinical dopamine-response of resting tremor failed to show a normal distribution, and fitted the distribution during cognitive co-activation. Comparison of the extreme groups of clinically most dopamine-responsive (improvement: 73-100%; n=16) and most dopamine-resistant tremor patients (improvement: 0-10%; n=15) revealed a higher prevalence of women (62.5% vs. 20%; p<0.02) in the dopamine-responsive group, with longer disease duration (3.44y vs. 2.21y; p<0.02), lower FAB scores (16.88 vs.17.53; p<0.05), and higher prevalence of dyskinesias (50% vs. 0%; p<0.01).

Conclusions: Unlike bradykinesia, the clinical dopamine response of resting tremor is not normally distributed. This effect appears to be modulated by the presence of cognitive stress, which makes the distribution more "abnormal". The findings suggest that the dopamine-response of resting tremor is context-dependent, which argues against a clear division of resting tremor across two phenotypes. Female gender and the presence of dyskinesias is associated with a better dopamine-response of resting tremor.

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Towards responsive deep brain stimulation for medically refractory freezing of gait in Parkinson's disease *R. Molina, J. Shute, E. Opri, K. Sowalsky, J. Roper, D. Martinez-Ramirez, K. Foote, C. Hass, M. Okun, A. Gunduz* (Gainesville, FL, USA)

Objective: Medically refractory FoG presents an unmet and pressing need to develop novel therapeutic strategies. We seek to describe the electrophysiology of the pedunculopontine nucleus (PPN), a brain stem structure found to excite spinal central pattern generators and the globus pallidus interna (GPi), in human walking. We will identify the underlying neural mechanisms and pathogenesis of FoG for real-time detection of FoG episodes. A real-time, onboard detector will be designed using the extracted features, stimulation will be delivered in response to positive detection, and the delivered therapy effectiveness will be assessed via clinical scoring standards.

Background: Freezing of gait (FoG) is a poorly understood and an often intractable symptom of Parkinson's disease (PD) affecting patients regardless of disease progression or medical therapy. Dopamine therapies or deep brain stimulation (DBS), often do not provide adequate management of FoG.

Methods: All participants must meet the inclusion criterion, including minimum scores on FoG-Q and a minimum of 5 freezing episodes incited by FoG provocation tasks. A total of five participants will receive bilateral GPI and PPN DBS electrode implantation with two Activa PC+S Neurostimulation system, (Medtronic, Minneapolis, MN. These novel devices are capable of capturing data while simultaneous delivering stimulation to the depth electrodes. Concurrently, data will be collected from multiple EMG+acceleration sensors (Delsys, Inc., Natick, MA), a 10-camera motion capture system (Vicon Peak, Oxford, UK), and ground reaction forces (Bertec, Newton, MA) over two-day monthly visits over a span of a year.

Results: We have observed a correlation between medication state and task intensity and the mu-low beta activity in GPi. Similarly, low frequency activity (<10Hz) in the PPN changes with medication and is positively correlated with the intensity of the task. Clinical labels of FoG have also been identified to correlate to FoG episodes and the low frequency activity. A neurologist's time-aligned labeling of onset and cessation of FoG episodes during a continuous walking task was compared to the onboard threshold detector.

Conclusions: Our initial results are promising and consistent across 4 subjects. The fifth patient was levadopa non-responsive, and may explain why similar patterns were not observed.

Istradefylline and Preladenant as adjuvant therapies for patients with Parkinson's disease

A. Negida, Z. Hassan, H. Ahmed, O. Hassan, A. Elsherbiny, S. Azzam, O. Osama, Y. Ibrahim (Zagazig, Egypt) **Objective:** The aim of this meta-analysis is to synthesize evidence about the efficacy of the adenosine receptor antagonists (Istradefylline and Preladenant) for patients with Parkinson's disease.

Background: Multiple A2a receptor antagonists have been developed for the treatment of PD and their efficacy has been assessed in multiple clinical trials.

Methods: We searched PubMed through, November, 2015, using relevant keywords. Records were screened for relevant studies and data were extracted to online data extraction sheet and were analyzed. Outcomes of (off time, on time without troublesome dyskinesia, on time with troublesome dyskinesia, UPDRS III, and UPDRS II) were pooled as mean difference or weighted mean difference between the two groups from baseline to endpoints. Statistical analyses were conducted by RevMan version 5.3 for windows and Open[Meta-analyst].

Results: Ten RCTs (Istradefylline: 7 RCTs, n=2231; and Preladenant: 3 RCTs, n=1507 patients) were included. The overall effect estimate favored Istradefylline than placebo in terms of: (1) daily time off (20 mg/day: WMD -0.62, 95% CI -1.06 to -0.17; 40 mg/day: WMD -0.80, 95% CI -1.22 to -0.38); (2) on time without troublesome dyskinesia (20 mg/day: WMD 0.74, 95% CI 0.31 to 1.18; 40 mg/day: WMD 0.85, 95 % CI 0.40 to 1.31); and (3) UPDRS III "on state" (20 mg/day: WMD -0.91, 95% CI -1.71 to -0.11; 40 mg/day: WMD -1.61; 95 % CI -2.49 to -0.73). However, the overall effect estimate did not favor Istradefylline over placebo in terms of: (1) on time with dyskinesia (20 mg/day: WMD 0.89, 95% CI -0.66 to 2.44; 40 mg/day: WMD 0.98, 95 % CI -0.08 to 2.048); (2) UPDRS II during off state (20 mg/day: WMD -0.48, 95% CI -1.13 to 0.15; 40 mg/day: WMD -0.51, 95 % CI -1.30 to 0.26); and (3) UPDRS II during on state (20 mg/day: WMD 0.09, 95% CI -0.54 to 0.73); 40 mg/day: WMD -0.18, 95 % CI -0.49 to 0.11). For the Preladenant, the overall effect size favored Preladenant than Placebo in terms of "daily time off" and "on time without dyskinesia" but this effect size was not significant for the 2 mg, 5 mg, and 10 mg doses compared to placebo.

Conclusions: Istradefylline could improve the motor functions during the "on state" and it was effective in reducing the "off time" without increasing the "on time with troublesome dyskinesia". Current evidence suggests that Preladenant can reduce the "off time". However, further randomized controlled trials on Preladenant are needed.

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Effect of deep brain stimulation on visuospatial impairment in Parkinson's disease

Y. Okahara, Y. Higuchi, K. Aoyagi, M. Abe, T. Yamamoto, Y. Yamanaka, S. Hirano, Y. Iwadate (Chiba, Japan) **Objective:** We evaluated postoperative change of visuospatial impairment in the patients with Parkinson's disease (PD) underwent deep brain stimulation (DBS) to assess the impact of chronic stimulation and discussed factors associated with DBS-related change.

Background: PD patients commonly have cognitive impairments including executive, memory, and visual perception deficits¹. Visuospatial perception deficits in PD might relate to symptoms of freezing of gait or visual hallucinations. To date, there are previous reports on cognitive outcome after subthalamic nucleus (STN) DBS²; however, the effects of surgery on visuospatial cognitive function are still the subject of controversy. In this study, we investigated the effect of DBS to visuospatial cognition in PD patients.

Methods: Thirty consecutive patients with PD who underwent bilateral STN (n=27) or Globus pallidus internus (n=3) DBS were included in this study. The median age was 66.5 years (IQR 61-68). The median disease duration was 13 years (IQR 10- 15 years). Mean Unified Parkinson's Disease Rating Scale (UPDRS) Part III was (on/off) $17.2 \pm 7.9/44.1 \pm 14.3$ (mean \pm S.D.). L-dopa equivalent dose (LED) was 1090 \pm 263 mg. Median MMSE was 30 (range 26-30). We performed Rey-Osterrieth Complex Figure Test (ROCFT) before and one year after surgery. Clinical factors, such as age, gender, preoperative cognitive function (Wechsler Adult Intelligence Scale [WAIS] III), family history, and disease duration were also evaluated.

Results: We found significant deterioration in copy accuracy of ROCFT after surgery (p=0.028), however no significant difference in immediate recall accuracy between before and after surgery. An over 10% decrease in copy accuracy correlated with the low scores of verbal comprehension, working memory in preoperative WAIS III (Spearman's rank correlation coefficient, p=0.017, 0.047). Age, disease duration, gender or preoperative motor scores were not associated with deterioration of copy accuracy.

Conclusions: Chronic stimulation might affect visuospatial cognition in PD patients. The pre-existing impairment of cognitive function might be a risk factor for deterioration of visuospatial impairment.

A novel paradigm of variable frequency deep brain stimulation to improve freezing of gait in Parkinson's disease

F. Jia, A. Wagle Shukla, w. Hu, L. Almeida, M. Okun, L. Li (Beijing, Peoples Republic of China) **Objective:** To determine the effects of a novel deep brain stimulation (DBS) paradigm of combining high and low frequency stimulation in varying patterns (VFS) for freezing of gait (FOG) and appendicular motor symptoms in Parkinson's Disease (PD).

Background: DBS is a well-established therapy for PD and is conventionally delivered in a high frequency range (130-180 Hz, HFS). HFS DBS is found to have suboptimal effects on FOG symptoms. Low frequency stimulation (60-80 Hz, LFS) is an alternate option however the benefits are noted as transient, inconsistent and may not have effective control of appendicular motor symptoms. We sought to examine the effects of a novel frequency based (VFS DBS) programming.

Methods: Twenty-eight PD patients (16 males, 12 females) with bilateral STN DBS (PINS system) were enrolled. These patients were optimized on HFS therapy for control of tremor, rigidity and bradykinesia however complained of a persistent FOG. Unified Parkinson's Disease Rating Scale (UPDRS) and a 10 meter timed up and go (TUG) task was used for comparisons while patients received one hour of HFS, one hour of LFS and one hour of VFS therapy. All evaluations (off dopaminergic medications) were performed by blinded video raters. These patients were sent home on VFS and followed-up at 6 and 12 months. Repeated measures ANOVA and post hoc comparisons with Bonferroni corrections were performed.

Results: Total time on the TUG task with VFS (27.4 seconds) was significantly lower compared to HFS (43.0 seconds, p = 0.005) and LFS (53.0 seconds, p = 0.005) therapy (Fig. A). Similarly, the number of freezing episodes significantly reduced with VFS (0.3 episodes) compared to HFS (1.7 episodes, p = 0.004) and LFS (1.5 episodes, p = 0.004) (Fig. B). VFS DBS also significantly reduced tremors (HFS, p = 0.005; LFS, p = 0.001) (Fig. D), improved bradykinesia (HFS, p = 0.001; LFS p = 0.001) (Fig. E) and rigidity (HFS, p = 0.001; LFS, p = 0.001) (Fig. F). The VFS effects on gait and motor outcomes remained sustained at 6 and 12 months follow-up (Fig.).



Conclusions: A combination of HFS and LFS DBS effectively controls gait as well as appendicular motor symptoms in PD. VFS benefits are noted to remain sustained at one year follow-up. A larger follow-up study is required to further confirm these results.

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Deep brain stimulation of subthalamic nucleus selectively modulates striato-thalamo-cortical circuit in Parkinson's disease: A systematic review and ALE meta-analysis *H. Chen (Beijing, People's Republic of China)* **Objective:** To investigate pooled effect of STN-DBS effect on brain activity in Parkinson's disease (PD), and to address the result inconsistency across previous functional image studies.

Background: Deep brain stimulation of subthalamic nucleus (STN-DBS) has been becoming an effective treatment strategy for patients with PD. However, the biological mechanism underlying the DBS treatment remains poorly understood. Functional brain imaging techniques provide unique opportunities to ascertain how STN-DBS modulates brain activity, but results often varied across studies. Activation likelihood estimation(ALE) meta-analysis allows a quantitative summarization by synthesizing a spatial activation map based on reported coordinates. **Methods:** In the present study we performed ALE meta-analysis in which functional imaging studies concerning STN-DBS effects on either resting-state or task-evoked brain activity in PD were searched. The STN-DBS meta-analyses were conducted by using GingerALE version 2.3.3 (http://brainmap.org/ale/). We further performed functional connectivity analysis in healthy individuals. To our knowledge, this is the first ALE meta-analysis that explored STN-DBS effect on brain activity.

Results: First, meta-analysis based on thirteen resting-state functional imaging studies in Parkinson's disease revealed that STN-DBS elevated brain activity in the STN and thalamus, and reduced activity in the caudal supplementary area and primary motor cortex during rest (Figure 1). Functional connectivity analysis based on a group of resting-state functional MRI data in healthy adults revealed that these treatment-related brain areas were functionally connected within a motor-related circuit. Second, meta-analysis based on five motor-control functional imaging studies in Parkinson's disease revealed that STN-DBS elevated brain activities in the globus pallidus internus, and decreased activities in the caudal supplementary area and paracentral lobule (Figure 1).



Conclusions: STN-DBS increased brain activity in the subcortical regions (i.e. STN, GPi and thalamus), and decreased brain activity in the motor cortex (i.e. SMA and M1). In conclusion, we postulate that STN-DBS may activate the basal ganglia and disrupt the information flow in the STC circuit in the meanwhile (Figure 2).



Impaired sensorimotor and visual networks in drug naive Parkinson's disease based on graph theoretical analysis

H. Chen (Beijing, People's Republic of China)

Objective: We aim to investigate topographic structure in drug naive patients with Parkinson's disease (PD). **Background:** Resting state functional magnetic resonance imaging (rs-fMRI) provides valuable insights into alteration of brain network in PD. Graph theoretical analysis, originated from mathematical study of networks, has been applied to compute a complex brain network to transfer complex brain network into nodes, edges and lines. The combination of rs-fMRI and graph theoretical analysis allows revealing small-world, modularity and hub properties in the complex human brain network.

Methods: Twenty six drug naïve PD and 19 age- and gender- matched healthy controls (HC) were included in our analysis. Small-world property and topographic profiles (nodal degree, global efficiency, local efficiency, cluster coefficient, shortest path length, betweenness centrality) were measured and compared between groups, with age and gender as covariates. We also performed correlation analysis between topographic features with motor severity measured by UPDRS III.

Results: Small-world property was present in PD (Figure 1). Nodal degree, global efficiency, local efficiency and characteristic path length consistently revealed disruptive sensorimotor network, and visual network to a less degree in PD (Figure 2). By contrast, default mode network (DMN) and cerebellum in PD showed higher nodal degree, global efficiency and local efficiency, and lower characteristic path length. Global and local efficiency in the midbrain was higher in PD excluding substantia nigra (Figure 2C and 2D). PD group also exhibited lower cluster



coefficient in the subcortical motor network (thalamus and caudate nucleus) than HC (Figure 2E). No significant correlation was found between topographic properties and motor severity.



Conclusions: Disruptive sensorimotor network and visual network may be a potential biomarker of PD. Unlike Alzheimer's disease targeting DMN, PD pathophysiology may specifically target sensorimotor and visual networks. DMN, cerebellum and a certain areas in the midbrain may play compensatory effect for disruptive networks.

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Interactions between amyloid-ß and microglial activation in Parkinson's disease

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Objective: To evaluate the relationship between microglial activation and amyloid-ß deposition in the brain using positron emission tomography (PET) in Parkinson's disease (PD) with normal and impaired cognitive function. **Background:** Neuroinflammatory processes such as activated microglia have been reported to play an important role in PD. Deterioration of cognitive performance has been connected with elevated beta-amyloid accumulation. Accumulation of amyloid- ß may contribute to microglial activation and disease progression.

Methods: We recruited 17 PD patients, 11 PD patients with mild cognitive impairment (MCI) and 11 healthy controls (HCs) to measure the impact of amyloid- β deposition in the brain with [¹¹C] Pittsburgh compound B (PIB) on microglial activation using the translocator protein 18-kDa (TSPO) radioligand [¹⁸F]-FEPPA. PIB distribution volume ratio (DVR) was measured in cortical and subcortical regions. A DVR of 1.2 was set to divide each brain region into PIB-positive or PIB-negative. FEPPA total distribution volume (V_T) values were compared for each brain region to evaluate the effect of PIB positivity while adjusting for TSPO rs6971 polymorphism (which is implicated in differential binding affinity).

Results: Preliminary analyzes revealed a significant main effect of PIB positivity in the striatum ($F_{(2, 32)}$ = 5.9, p = 0.006). Besides the striatum (p=.019), the dorsolateral (p=.012) and prefrontal cortex (p=.002) as well as the temporal (p=.004) and frontal lobe (p=.006) showed a significant interaction effect. In these regions the effect of PIB positivity was only significant in the PD-MCI group. In the frontal lobe the effect of PIB positivity was also

significant in the PD group (p=.011). Further, PIB-positive PD-MCI patients showed significantly higher V_T values than PIB-positive HCs in the striatum (p=.019), temporal (p=.012) and frontal lobe (p=.031) as well as significantly higher V_T values than PIB-positive PDs in the striatum (p=.028), prefrontal cortex (p=.004) and temporal lobe (p=.011).

Conclusions: Our results indicate an interaction between amyloid-ß deposition and microglial activation in PD. Further investigations are necessary to evaluate if amyloid deposits cause neuroinflammation and further neurodegeneration or if increased microglia activation develops as a protective response.

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Understanding neural activation in semantic fluency in Parkinson's disease with mild cognitive impairment *J.H. Julia, K. McMahon, D. Copland, G. Byrne, A. Toft, L. Mithcell, J. O'Sullivan, N. Dissanayaka (Herston, NSW, Australia)*

Objective: To identify neural mechanisms relating to semantic fluency deficits in PD-MCI and to establish possible neuroimaging markers for Parkinson's disease (PD) with dementia.

Background: Patients with PD are found to experience a plethora of symptoms ranging from subtle cognitive complaints to severe cognitive dysfunction leading to dementia. The cognitive dysfunction detrimentally impacts patients' quality of life and contribute to a high disease burden. Impairment in semantic fluency is reported to be associated with PD with mild cognitive impairment (PD-MCI) and is thought to be a risk factor for developing dementia in PD. Therefore, the aim of this study is to identify neural mechanisms relating to semantic fluency deficits in PD-MCI.

Methods: Sixteen non-demented PD patients and 6 age and gender-matched healthy controls (HC) participated. PD group was subdivided to the presence of MCI using a comprehensive cognitive battery according to the recommended diagnostic criteria (Litvan et al. 2012). Participants were scanned in 3T Siemens PRISMA using event-related fMRI to measure differences in semantic fluency between groups. The task was composed of rest, automated, category generation, and category switching. fMRI data was analysed using SPM12 and whole brain analysis. Significant was determined as p<0.001 uncorrected, with cluster level FWE correction (p<0.05).

Results: Ten PD patients were diagnosed with MCI with 1.5SD below norms. Behavioural data showed that an average number of items in all conditions were relatively smaller in PD-MCI compared to other groups. Using whole brain fMRI, the main effect of group for category generation highlighted right medial cingulate cortex, bilateral operculum including insular lobe, supramarginal gyrus, bilateral cerebellum and right precuneus. PD-MCI showed alteration in left temporal pole compared to PD-nMCI.

Conclusions: PD-MCI showed decreased activity in cerebellum compared to HC which may relate to its role of contributing in language processing. Also, there were differences in activation in the left temporal pole between PD-MCI and PD-nMCI. The left temporal pole deficits have been linked to semantic dementia. Our results demonstrate a possible involvement of this region with respect to impairment in semantic fluency in PD-MCI and potentially serve as a marker for dementia. This abstract is also submitted to OHBM 2017 Conference.

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Resting state modulations of EEG low frequency bands in Parkinson's disease.

A. Pal, N. Mehta, R. Sharma (New Delhi, India)

Objective: Dynamics in EEG activity such as slowing in low-frequency bands has been reported in Parkinson's disease (PD). The objective of the present study was to find out the activity pattern (power and cortical sources) in lower bands of EEG in PD with or without dementia.

Background: In Parkinson's disease, dysfunction in various cortical and subcortical pathways lead to the alteration in activity of brain depicted by EEG waves. Alteration in the EEG activity pattern and the sources of delta and theta bands may cause deficits in information processing in PD. Pathologically altered activity of these bands may predict the severity and stage of the disease and could serve as a noninvasive biomarker for early and accurate diagnosis of cognitive impairment as well as of dementia.

Methods: Parkinson's Patients with MMSE scores = 24 PD demented (PDD, n=28); MMSE score >24 as PD nondemented (PDND, n = 30) and Controls with MMSE score > 26 as Controls (Con, n=28) were taken for the study. EEG was recorded for 5 min each during Eyes closed and Eyes open conditions by using 128 channel EEG net . Absolute mean power was calculated using FFT algorithm in MATLAB. Source localization analysis was done using sLORETA software. Kruskal test followed by rank sum test in MATLAB was used. EEG sources compared by t-tests. Significance was determined with a *p*-value of <0.05. **Results:** At rest, EEG power in delta and theta bands was significantly higher in PDD compared to Control as well as PDND. In PDND compared to Control, power was present in theta band only. In PDND compared to Controls, EEG sources in delta band showed higher activation in frontal, limbic, occipital, temporal and sub lobar lobes, except in parietal lobe (Precuneus gyri BA, 7) where predominantly lower activation was seen. In theta band higher activation in medial frontal Gyrus (BA 47), anterior cingulate gyrus (BA 24, 32), and lower activation in medial frontal gyrus (BA 6), middle frontal gyrus (BA 10). PDD compared to Control as well as PDND primarily had higher activation in medial frontal gyrus (BA 10) and middle temporal lobe (BA 21) in both delta and theta bands.

Conclusions: Higher power and differential pattern of cortical source activation in slow bands (delta and theta) is an indicator of altered brain activity in PDD patients. Algorithms used for the present study could be used to differentiate the onset and progression of dementia from PDND to PDD.

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Evolution in Dopamine Transporter (DaT) Scan Utilization Patterns and its Effect on Treatment Decisions: Results of the Next 200 Scans

X.X. Yu (Cleveland, OH, USA)

Objective: To describe further changes in DaT scan utilization and its influence on management following our initial experience.

Background: We previously reported our DaT scan experience for the first 175 patients and showed: 1) high scan utilization rate and scan utilization variability amongst clinicians (5 to 33 per 100 new patients); 2) surprisingly low pre-scan *diagnostic accuracy rate* (i.e. compatibility percentage of the working diagnosis to scan results)-- 57% for neurodegenerative parkinsonism, 65% for non-neurodegenerative parkinsonism, 79% for essential tremor (ET), and 47% for psychogenic movement disorder; and, 3) high *treatment discrepancy rate* (i.e. the percentage of inconsistency of treatment with scan results) especially among patients with normal scans (24% continued on anti-parkinson medication).

Methods: We conducted a retrospective review of the next set of consecutive patients, evaluated by movement disorder neurologists, who received a DaT scan from November 2012 to May 2014.

Results: A total of 200 (out of 240) scans performed during the 19-month period were included in our analysis. The rates of scan utilization decreased to 0 to 13 per 100 new patients, although utilization variability remained wide. Clinicians' pre-scan diagnostic accuracy improved (i.e. when neurodegenerative parkinsonism was suspected (N=97), the scan was abnormal in 73.2% of the cases.; when non-neurodegenerative parkinsonism was suspected (N=40), the scan was normal in 80% of cases; this included psychogenic movement disorders (N=19) with a normal scan in 79%; and, when ET was the pre-scan diagnosis (N=28), the scan was normal in 86%). Treatment discrepancy reduced especially with normal scan results (i.e. only to 7% ofpatients with a normal scan remained on PD medications).

Conclusions: While scan utilization rates among specialists reduced over time, utilization variability remained wide and treatment became more concordant with DaT scan results. Surprisingly, with continued experience using DaT scans, our clinicians' pre-scan diagnostic accuracy improved over time.

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Hypometabolism in orbitofrontal and perirhinal cortex is associated with impulse control disorder In Parkinson's disease

I. Navalpotro-Gomez, A. Botas-Peñín, F. Molinet-Dronda, C. Gasca-Salas, M. Carmona-Abellán, H. Jiménez-Urbieta, M. Delgado-Alvarado, A. Quiroga-Varela, B. Gago, M.C. Rodríguez-Oroz (San Sebastian, Spain) **Objective:** (i) To elucidate the metabolic correlates sub-serving the clinical expression of ICD in PD and (ii) to evaluate the association between the glucose metabolism and the ICD scores.

Background: A substantial subset of Parkinson's disease (PD) patients suffers from impulse control disorders (ICD)¹. Previous metabolic/ functional neuroimaging studies exhibit a differential activation of reward-related cerebral areas but their methodological heterogeneity makes it difficult to provide firm conclusions².

Methods: Twenty-two PD-ICD patients according to the QUIP-RS scale, and nineteen healthy controls (HC) underwent [¹⁸F]-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET) in "on drug" state in resting condition. Regional glucose metabolism and its correlations with the QUIP-RS score were assessed using SPM8. **Results:** As PD-ICD patients [19 male, 3 female; 59.9±8.7 years old; 8.5±4.2 years of disease evolution; UPDRS ON motor score 19.2±2.29; Daily LED_{TOTAL} 1446 mg ±129.87] differed from healthy controls (10 male, 9 female; 68. ±3.2 years old) in age and sex, we included them as covariates for comparisons. PD-ICD patients exhibited

lower FDG uptake bilaterally in the orbitofrontal cortex (OFC), and to a lesser extent in the left perirhinal cortex than HC without any region of hypermetabolism. QUIP-RS score correlated negatively with FDG uptake in the medial OFC.

Conclusions: There is a bilateral and non-task related hypometabolism in stimulus-reward association areas in PD-ICD patients compared to HC, which is negatively correlated with the severity of this behavioral disorder.

*This abstract has not been previously published. It has been sent to the "13th International Conference on Alzheimer's & Parkinson's Disease" which will take place from March 29 to April 2, 2017 in Vienna, Austria.

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F-18-DOPA-PET predicts impulsive behavior under dopaminergic therapy in Parkinson patients

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Objective: The aim of this study is to investigate the influence of the intensity of dopaminergic projections to the ventral striatum (VS) measured with F-18-DOPA-PET in the development of impulse control disorders (ICDs) in patients with Parkinson's disease (PD).

Background: ICDs including gambling, hypersexuality etc. are a frequent side effect of dopamine replacement therapy in patients with PD. Cilia et al. and others have shown that ICD patients show a reduced signal in FP-CIT-SPECT in the VS, reflecting either a reduction of mesolimbic projections or, alternatively, a lower membrane dopamine transporter (DAT) expression on presynaptic terminals.

Methods: 59 participants, 46 of which with PD underwent a 90 minute dynamic F-18-DOPA-PET scan. Scans were spatially normalized to a DOPA-PET-template (García-Gomez et al, 2013) using SPM12. Patlak slopes (Ki) for each voxel were calculated with a custom built script using the occipital cortex as reference region. Ki in 7 striatal regions derived from the FSL striatum connectivity atlas were extracted. All participants completed the QUIP-RS questionnaire, a well-validated test to detect and quantify ICD behavior in PD (Probst et al., 2014).

Results: 17 Patients had a QUIP-RS score of greater than 8 and were therefore classified as having an ICD. In this group, a negative correlation was found between average Ki and QUIP-RS score in regions connected to the limbic system, i.e. mainly the VS (r=-0.52, p=0.03) and in regions connected to the executive system, i.e. the rostral caudate nucleus (r=-0.60, p=0.01). Similar results could be obtained by analyzing the static time frame from 80-90 minutes using the same reference region.

Conclusions: PD patients with symptoms of ICD show decreased F-18-DOPA-PET signal in the VS and the rostral caudate nucleus. The intensity of PET signal reduction in these regions correlated well with the severity of ICD symptoms. We conclude that a reduction in dopaminergic projections to the striatum rather than a functional downregulation of DAT could be responsible for the development of ICDs.

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99mTc-TRODAT-1 SPECT imaging in early and late onset Parkinson's disease

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Objective: In this study we tried to determine the TRODAT SPECT findings in EOPD as compared to LOPD. **Background:** 99mTc-TRODAT-1, which binds to the dopamine transporter, could be used to image the dopaminergic system and diagnosis of Parkinson's disease (PD). PD can be classified into two groups: late-onset Parkinson's disease (LOPD) and early onset Parkinson's disease (EOPD) that occurs in early life.

Methods: Fifteen patients were studied. The diagnosis of PD was defined by clinical criteria based on UK Parkinson's Disease Society Brain Bank criteria. Six patients whose age at onset of PD were younger than 50 were defined as patients with EOPD and 9 patients with older than 50 years were defined as patients with LOPD. All patient underwent 99mTc-TRODAT Brain SPECT.

Results: No significant difference was noticed between EOPD and LOPD in disease stage and symptoms. In visual analysis, 20 (66.67%) caudate nucleuses had decreased tracer uptake while all 30 (100%) putamens had decreased or absent tracer uptake. No significant difference between EOPD and LOPD was noticed in visual analysis. Striatum, Caudate and Putamen uptake ratio were calculated. No significant difference was noticed between EOPD and LOPD in these ratios. However there was significant difference in visual analysis (tracer uptake) as well as in uptake ratio between putamen and caudate nucleuses in both groups (P=0.001).

Conclusions: 99mTc-TRODAT-1 SPECT imaging showed lower presynaptical dopaminergical terminals density in both EOPD and LOPD. We didn't find in TRODAT uptake between two groups. Putamen showed more involvement and diminished TRODAT uptake.

Post-movement beta rebound inhibits future movement

E. Rhodes, A. Kharko, W. Gaetz, S. Hall (Plymouth, United Kingdom)

Objective: To evaluate the potential inhibitory effect of post-movement beta rebound (PMBR) on future movement production.

Background: Changes in the cortical power of beta oscillations within the primary motor system have been shown to correlate with various stages of movement production. During the preparation and execution of an action there is an event-related desynchronisation (ERD) of cortical beta power, then, following the cessation of movement there is a resynchronisation of the motor networks resulting in PMBR (Jurkiewicz et al., 2006). Previous research has shown that during serial movement there is an abnormal augmentation of PMBR within Parkinson's Disease (PD) patients not seen in healthy individuals. We suggest that this cumulative increase in beta power inhibits and impairs future movement, driving bradykinesia. Therefore it is a vital step to investigate whether PMBR inhibits future movement even in healthy individuals.

Methods: EEG was recorded from 50 healthy subjects as they performed a simple single-digit, isometric buttonpress task. For each individual, the EEG data was then analysed to find peak PMBR latency allowing us to design our follow-up study and time our TMS stimulation. Subjects performed the same button-press task in the follow-up study whilst motor evoked potentials (MEPs) were generated using single-pulse TMS at peak PMBR, 100ms prepeak PMBR and 100ms post-peak PMBR. MEPs for each timepoint were compared to an average of MEPs collected during a period of rest.

Results: Preliminary results suggest that average MEP amplitude is greatly reduced during PMBR. MEPs timed during peak PMBR exhibit the greatest reduction in amplitude.

Conclusions: These data suggest that PMBR does indeed inhibit future movement production. This adds weight to our suggestion that abnormal augmentation of PMBR drives the bradykinesia exhibited by PD patients during serial movement.

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Altered attentional brain network in Parkinson's disease with mild cognitive impairment

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Objective: To investigate alterations in the attention network in Parkinson's disease patients with mild cognitive impairment (PD-MCI).

Background: MCI is a risk factor for dementia in PD. Impairments in cognitive domains such as attention and executive processing are commonly observed in PD-MCI; however, neural mechanisms underpinning these deficits are poorly studied in PD. The present study aims to use task dependent fMRI to identify neural basis for deficits in attention and executive function in PD-MCI. This will assist with establishing neuroimaging markers for PD with dementia

Methods: Seventeen PD patients and 7 age and gender-matched healthy controls participated. PD was further subdivided to the presence of MCI using a comprehensive cognitive battery according to the recommended diagnostic criteria (Litvan et al. 2012). Participants were scanned (3T Siemens PRISMA) using event-related fMRI to measure differences in attention network test between groups. Three different attention components of alerting, orienting, and executive control were calculated (Fan et al. 2005). Behavioural reaction time and accuracy were analysed. Functional MRI data was analysed using SPM12 and whole brain analysis. Significance was determined as p<0.001 uncorrected, with cluster level FWE correction (p<0.05).

Results: Ten PD patients were diagnosed with MCI with 1.5SD below norms. In alerting, PD-MCI showed increased activation in the medial cingulate cortex, inferior frontal gyrus and prefrontal and temporal thalamus compared to PD-nMCI. PD-nMCI showed increased activation in right occipital regions including calcarine gyrus and precuneus; bilateral hippocampus and cerebellar vermis. In executive control, PD-MCI also showed increased activation left posterior-medial prefrontal cortex, left insular, bilateral inferior frontal gyrus and right prefrontal thalamus.

Conclusions: Increased activation posterior and frontal regions found in the PD group may indicate impaired deactivation of default mode network in PD particularly in PD-MCI compared to controls. Whilst, thalamus plays a major role in alerting and executive function, excessive activation observed particularly in PD-MCI may relate to compensatory activation in order to complete the task. This abstract is also submitted to OHBM 2017 Conference.

Neural correlates underlying reward processing and decision-making in impulse control disorder in Parkinson's disease

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Objective: To investigate the functional neural basis of decision-making in PD-ICD subjects using a modified version of the Iowa Gambling Task (IGT) paradigm.

Background: Impulse Control Disorders (ICD) is a frequent and severe psychiatric complication in Parkinson's disease (PD)1 whose physiopathology is poorly understood2

Methods: 18 PD-ICD patients, 17 PD non-ICD patients and 18 healthy controls (HC) matched for age, gender and education, underwent functional MRI (fMRI) scanning while performing a modified version of the IGT using a block experimental design. The task was divided in 3 sections: response to positive, negative and mixed feedback. Whole-brain, Region- of-Interest (ROI) and multivariate functional connectivity analyses were performed. **Results:** The PD-ICD group showed increased activation across the 3 conditions compared to HC in prefrontal cortex (PFC) (bilateral frontal superior medial gyrus, left middle frontal gyrus and left mid-orbitofrontal cortex), motor regions (bilateral pre-supplementary area), left middle temporal gyrus, parietal cortex (left inferior and superior giri) and bilateral putamen. Compared to PD non-ICD, PD-ICD patients showed enhanced activation in left inferior parietal cortex, right precuneus and bilateral putamen. Time course analyses revealed a Group by Condition interaction in the left and right insula, and right inferior frontal gyrus, where PD-ICD patients had lower activation in the mixed feedback condition than the other groups. Group differences in functional connectivity with the striatum were observed. Relative to HC, PD-ICD patients had stronger coupling with the bilateral dorsolateral PFC, and PD non-ICD patients had stronger connectivity with the orbitofrontal cortex/ventromedial PFC.

Conclusions: PD-ICD patients show altered activation of the cortex (insula and inferior frontal gyrus) and abnormal functional connectivity (striatum-PFC regions) in structures involved in risk and uncertainty during reward-based decision-making. Differences in the response to mixed feedback decision could be associated with a difficulty of acquisition of probabilistic contingencies in the learning phase in comparison to a non ICD population.

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Does smoking impact dopamine neuronal loss in de novo Parkinson's disease?

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Objective: To investigate whether smoking impacts striatal dopamine neuronal degeneration in Parkinson's disease (PD), we compared striatal subregional dopamine transporter (DAT) binding between current-smokers and never-smokers with *de novo* PD.

Background: Cigarette smoking is inversely associated with the risk of PD. Cigarette smoke has been shown to protect against toxin-induced dopamine neuronal damage in experimental animals; however, its effect on dopamine neuronal degeneration in humans with PD is yet to be demonstrated.

Methods: We analyzed the data of 282 male patients with *de novo* PD (mean age, 66.2 ± 10.1 years; range, 38-89 years) with documented smoking history, who underwent DAT positron emission tomography scans. Among them, 105 ex-smokers were excluded from the analysis.

Results: Current-smokers (n = 44) showed higher depression score compared with never-smokers (n = 133), but other clinical variables were comparable between the two groups. DAT binding to the posterior and ventral putamen was higher, and inter-subregional gradients of the anterior putamen/posterior putamen and the ventral striatum/posterior putamen were lower in current-smokers than in never-smokers. A general linear model showed that Unified Parkinson's Disease Rating Scale (UPDRS)-motor scores were comparable between the two groups after controlling for DAT binding to the posterior putamen and other potential confounding variables, but the interaction effect between smoking status and DAT binding to the posterior putamen on UPDRS-motor score was different, showing a steeper slope in current-smokers than in never-smokers.

Conclusions: These results demonstrate that current-smokers with PD has a different dopamine depletion pattern compared to never-smokers with PD and show a trend toward no protective effect of smoking on dopamine neuronal degeneration, suggesting that current-smokers with PD may represent a different PD subtype.

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Aberrant resting state functional brain networks in patients with Parkinson's disease and visual hallucinations

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Objective: To explore the neural correlates of visual hallucinations (VH) in patients with Parkinson's disease (PD). **Background:** Psychosis is one of the commonly observed non-motor symptoms of PD. It usually manifests as visual hallucinations (VH) and minor hallucinations. The neural correlates of VH are not fully understood. Early identification of PD patients at risk of developing psychosis is imperative as psychosis significantly worsens the quality of life of patients with PD. Hence it is crucial to explore the signature alterations in neural networks in patients with PD having VH.

Methods: This study included 40 subjects with PD [20 with VH (PD+VH), 20 without VH (PD-VH)]. MR images were obtained for all subjects in a 3T scanner. Mini Mental Status Examination (MMSE) was done to screen for cognitive impairment and a score < 26 was set as an exclusion criteria. Severity and stage of PD were assessed by using the Unified Parkinson's Disease Rating Scale (UPDRS III) and the Hoen and Yahr (H&Y) scale respectively. Graph theory based analysis was used to compare the pattern of functional connectivity between the two groups. **Results:** There was no significant difference in the age, duration of illness, and gender distribution between the two groups. Comparison of the global graph metrics revealed significantly increased clustering coefficient (CC) and decreased path length in PD+VH group. Comparison of the graph metrics of individual seeds revealed significantly higher CC in structures corresponding to several resting state networks such as default mode network (superior frontal gyrus, precuneus, inferior temporal gyrus, inferior parietal sulcus, angular gyrus), fronto-parietal network (dorsolateral and ventrolateral prefrontal cortex), and parahippocampal gyrus in PD+VH group. PD+VH group had significantly lower clustering coefficient in the anterior cingulate cortex, which is a component of cingulo-opercular network.

Conclusions: Patients with VH have significantly higher small-worldness compared to those without VH. Several structures corresponding to the default mode network, and fronto-parietal network have a higher clustering coefficient in PD+VH group whereas the cingulo-operacular network had reduced clustering coefficient in patients with VH.

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Subcortical local shape volume analysis of progressive mild cognitive impairment in Parkinson's disease *S.J. Chung, J.H. Shin, K.H. Cho, Y. Lee, H.S. Yoo, S.J. Chung, Y.H. Sohn, J.K. Seong, P.H. Lee (Seoul, Korea)* **Objective:** We evaluated the role of subcortical structures in ongoing dementia in Parkinson's disease (PD). **Background:** Cortical neural correlates of ongoing cognitive decline in PD are suggested, however, the significance of subcortical structures in the development of dementia in PD has not been fully studied.

Methods: One hundred eighty-two patients with PD-mild cognitive impairment (PD-MCI) were classified as PD-MCI converters (n = 74) or PD-MCI non-converters (n = 108) based on whether they were subsequently diagnosed with dementia. We explored automatic analysis of subcortical brain structures using a computerized segmentation procedure.

Results: PD-MCI converters had a smaller local shape volume than PD MCI non-converters in bilateral putamen, bilateral thalamus, right caudate and right hippocampus. The thalamic local shape volume was closely associated with cognitive performance of semantic fluency and attention in patients with PD-MCI converters.

Conclusions: Subcortical local shape volumes in the basal ganglia and thalamus may serve as an important predictor for the development of dementia in PD.

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White matter microstructural features of motor subtypes in de novo, drug naïve Parkinson's disease patient *M.C. Wen, H. Heng, Z. Lu, Z. Xu, L.L. Chan, E.K. Tan, L. Tan (Singapore)*

Objective: The objective of this study was to determine how white matter (WM) microstructure is altered in early tremor dominant (TD) and postural instability and gait difficulty (PIGD) subtypes of Parkinson's disease (PD) before administration of medications.

Background: One of the common classifications in PD is TD and PIGD subtypes. To date, little is known about the white matter (WM) microstructural features of the two subtypes in early drug naïve PD.

Methods: 52 TD and 13 PIGD patients with consistent subtypes at baseline and one-year follow-up and 61 wellmatched controls underwent MRI scanning at baseline. Whole-brain voxel-based morphometry (VBM) and tractbased special statistics (TBSS) were used to compare gray matter (GM) and WM features between TD, PIGD, and control groups.

Results: TD patients showed increased fractional anisotropy (FA), but decreased radial and axial diffusivities (RD and AD) in multiple projection, association, and some commissural WM tracts, compared with PIGD patients or controls. Correlating the DTI values of the significant tracts with general motor severity in PD indicated mild-to-

moderate correlations of FA and RD in the genu of the corpus callosum in TD patients, but strong correlations of FA and RD in multiple association tracts, including bilateral inferior longitudinal fasciculi, in PIGD patients. These results cannot be explained by GM changes.

Conclusions: Increased FA but decreased diffusivities in TD patients suggest neural compensation. In contrast, PIGD patients with similar disease stage and duration had more WM degradation. Findings from our study demonstrate differentiable WM features between TD and PIDG subtypes in early drug naïve PD patients.

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Writing training enhances neural connectivity in Parkinson's patients with micrographia

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Objective: To study network interactions of patients with Parkinson's disease (PD) and healthy controls (CT) during handwriting with and without external visual cues and to investigate the effect of long-term visually-cued writing training on network interactions in PD.

Background: A common motor symptom of PD is micrographia, characterized by a decrease in writing amplitude. Despite the relevance of this impairment, the underlying neural network abnormalities and the impact of training interventions on brain connectivity are mostly unknown.

Methods: We analyzed fMRI-data using dynamic causal modeling to investigate neural network dynamics of amplitude training for micrographia compared to placebo training. We also examined the effects of visual cues. At baseline, 28 patients with early PD on dopaminergic medication and 14 age-matched CTs performed a pre-writing task in the presence and absence of visual cues in the scanner. Subsequently, patients were randomized to an experimental writing training and a placebo intervention of six weeks, after which they underwent the same scanning procedure.

Results: At baseline, patients displayed weaker right visuo-parietal coupling during writing, suggesting that impaired right hemispheric visuomotor integration may contribute to micrographia. During cued writing both groups displayed stronger excitatory coupling onto the left superior parietal lobe from visual and premotor areas, largely consistent with previously identified 'external' motor control pathways. In the absence of cues, there was stronger coupling in the motor control network, with increased parieto-premotor, premotor-cerebellum and premotor-M1 connectivity. The most important results pertained to the impact of training. We found that intensive writing training propagated connectivity via the left hemispheric visuomotor stream to an increased coupling with the supplementary motor area. This pattern was not apparent in the placebo group. Interestingly, training did not lead to normalization of network interactions.

Conclusions: Our findings imply that training effects rely on the functional reserve of brain networks, which remain relatively unaffected by the disease. We conclude that in early PD experience-dependent brain reorganization remains possible in cortical networks after prolonged training and induce clinical improvement in concert with dopaminergic treatment.

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Structural brain abnormalities associated with preclinical cognitive impairment in idiopathic Parkinson's disease.

C. Lambert, O. Williams, L. Ricciardi, F. Morgante, T. Barrick, M. Edwards (London, United Kingdom) **Objective:** Using the Progressive Parkinson's Initiative (PPMI) data, clinical and structural differences between individuals destined to develop PD cognitive impairment was defined.

Background: Cognitive dysfunction in PD is often associated with disease progression. However, subtle deficits can be detected in 24% of individuals at diagnosis¹, suggesting that damage is already present.

Methods: COHORT SELECTION: Individuals with PD and a 3T T1-weighted MRI at baseline were selected and divided into three groups based on their eventual cognitive status: No dementia (PD-NON, N=207), mild cognitive impairment (PD-MCI, N=102), or dementia (PDD, N=9). IMAGE PRE-PROCESSING: The T1 weighted MRI was segmented into grey matter (GM) and white matter (WM) using SPM12 and used for voxel-based morphometry (VBM), applying a 6mm FWHM Gaussian smoothing kernel. IMAGE ANALYSIS: Structural differences were tested using a one-way ANOVA in SPM12, controlling for age, gender, handedness, years of education, TIV and study center. Significance was set at peak voxel Family Wise Error (FWE) P < 0.05. CLINICAL DATA Group differences were assessed using a Kruskal-Wallis test.

Results: CLINICAL: The PD-MCI and PDD groups were significantly older with more severe motor and non-motor symptoms (anosmia, RBD and depression). VBM: GM Widespread areas of reduced GM were observed between

PD-NON vs. PDD and PD-MCI vs. PDD, particularly in the bilateral hippocampi, primary olfactory cortex, posterior cingulate and cerebellum. Fewer abnormalities were observed between PD-NON vs. PD-MCI, and included the temporal-parietal junction and cerebellum (Figure 1). VBM: WM several areas of reduced WM were observed between PD-NON vs. PDD and PD-MCI vs. PDD, particularly in the parietal WM.



Conclusions: 1. There are no significant differences surviving multiple comparison correction in the baseline cognitive profile or disease duration between the three groups. 2. Those who develop PD-MCI or PDD are significantly older with more severe motor and non-motor symptoms (anosmia, RBD and depression). 3. The average time to MCI is no different between the PD-MCI and PDD groups. 4. Extensive grey and white matter loss is present at least three years before dementia clinically manifests in PD. 5. Abnormalities in pre-clinical PD-MCI overlap with preclinical PDD, suggesting an intermediate stage.

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Associations of DAT SPECT and TCS with prodromal features of Parkinson's disease: Results in PREDICT-PD participants

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Objective: To examine whether changes on dopamine reuptake transporter (DAT) SPECT and transcranial sonography (TCS) correlated with Parkinson's disease (PD) risk scores and other prodromal features in the PREDICT-PD study.

Background: DAT SPECT and TCS have been proposed as imaging markers of prodromal PD. PREDICT-PD aims to define a group at higher risk of PD using an algorithm comprised of risk factors and early non-motor features identified through systematic review (1). Subjects aged between 60-80 years at baseline have been tested annually since 2011, predominantly via the internet, using questionnaires (including the Rapid Eye Movement sleep Behaviour Disorder (RBD) Screening Questionnaire; RBDSQ), objective smell tests (University of Pennsylvania Smell Identification Test; UPSIT) and the BRAIN-tap test (which measures alternate finger taps in 30 seconds) (2). **Methods:** Participants in this imaging sub-study were drawn from the wider PREDICT-PD cohort (1,323 UK residents recruited at baseline and free from known neurodegenerative disease). Forty-six participants that had completed all assessments (online screening questionnaire, UPSIT, RBDSQ, BRAIN-tap test, and clinical examination using the MDS-UPDRS) underwent DAT SPECT and TCS. Linear regression was used to examine associations between imaging modalities and PD risk scores, intermediate markers of prodromal PD (i.e. UPSIT and

RBDSQ scores, and the number of alternate finger taps) and MDS-UPDRS scores. Risk was expressed as the log odds of PD.

Results: Striatal Binding Ratio (SBR) was associated with MDS-UPDRS motor scores (p=0.009), UPSIT scores (p=0.002), RBDSQ scores (p=0.024), tapping speed (p=0.024) and PD risk estimates (p=0.040). Using TCS, the size of nigral echogenic area was associated with MDS-UPDRS motor scores (p=0.027) and PD risk estimates (p<0.001), but not UPSIT, RBDSQ or tapping speed. Modeling PD risk estimates along with UPSIT, RBDSQ and finger tapping scores explained 26% of variation in SBR (r2 = 0.258), which was significantly more than any factor on its own.

Conclusions: SBR is associated with prodromal motor and non-motor features of PD, and TCS hyperechogenicity with risk estimates and motor scores. Combining assessments for risk markers may better predict those in the prodromal stages of PD.

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Altered intrinsic brain functional connectivity in drug-naïve Parkinson's disease with LRRK2 mutation *Y. Hou, C. Luo, J. Yang, R. Ou, W. Song, Y. Chen, Q. Gong, H. Shang (Chengdu, People's Republic of China)* Objective: This study aimed to compare the alterations in the cortico-striatal functional connectivity (FC) of drugnaïve Parkinson's disease (PD) patients with the leucine-rich repeat kinase 2 (*LRRK2*) mutation in the ethnic Han-Chinese PD population using voxel-based analysis of neuroimaging data.

Background: *LRRK2* has been recently identified as a causative gene of PD, with the most common mutations of R1628P and G2385R in the ethnic Han-Chinese PD population. However, the pathogenic mechanism of the *LRRK2* mutation remains largely unknown.

Methods: Resting-state fMRI was used to assess FC focusing on striatal subregions of 11 PD patients with the *LRRK2* mutation, 11 PD patients without such mutation, and 22 healthy control subjects in the ethnic Han-Chinese PD population.

Results: When compared with the healthy control subjects, both subgroups of PD patients showed alterations in FC within sensorimotor-striatal and posterior putamen-striatal circuits. However, relative to the subgroup of patients without the *LRRK2* mutation, the subgroup of patients with the *LRRK2* mutation exhibited decreased FC between putamen and bilateral superior frontal gyri, precuneus and calcarine gyri. Furthermore, the FC between putamen and bilateral superior frontal gyri decreased with age in *LRRK2* mutation carriers but not in noncarriers.

Conclusions: The differences of FC between PD patients with and without the *LRRK2* mutation may support the further research of the distinct pathological mechanism resulting from the *LRRK2* mutation in the ethnic Han-Chinese PD population. Our result is preliminary and further investigations are needed.

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Resting state functional connectivity in Parkinson's disease patients with and without freezing of gait

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Objective: To investigate resting state functional connectivity (rsFC) abnormalities in patients with Parkinson's disease (PD), either with (PD-FOG) or without freezing of gait (PD no-FOG).

Background: Patients with PD develop several gait disturbances including FOG, a common symptom that deteriorates daily mobility leading to increased risk of falls and related injuries. Pathophysiological and neuroimaging studies demonstrated abnormalities in several brain areas involved in gait inhibition in PD [1-2]. In this study, we aimed to assess possible disturbances associated with intra-network and inter-network rsFC in patients with PD, PD-FOG and PD no-FOG.

Methods: Thirty-one PD patients, (15 PD-FOG and 16 PD no-FOG), and 16 healthy subjects (HS) underwent resting-state fMRI. The preprocessing steps included high pass filtering, spatial smoothening, motion correction, and normalization. Resting-state networks (RSNs) were further extracted to evaluate the within- and between-network rsFC using Melodic and FSLNets software packages. Group level differences were reported after correcting for multiple comparisons at p<0.05.

Results: PD patients, both PD-FOG and PD no-FOG groups, showed higher within-network rsFC than HS [figure1]. A larger number of RSNs was involved in PD-FOG, both when compared to HS [figure2] and to PD no-FOG [figure3]. PD no-FOG did not show increased rsFC in any of the RSNs relative to PD-FOG. With respect to HS, the between-network rsFC among the anterior default mode network and sensory motor network decreased in PD as well as PD-FOG and PD no-FOG groups considered separately. Furthermore, PD-FOG showed increased rsFC

between salience and auditory network as well as decreased rsFC between executive control network and right frontoparietal network compared with HS [figure4].



Figure 1: Increased within-network functional connectivity in PD patients than in HS. *Yellow* indicate the components derived from whole group of participants; *Blue* represents increases in PD patients compared with HS. pDMN = posterior default mode network; OVN = occipital visual Network; SMN = sensory motor network; ISMN = left sensorimotor network; rSMN = right sensorimotor network; CBN = cerebellar network; OFN = orbitofrontal network; FN = frontal network; BGN = basal ganglia network



Figure 2: Increased within-network functional connectivity in PD-FOG patients than in HS. *Yellow* indicate the components derived from whole group of participants; *red* represents increases in PD-FOG patients compared with HS. pDMN = posterior default mode network; 1FPN = left fronto-parietal network; OVN = occipital visual network; SMN = sensory motor network; aDMN = anterior default mode network; ISMN = left sensorimotor network; rSMN = right sensorimotor network; SN = salience network; CBN = cerebellar network; OFN = orbitofrontal network; FN = frontal network; BGN = basal ganglia network



Figure3: Increased within-network functional connectivity in PD-FOG than in PD no-FOG. Yellow indicate the components derived from whole group of participants; green represent increases in PD-FOG patients compared with PD no-FOG patients. IFPN = left frontoparietal network; INS = insular network; SMN = sensory motor network; OFN = orbitofrontal network; FN = frontal network; BGN = basal ganglia network



Figure 4: Matrix of partial correlation of 18 RSNs time courses. Images at the top represent between-network correlation maps in PD patients; PD-FOG; PD no-FOG and healthy subjects (HS); images at the bottom represent the t-test values when the patient groups were compared with HS. Stars represent significant differences in between-network connectivity after group comparisons; red and blue squares represent increased and decreased between-network rsFC, respectively; pIDMN = posterior default mode network; rFPN = right frontoparietal network; IFPN = left frontoparietal network; IFPN = left frontoparietal network; ISN = insular network; OVN = occipital visual network; MVN = medial visual network; ECN = executive control network; SMN = sensory motor network; aDMN = anterior default mode network; ISMN = left sensorimotor network; AN = auditory network; rSMN = right sensorimotor network; SN = salience network; CBN = cerebellar network; OFN = orbitofrontal network; FN = frontal network; BGN = basal ganglia network

Conclusions: The within- and between-network findings clearly indicate a functional brain reorganization occurring in PD patients, with more severe abnormalities in PD-FOG compared with PD no-FOG. Decreased betweennetwork rsFC between default mode network and sensory motor network in PD-FOG as well as in PD no-FOG may represent the functional substrate underlying motor and cognitive impairment in PD patients. Altered rsFC between salience and auditory network as well as between executive control network and right frontoparietal network may represent a specific pattern of rsFC in PD-FOG.

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Longitudinal comparison of 11C-PE2I and 18F-DOPA PET for assessing severity and rate of disease progression in patients with Parkinson's disease

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Objective: To directly compare 18F-DOPA with a highly specific dopamine transporter radioligand 11C-PE2I, for the assessment of motor severity and rate of progression in Parkinson's disease (PD).

Background: 18F-DOPA positron emission tomography (PET) is considered the 'gold standard' for measuring the integrity of dopaminergic function in PD. However, 18F-DOPA metabolism in non-dopaminergic neurons and disease-related compensatory upregulation of amino acid decarboxylase (AADC) may result in underestimation of dopamine cell loss.

Methods: Thirty-three mild-moderate PD patients underwent PET at baseline (Age= 55.1 ± 7.0 ; Duration= 5.9 ± 2.2); twenty-three were followed-up at 19.4 ± 3.3 m (Age= 56.8 ± 7.1 ; Duration= 7.2 ± 2.0). Striatal 18F-DOPA Ki and 11C-PE2I BPND were quantified using Patlak graphical method (t*=30) and simplified reference tissue model respectively, with cerebellar reference.

Results: Standard multiple regression at baseline indicated that 11C-PE2I BPND significantly predicted total UPDRS-III (β =-0.474, p<0.05) and bradykinesia scores (β =-0.610, p<0.01), whereas 18F-DOPA Ki did not significantly contribute to either model. Voxel-wise analysis revealed large clusters showing negative correlation between 11C-PE2I BPND and motor severity extending across putamen, caudate and ventral striatum bilaterally. 18F-DOPA Ki voxel-wise analysis revealed smaller clusters restricted to most affected putamen and caudate.

Longitudinally, significant negative correlations were found between striatal ?11C-PE2I BPND, ?UPDRS-III [rs(21)=-0.43, p=0.040] and ?bradykinesia [rs(21)=-0.44, p=0.035]. No associations were found between ?18F-DOPA Ki, ?UPDRS-III [rs(21)=-0.053, p=0.81] and ?bradykinesia [rs(21)=0.026, p=0.91].

Conclusions: Results suggest striatal DAT is more closely associated with clinical severity and rate of disease progression than AADC and 18F-DOPA-derived measures of striatal dopamine storage capacity. 11C-PE2I PET may be useful for objectively evaluating efficacy of neuroprotective treatments in PD.

1494

Serotonin-to-dopamine transporter ratios in Parkinson's dyskinesias: The longitudinal study

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Objective: This study was designed to detect whether in Parkinson's disease (PD) the putaminal serotonin–over–dopamine transporter ratio has a threshold that is critical for the development of levodopa–induced–dyskinesias (LIDs).

Background: Serotonergic terminals play an important role in LIDs. Both an increased SERT–over–DAT terminal ratio in the putamen and longer disease duration have been proposed to be risk factors for the appearance of dyskinesias in PD patients treated with levodopa. Nonetheless, it remains unclear whether there is a critical threshold in the terminal ratio for the appearance of dyskinesias.

Methods: PET imaging with 5[11C]-3-amino-4-(2-dimethylaminomethylphenyl-sulfanyl)-benzonitrile (11C–DASB), and [11C]N-(3-iodoprop-2E-enyl)-2ß-carbomethoxy-3ß-(4-methyl-phenyl)nortropane (11C–PE2I), which are specific *in vivo* markers of the serotonin (SERT) and dopamine transporter (DAT), were used to assess the SERT–to–DAT terminal ratio. We studied 17 PD patients with stable response to levodopa and 7 PD patients with LIDs. Of the 17 stable patients, 12 were followed up clinically and had repeated 11C–DASB and 11C–PE2I PET imaging after 17 months. We analysed PET data using the simplified reference tissue model and cerebellum as the reference region. 11C–DASB–to–11C–PE2I binding ratios were calculated for the putamen.

Results: At baseline, and in line with previous studies, the PD patients with LIDs (N=7) had higher SERT-to-DAT ratios (mean= 0.99 ± 0.02) as compared to the non-dyskinetic patients (N=17) (0.74 ± 0.01 ; p<0.001). At follow-up, 3 of the 12 stable patients had developed LIDs. Each of these 3 patients had a putaminal SERT-to-DAT ratio that was within the range of the group of patients who were dyskinetic (N=7) at baseline (range: 0.85-1.25). **Conclusions:** Our findings suggest that the SERT-over-DAT putaminal ratio may have a threshold value of 0.85, above which PD patients treated with levodopa are likely to be dyskinetic.

1495

18F-AV-1451 PET imaging in pre-dementia Parkinson's disease

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Background: The radioligand 18F-AV-1451 binds tau protein, primarily in the form of paired helical filaments, which is present in increasing amounts in Alzheimer's disease from pre-dementia stages until death. In varying degrees, 18F-AV-1451 also binds to pathological tau in Parkinson's disease dementia and dementia with Lewy bodies; to straight tau filaments seen in progressive supranuclear palsy and corticobasal degeneration; and to neuromelanin-containing cells in the substantia nigra. We previously demonstrated decreased 18F-AV-1451 binding in the substantia nigra of patients with Parkinson's disease, thought to reflect loss of neuromelanin-containing dopaminergic neurons.

Methods: Twenty-six Parkinson's disease patients and 24 healthy age-matched controls had 18F-AV-1451 positron emission tomography (PET) and most Parkinson's disease patients also had dopamine transporter imaging, using 123I-FP-CIT. Neuropsychological evaluation as recommended by Litvan et al. was performed to detect the presence of PD-MCI. Voxel-wise comparisons between groups were conducted using SPM12. Regional analysis of 18F-AV-1451 PET was performed using PMOD, and regional analysis of dopamine transporter imaging was performed using Hermes BRASS.

Results: Nine Parkinson's disease patients were identified as PD-MCI and 17 as PD-nonMCI. Using 18F-AV-1451, no significant differences between groups were found in cortical areas. In the substantia nigra, PD-nonMCI patients displayed significantly lower 18F-AV-1451 signal than healthy controls, and PD-MCI patients had even lower signal than PD-nonMCI. No differences were found in other sub-cortical areas using 18F-AV-1451. Voxel-wise analysis of 18F-AV-1451 PET uptake failed to reveal any differences surviving family-wise error correction.

Comparing PD-MCI and PD-nonMCI using dopamine transporter imaging, PD-MCI patients were found to have a significant decrease of presynaptic dopamine transporter density in the combined striatae.

Conclusions: Our results indicate that cortical binding of the tau radioligand 18F-AV-1451 is rare in pre-dementia Parkinson's disease. However, lower 18F-AV-1451 signal of the substantia nigra likely reflects progression of nigrostriatal dysfunction in PD-MCI compared to PD-nonMCI.

1496

SPECT imaging of striatal DAT availability in Parkinson's disease: Changes over time and relevance to dyskinesias

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Objective: This study was designed to explore in Parkinson's disease (PD) the role of dopamine transporter (DAT)-specific single photon emission computed tomography (SPECT) imaging as a prognostic marker of levodopa-induced dyskinesias (LIDs).

Background: As PD progresses, the density of the DAT in the striatal dopaminergic terminals continues to decline, while patients with PD are at risk for developing LIDs.

Methods: We retrospectively selected 42 PD patients who underwent SPECT imaging with 123I-Ioflupane (DAT-specific *in vivo* marker) approximately five years ago during the diagnosis of PD.Fifteen patients of the 42, were rescanned with 123I-Ioflupane SPECT 6.3 ± 3.0 years after their first scan. We divided the PD patients according to the presence or absence of dyskinesias as LIDs and non-LIDs. SPECT data were analysed for the putamen by a semi-quantification approach using the occipital cortex as a reference.

Results: Ten PD patients had developed LIDs, while 32 were non-dyskinetic. The putaminal mean 123I-Ioflupane uptake in the LIDs (1.7 ± 0.4) group was not statistically different as compared to the non-LIDs group $(1.7\pm0.5; p>010)$. All 15 PD patients who had a second SPECT scan had significant reductions in the putaminal 123I-Ioflupane uptake (p<0.001) as compared to the first scan. Within the group of 15, the LIDs (N=8) had significantly lower DAT uptake (1.1±0.3) as compared to the non-LIDs group (N=7); (1.5±0.5; p<0.05).

Conclusions: 123I-Ioflupane SPECT imaging in *de novo* PD, cannot predict the onset of LIDs within five years from diagnosis. As shown in the subgroup that repeated 123I-Ioflupane SPECT imaging, an onset of LIDs may be linked to a faster decline of putaminal DAT availability.

1498

Multicenter validation of disease- related Parkinson's disease pattern with resting state functional MRI

K. Schindlbeck, A. Vo, Y. Ma, S. Peng, K. Poston, H. Hurtig, N. Dahodwala, D. Eidelberg (Manhasset, NY, USA) **Objective:** To validate Parkinson's Disease-related network topography characterized with resting-state functional MRI (rs-fMRI) in two multicenter based cohorts of idiopathic Parkinson's disease (IPD) patients.

Background: We recently developed a novel method, using independent component analysis in conjunction with bootstrap resampling to characterize specific network topographies associated with IPD (Vo et al, 2016). The functional PD-related pattern (fPDRP) discriminated normal controls (NC) from IPD patients and showed a similar topography compared to the previously characterized pattern identified using metabolic PET imaging.

Methods: We studied two independent cohorts of IPD patients of three different sites (Center(C) 1 Northshore University Hospital, C2 University of Stanford & Pennsylvania) and NC subjects with rs-fMRI in a medication-free (off) state. Subject scores and temporal dynamics were estimated for prospective cases with dual regression using the spatial maps generated from the derivation set (Vo et al, 2016). Individual values were z-scored with respect to corresponding values from the healthy control group. Motor symptoms were assessed in all IPD subjects using the Unified Parkinson's Disease Rating Scale (UPDRS).

Results: We scanned 30 IPD patients, divided into two different cohorts (C1 n=19, C2 n=11), and 18 age- and gender matched healthy controls. Expression values for fPDRP were significantly elevated in both testing cohorts (C1 p<0.001; C2 p=0.02) compared to normal controls (Figure 1). Subject scores correlated with subscale ratings for akinesia-rigidity (r=0.47, p<0.002) but not tremor (r=0.14, p=0.51) in this multicenter testing cohort (Figure 2).



Conclusions: Our findings reveal that fPDRP represents a replicable imaging marker across independent multicenter cohorts of IPD patients. These results provide further support for the stability of the fPDRP topography as well as the consistency of its relationship to motor symptoms across different patient populations.

1500

A neuroimaging-based model for disease progression in Parkinson's disease

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Objective: We model the rate of disease progression over 4 years in subjects with Parkinson's disease based on neuroimaging features acquired at baseline.

Background: DaTSCAN is a radiotracer with high affinity for the presynaptic dopamine transporter (DAT) in the striatum. The putamen binding ratio (PBR) is the ratio of the tracer uptake between the putamen and the reference region (the occipital cortex). We use PBR data from 95 PD subjects from the PPMI database that have completed scans at baseline (year 0) and at years 1, 2 and 4. At baseline, PBR values were found to be significantly correlated with UPDRS motor score (Figure 1).



Figure 1. Cross-sectional correlation of the of the PBRs and the motor score (measured at baseline). The motor score is split into (better side + common) and (worse side + common) and correlated with the corresponding imaging side. The Spearman rho correlation was computed.

Methods: A hierarchical model is fitted to estimate the rate of progression as estimated by the change in PBR values. Our assumption is that the imaging data would contain relevant and objective information on disease progression as related to dopaminergic deficit. We identify the following image features, <u>all measured at baseline</u>: 1) PBR values for the more and less affected sides, 2) difference between the PBR values of the better and worse sides, and 3) difference between the putamen and caudate binding ratios (PBR – CBR). The model parameters were obtained in a training phase using a subset of the data. Next, the predicted yearly change of the PBR is estimated for each subject based on the baseline image features only and the estimated model parameters. This yearly change is used to predict the PBR at years 1, 2 and 4 (see Figure 2 for examples). The model is applied separately to the better and to the worse sides of the putamen. Cross-validation (5 folds) was used to estimate the error rate for year-4 PBR predictions.



Figure 2. Examples of the measured PBR values (red points) and the predicted progression (green band) for two subjects in the study.

The model predicts the yearly change in PBR which is the slope of the green band in the figure. Only baseline imaging metrics are used to estimate the slope for the next 4 years.

Results: The median error for year-4 predictions is 18% for the better side and 24% for the worse side (Figure 3) and smaller errors were observed at years 1 and 2. The most important image feature for predicting the progression is the PBR value at baseline. The best predictor is obtained using the better side with the baseline PBR values (p < 0.001) and the PBR difference between the better and worse (p < 0.01). The (PBR – CBR) term is not significant.



Figure 3. Comparing predicted values and measured values for the year-4 PBRs. Left: better side $R^2 = 0.53$, Median error = 18% Right: worse side $R^2 = 0.34$, Median error = 24%

Conclusions: A model is developed that predicts disease progression over 4 years as quantified by PBR values with 18% accuracy. In addition to baseline PBR values, this model includes the feature reflecting the side-to-side asymmetry. Such asymmetry is known to be a function of disease manifestation and progression.

1502

Serotonergic, dopaminergic disruptions and related non-motor features throughout the course of Parkinson's disease: a transversal pet study

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Objective: To explore the progression of DA and 5-HT lesions during the course of Parkinson's disease (PD) and their respective contribution to the pathogenesis of neuropsychiatric signs.

Background: Many evidences suggest a disruption of several neurotransmitters in PD, beyond the dopaminergic (DA) one (1). A link between serotonergic (5-HT) alteration and occurrence of neuropsychiatric symptoms has been especially highlighted, from the early stages of disease (2). However, the respective evolution of DA and 5-HT lesions in PD course, as well as their specific role in related symptomatology, had never been simultaneously explored. Our aim was therefore to fill this gap by combining clinical and Positron Emission Tomography (PET) imaging approaches.

Methods: Sixty PD patients, i.e., 30 drug-free *de novo* patients (less than 2 year-disease duration), 15 mid-stage patients (4-7 year-disease duration), and 15 advanced patients (8-10 year-disease duration), as well as fifteen agematched healthy controls, were enrolled. Fifteen *de novo* patients specifically presented apathy (LARS score = -21). All subjects underwent detailed neurological and neuropsychological assessments, as well as two PET-scans using DAT and SERT transporters ligands ([11C]-PE2I and [11C]-DASB, respectively). Voxel-based approach was used to compare DA and 5-HT innervation between groups and to explore correlations with neuropsychiatric signs. **Results:** All patients exhibited DA disruption in the nigrostriatal pathway, relative to controls. DA lesions were more pronounced in caudate nuclei in *de novo* apathetic patients and in more advanced ones. PD-group comparisons revealed worsening of DA depletion in the nigrostriatal projection targeting the posterior striatum (putamen) and pallidum with PD progression. The 5-HT system was also impacted by PD evolution, affecting progressively and widely the meso-cortical areas, thalamus and striatum. Interestingly, *de novo* apathetic patients elicited a 5-HT denervation pattern close to those of moderate-to-advanced ones [*Figure*]. Our data moreover suggest a link between the severity of anxiety and a 5-HT disruption in the subgenual ACC. The degree of fatigue was related to combined DA and 5-HT lesions in several cortical limbic areas.



Brain distribution of the dopaminergic ([11C]-PE2I) (*left panel*) and the serotonergic ([11C]-DASB) (*right panel*) tracers among the control group (line 1), the *de novo* non-apathetic PD patient group (line 2), the *de novo* apathetic PD patient group (line 3), the moderate PD patient group (line 4), and the advanced PD patient group (line 5).

Conclusions: These findings highlight progressive combined DA and 5-HT disruption in PD, which correlates with neuropsychiatric manifestations.

1503

Utility of susceptibility weighted imaging in the objective diagnosis of idiopathic Parkinson's disease: Is DaTscan necessary?

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Objective: To assess the utility of susceptibility weighted imaging (SWI) in the diagnosis of idiopathic Parkinson's disease (IPD) from the movement disorders clinics at the Walton Centre, UK.

Background: The hallmark pathological manifestation of IPD is the deposition of Lewy bodies and loss of striatal dopaminergic neurons of the substantia nigra (SN). Damier *et al* described patterns of dopamine-containing neuron loss in 5 compartments within the SN, the main of which is nigrosome-1. Maximal cell loss occurs in nigrosome-1 and has been identified as a potential pathoanatomical correlate of IPD pathology on susceptibility-weighted 3T magnetic resonance imaging. It is proposed that absence of normal nigrosome-1 signal on 3T MR SWI has a high sensitivity and specificity for IPD.

Methods: Twenty-one PD patients who met the UK PDS Brain Bank criteria for IPD were identified who had undergone 3T SWI MRI in our unit. A neuroradiologist, blinded to the clinical details, reviewed the imaging to

determine the presence or absence of the nigrosome-1 complex on each side. This data was correlated against the clinical presentation.

Results: Four scans were excluded due to unacceptable movement artefact, so 17 scans were analysed. The median interval between symptom onset and imaging was 12 months. Eighty-eight and two tenths percent demonstrated abnormal nigrosome-1 complexes on SWI MRI. Of the abnormal scans 52.9% had absent nigrosome-1 complexes bilaterally, whilst the rest demonstrated unilateral changes. There was not a correlation between the clinically most affected side and the absence of the contralateral nigrosome-1 complex.

Conclusions: These findings support those reported in the current literature. SWI MRI has the potential to provide objective imaging support in the diagnosis of IPD. Advantageously this imaging modality does not carry the potential risks associated with DaTScan and is often more readily available. However, further studies are required to assess the use of this imaging modality in the diagnosis of IPD. We propose a matched case-control study against normal controls and 'Parkinson-Plus' disorders to determine the sensitivity and specificity for idiopathic PD. A longitudinal study of serial SWI MRI in an 'at-risk' population, such as REM-sleep disorder patients, could help establish whether the imaging changes are present in the pre-motor stages and whether they have value in predicting the development of IPD.

1504

Brain structural and functional changes associated with frequent falls in Parkinson's disease

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Objective: We investigated brain structural and functional changes associated with falls.

Background: Gait and balance disorders are one of the common clinical features of Parkinson's disease (PD) and falls in PD have great impact on patient's activity of daily living (ADL) and quality of life (QOL).

Methods: We recruited 91 PD patients (38 men and 53 women, age 69.0 ± 8.8 , Hoehn-Yahr (H-Y) 2.9 ± 1.0) admitted to our hospital. In addition to background characteristics, we evaluated gait and balance ability, motor symptom, and cognitive function. As an imaging analysis, we obtained 3D T1-weighted images of all patients and resting state functional MRI data of 58 patients using 3 Tesla MRI scanner (GE Healthcare). We performed VBM analysis using Statistical Parametric Mapping 8 (SPM8) and compared the gray matter volume of the patients with and without falls. We included age, gender, H-Y stage, MDS-UPDRS part 3, and freezing severity as covariates. We also investigated functional connectivity alterations using the CONN-fMRI Functional Connectivity toolbox v16 (http://www.nitrc.org/projects/conn).

Results: Among 91 patients, 55 patients had experienced falls. There were significant differences in clinical measures between patients with and without falls, including severity of freezing of gait, disease duration, MDS-UPDRS part 1, part 2, part 3, part 4, Berg Balance Scale, Frontal Assessment Battery, and Hamilton rating scale for depression. In patients with falls, significant gray matter volume reduction by the VBM analysis controlling several confounding factors in the right supra temporal gyrus (STG) and the right inferior parietal lobule (IPL). Resting state fMRI analysis showed decreased functional connectivity among the right posterior perisylvian region including IPL and STG, bil. Pallidum, and bil. supplementary motor area.

Conclusions: These findings suggested that the impaired brain network including the right IPL, STG, and bil basal ganglia is associated with frequent falls. Considering the suggested function of the right IPL, STG, impaired sensory integration and visuospatial attention might associate with the frequent falls in PD. Although future studies would be needed, above-mentioned cortical areas might be future therapeutic targets in neuromodulative intervention for fall prevention.

1506

The effect of expectation on Parkinson's disease: An EEG study

E. Carlino, A. Piedimonte, G. Guerra, A. Romagnolo, E. Frisaldi, S. Vighetti, L. Lopiano (Turin, Italy) **Objective:** The aim of the present study is to determine how the expectation of receiving a therapeutic treatment influences Parkinson's disease (PD) symptoms.

Background: The placebo effect can be observed in different medical conditions, including PD. In particular, it has been shown that the expectation of receiving an anti-parkinsonian drug produces clinical benefits similar to real treatments. Moreover, after previous exposures to effective treatments, the administration of a placebo produces robust clinical improvements. In the present study we investigated the influence of positive expectations on different outcome measures. Beside the traditional clinical outcome, we investigated two common problems in PD patients: perceived fatigue and difficulties in motor preparation.

Methods: Thirty-eight PD patients were recruited for the study. They were asked to lift a load with their index finger and to repeat the movement until exhaustion in two different conditions: an OFF condition (without L-Dopa) and an ON condition (with L-Dopa). Patients were randomly assigned to two different groups: 100% group or 50% group, based on the percentage of L-Dopa received. Patients in 100% group received their standard L-Dopa dose, whereas patients in the 50% group received the 50% of their standard dose. Both groups were informed that they would have received their standard daily dose of L-Dopa, in order to induce the expectation of clinical and motor improvement. Different motor and clinical parameters have been recorded. EEG has been used to measure the Readiness Potential (RP), an event-related potential involved in motor preparation and influenced by fatigue. Number of repetitions and rate of perceived exertion were recorded to assess the motor improvement. Clinical symptoms were assessed using the UPDRS.

Results: In the ON condition, we found that the 100% group improved in both clinical and motor parameters (decrease in perceived fatigue, increase of motor repetitions and reduction of RP amplitude). The same results were obtained in the 50% group. More importantly, no significant differences between groups were observed. **Conclusions:** These data indicate that expectations and previous experiences plays a crucial role in placebo responsiveness. This study opens important clinical implications, such as the possibility to reduce L-dopa intake alternating drugs with placebos, maintaining a good clinical condition during the standard PD treatment.

1507

Decreased fronto-parietal connection is associated with face pareidolia in Parkinson's disease.

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Objective: To investigate the neural mechanism of face pareidolia in Parkinson's disease (PD) patients using resting state functional magnetic resonance imaging (rs-fMRI).

Background: Face pareidolia is a complex visual illusion in which one perceives an ambiguous non-human object as a face. Although face pareidolia may occur in healthy subjects, previous studies reported PD patients experience it much frequently. However, neural mechanism and clinical relevance of pareidolia is unclear.

Methods: Seventy-six PD patients who admitted to Osaka University hospital from Sep. 2015 to Nov. 2016 were included to this study. All patients underwent clinical evaluations including MDS-UPDRS (part1-4), MMSE, FAB, MoCA, Benton judgement of line orientation test, and the Pareidolia test. In the Pareidolia test, patients who experienced at least one pareidolic response were considered as pareidolia-positive, and the rest were considered as pareidorlia-negative. All patients also underwent MR scans including rs-fMRI by using 3-T magnetic resonance scanner (GE Medical Systems, WI). Resting Functional connectivity analyses were performed by using the CONN-fMRI Functional Connectivity toolbox v17. Local ethical committee approved this study and written informed consent was obtained from all participants.

Results: Thirty-five patients were pareidolia-positive, and forty-one were pareidolia-negative. Pareidolia-positives were older and worse in cognitive status than pareidolia-negatives. ROI based analysis revealed left-dominant decreased functional connectivity in bilateral fronto-parietal networks, including left frontal operculum cortex (FO) and left superior parietal lobule (SPL), bilateral superior temporal gyrus and left temporo-parietal junction (TPJ). Seed based analysis using left FO as seed also revealed the decreased connectivity between left FO and both left SPL and left TPJ.

Conclusions: Because of its importance for social activity, previous researches has emphasized the fast and sensitive nature of face-recognition network, which could lead to pareidolic reaction. Considering previous findings revealing SPL role in visual attentional control and TPJ role in detecting salient visual stimulus, our findings may suggest that top-down attentional modulation to visual processing pathway via fronto-parietal network involved in pareidolic reaction, and impaired appropriate modulation may lead to frequent face pareidolia in PD.

1509

Neural correlates of minor hallucinations in Parkinson's disease: A multimodal imaging study

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Objective: To explore the neural correlates sub-serving isolated minor hallucinations in Parkinson's disease (PD) through a multimodal structural and functional neuroimaging approach based on grey matter volume (GMV) voxel-based morphometry (VBM) and resting-state fMRI (rs-fMRI).

Background: Minor hallucinations are a frequent symptom in PD. They occur in up to 50% of patients and can evolve into well-structured hallucinations as disease progresses [1]. Isolated minor hallucinations in PD have been

associated with structural changes in the dorsal visual pathway in a single study using voxel-based morphometry [2]. However the neuroanatomical substrate of minor hallucinations remains poorly understood.

Methods: We studied a sample of 14 non-demented PD patients, with (PDmH, n = 7) and without (n = 7) minor hallucinations, matched by age, education, medication and cognition. Participants underwent (i) clinical and neuropsychological assessment; (ii) MRI scan using whole-brain VBM; and (iii) rs-fMRI seed-to-whole brain techniques. We compared GMV and functional connectivity relative to precuneus in both groups. Significance was set at p<0.005; k=50.

Results: Minor hallucinations were associated with GMV loss in dorsal and ventral visual pathways and in frontal areas [figure 1]. In the PDmH group, increased functional connectivity was found between precuneus and (i) dorsal and ventral visual pathways (superior parietal lobe, fusiform, lingual and inferior temporal gyrus); (ii) sensory processing transmodal areas (supramarginal gyrus, insula, superior temporal pole); and (iii) dorsal attention network (dorsolateral prefrontal cortex, intraparietal sulcus) [figure 2]. Conversely, decreased functional connectivity was found between precuneus and ventral attention network (anterior cingulate cortex, superior frontal gyrus) [figure 3].





Conclusions: Minor hallucinations are associated with structural and functional changes in sensory processing areas and attention networks. In addition to volume loss in both visual pathways, PDmH showed an increased functional connectivity between precuneus and posterior cortical regions (visuoperceptive integration areas and dorsal attention network) and decreased functional connectivity between precuneus and distant brain regions of ventral attention network.

1514

In vivo mapping of nigro-striatal dopamine transporter (DAT) availability in early Parkinson's disease patients using [18F]FE-PE2I and high-resolution positron emission tomography.

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Objective: The objective of the present work was to evaluate *in vivo* with high resolution positron emission tomography (PET), the relative loss of the dopamine transporter (DAT) in the axonal terminals as compared with the cell bodies and axons, in early stages of Parkinson's disease (PD).

Background: DAT is enriched in nigrostriatal dopaminergic neuron and it regulates the dopamine-related signaling. To date the nigrostriatal terminals in the striatum have been the main target for DAT imaging in early stages of PD (1). DAT is enriched at the level of the striatal terminals and on cell bodies of dopaminergic neurons in the substantia nigra but also in dendritic and axonal plasma membranes (2).

Methods: Nineteen PD patients (14M/5F, 61.8±8.4y, disease duration 2.9±2.6y; UPDRS-m: 19.4±6.5) and 14 control subjects (CS) (12M/2F, 60.6±6.8y) underwent PET measurements with the DAT radioligand ¹⁸F-FE-PE2I using the high resolution research tomography (HRRT) system. Voxel-based BP_{ND} maps were generated for all subjects (fig.1). Template-based regions of interest (ROIs) based on DAT binding pattern and anatomical information from MRI were first delineated for the substantia nigra (SN), the striatum (STR) and for the nigro-striatal (NST), nigro-pallidal (NPT) and nigro-thalamic (NTT) tracts. The ROIs were then applied to each parametric image to obtain individual BP_{ND} estimates. Differences between groups were assessed with unpaired t-test (p<0.05) and by calculating the effect size (Cohen's *d*).

Results: In PD patients, significantly lower BP_{ND} values compared with CS (p<0.001) were observed in STR (1.7±0.7 vs 4.0±0.5) and SN (0.6±0.1 vs 0.8±0.1). No statistically significant differences of DAT availability between groups were measured along the tracts (PD: 0.41±0.1, CS: 0.44±0.1). Cohen's *d* between groups (PD vs HC) were larger for the STR (3.2), moderate for the SN (1.8) and small for the tracts (0.2).



Fig.1 High resolution binding potentials maps (BP_{ND}) of DAT availabilities (Axial and coronal views) in two representative subjects: PD patient (lower panel) and healthy control (upper panel).

Conclusions: The findings of this study demonstrate that in early PD DAT availability is mainly decreased in the striatal terminals and to a much lower degree at the level of the cell bodies in the SN and preserved along the tracts. These results confirm earlier reports from post-mortem studies suggesting that in early PD a large proportion of dopaminergic neurons in the SN are still viable.

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Non-motor symptoms in Parkinson's disease and putamen dopamine transporter uptake (DaTscan) uptake: A survey of 85 patients

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Objective: We addressed association between 30 non-motor symptoms (NMS) (using the validated Parkinson's disease (PD) NMS Scale (NMSS)), and DaTscan putamen uptake ratios as part of a large-scale multicentre naturalistic NMS study.

Background: NMS in PD are heterogeneous and have been proposed to have both dopaminergic and nondopaminergic pathophysiology. Pre-synaptic striatal dopamine transporter (DaTscan) may thus provide a surrogate marker for some dopaminergic NMS.

Methods: Data was collected from the UK arm of the NMS International Longitudinal Study (NILS, UKCRN No 10084), 85 PD patients who had undergone a battery of motor and non-motor assessments as well as DaTscan (¹²³I FP-CIT, Ioflupane) imaging were analysed. Association between NMS and DaTscan uptake was calculated using Spearman's rank correlation.

Results: PD patients (71.8% male, mean age 62.05 ± 12.05 years, mean disease duration 3.28 ± 3.43 years, age of PD onset 58.77±12.27 years) had a mean NMSS total score of 50.35 ± 40.62 and a mean NMS Questionnaire total score of 7.44 ± 6.51 . NMS and DaTscan putamen uptake correlation was statistically significant for visual hallucinations, delusions, dribbling of saliva, and olfaction (table 1). NMS burden and DaT uptake had a "very weak" correlation (right putamen r=-0.191, p=0.080; left putamen r=-0.231, p=0.033).

Table 1: Association	Right Putame n	Left Putame n
NMS1 Orthostatic hypotention	0.147	0.098
NMS2 Blackout	-0.209	-0.202
NMS3 Daytime sleepiness	-0.073	-0.147
NMS4 fatigue	-0.147	-0.146
NMS5 Difficulty sleeping	0.204	0.044
NMS6 restless legs	-0.016	-0.148
NMS7 Loss of interest	-0.131	-0.101
NMS8 lack motivation	-0.201	-0.181
NMS9 nervous	-0.080	-0.024
NMS10 Depressed	-0.006	0.089
NMS11 Flat moods	-0.051	-0.143
NMS12 pleasure problems	-0.035	0.029
NMS13 visual hallucinations	-0.238	-0.287*
NMS14 Delusions	-0.230 ⁺	-0.203
NMS15 double vision	-0.022	-0.137
NMS16 Concentration problems	-0.108	-0.167
NMS17 Short-term memory problems	-0.011	-0.111
NMS18 Memory problems	-0.042	-0.058
NMS19 Dribbling of saliva	-0.264*	-0.253
NMS20 Swallowing difficulty	-0.119	-0.161
NMS21 Constipation	-0.138	-0.202
NMS22 Urinary urgency	-0.099	-0.156
NMS23 Urinary frequency	-0.044	-0.036
NMS24 Nocturia	-0.018	-0.056
NMS25 Altered sex interest	0.082	-0.032
NMS26 Problems having sex	-0.056	-0.023
NMS27 Pain	0.023	0.007
NMS28 Olfactory changes	-0.362	-0.151
NMS29 Weight change	-0.102	-0.049
NMS30 Excessive sweating	-0.127	-0.122
NMSS Total	-0.154	-0.213

Conclusions: Although a minority of 30 NMS and NMS burden do correlate with striatal DaT scan uptake, the association if very weak and largely not significant. This suggests that the dominant pathophysiology of NMS is predominantly non-dopaminergic.

Longitudinal cortical thickness changes in Gba-positive relative to gba-negative Parkinson's disease patients with hemiparkinsonism

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Objective: This study investigated the longitudinal changes of the cortical grey matter in Parkinson's disease (PD) patients with hemiparkinsonism, with (GBA-positive) and without (GBA-negative) glucocerebrosidase gene (GBA) mutations.

Background: GBA mutations are the greatest genetic cause of PD. Compared with noncarriers, heterozygous GBA-PD patients are characterized by an earlier age-of-onset, a better response to L-Dopa and an increased likelihood to experience cognitive symptoms, neuropsychiatric disturbances, and autonomic dysfunction.

Methods: Eleven GBA-positive PD patients with hemiparkinsonism (Hoehn and Yahr 1.0 or 1.5) were compared with 24 GBA-negative PD patients matched for age, sex, disease duration and severity. Patients underwent clinical and neuropsychological evaluations and MRI scans at baseline and once a year for 3 years. Twenty-five healthy controls underwent evaluations at baseline. The pattern of cortical thinning was investigated in PD patients relative to healthy controls at baseline. Longitudinal cortical changes were assessed in the GBA-positive and GBA-negative PD patients.

Results: At baseline, GBA-positive PD patients showed a greater left side predominant cortical atrophy in motor, frontal, temporal and occipital areas relative to both healthy controls and GBA-negative subjects matched for disease duration and severity. Overtime, the GBA-negative group showed a higher rate of cortical thinning relative to GBA-positive patients; however, the pattern of cortical thinning in GBA-negative cases did not reach the severity shown by GBA-positive patients after 3 years.

Conclusions: GBA-positive PD patients showed a greater and earlier cortical thinning relative to GBA-negative cases with the same disease duration and severity.

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Cognitive changes and cortical thinning evolution of Parkinson's disease patients: 4-year-follow up

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Objective: The aim of the study was to investigate differences in the progression of cognitive decline and cortical thinning evolution in Parkinson's disease (PD) patients compared to healthy controls (HC).

Background: Although PD is a degenerative illness, changes over time in cognition are mild. Longitudinal studies have reported impairment in speed of processing, memory and verbal fluency. Cortical changes related to cognitive decline have been poorly investigated.

Methods: Forty-four PD patients and 22 HC underwent neuropsychological and magnetic resonance imaging assessment (scan interval μ =45.7 months). Repeated measures ANOVA were performed from adjusted *z*-scores. Patients were classified as having mild cognitive impairment (MCI) according to recent diagnostic criteria. FreeSurfer software was used for cortical thickness analyzes and results were corrected for multiple comparisons using pre-cached cluster-wise Monte Carlo simulation with 10,000 iterations. Reported cortical regions reached corrected significance level of p < 0.05.

Results: There were significant interactions group per time in Trail Making Test Part A (F=4.533; p=.037), Symbol Digit Modalities Test (F=8.313; p=.005), delayed recognition from Rey's Auditory-Verbal Learning Test (F=5.158; p=.027) and Stroop Color (F=5.928; p=.018). Over 4 years, 20 (45.5%) patients had PD-MCI from which 11 (39.9%) were cognitively preserved at baseline and 2 (4.5%) PD-MCI patients converted to PD dementia. Comparison of whole brain cortical thickness maps showed that both groups had progressive significant cortical thinning in several regions of the posterior cortex. Significant cortical thinning in PD patients was found, specifically in left isthmus posterior cingulate and right inferior parietal. In controls, changes over time were seen in the left lingual gyrus and insula, right caudal middle frontal and lateral occipital regions. However, no significant interaction group per time effects was seen between controls and patients.

Conclusions: PD patients had significant decline of memory and processing speed and an increased rate of MCIs over time. According the cortical thickness measures, in our 4-year study there are evidences of progressive atrophy, but this atrophy was similar for patients and controls.

EEG shows subclinical motor preparation deficits in Parkinson's disease patients with freezing of gait during locomotion

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Objective: Investigate motor preparation and cognition in Parkinson's disease (PD) patients with and without freezing of gait (FOG) while sitting and stepping with EEG.

Background: FOG pathophysiology is poorly understood but is associated motor preparation and executive deficits. Event-related potentials (ERPs) are EEG potentials in response to an event. ERPs can correlate with executive function (e.g. P3b) while others are movement-related potentials which precede voluntary movement (lateralized readiness potential (LRP)). We examine these ERPs for a simple motor task in PD with and without FOG and consider the effect of locomotion on these ERPs.

Methods: We recruited 20 PD patients (10 with FOG) to perform a two-stimulus oddball task sitting and stepping in place. Participants pressed a button once a target stimulus was seen but ignored the standard stimulus and synchronous 128-channel EEG was recorded. Response times (RTs) were calculated for sitting and stepping conditions. ERPs were calculated over centroparietal areas (for P3b responses) as well as over frontocentral areas (for LRPs).

Results: RTs while stepping were slower than while seated for the patients with FOG. However, RTs were *faster* while stepping for the non-freezers. In both conditions, there was no difference in the P3b ERP between groups but LRP onset is earlier in FOG, with a greater amplitude. When sitting was compared to stepping, freezers displayed an earlier onset of the LRP while stepping. There was no difference in these potentials between sitting and stepping in non-freezers.

Conclusions: This is the first study of ambulatory ERPs in Parkinson's disease. The faster stepping RTs in the non-freezers suggests they recruit more attentional resources to perform a dual-task. The slower stepping RTs suggest the freezers are unable to do this. Although there was no difference in the P3b ERP, the longer and larger LRP implies freezers need to recruit greater frontal resources to achieve equivalent RTs to non-freezers while seated. As frontal networks become overloaded during stepping, freezers initiate movement earlier but are unable to compensate sufficiently, resulting in slower RTs.

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Connectivity patterns in frontal cognitive regions in Parkinson's disease

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Objective: Evaluate the changes in brain connectivity between Parkinson's disease (PD) with and without mild cognitive impairment (MCI).

Background: Up to 40% of PD patients have MCI early in the disease. Previous studies showed extensive structural and functional brain changes associated with cognitive performance in PD patients. By analyzing the MCI-non-PD patients we can distinguish better the patterns specifically associated with cognitive deficits in PD.

Methods: We analyzed the connectivity patterns in 17 PDN, 19 PD-MCI, 13 MCI-nonPD patients and 27 healthy volunteers (HV) using the bootstrap analysis of stable cluster method to mathematically compute the regions of interest (ROI) in the brain. We concentrated only on the frontal cognitive regions (dorsolateral (DLPFC), ventrolateral (VLPFC) and ventromedial (VMPFC) prefrontal cortices). All participants underwent a neuropsychological assessment based on the level II MDS-Task Force criteria for MCI in PD and the MCI criteria for assessing Alzheimer's disease. ROIs were selected in data-driven way across different cluster resolutions. The strength of the connectivity between all the ROIs were compared across groups.

Results: PDN had increased connectivity compared with HV and PD-MCI between the VMPFC-supplementary motor area (SMA), VMPFC-motor regions as well as DLPFC-superior temporal gyrus and DLPFC –hippocampus, at resolutions 19 and 180. MCI-nonPD showed the same patterns with decreased connectivity compared to PDN and HV in the VMPFC-motor, DLPFC-superior temporal connections, but not in the VMPFC-SMA pathway. PDN vs. HV had increased VMPFC-posterior cingulate connectivity at resolution 180. PD-MCI vs. HV showed increased connectivity between VLPFC-caudate nucleus and VLPFC-posterior cingulate regions, and decreased connectivity between right and left VLPFCs at resolution 180.

Conclusions: Our data reveal a significant increase in connectivity between DLPFC, VMPFC in PDN compared to HV and a significant decrease in PD-MCI patients compared to PDN. These patterns might reflect a compensational effect in PDN patients, which allows them to have a cognitive performance at the same level as healthy individuals.
In the PD-MCI patients this compensational mechanism is weakened. Finally, the results indicate that the integrity of the functional connection between VMPFC and SMA is more crucial for the maintenance of cognitive function in PD than in non-PD individuals.

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Dopamine depletion impairs gait automaticity by altering cortico-striatal and cerebellar processing in Parkinson's disease

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Objective: Investigating the role of dopaminergic medication on the neural mechanisms underlying lower limb motor automaticity during fMRI in 23 patients with PD that were measured both on and off dopamine. **Background:** Impairments in motor automaticity cause patients with PD to rely on attentional resources during gait¹, resulting in greater motor variability and a higher risk of falls¹⁻². Although dopaminergic circuitry is known to play an important role in motor automaticity¹⁻², little evidence exists on the neural mechanisms underlying the breakdown of locomotor automaticity in PD¹⁻². This impedes clinical management and is in great part due to mobility restrictions that accompany the neuroimaging of gait.

Methods: Participants performed a virtual reality gait paradigm during fMRI by operating foot pedals to navigate a corridor (*'walk'* condition) or watching the screen while a researcher operated the paradigm from outside the scanner (*'watch'* condition). Step time variability during *walk* was used as a surrogate measure for motor automaticity (where higher variability equates to reduced automaticity).

Results: Patients demonstrated increased step time variability during the "off" state and showed increased BOLD response in the bilateral orbitofrontal cortices (*walk>watch*). A parametric modulator analysis revealed that patients on medication recruited the cerebellum during periods of increasing variability, whereas patients off medication instead recruited cortical regions implicated in cognitive control. Finally, a main effect of medication was found for functional connectivity within an attentional motor network and a significant condition by medication interaction for functional connectivity was found within the striatum. Furthermore, functional connectivity within the striatum correlated strongly with increasing step time variability during *walk* in the off state (r=0.616, p=0.002), but not in the on state (r=-0.233, p=0.284). Post-hoc analyses revealed that functional connectivity in the dopamine depleted state within an orbitofrontal-striatal limbic circuit was correlated with worse step time variability (r=0.653, p<0.001).

Conclusions: Overall, this study showed that dopamine ameliorates gait automaticity in Parkinson's disease by altering striatal, limbic and cerebellar processing, and thereby informing future therapeutic avenues for gait and falls prevention.

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Altered resting-state functional interhemispheric connectivity in Parkinson's disease

X. Dan, S. Lin, A. Liu, J. Wang, T. Wu, P. Chan, M. McKeown (Beijing, People's Republic of China) **Objective:** To examine direct interhemispheric functional connectivity (FCi) in Parkinson's disease (PD) during resting-state fMRI and to investigate the relations between observed connectivity changes and performance on clinical features.

Background: FCi, important for a variety of functions has typically been seen to be unaffected in PD as anatomically connectivity is typically intact. Recent studies have challenged that view, and suggested that tremor and PIGD subtypes may be differentiated based on FCi patterns[1].

Methods: We performed both exploratory and hypothesis driven analyses on FCi patterns derived from resting state fMRI from 50 subjects (PD=26, N=24). We jointly examined instantaneous correlations as well as lag1 correlations between the two hemispheres in 28 pairs of homologous regions.







Results: With the data-driven approach, Principal Component Analysis (PCA) was performed on the FCi correlation values. The PCs that discriminated between PD and controls had prominent interhemispheric connections (Fig.1). In a hypothesis driven approach, we determined if interhemispheric connectivity predicted clinical indices. FCi values accurately predicted disease duration but not cognitive performances on the MMSE. Significant gender differences were found in FCi that interacted with PD status. Smell detection was predicted with FCi with similar patterns between PD and controls. FCi predicted smoking, with differences between PD and controls. Similarly, we confirmed a prior report that tremor predominance can also be predicted by FCi.

Conclusions: Our results suggest that FCi is widely disrupted in PD, and associated with a variety of clinically relevant symptomatology.

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EEG Markers for Emotional Inhibition in Parkinson's Disease

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Background: There is a need for better diagnostics and monitoring of neural and cognitive changes during the progression of PD. In previous literature, neural disruptions to emotional processing in PD have been reported.¹ A non-invasive method to study such neural changes is to record ERPs in an EEG during participation in a cognitive task.

Methods: Twenty-two non-demented PD patients and 13 healthy age matched controls were tested using a visual Go/Nogo task with affective words (positive, negative, and neutral) as distractors and targets whilst ERPs were recorded.

Results: Behavioural findings and ERPs differentiated PD from healthy older people: (i) PD took consistently longer to respond to targets across all conditions ($F_{1, 29} = 9.30$, p = .005), and were significantly less accurate in both Go and Nogo trials ($F_{1, 29} = 5.70$, p = .024); (ii) N2 amplitude was significantly higher ($F_{1, 33} = 6.15$, p = .018), and P3 amplitude was significantly lower ($F_{1, 33} = 4.95$, p = .033) and occurred significantly later in PD ($F_{1, 33} = 6.0$, p = .019). Support for ERP differentiation due to affective valence between PD and controls was not observed, however, these results and a consideration of study limitations provide new directions for future research. **Conclusions:** This study has provided support for the utility of N2 and P3 recordings during participation in an affective Go/Nogo task as potential biomarkers of PD progression and diagnosis.

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Sleep disturbance may alter white matter and resting state functional connectivities in Parkinson's disease *S.J. Chung, Y.H. Choi, H. Kwon, Y.H. Park, H.J. Yun, H.S. Yoo, Y.H. Sohn, J.M. Lee, P.H. Lee (Seoul, Korea)* **Objective:** To clarify whether sleep disturbance would alter the patterns of structural and functional networks underlying cognitive dysfunction in patients with Parkinson's disease (PD).

Background: Ample evidence has suggested that sleep disturbance may have a detrimental impact on neurodegenerative process responsible for cognitive performance in general population or patients with Alzheimer's disease. However, it remains unclear whether poor sleep contributes to cortical or subcortical structural changes underlying cognitive impairment in patients with PD.

Methods: Among the 180 patients with non-demented PD in our cohort, 45 patients were classified as the group with sleep disturbance according to the 5-item Scales for Outcomes in Parkinson's disease-nighttime scale. Based on propensity scores, another 45 PD patients without sleep disturbance were matched to this group. We performed a comparative analysis of cortical thickness, diffusion tensor imaging-based white matter integrity, resting-state functional connectivity, and cognitive performance between PD patients with and without sleep disturbance. **Results:** PD patients with sleep disturbance showed poorer performance in attention and working memory, and a tendency towards a lower score in frontal executive function relative to those without sleep disturbance. The PD with sleep disturbance group (figure 1), although there were no significant differences in cortical thickness between the PD subgroups. On functional network analysis, PD patients with sleep disturbance exhibited less severely decreased cortical functional connectivity within the default mode network, central executive network, and dorsal attention network when compared with those without sleep disturbance (figure 2).



Conclusions: The present study suggests that sleep disturbance in PD patients could be associated with white matter and functional network alterations in conjunction with cognitive impairment.

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Olfactory Impairment in Parkinson's Disease and White Matter Abnormalities in Central Olfactory Areas S. Sobhani, M. Aarabi (Tehran, Islamic Republic of Iran)

Objective: To determine white matter abnormalities in PD patients with various degrees of olfactory impairment. **Background:** Neuroimaging results of PD brain based on diffusion tensor imaging (DTI) correlate well with the olfactory loss in PD patients. In the present study we aim to determine whether white matter integrity measured based on DTI method is associated with odor identification test scores in PD patients.

Methods: Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database. Odor identification was assessed using the University of Pennsylvania Smell Identification Test (UPSIT). Five groups, total 85 subjects (18 anosmia, 26, 17 and 12 PD patients with severe, moderate and mild microsmia, respectively and 12 PD patients with normal olfactory status) were recruited with similar age, sex ratio, GDS, MoCA, handed and NHY. The Diffusion MRI data were corrected for subject motion, eddy current distortions, and susceptibility artefacts due to the magnetic field inhomogeneity using Explore DTI toolbox [2]. Diffusion MRI connectometry was conducted in all subgroups using a multiple regression model considering UPSIT, sex, age and the local significant connectomes.

Results: The between-group Connectometry revealed that individuals with PD-Anosmia had lower QA(FDR=0.02123)in body of the corpus callosum (CC),bilateral corticospinal tracts,middle cerebellar peduncles,right and left cingulate cortex,left fornix,Genu and splenium of corpus callosum compared to patients with mild microsmia[Figure 1].A significant difference(FDR=0.04683)was observed in body,Genu and Splenium of the corpus callosum(CC)and bilateral corticospinal tracts between PD-anosmia and patients with moderate microsmia[Figure 2].individuals with Severe microsmia had alterations in FA in multiple regions(FDR=0.07658),including the right and left cingulate cortex, bilateral corticospinal tracts, middle cerebellar peduncles and left inferior longitudinal fasciculus(ILF)compared to mild microsmia patients[Figure 3].





Conclusions: This study shed light on the microstructural changes in bilateral cingulum, CC, IFOF, CST and MCP areas associated with olfactory impairment in early diagnosed PD patients. Since smell insufficiency is the precursor to PD, microstructural changes regarding reduced FA values in olfactory regions might reflect the primitive alterations in Parkinsonic brain.

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The influence of LRRK2 mutations on cholinergic system in manifest and prodromal stage of Parkinson's disease: a positron emission tomography study

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Objective: To evaluate the effects of leucine-rich repeat kinase 2 (*LRRK2*) mutations on the central cholinergic system in both manifesting and non-manifesting carriers using PET and MRI.

Background: *LRRK2*-PD has been reported to result in slower progression of motor symptoms, lower prevalence of REM sleep behavior disorder (RBD), less cognitive decline and better olfactory performance compared to idiopathic PD. Previous PET studies have suggested increased dopamine turn-over and preserved serotonergic innervation, but the influence of *LRRK2* mutations on the central cholinergic system has never been examined.

Methods: 14 *LRRK2*-PD patients, 16 non-manifesting *LRRK2* mutation carriers, 8 idiopathic PD patients, 5 idiopathic RBD patients and 11 controls underwent N-¹¹C-methyl-piperidin-4-yl propionate PET scans. Acetylcholinesterase (AChE) hydrolysis rates were calculated using the striatal input method; age-expected control values for *LRRK2*-subjects, idiopathic PD and RBD subjects were derived from linear regression analyses of AChE

values for *LRRK2*-subjects, idiopathic PD and RBD subjects were derived from linear regression analyses of AChE hydrolysis rates on age performed in healthy control subjects. Voxel-based morphometry was conducted to control for a possibly difference in brain atrophy.

Results: We found significantly increased thalamic AChE hydrolysis rates in the non-manifesting *LRRK2* mutation carriers compared to age-expected values ($108.0 \pm 9.1\%$, P = 0.036). The increase of AChE activity was widespread through cortical regions in manifest stage (average cortex $113.6 \pm 17.2\%$, P = 0.015), especially in regions associated with default mode and limbic networks ($113.2 \pm 17.4\%$, P = 0.013; $112.3 \pm 15.1\%$, P = 0.012); the increase was positively correlated with Hoehn & Yahr stage. Thalamic cholinergic activity was significantly decreased in idiopathic PD ($93.3 \pm 8.8\%$, P = 0.033) and non-significantly decreased in RBD ($94.1 \pm 14.4\%$, P =



0.338). Voxel-based morphometric analysis failed to detect any significant differences in gray matter volume between groups after family wise error correction.

Conclusions: *LRRK2* mutation is associated with significantly increased cholinergic activity in the brain even in non-manifesting carriers and the effect is more prevalent through cortical regions once disease becomes manifest; while idiopathic PD or RBD is associated with decrease of cholinergic activity. Changes in cholinergic activity are unlikely to reflect the effects of atrophy.

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Substantia nigra area evaluated by neuromelanin-sensitive MRI as an imaging biomarker of disease progression in Parkinson's disease

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Objective: To investigate the pattern of substantia nigra - neuromelanin (SN-NM) area loss and contrast ratio (CR) intensity changes in late-stage Parkinson's disease (LSPD) patients, compared to *de novo* PD patients and PD patients with a 2-5 year disease duration in order to evaluate NM changes throughout disease progression. **Background:** A specific T1-weighted magnetic resonance imaging (MRI) sequence has been shown to detect SN-NM signal changes that accurately discriminate PD patients from controls, even in early disease stages. However it is unclear what happens to these SN changes in later stages of the disease.

Methods: A comparative cross-sectional study was performed, analyzing SN-NM MRI signal in LSPD defined as Schwab and England ADL Scale < 50 or Hoehn Yahr Stage (HY) >3, comparing them with other disease stages, i.e. *de novo*, 2-5 year PD and controls. For all the groups SN-NM signal area and CR values for the internal and lateral SN regions were obtained with semi-automated methods.

Results: 13 LSPD, 12 *de novo* patients with PD, 10 PD patients with a 2-5 year disease duration, and 10 controls were included. NM signal area was significantly decreased in de novo PD patients compared to LSPD ones (*P-value* = 0.005; sensitivity: 75%; specificity 92% and AUC: 0.86) and in PD patients compared to controls (P-value < 0.002). In the lateral SN region, a decrease in the CR was detected in all the PD groups compared to controls; also, despite not reaching statistical significance, a slight increment was observed comparing LSPD to 2-5 year PD patients. NM signal area had a significant correlation with HY (R= -0.37; P < 0.05) and MDS-UPDR part II (R= -0.4; P < 0.05) while a weak correlation was found with MDS-UPDRS part III (R= -0.26; P: 0.1).

Conclusions: SN area evaluated by NM-sensitive MRI may be a promising biomarker of nigral degeneration and disease progression in PD patients. Further longitudinal studies on a larger population and the use of consensus acquisition and analysis protocols are warranted in order to replicate our results and verifying if SN-NM area could be considered as a disease progression imaging biomarker in clinical trials.

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Alterations in Dynamic Brain Connectivity Patterns in Parkinson's Disease

X. Dan, A. Liu, J. Wang, M. McKeown, T. Wu, P. Chan (Beijing, People's Republic of China) **Objective:** To explore the time varying brain connectivity networks in Parkinson's disease (PD) during resting-state fMRI and to investigate the correlate between connectivity dynamics and performance on the clinical features. **Background:** Most brain connectivity studies in PD are based on the stationary assumption where the brain connectivity networks are assumed to be time invariant. However, the dynamics of brain connectivity have been increasingly recognized as being important.

Methods: We compared the connectivity dynamics between PD groups (N=26) and normal control (N=24) with selected window length (16, 30, 32, 50, 64, 80, 100, 128 respectively) using sliding window strategy. The network variation and connectivity power were compared.

Results: The PD group demonstrated the lower connectivity power compared with that of normal group at all the window length.(Fig.1) The variations of brain connectivity was decreasing with the increasing of the window length (Fig.2). The bilateral connections have less variability while the cross hemisphere maintain higher variations(Fig.3,4). The differences between normal and PD groups has become less obvious with the increasing of the window length (Fig.5,6,7). At all the window length, the loading weights of first eigenconnectivity were correlated with the network dynamics(Fig.8). The age, gender and smoking were found to be correlated with the network power at all the window length.

Comparison across groups with different window lengths



Comparison across groups with different window lengths







Comparison across groups with different window lengths





Conclusions: The differences in flexibility revealed by brain time varying networks may further provide us the insights into brain function altered in PD.

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The role of phosphodiesterase 4 in sleep disturbances in Parkinson's disease

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Objective: We aimed to assess the association between phosphodiesterase 4 (PDE4) expression and sleep disturbances *in vivo* using combined multimodal magnetic resonance imaging (MRI) and PET molecular imaging with [¹¹C]rolipram in Parkinson's disease (PD).

Background: Sleep disturbances are very common in patients with PD. Animal and genome-wide association studies have suggested a link between cAMP/PKA signalling, PDE4 expression (an enzyme which hydrolyses cAMP) and daytime sleepiness.

Methods: 12 PD patients and 5 healthy controls underwent clinical and imaging assessments. Sleep disturbances were assessed with the Parkinson's disease sleep scale (PDSS), Epworth Sleepiness Scale (ESS) a measure of excessive daytime sleepiness (EDS), UPDRS-I single items for sleep and fatigue, and non-motor symptom scale (NMSS) domain 2 sleep/fatigue. MIAKATTM was used to generate parametric images of [¹¹C]rolipram volume of distribution (V_T) with the Logan plot. FMRIB's diffusion toolbox (FDT) was used to perform probabilistic tractography on each subjects' diffusion data to functionally parcellate the striatum according to cortico-striatal projections to generate connectivity maps for limbic, cognitive and sensorimotor subdivisions of the striatum.

Results: PD patients with EDS had significantly increased V_T values compared to those without EDS. Higher ESS scores, indicating greater EDS, correlated with higher PDE4 V_T in cortical regions involved in the limbic loop [amygdala (r=0.670), hippocampus (r=0.813), orbitofrontal (r=0.685), cingulate (r=0.663) and temporal cortex (r=0.809)], striatum (0.713), thalamus (r=0.660), hypothalamus (r=0.819) and accumbens (r=0.738). Furthermore, higher EDS was associated with specific increases in PDE4 within limbic portions of the striatum (connectivity based analysis, (r=0.788).

Conclusions: Our findings indicate converging evidence for an association between daytime sleepiness and elevated PDE4 in cortical and subcortical limbic regions, implicating PDE4 in the pathophysiology of sleep disturbances in PD.

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Assessing cholinergic innervation in Parkinson's disease using the PET imaging marker [18F]Fluoroethoxybenzovesamicol

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Objective: To validate [¹⁸F]Fluoroethoxybenzovesamicol ([¹⁸F]FEOBV) imaging in healthy volunteers by dynamic scanning. The secondary objective of this study was to evaluate the differences in [¹⁸F]FEOBV binding between PD patients and healthy control subjects, in order to evaluate the clinical feasibility of [¹⁸F]FEOBV as a cholinergic imaging ligand in PD.

Background: Cholinergic neuronal degeneration is an important contributor to several neurodegenerative diseases, including Parkinson's disease (PD), but the rate and extent of this cholinergic neuronal degeneration in the course of PD is unknown. Previous PET studies on the cholinergic system in PD used indirect PET markers, showing pre- as well as post-synaptic binding. However, to get a better understanding of cholinergic depletion, a more selective, presynaptic marker is needed. Preclinical studies showed promising data on the vesicular acetylcholine transporter (VAChT) tracer [¹⁸F]FEOBV, in detecting cholinergic deficits in vivo. The use of [¹⁸F]FEOBV as a PET imaging marker of cholinergic innervation has been studied only preclinically and in healthy human volunteers.

Methods: The study population comprised 20 subjects in total, of which 10 healthy control subjects and 10 PD patients. Three healthy control subjects underwent dynamic scanning in 3 imaging sessions at 0-120, 150-180, 210-240 min after injection of [¹⁸F]FEOBV. The addition 7 healthy controls and 10 PD patients underwent a short static [¹⁸F]FEOBV scan.

Results: The dynamic scans showed a [¹⁸F]FEOBV distribution which was comparable to previous findings, showing the highest binding in striatum and thalamus, and a lower binding to the cortex. The most optimal late static scanning period derived from these data was thought to be best at 210 minutes after injection and 30 minutes in duration. [¹⁸F]FEOBV binding data of PD patients and controls will be shown.

Conclusions: [¹⁸F]FEOBV shows a high binding to striatum and thalamus and lower binding to the cortex. The dynamic scan data suggest that static scans of 30 minutes should be sufficient to generate adequate cholinergic

binding data, which makes [¹⁸F]FEOBV very feasible as a cholinergic marker, also supported by the binding data of PD patients and controls.

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High-Pass Filtered Phase Mr Imaging to Detect Longitudinal Motor Associations of Iron Accumulation in Parkinson's Disease

A. Martin-Bastida, N. Lao-Kaim, Y. Xing, C. Loane, A. Roussakis, S. Schwarz, N. Valle-Guzman, P. Mahlknecht, X. Li, G. Paul-Visse, H. Widner, M. Politis, T. Foltynie, R. Barker, D. Auer, P. Piccini (London, United Kingdom) **Objective:** To assess whether longitudinal changes in deep grey matter nuclei iron content are associated with declining motor function in Parkinson's disease over a period of 18 months.

Background: Iron accumulation plays an important role in neurodegeneration in Parkinson's disease. Susceptibility weighted imaging (SWI) is a high-resolution MR-based imaging technique for quantifying iron depositions in vivo. Phase images offer greater specificity in quantifying brain iron load. We hypothesised that high-pass filtered phase imaging may be a useful monitoring tool for longitudinal clinical characterization of PD, and we sought to investigate the clinical associations of iron depositions in deep grey matter nuclei.

Methods: We evaluated forty-two PD subjects and six age and gender matched healthy volunteers (HV) longitudinally with high-pass filtered phase imaging at baseline and after 18 months. Average phase shifts (radians) in the caudate nucleus, putamen, globus pallidus, substantia nigra (SN) and dentate nucleus (DN) were analysed using SPIN software. Longitudinal changes of bilateral radians (radians) were calculated by subtracting baseline values from follow up values. Parametric correlations of regional radians were conducted with UPDRS part III, tremor and bradykinesia-rigidity sub-scores. Correlations were considered significant only if p f p<0.05 following Benjamini-Hochberg FDR adjustments.

Results: PD patients showed significant higher radians in the SN (p<0.001) after 18 months, without significant change in controls. No significant longitudinal iron deposition changes were found in striatal and dentate nuclei. SN radians positively correlated with UPDRS-III (r=0.650, p<0.001) and bradykinesia-rigidity subscores (r=0.523, p=0.001). In addition DN correlated with tremor subscores (r=0.464, p=0.008).

Conclusions: Our results show that high-pass filtered phase imaging might offer an interesting monitoring tool to evaluate longitudinal progression of motor severity and clinical phenotypes in PD, and could be useful to assess the effect on these structures of iron chelation therapies.

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Altered Pde10a Expression Detectable Early in Untreated Parkinson's Disease Patients

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Objective: To investigate *in vivo* whether loss of PDE10A expression in Parkinson's disease (PD) is an early phenomenon in early untreated PD patients using positron emission tomography (PET) molecular imaging with [¹¹C]IMA107, a highly selective PDE10A radioligand.

Background: The mechanisms underlying neurodegeneration and loss of dopaminergic signalling in Parkinson's disease are still only partially understood. PDE10A is a basal ganglia expressed dual substrate enzyme, which regulates cAMP and cGMP signalling cascades, thus having a key role in the regulation of dopaminergic signalling in striatal pathways, and in promoting neuronal survival.

Methods: We studied a cohort of 16 early untreated PD patients compared to a group of 16 healthy controls. Subjects undertook one [¹¹C]IMA107 PET and one 3-T MRI scan. Image processing and kinetic modelling was carried out using MIAKATTM. Parametric images of [¹¹C]-IMA107 binding potential relative to nondisplaceable binding (BP_{ND}) were generated from the dynamic [¹¹C]IMA107 scans using the simplified reference tissue model with the cerebellum as the reference tissue.

Results: Region of interest analysis showed lower mean [¹¹C]IMA107 BP_{ND} in the caudate (38%, P<0.001) and putamen (14%, P<0.001) in PD patients compared to healthy controls, which was confirmed with voxel-based analysis. At structural MRI, PD patients showed no volumetric changes in caudate or putamen but loss of structural connectivity (loss of mean diffusivity in caudate=9%,P=0.005 and putamen=7%, P=0.037). Loss of PDE10A showed no lateralization. Higher Unified Parkinson's Disease Rating Scale part-III motor scores correlated with lower [¹¹C]-IMA107 BP_{ND} in the caudate (r=-0.676; P=0.006) and putamen (r=-532; P=0.041).

Conclusions: Our findings demonstrate that loss of PDE10A expression is an early phenomenon in the course of PD over and above structural connectivity changes and is associated with the severity of motor symptoms,

independently of levodopa treatment. These data demonstrate that the previous reductions reported in PD are not due to the effects of medication.

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Assessing Nigral Functional Connectivity in Parkinson's disease With Resting State Functional MRI

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Objective: To evaluate functional connectivity of SN with basal ganglia and motor cortex in Parkinson's disease (PD) using resting state functional MRI (RS fMRI).

Background: The clinical manifestation of neurodegenerative diseases is thought to result from disrupted functional brain networks. Parkinson's disease is a neurodegenerative disorder characterised by progressive dopaminergic neuronal loss of SNc with further dysfunction of striatal-thalamic-cortical loops. To investigate the pattern of network dysfunction resulting from SN neurodegeneration we subsequently performed a resting state fMRI cross-sectional study of nigral functional connectivity.

Methods: Twenty-nine early stage PD subjects during medication off state and twenty-six age and sex matched healthy controls were studied with resting state (RS) fMRI. Spontaneous low-frequency (0.08-0.1 Hz) blood oxygenation level-dependent (BOLD) signal intensity fluctuations of SN were used to identify significant temporal correlations with a priori striatal and motor cortical regions. For each individual the mean SN time series were correlated with the time series of striatal nuclei and the regions of the Human Motor Area Template (HMAT). Nigral seeds were divided into more and less affected sides according to clinical motor severity as assessed with UPDRS part III.

Results: Nigral seed regions showed positive functional connectivity with thalamus, globus pallidus and putamen and was anticorrelated with sensorimotor cortex in both PD and HC groups. In contrast, additional negative connectivity was shown in premotor cortex (SMA and premotor dorsal areas) in PD group. Further decline of functional connectivity in premotor cortex were found in most affected SN when compared to the less affected. Bilateral reductions of functional connectivity in dorsolateral prefrontal, premotor and parietal superior and inferior cortices were found in PD group when compared to HC.

Conclusions: Our results demonstrate the *in vivo* disrupted nigral functional connectivity using RS fMRI with the striato-thalamo-cortical structures in early PD patients, in keeping with the dopaminergic neurodegeneration.

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Pathway Selective Deep Brain Stimulation Derived from Patient-Specific Models

K. Gunalan, B. Howell, R. Patriat, Y. Duchin, G. Sapiro, N. Harel, C. McIntyre (Cleveland, OH, USA) **Objective:** The goal of this work is to quantify the specific pathways directly activated by clinical DBS settings. **Background:** Deep brain stimulation (DBS) of the subthalamic region is an established clinical therapy for the treatment of late stage Parkinson's disease. A fundamental biophysical effect of DBS is the generation of action potentials in axons surrounding the stimulating electrode. The subthalamic region is made up of multiple axonal pathways, and it is unclear which of these pathways are directly responsible for the therapeutic benefit (or side effects) generated by DBS.

Methods: A patient-specific computational model of DBS was created based on 7T MRI data. Subcortical nuclei were segmented from T1-weighted, T2-weighted, and susceptibility-weighted images. Axonal pathways representing the hyperdirect, subthalamopallidal, pallidothalamic, and cerebellothalamic pathways, as well as the internal capsule were reconstructed by conducting tractography with diffusion-weighted images. Each of the 5000 axons reconstructed were modeled as a multi-compartment cable structure. The voltage distribution generated by the DBS electrode was calculated using a finite element method; this voltage distribution was then used to stimulate the model axons; and the response of the axons to DBS was quantified. [figure1]



Patient-specific computational model of deep brain stimulation. A) Anatomical model including a T2-weighted image, electrode, thalamus (yellow), subthalamic nucleus (green), globus pallidus externus (light blue), globus pallidus internus (dark blue), and red nucleus (red). B) Axon pathways in the subthalamic region reconstructed with tractography (internal capsule - white; hyperdirect - purple; subthalamopallidal - green; pallidothalamic - blue; cerebellothalamic - orange).

Results: Recruitment curves were created for each electrode contact to calculate the effects of different amplitudes on the activation of each pathway. The clinically-defined therapeutic stimulation setting (contact 2, 2 Volts, 60 microseconds) activated the hyperdirect, subthalamopallidal, pallidothalamic, and cerebellothalamic pathways. The relative proportion of activated pathways could be most effectively biased by selecting different contacts. **Conclusions:** Clinically effective stimulation most likely activates multiple pathways. Preferential stimulation of different pathways is possible but is dependent upon the patient-specific anatomy, electrode position, and stimulation parameter settings.

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Modulation of executive motor network after neurofeedback training in Parkinson's disease

N. Smulders, D. Mehler, L. Subramanian, D. Linden, J. Whittaker (Cardiff, United Kingdom) **Objective:** To identify changes in effective (i.e. directed) connectivity in the executive motor network during finger tapping. To compare the effects of two rehabilitation strategies.

Background: Current rehabilitation strategies for Parkinson's disease (PD) include motor training (MOT) and motor imagery (MI). A more recent development is neurofeedback (NF) training during which patients are provided with real-time feedback from motor regions involved in MI. The current study assessed the effect of NF + MOT vs MOT on the effective connectivity between motor regions during a motor task in PD patients.

Methods: 26 PD patients had completed a 10-week randomized controlled trial that evaluated the clinical efficacy of real-time fMRI-NF training as described previously [1]. Briefly, patients were randomly assigned to one of two intervention groups matched for age, gender and medication. One group completed MI based NF combined with MOT (NF group), the other group completed MOT training only (MOT group) using a Nintendo Wiifit® machine. Before and after the intervention, both groups completed a visually cued right-hand finger tapping task "off" medication during which fMRI data were acquired. After quality control of fMRI data, scans from 21 early stage (Hoehn & Yahr stages I-III) PD patients (4/16/1, respectively) were included. Dynamic causal modelling (DCM) was applied to the fMRI data to estimate the effective connectivity between brain regions of the motor network involved in this task [2]. Bayesian Model Selection was used to determine which connectivity models best explained the data.

Results: Network analyses revealed that in both the NF group and MOT group, global connectivity strength pre-post intervention has increased. Further, model comparison between pre-post intervention showed a change in the network structure for the NF group. The preferred model post intervention included new connections from primary motor area (M1) to the cerebellum and from M1 to the putamen. In contrast, no change in network structure was observed in the MOT group.

Conclusions: Both NF and MOT training led to increased connectivity between brain regions of the executive motor network. Further, changes in network structure were only observed in the NF group. Given that only the NF group showed significant clinical improvement as reported earlier [1], we suggest that NF can potentially enhance compensatory network organization in PD.

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Prospective Analysis of Morphological Markers of Development of Impulsive Compulsive Behaviors in De Novo Parkinson's Disease

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Objective: Aim of this study was to determine whether structural imaging features present at disease onset or over disease course predict the development of ICB in patients with de novo PD

Background: Previous studies have reported structural brain abnormalities in Parkinson's disease (PD) patients with impulsive compulsive behavior (ICB). Yet, it is not clear whether these structural abnormalities underlie the predisposition to develop ICB or if they are secondary phenomena associated with established ICB

Methods: From a cohort of 1116 subjects (PD=629; healthy controls, HC=195) from the Parkinson's Progression Marker Initiative (PPMI) database, we built a MRI dataset selecting those who underwent 3T-MRI and had a T1-MPRAGE acquisition at baseline. This provided 421 subjects (253 PD, 11 HC). For the purpose of this study, we included de-novo, drug-naive PD patients who screened negative for ICB at baseline and converted to positive screening at any follow-up time. We identified 42 PD patients converting to ICB (PD-ICB) who were matched by age, gender and disease duration with 42 PD patients who did not develop ICB at follow-up (PD-no-ICB); 42 HC matched by age and gender were also included. Grey matter (GM) and white matter (WM) voxel-based morphometry (VBM) and cortical thickness voxel-based quantification (VBQ) were compared among the three groups at baseline using SPM 12 (cross-sectional analysis). For the longitudinal analysis, MRI scans obtained after the onset of ICB were available from 27 PD-ICB; these scans were compared with those of 32 PD-no-ICB and 35 HC performed at time-points to match the ICB group

Results: At baseline, no significant difference was observed between HC and PD and between PD-no-ICB and PD-ICB in any of the analysis. In the longitudinal analysis, significant differences were found between HC and PD in the rate of grey and white matter atrophy, particularly in the hippocampus and striatum bilaterally.

Conclusions: When comparing PD groups, a region of increased atrophy in the anterior limb of the left internal capsule adjacent to the head of the left caudate nucleus was found in PD-ICB, not surviving correction for multiple comparison. Our study suggests that standard structural imaging is not sensitive to demonstrate structural brain abnormalities to identify patients at risk at the time of PD diagnosis.

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A quantitative meta-analysis study of Impulse control disorders in patients with and without Parkinson's disease

A. Faust- Socher, M. Criaud, A. Mihaescu, A. Lang, S. Cho, S. Houle, A. Strafella (Toronto, ON, Canada) **Objective:** Evaluating through meta-analysis brain activations associated with impulse control disorder in patients with and without Parkinson's disease.

Background: Impulse control disorders (ICDs) in the general population also known as "behavioral addictions" may share some clinical features with substance addictions. Parkinson's disease (PD) patients receiving dopaminergic therapy are susceptible to develop similar pathological behaviors. Imaging studies have showed that frontal and striatal areas are involved in the pathophysiology of these disorders in different populations. There are no known studies directly comparing brain activation in PD-ICD versus non PD-ICD.

Methods: We searched the literature through "Pubmed" and "Web of sciences" from 1.2000-1.2016, for imaging studies involving PD-ICD patients or non-PD ICD subjects. fMRI, SPECT (Tc^{99}), and PET (H_2O^{15}) studies were considered. Clinical and demographical data including cognitive state were extracted. For the PD patients we collected UPDRS scores, Levodopa equivalent daily dose. A coordinate-based quantitative meta-analysis ("activation likelihood estimation") was performed.

Results: A total of 56 experiments and 384 foci were included. For the PD group, we found 16 experiments with 117 significant foci. For the non-PD group, we found 40 experiments with384 significant foci. PD subjects were older than the non-PD subjects, but most experiments included a normal control group age matched to the study group, thus controlling for the "age effect". Cluster analysis demonstrated activation of the Lt. Insula, Lt. Putamen, Bil.Pallidum in the Non-PD ICD group. Additional significant clusters were found in the PD-ICD group including: Lt. Caudate, Anterior Orbital gyrus, Rt. Posterior and Inferior orbital gyri.

Conclusions: This study suggests that several brain circuits are shared between non-PD patients with ICD and PD patients associated ICD .However, activation of frontal brain areas was exclusively seen in PD-ICD patients. Our results contribute to a better understanding of PD associated ICD pathophysiology, which may differ from the one among ICD non-PD patients.

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Clinical utility of visualization of Nigrosome-1 in patients with Parkinson's disease

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Background: Detection of Nigrosome-1 has recently emerged as a surrogate neuroimaging biomarker for evaluation of PD. Studies using 7T and 3T-MRI have reported poor visualization of Nigrosome-1 to be a fairly consistent neuroimaging feature in patients with PD with high diagnostic accuracy, sensitivity and specificity. There is only limited data available on the inter-rater reliability and relationship between poor visualization of Nigrosome-1 and clinical asymmetry in PD.

Methods: 3T High resolution Venobold sequences of 67 patients with PD and 63 matched controls were reviewed by two radiologists blinded to the clinical details of subjects. All subjects were classified into abnormal and normal groups based on visualization of Nigrosome-1. Subjects with abnormal Nigrosome-1 were reclassified based on whether the abnormality was symmetrical or asymmetrical in either side of mesencephalon. Inter-rater reliability was calculated using Cohen's kappa at each level of classification. Relationship between poor visualization of Nigrosome-1 and clinical asymmetry was also assessed.

Results: There was good inter-rater reliability of Nigrosome-1 visualization among the reviewers at each level of classification (k=0.75 - 0.92). Poorly visualized abnormal Nigrosome-1 and clinical asymmetry were contralaterally related in 73.9 % of subjects (p=0.003). Patients with bilaterally symmetrical Nigrosome-1 abnormality were also found to have clinical asymmetry in 50 % patients.

Conclusions: There was good inter-rater reliability of abnormal Nigrosome-1 detection by the reviewers. There was also significant agreement on clinical asymmetry and poor visualization of Nigrosome-1. However, caution should be exercised while interpreting visualization of Nigrosome1. Further studies are needed to explore the potential of Nigrosome-1 detection as a surrogate neuroimaging biomarker in PD.

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Non-motor symptom burden is associated with thalamic atrophy in Parkinson's disease

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Objective: To investigate whether non-motor symptoms burden is associated with cortical and subcortical morphological changes in PD patients.

Background: Non-motor symptoms are common aspects of Parkinson's disease (PD) occurring in prodromal PD and greatly affecting the quality of life. The global impact of non-motor symptoms can be graded using the non-motor symptoms burden classification system and can be used to address the neural correlates of non-motor symptoms burden, which is an unmet need.

Methods: We studied 41 non-demented PD patients (24M, mean age: 64.0 ± 9.3 years). Non-motor symptoms burden was assessed using the Non-Motor Symptoms Scale gradings (NMSS). Cortical thickness and subcortical nuclei volume analyses were carried out using the automated surface-based analysis package Free-Surfer (version 5.3.0). PD patients were divided into two groups according to the NMSS grading: mild to moderate (NMSS: 0-40) and severe (NMSS: =41) non-motor symptom burden.

Results: Thalamic atrophy was associated with worse NMSQ (r=-0.42, P=0.042) and NMSS (r=-0.47, P=0.014) total scores. The non-motor symptoms that drove this correlation were sleep/fatigue (r=-0.36, P=0.042) and gastrointestinal tract dysfunction (r=-0.36, P=0.042). When the PD patients were divided into two groups, we found that PD patients with severe non-motor symptom burden had significant thalamic atrophy compared to the group with mild to moderate non-motor symptom burden (P=0.048).

Conclusions: Our findings show that greater non-motor symptom burden is associated with thalamic atrophy in PD. Thalamus plays an important role in processing sensory information including visceral afferent from the gastrointestinal tract and in regulating states of sleep and wakefulness.

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Exercise alters response of reward anticipation in the ventral striatum of subjects with Parkinson's disease *M. Sacheli, D. Murray, N. Vafai, E. Shahinfard, M. Cherkasova, K. Dinelle, N. Neilson, J. McKenzie, S. Appel-Cresswell, M. McKeown, V. Sossi, A. Stoessl (Vancouver, BC, Canada)*

Objective: To investigate the effects of exercise on reward circuitry in Parkinson's disease (PD). **Background:** The benefits of exercise in PD have been linked to enhanced dopamine (DA) transmission in the striatum. It is hypothesized that exercise induced changes in DA function may also alter reward signaling in the ventral striatum (VS).

Methods: We examined VS activity during reward anticipation in an fMRI monetary incentive task. Subjects were asked to select 1 of 4 cards during a trial. Each block (20 trials), had a different probability of reward 0, 50, 75, 100%. For each successful choice the subject received \$0.50. Percent signal change of the blood oxygen level dependent (BOLD) signal in the VS was calculated during the anticipatory phase (10 second before the reward was revealed). The effects of exercise on reward response were examined in two different ways: Sedentary subjects (SED) vs. habitual exercisers (HAB) – 22 male subjects with PD were recruited, 15 SED subjects and 7 HAB exercisers. t-tests were conducted for each probability. Aerobic cycling (AER) vs. control/stretching (CON) – 21 sedentary subjects with PD were randomly allocated into AER (n=14) or CON (n=7) exercise interventions. Both groups exercised 60 min/ session, 3 x/week for 36 sessions. RM-ANOVA (time x probability x group) was conducted to determine the effects of the different exercise interventions on VS activity.

Results: SED vs. HAB – HAB had significantly higher BOLD signal at 75% reward probability compared to SED t(20)= 2.27, p<0.05) (Fig 1). AER vs CON - Significant time x prob x group interaction was observed. Fishers LSD post hoc tests showed a significantly reduced BOLD signal at 50% probability pre to post in only CON and at 75% probability a significantly increased BOLD signal pre to post in only AER (p<0.05) (Fig 2).



Figure 1. Percent signal change (PSC) in the ventral striatum of sedentary subjects and habitual exercisers with Parkinson's disease. PSC = percent change in BOLD signal from baseline during the anticipation phase. Anticipation phase = the 2 second time period immediately prior to the reveal of the reward. Habitual exerciser = Subjects who exceed 4 counts of moderate to vigorous exercise and 120 minutes of exercise per week, Sedentary are any subjects who fall below the threshold. * p<0.05, error bars denote standard error of the mean



Figure 2. PSC in the ventral striatum before (pre) and after (post) either a control or aerobic exercise intervention. Both interventions consisted of 3-sessions/week, 45-60 minutes/ session for a total of 36 sessions. Control intervention = seated stretches, breathing and social interaction, aerobic intervention = stationary cycling at 60-80% of VO₂ max at 60 RPMs. PSC = change in BOLD signal from baseline during the anticipation phase. Anticipation phase = the 2 second time period immediately prior to the reveal of the reward. * p<0.05, error bars denote standard error of the mean.

Conclusions: At the 75% probability of monetary reward habitual exercisers had a greater BOLD signal in the VS compared to sedentary subjects. Interestingly, a similar response at 75% probability is seen after 3 months of aerobic exercise. The BOLD signal in the VS increases after 3 months of aerobic exercise, with no difference in the control group. This study suggests that aerobic exercise alters the function of reward circuitry, potentially through changes in the mesolimbic DA system. Future analysis will examine forebrain connectivity patterns associated with reward processing and learning.

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Globus Pallidus and Pedunculopontine Nucleus Oscillations during Executed and Imagined Gait in Patient with Parkinson's Disease and Freezing of Gait Symptoms.

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Objective: To explore neurophysiological markers of intentional executed and imagined movement in both Globus Pallidus Internus (Gpi) and Pedunculopontine Nucleus (PPN) in patients with Parkinson's Disease (PD) and Freezing of Gait symptoms (FoG).

Background: Freezing of Gait (FoG) is a unique and poorly understood clinical phenomenon affecting ~53% of the patients with Parkinson's disease (PD), and it is characterized by a sporadic inability to step forward. Although the pathophysiological basis of PD and FoG remain unknown, it has been shown that Deep Brain Stimulation (DBS) in the Gpi can decrease the FoG episodes and alleviate other PD phenotypes. There is pressing need to reach a better understanding of the network involved in gait initiation, to be able to shed light on the pathology and potentially use newfound biomarkers as control features for responsive DBS therapies.

Methods: Two patients were implanted in both Gpi and PPN regions as part of an explorative closed-loop DBS cohort with Medtronic PC+S neurostimulators. The patients were asked to "walk" by moving their feet with a simulated gait motion while intermittently touching a pad that was acting as ground. Leveraging the inertial and EMG sensors data, it was possible to explore neurocorrelates with movement intention/execution. The absence of movement during the cued motor imagery task (imagine walking/rest) allow us to evaluate intention without the peripheral feedback as confounding factor.

Results: The simulations executed on intraoperatively collected data from PD patients shows that is possible to reliably detect movement execution in both Gpi and PPN. Furthermore, it appears that during the motor imagery task only the Gpi shows reliable and significant modulation that correlates with the cues.

Conclusions: Our results suggest that gait initiation modulates Gpi activity during both imagined and executed gait task. PPN instead seems to have significant modulation only during executed tasks, suggesting an involvement with the execution but not the planning of movement, or a feedback evoked activity. The results suggest that it would be

possible to use gait onsets as feature to modulate a responsive DBS activation, to stimulate only during gait, decreasing stimulation evoked side effects and battery depletion.

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Volume analysis and localization of midbrain hyperechogenecities via TCS and MRI

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Objective: We are presenting follow-up results on our previous study for 3D volumetric measurements of SN hyper-echogenicities, to differentiate PD patients from healthy controls (HC). Additionally, and for the first time, we show detailed information about the 3D positional distribution of hyper-echogenicities via co-localization with MRI. **Background:** Transcranial sonography (TCS) has become an additional tool to diagnose movement disorders like Parkinson's disease (PD). In PD patients, hyper-echogenicities have been detected at the area of the substantia nigra (SN). So far, 2D measurements of these 3D structures are used for diagnosis.

Methods: 3D-TCS as well as MRI was performed for 20 PD patients and 24 healthy controls (HC). 3D datasets were segmented manually, concerning ipsi-lateral hyper-echogenicities and the midbrain. Extracted features for differentiation were i) the maximum 2D area ("2.5D"), and ii) the 3D volume of all slices of 5.5mm length along the 3D axial direction. TCS and MRI were aligned semi-automatically in 3D, via an image-based registration algorithm and comparison of voxel grey-level intensities. Additionally, a novel group-MRI-atlas was generated for our cohort. It was then possible to fuse all individual 3D-TCS scans into a volumetric TCS-atlas for the first time. The fusion was based on a concatenation of the multi-modal transformations of TCS-to-MRI and MRI-to-atlas.

Results: A cut-off was detected for the bi-lateral 2.5D and the 3D features in order to classify between PD and HC via a ROC-analysis. Our results were able to achieve a sensitivity of 85.7% and a specifity of 88%. All TCS volumes could be registered into the multi modal group atlas. First group-based volumetric localization results regarding the TCS hyper-echogenicities were gained.

Conclusions: Our results demonstrate a good classification of HC versus PD patients with the help of the 2.5D as well as the 3D features. Our aim is to generate a fully automated segmentation, which could help in clinical practice. Interestingly, hyper-echogenicities in PD patients are located in the area of the Nucleus parabrachialis pigmentosus cranially. Caudally, they are rather located in the pars compacta of the SN. Especially hyper-echogenicities in the area of the nigrosome seem to underline a certain importance of those structures in the degeneration process in PD.

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Abnormal DaTscan in a case of Anoxic brain injury

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Objective: To study the utility of DaTscan in anoxic brain injury.

Background: Parkinsonism is a clinical syndrome seen in Parkinson's disease (PD) which includes tremors, bradykinesia, rigidity, and gait disturbance. Secondary Parkinsonism is explained by a specific etiology. DaTscans are abnormal even in the earliest presentation of the PD associated with nigrostriatal degeneration [1], but little is known about their role in revealing dopaminergic deficits in parkinsonism secondary to non-degenerative causes. **Methods:** A 26-year-old woman presented with right arm tremor and stiffness, slowed speech, difficulty swallowing, difficulty opening eyes, and gait disturbance. Two months prior to the presentation, the patient was admitted for a heroin induced cardiac arrest and subsequent anoxic brain injury (ABI) as evidenced on brain imaging. She had no notable neurological deficits at that time. One month after her discharge, she started having above symptoms. Physical examination showed increased tone on extremities with intermittent involuntary movements of the right arm, and severe eyelid apraxia. Her gait was wide based and unsteady. A brain MRI showed abnormal T 2 hyperintensity in the bilateral globus pallidus, posterior internal capsule, and caudate head (figure1), compatible with ABI. The DaTscan revealed markedly decreased radiotracer activity in the right putamen and slightly reduced activity in the right caudate head and left putamen, supporting the diagnosis of a parkinsonian syndrome.



Results: To the best of our knowledge, this is the first report of abnormal DaTscan in secondary parkinsonism caused by ABI. The development of this condition most likely reflects the vulnerability of the globus pallidus and the substantia nigra-pars-reticularis to hypoxia/ischemia. The clinical diagnosis of post-hypoxic Parkinsonism in our patient was based on her young age, no history of anticonvulsant or antipsychotic medicine use, no family history of movement disorders and development of parkinsonian symptoms after ABI. DaTscan verified dopaminergic deficits in this patient with secondary parkinsonism due to ABI and therefore guided our treatment with Carbidopa.

Conclusions: In conclusion, we suggest that DaTscan should be considered to evaluate parkinsonism features in the setting of ABI.

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Syndenham's chorea in Senegalese children: A case series

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Objective: To describe clinical profile and treatment outcome of Sydenham's chorea (SC) in children attending a tertiary care hospital in Dakar, Senegal.

Background: SC is a rare complication of acute rheumatic fever (ARF). It can occur after an untreated group A β hemolytic streptococcus infection (1). SC is the commonest cause of acquired chorea in childhood. Although it is few reported in developed countries because of the treatment improvement, literature still found cases in developing countries (2). **Methods:** A retrospective study was conducted at the Neurology Department of Fann National Teaching Hospital. All records of children under 15 years old, diagnosed with SC between July 2003 and July 2009 were reviewed. Age at onset, clinical features, investigations, treatment given and outcome data were collected.

Results: Overall 10 children records were reviewed. The mean age at onset of SC was 8.7 years (range 7-10) with a female predominance (60%). No history of throat infection was found and 1 child had family history of ARF. Onset symptoms was subacute in all. Chorea was generalized in 9 children (90%) and 1 child had hemichorea. Other neurological disorders included axial hypotonia (100%) and no psychiatric signs were present. Laboratory findings were elevated serum level of: antistreptolysin O in 5 children; erythrocyte sedimentation rate and /or C-reactive protein in 8 children. Echocardiogram showed mitral regurgitation (50%). Brain imaging was not done. Chorea treatment in the 10 children included haloperidol (0.075 mg/kg/day for an average of 5 months). Etiological treatment included penicillin for ten days and antibiotic prophylaxis. Cessation of chorea 3 months after the treatment initiation was observed in 90 % of cases.

Conclusions: SC is still present in this senegalese population children. Promptly managed, the outcome was favorable in our study but primary prevention remains the best treatment.

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Pilot evaluation of pseudoelastic orthoses for supporting motor control in children with secondary dystonia and dyskinesia

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Objective: The study reports preliminary observations on the use of orthotic devices with nonlinear spring properties prescribed with the aim to stabilise posture and improve upper-limb motor control in young patients with Movement Disorders (MD).

Background: Cerebral palsy and other cerebral lesions are at the basis of secondary paediatric MD, carrying along control deficits, ill posture and functional disability. Drugs may be ineffective in some cases and alternative treatments are sought. Viscoelastic force fields are known to affect muscular synergies and may enhance

proprioceptive feedback. Orthoses based on pseudoelastic alloys were developed to provide that dynamic action. **Methods:** With Ethics Committee's approval, we recruited five children (12.2±5.6 years old) with complex MD pictures comprising secondary dystonia and dyskinesia of various aetiology. They were evaluated prior to and after a 30-days' elective treatment with a new functionally-personalised orthosis. Passive range of motion, Modified Ashworth Score and motor function (Melbourne Upper-Limb Scale) were evaluated. The subjects also carried out the reach-forward and hand-to-mouth tasks under optoelectronic monitoring (figure 1), and upper-limb kinematics was analysed. PedsQL was used to assess patients' perceptions about the therapy, and anecdotal observations were recorded.



Results: The orthotic treatment was very well accepted. There were no adverse effects. Clinical results differed according to the main trait, with prevalently dystonic patients improving more in the postural domain, and dyskinetic ones developing better movement stability with segmental kinematics becoming more task-related. One dyskinetic patient obtained promising results also during daily activities, as documented by footages shot at home. In this case, the Melbourne Scale score improved from 7.3% to 16.4%.

Conclusions: The current study does not possess statistical generality. The patients, taken singularly, did display improvements in life quality as a correlate of better posture, less pain and better functional abilities in some domains. The overall improvement was mild; patients' perception was good. The preliminary clinical impressions support an indication for pseudoelastic devices, as adjuvant in the treatment of MD in the young, but longer treatment durations and larger cohorts, are needed to confirm efficacy.