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Late-Breaking Abstracts, MDS Study Group Abstracts and Guided Poster Tour Information
Objective: To characterize demographic and clinical features of the young-onset Parkinson disease (YOPD) population using the large data set derived from the National Parkinson Foundation Quality Improvement Initiative (NPF-QII); a prospective multicenter ongoing study.

Background: Parkinson disease (PD) is the second most common neurodegenerative disorder. A distinct subset of PD patients referred to as Young Onset PD (YOPD) has been arbitrarily defined by an age of onset (from 20 to 40, or <50 years old). Studies show that YOPD patients have different initial symptoms, environmental risk factors, rate of progression, motor symptoms, non-motor symptoms, choice of DBS target, and quality of life (QOL) impairment as compared to later onset PD (LOPD). Although some distinguishing characteristics have been identified, the clinical phenotype has not been fully characterized.

Methods: Subjects were recruited without exclusions from the NPF-QII database. NPF-QII is a prospective observational clinical study with 8,110 patients with PD and caregivers followed longitudinally with annual systematic evaluation at 20 NPF Centers of Excellence. Data collected includes demographics such as age of onset, disease duration, gender, and a clinical evaluation including collection of comorbid conditions, PDQ 39, Time up and go (TUG) score, H&Y stage, hospitalization, ability to stand unaided, cognitive score (immediate recall, delayed recall and verbal fluency), falls and modified caregiver strain index (MCSI). NPF-QII data collected from June 2009 to March 2016 was analyzed. Analyses were conducted using a strict definition of onset under 40 to define YOPD. In all comparisons, after adjustment for sex and comorbidities a weighted average by duration was computed to control for non-linear relationships. Confidence intervals were computed using a binomial confidence interval for binary and a Gaussian approximation for continuous variables, and Cohen’s D is presented for significant relationships versus 3,846 individuals in a typical onset reference group with onset from 55 to 70.

Results: Overall, the study included 505 individuals with YOPD and 7,605 individuals with onset after 40. The average age of onset in the YOPD group was 34.6 years (SD: 5.2) and the average and median disease duration was 16.6 years (IQR: 9.3—22.7). The YOPD cohort was 67% male, with increasing male to female ratio at younger age: participants with onset under 30 were 75% male (p<0.05 vs reference, which was 63% male) (Figure 1). The YOPD cohort had fewer comorbidities (72% had no symptomatic comorbidities versus 58% in the reference group, p < 0.01). In the cognitive assessment, from diagnosis through four years disease duration, YOPD patients were no different from the reference group. However, after four years YOPD patients demonstrated significantly better cognition than the reference group, with Cohen’s D increasing from 0.34 at 6 years duration to 0.55 at 12 years (Figure 2). Caregiver strain and falls were similar in the YOPD and reference groups. There was a noted relationship of duration of disease with caregiver strain and also with falls (Figures 3 and 4). Analysis revealed that comorbidity burden (p < 0.01), hospitalization rate (p < 0.05), mobility (TUG scores, p < 0.01) and ability to stand unaided (p < 0.01) were superior in the YOPD versus reference group. YOPD patients experienced a worse reported quality of life as measured by PDQ-39 compared to LOPD despite having milder motor symptoms.

Conclusions: Our results show a novel and significantly higher male proportion in the YOPD group as compared to the LOPD group, and this finding has not been reported in prior studies. YOPD patients over time had better cognition than those with typical age of onset for similar disease duration. However, unlike some previous reports, the risk of falls and caregiver strain were correlated with duration of PD rather than with age of onset. Given the large number of long-duration YOPD patients, the risk of falls and caregiver strain should both be management
concerns. These results highlight some interesting findings and differences in the YOPD population. Further studies will be needed to confirm these findings and to determine contributing factors.
LBA 2
PD_manager European Parkinson Project: A pilot multicenter study using mHealth devices for symptom
smart monitoring

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Objective: To develop an algorithm for automatic detection and monitoring of motor symptoms in PD as well as to
record specific non-motor features such as cognitive abilities and perform speech analysis.

Background: Parkinson’s disease (PD) current clinical management is mostly based on the patient’s subjective
report on the effect of treatment. This traditional approach requires time, it is biased by patient’s judgment and is
often not completely reliable. The main purpose of the EU funded project PD_manager (Horizon 2020, Grant
Agreement n° 643706) is to build and evaluate an innovative, m-health, patient-centric system for PD remote
monitoring. The system will recognize symptoms and feed a decision support system to trigger decisions by
healthcare professionals. Here we present the results of a pilot study in 20 PD patients (14 men and 6 women),
investigated at 3 institutions: IRCCS Fondazione Ospedale San Camillo, IRCCS Santa Lucia Foundation and
University Hospital of Ioannina –Greece. The study was approved by the Ethic committee in Venice.

Methods: We used mobile and wearable devices (smartband, smartphone and sensor insoles) along with video
recordings. A specifically developed Cognitive App has also been tested. To evaluate the effectiveness of our
devices, all recordings were performed in a standardized setting, using a dedicated protocol. Measurement
concerned motor activity during simple and ecological task (e.g. walking, rising from a chair, lying on a bed etc...) and
occurred in controlled ON and OFF state, 4 times for each of the 20 patients. All patients worn devices with
built-in movement sensors : a smartband, placed in the more affected side arm and connected to a recording
smartphone placed in the trousers’ pocket, and a pair of sensor insoles, inside the shoes, recording weight force on feet surface and gait parameters. Moreover a number of long continuous recordings (3-5 days), in an ecological context, has been collected to compare the output of the PD_manager algorithms with patient diaries.

**Results:** The mean age of patients was $68 \pm 10.69$ years and the mean disease duration was $10 \pm 5.35$ years. A total of 140 (69 in ON state, 71 in OFF) session were recorded. For the subset of 5 patients with significant tremor, constancy was found higher ($p=0.0074$) in OFF periods. Tremor amplitude was also higher but it did not reach statistical significance ($p=0.12$). In patients with mild dyskinesia the wrist gyroscope energy averaged on 5-min intervals was statistically higher ($p<0.01$) during ON periods compared to OFF periods.

![Box plot](image)

**Conclusions:** The defined recording protocol allowed to gather a large amount of labelled, homogeneous and synchronized data from sensor insoles, smartphone and wristband sensors. First results are promising and suggest that the use of a mHealth environment, allows detection of motor symptoms and differentiation between ON and OFF conditions.
Objective: The aim of this study was to evaluate whether 3 months of intranasal reduced glutathione, (in)GSH, results in improvement of total and/or motor Unified Parkinson's Disease Rating Scale (UPDRS) scores in individuals with Parkinson's Disease (PD).

Background: Reduced glutathione (GSH) is a nutrient depleted early in the course of PD and brain GSH augmentation was first proposed as a therapeutic more than three decades ago. A recent Phase I trial of (in)GSH in PD demonstrated a 4+ point improvement in total UPDRS following three months of study intervention; the goal of this study was to evaluate whether those improvements were reproducible.
Methods: 45 individuals with Hoehn & Yahr Stage 1-3 PD were randomized to receive placebo (saline), 300 mg/d, or 600 mg/d (in)GSH in three divided doses daily for three months, and observed over a one month washout.

Results: All cohorts improved over the three month intervention with both 600 mg/d and placebo groups having statistically significant improvements over baseline UPDRS total (mean (SD) -4.6 (4.7), P=0.0012 and -3.4 (6.2), P=0.0295, respectively). Only the 600 mg/d group had improvements in UPDRS motor subscore (mean (SD) -2.2 (3.8), P=0.0243). The 600 mg/d cohort also had statistically significant improvements in Non-Motor Symptom Score (NMSS) (mean (SD) -10.2 (13.2), P=0.0108).

Conclusions: These data contribute to the body of literature demonstrating a symptomatic effect of (in)GSH in some individuals with PD. This is the second study to demonstrate a 4+ point improvement in total UPDRS scores over baseline with 200 mg/ ml thrice daily. The placebo group experienced early and sustained improvement, and therapeutic benefit of (in)saline or study participation cannot be excluded. Whether long term use of (in)GSH leads to clinical improvements that are significantly different than placebo will require longer-duration studies in larger cohorts.

LBA 4
High genetic load in early-onset Parkinson's disease

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Objective: The aim of this study is to evaluate the genetic load in a group of 136 early-onset Parkinson's disease (EOPD) with onset under 35 years old.

Background: Mutational search in the genes involved in EOPD is a key step of diagnosis and has implications for prognosis. The elevated number of genes makes it a complex and laborious task. Next Generation Sequencing (NGS) allows the simultaneous analysis of hundred thousands of DNA fragments.
Methods: Target enrichment was performed through multiplex PCR using Agilent HaloPlex target enrichment assay and subsequent NGS on an Illumina platform, for 136 samples. A custom panel of 34 genes linked to PD, parkinsonisms and dystonia has been designed using Agilent SureDesign software and the bioinformatic analysis of the NGS data was performed on Galaxy - Orione Crs4 platform and IGV software (Broad Institute). The panel design consists of 9681 total amplicons, that cover for 99.7% a target region of 275.731 kbp. We validated the efficiency of this panel by screening patients with known mutations in blind. All results were confirmed. Quantitative analysis (MLPA, MRC-Holland) has been used to detect chromosomal rearrangements in all patients.

Results: The molecular analysis with NGS of the 136 EOPD patients revealed that 64% of them have at least 1 pathological variant: known mutations or novel pathogenic variants. 54% of patients had monogenic condition (recessive or dominant); 10% of patients had mutations in more than one gene suggesting a polygenic situation; 36% did not harbour mutations in any of the genes analysed.

Conclusions: Our data show that NGS approach is a suitable tool for the molecular characterization of gene involved in EOPD patients. The sequencing analysis suggests that the genetic component has a high burden in this kind of PD patients.

LBA 5
Tau [18F]AV-1451 PET Uptake in Patients with Suspected 4-Repeat Tauopathy

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Objective: To describe imaging results using tau-PET ligand [18F]AV-1451 in a multi-site study of individuals with suspected 4-repeat tauopathy (4Rtau), including progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).

Background: PSP and CBD are atypical parkinsonian disorders characterized by progressive parkinsonism and cognitive dysfunction due to underlying 4-repeat tau pathology. Regional distribution of 4Rtau is often observed in midbrain, cerebellar, and other subcortical structures and may be present in fronto-parietal neocortex. There is need for in vivo biomarkers of tau pathology in PSP, CBD and other neurodegenerative tauopathies. AV-1451 is a novel PET radiotracer that selectively binds to a spectrum of tau-positive inclusions in postmortem samples.

Methods: [18F]AV-1451-PET was performed in 20 mild-to-moderate, clinically-diagnosed PSP patients (Richardson’s Syndrome), 5 CBD patients, and 20 age and sex matched, cognitively normal controls (NC) recruited from five centers. All subjects were enrolled in the A09 clinical trial sponsored by Avid Radiopharmaceuticals. We created 75-105min SUVR images using a cerebellum reference region. For each subject, we calculated the mean SUVR uptake within globus pallidus (GP) and dentate nucleus of the cerebellum (DN), as well as the hemispheric asymmetry of uptake within these regions (asymmetry index [AI] = 200*(R– L)/(R+L)). Analyses were performed using t-tests, receiver operating characteristic (ROC) analysis. Correlations were also assessed between regional SUVR means, disease duration and clinical severity (PSP Rating Scale and subcomponent measures) in PSP patients.

Results: PSP patients had increased AV-1451 uptake in GP (1.84±0.20) and DN (1.32±0.10) relative to NC (GP=1.56±0.20; pL uptake in DN (AI=3.77±3.08, p=0.052). No correlations between ROI SUVR values and disease duration or clinical severity in PSP patients survived multiple comparisons correction.

Conclusions: At a group level, AV-1451 retention was elevated in GP and DN for PSP relative to NC. This is consistent with neuropathological studies suggesting that these regions harbor 4Rtau pathological inclusions. However, at the individual level diagnostic utility based on ROC analysis was only moderate. These findings
provide evidence that AV-1451-PET may be a useful in vivo biomarker of tau burden in PSP, but longitudinal follow-up and PET-to-autopsy validation are needed.

**LBA 6**
**Progression of Parkinson's disease: 5 year follow-up**

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**Objective:** To examine progression motor and non-motor symptoms in a clinical population-based sample of patients with Parkinson’s disease during 5-year follow-up.

**Background:** Parkinson’s disease (PD) is chronic neurodegenerative disease with progressive course and an average duration of approximately 15 years; the motor symptoms of PD have dominated the clinical pictures of the disease, but numerous non-motor symptoms are present at different stages of the disease.

**Methods:** A cohort of 360 PD patients from the academic clinical setting was followed up after 5-year. The assessment included motor scoring with Hoehn and Yahr staging and the Unified Parkinson’s Disease Rating Scale. Comprehensive psychiatric examination and neuropsychological testing were also applied.

**Results:** Expected progression of motor symptoms and motor complications of the disease were evidenced. The most frequent neuropsychiatric symptoms were apathy, anxiety and depression even after the 5 year follow-up. In comparison to the baseline the reduced number of patients with apathy (baseline-60% and follow-up-38.58%) was recorded. Approximately the same prevalence of depression (baseline-40.5% and follow-up-34.69%) and anxiety (baseline-23.33% and follow-up-17.12%) were recorded. Around 54.05% of PD patients were cognitively intact at follow-up in comparison to 72.50% at baseline. Almost one third of the cohort were diagnosed with MCI, whereas 20.26% at 5 year follow-up were diagnosed with dementia. Mortality rate after 5-year follow-up was rather high (29.17%).

**Conclusions:** These findings presented the complexity of PD as the motor disease with inevitable neuropsychiatric symptoms simultaneously. Although the treatment is available the mortality rate was higher in comparison to normal population.

**LBA 7**
**Interim Results of a Long-term Open-label Safety Study of ADS-5102 (amantadine HCl) Extended-Release Capsules for Treatment of Levodopa-Induced Dyskinesia (LID) (EASE LID 2 Study)**

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**Objective:** Characterize the long-term safety and tolerability of ADS-5102 (amantadine HCl) extended-release capsules, 340 mg once daily at bedtime, for the treatment of levodopa-induced dyskinesia (LID) in Parkinson’s disease (PD), including subjects with LID despite having undergone deep brain stimulation (DBS).

**Background:** LID is a long-term motor complication of levodopa therapy. The efficacy of ADS-5102 for treating dyskinesia has been demonstrated in two completed, randomized, placebo-controlled efficacy trials of up to six months duration. These trials excluded subjects with DBS.
Methods: In an ongoing open-label safety study conducted in North America and Western Europe (NCT02202551), PD subjects with LID received ADS-5102 340 mg once daily at bedtime for up to two years. Eligible subjects continued ADS-5102 treatment following conclusion of prior efficacy study, or initiated ADS-5102 treatment for subjects who had LID despite having undergone DBS and were naïve to ADS-5102. The primary outcome measure is safety and tolerability using standard safety assessments. Efficacy is measured by the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), Part IV.

Results: For this interim analysis, 129 subjects received ADS-5102 for a mean duration of 161 days (range: 10 – 441 days). The most common adverse events (AEs) included fall (20%), hallucinations (12%), abnormal dreams (7%), dizziness (7%), and peripheral edema (7%). Fourteen subjects (11%) discontinued dosing due to an AE; in these 14 subjects, the most common AEs resulting in discontinuation were fall (3 subjects) and visual hallucinations (2 subjects). Onset of neuropsychiatric AEs mostly occurred during the first 60 days. In subjects who continued ADS-5102 from the previous 6-month efficacy study, the decrease in MDS-UPDRS Part IV was maintained through Week 16 of this open-label study (representing a total of 41 weeks of continuous ADS-5102 treatment). DBS subjects also showed improvement in MDS-UPDRS, Part IV.

Conclusions: ADS-5102 was generally well tolerated and AEs are consistent with the safety data reported from previous ADS-5102 studies. In addition, ADS-5102 showed long-term efficacy in the treatment of LID.

LBA 8
Survival and dementia in GBA-associated Parkinson Disease: the mutation matters

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Objective: We compared survival and dementia in Parkinson Disease (PD) patients carriers of GBA mutations and non-carriers. In addition, we compared effects of severe and mild GBA mutations.

Background: Mutations on the GBA gene are a major risk factor for PD and were associated to earlier onset, increased cognitive impairment and family history. Severe GBA mutations (with a stronger reduction of enzymatic activity) increase the risk to develop PD more than mild mutations. On the other hand, no studies showed significant clinical differences between severe versus mild-mutations PD-carriers.

Methods: We studied 2764 unrelated consecutive PD patients: 123 GBA-carriers (67 mild-N370S, and 56 severe-L444P) and 2641 non-carriers. All subjects were followed at the Parkinson Institute, Milan-Italy from 2002 to 2013. We retrospectively recalled longitudinal clinical and demographic data available of all patients. All patients lost at follow up have been contacted during 2014-15 by telephone call to have information on survival (if deceased and when).

Results: GBA-carriers resulted to have an earlier onset (52±10yy vs 57±10yy), and increased frequency of dementia (34% vs 20%), a similar number of deceased cases (21% vs 22%). Kaplan-Meyer analysis showed a significant earlier onset of dementia as well as an earlier death in GBA-carriers. Multivariable analysis attributed to GBA-carriers a greater risk of dementia (HR=3.16, p<0.001) and of death (HR=1.85, p=0.002) being equal for gender, age at onset and disease duration. If we included dementia in the multivariable analysis, carriers still had a greater risk to die (HR=1.65, p=0.016), suggesting that reduced survival was not due only to increased dementia. GBA-carriers had a more severe progression at last UPDRS: in particular non-dopaminergic items resulted more severe, including dysphagia, freezing gait, and orthostatic hypotension. Comparison of Severe GBA mutations-carriers versus Mild GBA mutations-carriers showed that dementia was increased and earlier in severe-carriers, while no differences was seen on survival and other clinical features from last UPDRS available, possibly due to limited subjects number.

Conclusions: Survival is reduced in PD patients GBA-carriers compared to non-carriers mainly because increased and earlier cognitive decline and greater development of non-dopaminergic complications, including dysphagia
and orthostatic hypotension. Severe mutations associated to a greater reduction of enzymatic activity had also a stronger effect on dementia confirming that they works in a loss of function modality.

LBA 9
A Pilot Trial of Biphasic Pulses Deep Brain Stimulation for Dystonia: The BiP DBS Dystonia Study

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Objective: To evaluate the safety and tolerability of biphasic pulses in dystonia deep brain stimulation (DBS).

Background: DBS is a well-established therapy for dystonia patients who have a suboptimal response to oral medications and/or botulinum toxin injection. Dystonia patients often have inconsistent benefits that emerge over long time intervals and dystonia patients frequently require considerably higher DBS settings leading to the morbidity associated with premature neurostimulator battery drain and to repeat battery replacement surgery. Newer DBS programming strategies have the potential to improve clinical effectiveness and battery longevity. Modeling studies have suggested that biphasic pulse shaping could be applied to DBS patients, however only tremor and Parkinson’s disease have been previously explored.

Methods: The study design was a pilot safety trial of biphasic pulse shaping in a dystonia DBS clinic population. Primary dystonic syndromes (generalized or cervical dystonia) with bilateral GPi DBS implants were utilized for enrollment. The chronic clinic DBS programming parameters were used as the baseline settings. The stimulation mode was then modified from conventional continuous DBS to a biphasic waveform through a temporarily switching of the firmware on the already implanted neurostimulator. Safety was documented through clinician observation and case report forms with information derived from detailed interviews during the setting changes. Patients were videotaped for later evaluation by blinded raters on relevant motor scales (BMFDRS, UDRS, TWSTRS) and on the GAITRite (walking). The time points for ratings included baseline (chronic clinic programming parameters) and an immediate post- 30-minute washout after switching to a biphasic mode. The neurostimulator was left in biphasic mode and scales were collected at 1 hours and 2 hours. Continuous variables were examined as medians with respect to the interquartile range (IQR). Repeated measures were analyzed with the Friedman test, assuming a significance level of p=0.05.

Results: There were 10 subjects (generalized dystonia n=6 and cervical dystonia n=4). The mean age ranged from 24-72 years; 6 males. There were no side effects of biphasic stimulation reported by the patients or observed by the clinicians. The motor scales had a incremental improvement across time points reaching statistical significance for the TWSTRS [11.0 (IQR=10.5-18.0) when comparing value to baseline: 13.0 (IQR=10.5-22.5) at washout, 9.0 (IQR=7.0-19.0) at immediate post-, 10.0 (IQR=8.5-14.0) at 1h post- and 10.0 (IQR=8.0-13.0) at 2h post biphasic; 2=11.7, p=0.020]. Significance was not reached for the UDSS [15.5 (IQR=8.8-36.0) at baseline, 17.0 (IQR=11.0-25.0) at washout, 13.0 (IQR=5.8-23.3) at immediate post-, 11.5 (IQR=8.0-28.3) at 1h post- and 13.5 (IQR=7.8-24.0) at 2h post biphasic; 2=6.5, p=0.162] or for the BFMDRS [11.5 (IQR=9.5-23.5) at baseline, 14.0 (IQR=9.5-27.0) at washout, 12.5 (IQR=7.3-19.8) at immediate post-, 11.5 (IQR=6.0-20.5) at 1h post- and 11.5 (IQR=7.8-17.8) at 2h post biphasic; 2=3.9, p=0.415]. The GAITRite evaluations demonstrated incremental improvement across time points including velocity [109.3cm/s (IQR=91.6-137.3) at baseline, 105.3cm/s (IQR=85.1-132.6) at washout, 106.4cm/s (IQR=98.3-135.2) at immediate post-, 113.9cm/s (IQR=99.9-145.9) at 1h post- and 117.9cm/s (IQR=108.5-142.1) at 2h post biphasic; 2=16.8, p=0.002], cadence [104.7 steps/min (IQR=102.5-122.5) at baseline, 106.8 steps/min (IQR=99.1-113.1) at washout, 108.7 steps/min (IQR=99.0-120.0) at immediate post-, 111.3 steps/min (IQR=104.1-122.6) at 1h post- and 111.3 steps/min (IQR=105.5-125.9) at 2h post biphasic; 2=16.7, p=0.002] and average step length [62.3cm (IQR=47.6-74.0) at baseline, 60.4cm (IQR=54.0-69.7) at washout, 61.5cm (IQR=55.3-72.7) at immediate post-, 62.2cm (IQR=56.3-76.1) at 1h post- and 63.4cm (IQR=56.7-78.1) at 2h post biphasic; 2=10.0, p=0.040].

Conclusions: Biphasic stimulation was safe and well-tolerated in the acute setting for dystonia patients. There was evidence for incremental improvement on the cervical dystonia scale and in gait measurements. A larger and more
A focused study should be conducted. Additionally, biphasic pulses as a vehicle toward a more rapid clinical response will need to be studied in a chronic setting.

### LBA 10

**Launching the International Parkinson and Movement Disorder Society Genetic Mutation Database (MDSGene)**

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**Objective:** To build a publicly available database which provides a comprehensive and regularly updated overview of movement disorders phenotypes linked to causative gene mutations reported in the scientific literature.

**Background:** The number of identified genes and mutations causative for a broad range of different movement disorders has increased dramatically over the past years, and the growing number of publications makes it increasingly difficult to follow and interpret these results. Therefore, we have developed a comprehensive online resource, the International Parkinson and Movement Disorder Society Genetic Mutation Database (MDSGene; available at [www.mdsgene.org](http://www.mdsgene.org)), that systematically links reported mutations to movement disorder phenotypes.

**Methods:** The content of MDSGene is based on genetic and phenotypic/clinical data extracted from the relevant literature by an experienced team of movement disorder specialists and geneticists following systematic and regularly updated systematic Pubmed searches.

**Results:** MDSGene currently displays extensive data on mutations in Parkinson’s disease (i.e. PINK1, Parkin, DJ-1, SNCA, VPS35), paroxysmal movement disorders (i.e. SLC2A1, PNKD, PRRT2), and familial brain calcification (i.e. PDGFβ). MDSGene provides a comprehensive list of the available literature and an extensive summary of patients’ characteristics for each gene of interest using graphic and tabular data summaries. Furthermore, MDSGene allows symptom-based queries, which return possible diagnoses and reported mutations consistent with the selected combination of symptoms and supported by systematically sampled evidence.

**Conclusions:** The collaborative effort of bioinformatics and movement disorder specialists has resulted in a comprehensive online database, which is able to provide a systematic synthesis of the current knowledge of genotype-phenotype relations in hereditary movement disorders. This resource can be used to assist clinical diagnosis and will help guide research in the field of hereditary movement disorders.

### LBA 11

**DNA repair pathways as a common genetic mechanism modulating the age at onset in Huntington’s disease and other polyglutamine diseases**

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Objective: To investigate whether the modifying effects of variants in DNA repair genes, recently associated with Huntington’s disease (HD) age at onset, can be replicated and extended to other polyglutamine diseases.

Background: From over 30 human diseases that are caused by expansion of unstable microsatellite sequences, nine are due to expanded CAG repeats in different genes encoding polyglutamine tracts, and these are usually known as the polyglutamine diseases. This group includes HD, several spinocerebellar ataxias (SCAs), and spinal and bulbar muscular atrophy. Although there is an inverse correlation between the size of the CAG repeat tracts in the expanded alleles and the age at onset of the disease this does not account for all the variance in the onset, suggesting the existence of additional modifying factors.

Methods: An independent cohort of 1462 subjects with HD and polyglutamine SCAs was collected, and SNPs corresponding to the most significant hits in the HD GWAS study were genotyped.

Results: In a grouped pathway analysis of DNA repair genes, the most significant association with age at onset was found when grouping all polyglutamine diseases (HD+SCAs, p=1.43x10-5). Significant associations were also found for HD (p=0.00194), all SCAs (p=0.00107), SCA2 (p=0.0035), and SCA6 (p=0.00162). When testing individual SNPs, significant associations were found for rs3512 in FAN1 with HD+SCAs (p=1.52x10-5) and all SCAs (p=2.22x10-4), and rs1805323 in PMS2 with HD+SCAs (p=3.14x10-5). All these associations follow the same direction as in the HD GWAS.

Conclusions: This study shows that DNA repair genes significantly modify the age at onset not only in HD, but also in polyglutamine SCAs. This finding suggests a common genetic mechanism for these diseases, which could operate through the observed somatic expansion of repeats. Genetic manipulation of DNA repair pathways start to emerge and may offer novel therapeutic opportunities in multiple repeat expansion diseases.

LBA 12
Using Gene Ontology to characterise key players in Parkinson’s Disease

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Objective: Using the Gene Ontology to annotate proteins involved in processes that are dysregulated in Parkinson's, in order to underpin the rapid analysis of new experimental data, and help further elucidate the links between these processes and neurodegenerative disease.

Background: The avalanche of genetic data for neurodegenerative pathologies, including Parkinson's, requires curation in order to give them biomedical context. One of the key links between such data, the scientific literature and knowledge of gene functions, is the Gene Ontology (GO). GO is a community resource that uses a structured and controlled vocabulary to describe gene products in terms of their biological processes, cellular locations and molecular functions. We have been curating proteins involved in processes that are dysregulated in Parkinson's, and our focused GO annotation of two critical areas, autophagy and WNT signalling in the context of dopaminergic neuron development, recently became public (March 2016).

Methods: We have expanded the ontology by creating new terms, such as ‘midbrain dopaminergic neuron differentiation’, ‘Wnt signalosome’, ‘beta-catenin-TCF complex’ and ‘parkin-mediated mitophagy in response to
mitochondrial depolarization’, to reflect the way this biology is described in the literature. With new ontology terms in place, we were able to curate human genes more precisely, giving priority to those associated with Parkinson’s in genetic familial or population studies.

**Results:** The curation of proteins involved in autophagy, in particular focusing on mitophagy and chaperone-mediated autophagy, has led to the creation of 478 annotations associated with 347 proteins. Thirty-nine proteins were identified as key components of the WNT signalling pathway, and our curation of these proteins increased the number of manual annotations associated with this pathway to a total of 308.

**Conclusions:** Through extension and enhancement of the ontology and the curation of selected literature, we have developed and updated the representation of key biological processes relevant to Parkinson’s in the GO resource. This work can be used to underpin the rapid analysis of new experimental data, and help further elucidate the links between these processes and neurodegenerative disease.

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**LBA 13**

**Early add-on rasagiline to ropinirole monotherapy in newly diagnosed patients with Parkinson’s disease. Preliminary results of a prospective randomized single-blind delayed-start follow-up study**

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**Objective:** The aim of this prospective, randomized, single-blind, parallel group follow-up study was to assess the symptomatic and possibly neuroprotective effect and safety of the MAO-B inhibitor rasagiline as early or delayed add-on to ongoing ropinirole monotherapy, in comparison to the latter drug alone, in newly diagnosed Parkinson’s disease (PD) patients.

**Background:** Only few data are so far available on the therapeutic efficacy and safety of rasagiline as an adjunct to dopamine(DA)ergic agonists in patients with early PD.

**Methods:** Eighty six patients with early PD, mean age 63 ± 8.0 , mean disease duration at the inclusion 18.3 ± 7.7 months, Hohen & Yahr (H & Y) stage 1.5 to 2.5, on sustained monotherapy with ropinirole extended release for no longer than 6 months at a stable median daily dosage of 8 mg (range 6-8 mg) for at least 3 months, were randomized in 3 arms: early rasagiline 1 mg daily (Group A), delayed rasagiline 1 mg daily six months later (Group B) and carrying on ropinirole monotherapy (Group C). Efficacy outcomes of the symptomatic effect of rasagiline were change in UPDRS parts II and III, H&Y stage and PDQ 39 scores from baseline to 3 and 6 months for Group A in comparison with Groups B and C and change from 6 months to 12 months for Group B in the same rating scales. The symptomatic effect of rasagiline obtained in Groups A and B was also compared. The putative neuroprotective action of rasagiline was assessed by comparing the scores of the above mentioned scales at 12 months of follow-up among the three Groups of patients. Adverse events were recorded at each assessment time during the follow-up. Statistical analysis was performed by using Student t test, Anova and mixed-effects Anova correcting the significances for multiple comparisons (Bonferroni correction) when necessary, for paired or independent samples or non parametric analogues for not normally distributed data. SPSS v23 was used for all the analysis, setting at p < .05 the significance level.

**Results:** At the inclusion there was no significant difference between the Group A (n=26), Group B (n= 24) and Group C (n= 36) in terms of gender distribution, age, duration of PD, H&Y stage, UPDRS parts II and III and PDQ 39 scores, duration and daily dosage of ropinirole. There was not significant difference in the scores of UPDRS II, III, II plus III combined and PDQ39 between the inclusion and those at 3 and 6 months after the adjunct of rasagiline in Group A and between 6 and 12 months in Group B. In contrast, the scores of UPDRS II, III, and II
plus III combined at 3 and 6 months in Group B and at 6 months in Group C showed a significant worsening as compared to baseline.

There was not significant difference in the scores of UPDRS II, III and PDQ39 among the three Groups at the 12 months assessment, even though a clear-cut trend toward a worsening in the scores of the above mentioned rating scales was observed in Groups B and C as compared to Group A. Mild to moderate adverse effects were reported by 70 patients (81.4%) and 3 patients dropped out due to nausea and vomiting (Group A), psychosis (Group B), lower limbs oedema (Group C), respectively.

Conclusions: The main finding of this study is the stabilization (possibly symptomatic effect) of the scores of UPDRS II and III and PDQ39 in the first six months following the adjunct of rasagiline in Group A and Group B, in contrast with a progressive worsening of the the same scores in Group C. A neuroprotective effect of rasagiline could not be demonstrated at 12 month, even though the scores of the three rating scales in Group B were found to parallel those of Group C, showing a course divergent from that of Group A.

LBA 14
A Minipig Model of Parkinson’s Disease Induced by Proteasome Inhibition: A Multi-Tracer PET Imaging Study

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**Objective:** The objective of this study was to chronically inhibit the ubiquitin proteasome system (UPS) in minipigs to induce a model of Parkinson’s disease (PD). Non-invasive in vivo positron emission tomography (PET) on the dopaminergic, serotonergic and noradrenergic neurotransmitter systems was used to evaluate the feasibility and face validity of the minipig model as a progressive model of PD.

**Background:** To various degrees, both PD and aging are characterized by progressive decreases in the activity of the UPS presumably contributing to the pathological widespread cell death and protein aggregation (Lewy bodies) observed in PD. These cellular impairments are involved in several of the motor and non-motor aspects of PD related to multiple neurotransmitter systems. There is an urgent need to develop a reliable model that reproduces both the progression and clinical presentation of the idiopathic disease in addition to its pathological features.

**Methods:** Eight adult minipigs were implanted with an intracerebroventricular (ICV) catheter connected to a subcutaneous injection port. An UPS inhibitor, lactacystin, was injected weekly into the port. PET scans were performed with [11C]DTBZ (tracer of the vesicular monoamine transporter), [11C]Yohimbine (tracer of the alpha2-adrenergic receptor) and [11C]DASB (tracer of the serotonin transporter) at baseline and to date 5-6 of the animals have had follow up scans between 2 and 7 months after the start of lactacystin injections. The animals were longitudinally monitored for motor deficits.

**Results:** Our preliminary analysis of the first animals shows that lactacystin administration induced decreases in [11C]DTBZ and [11C]DASB binding in striatal regions compared to baseline, consistent with loss of dopaminergic and serotonergic brainstem neurons in PD. An increased volume of distribution of [11C]Yohimbine was detected in thalamic and cortical regions, likely reflecting upregulation of the receptors in response to loss of pontine adrenergic cell bodies. Moreover, impairments in motor performance were observed.

**Conclusions:** Our imaging data are consistent with Braak’s pathology staging of PD, which suggests a caudo-rostral gradient of deficits with serotonergic, noradrenergic and dopaminergic nuclei affected in PD. Prolonged UPS inhibition may provide a new, progressive model of PD useful in the investigation of both motor and non-motor deficits.
LBA 15
Predictors of outcome of STN-DBS in Parkinson’s disease with early motor complications

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Objective: To investigate the effects of age, disease duration, and disease severity on quality of life (PDQ-39-SI) after deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson’s disease (PD) with early motor complications.

Background: This was a study in patients with PD and recent onset of motor complications who were randomized to either STN-DBS plus best medical treatment (BMT) or BMT alone followed for 24 months. The EARLYSTIM trial[1] had intentionally chosen permissive inclusion criteria that allowed a rather broad population of PD patients to be included. Yet, the relative contributions of age, duration of disease, and severity of disease to the outcome of quality of life needed to be evaluated.

Methods: EARLYSTIM was a prospective randomized study comparing STN-DBS to BMT after 2 years follow-up with quality of life (PDQ-39-SI) as the primary endpoint. Mixed model repeated measures regression analyses of the baseline characteristics versus the change in quality of life at 5, 12, and 24 months were conducted. P-values ≤0.05 were considered statistically significant.

Results: No correlation was found of age at randomization, disease duration, and years with motor complications with change from baseline to follow-up in PDQ-39-SI in either treatment group. The severity of disease measured at baseline with the Unified PD Rating Scale (UPDRS-III off and on medications, UPDRS IV) did not correlate with the change from baseline to follow-up in PDQ-39-SI in either treatment group. The PDQ-39-SI at baseline was significantly correlated to the change from baseline to follow-up in PDQ-39-SI in both treatment groups (p<0.05). The higher the baseline score (worse quality of life) the larger the improvement in quality of life at 24 months.

Conclusions: In the EARLYSTIM cohort of relatively young patients with PD and early motor complications, STN-DBS improved quality of life independently from age, disease duration and disease severity. However, quality of life at baseline was a predictor for the change in quality of life.

LBA 16
Predictors of cognitive impairment in Parkinsons disease – first report from Belgrade PD Study

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Objective: To report the rates and predictors of progression to either mild cognitive impairment (MCI) or dementia, in PD patients, using standardized neuropsychological methods.

Background: More than half of Parkinson's disease (PD) patients develop some kind of cognitive impairment during the disease course, which significantly affects the quality of life, prognosis and mortality of these patients.

Methods: In this longitudinal study, a comprehensive neuropsychological battery covering five domains (attention/working memory, executive, verbal, and visual memory, language, and visuospatial) was administered to 132 nondemented PD patients and to 105 healthy matched controls (HC). MCI was diagnosed according to level 2 of the Movement Disorder Society Task Force criteria. Patients were classified as having normal cognition, MCI, or...
dementia at baseline and followed in yearly intervals for 2 consecutive years. Kaplan-Meier curves and Cox proportional hazard models were used to examine cognitive decline and its predictors.

**Results:** Patients averaged 66.8 years of age, 66% men, who had PD on average for 6.3 years. The cumulative incidence of cognitive impairment was 12.5% at year 2. 15% of incident MCI cases had progressed to dementia by the last follow up. In a multivariate analysis, predictors of future decline were older age (p<0.001), male sex (p<0.005), higher Unified Parkinson's Disease Rating Scale motor score (p<0.001), presence of freezing (p<0.005), worse global cognitive score (p<0.001) and REM sleep behavior disorder (p<0.005).

**Conclusions:** Transition from normal cognition to cognitive impairment, including dementia, occurs frequently in PD. Certain clinical and cognitive variables may be useful in predicting progression to cognitive impairment in PD.

**LBA 17**

**Direct autophagy inhibition induces dopaminergic deficits in the substantia nigra in rats**

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**Objective:** In this exploratory study, we investigated if unilateral nigral injections of a non-specific autophagy inhibitor were able to induce dopaminergic (DA) deficits in rodents.

**Background:** One of the landmarks of Parkinson’s Disease (PD) is the pathological accumulation of protein aggregates known as Lewy bodies. Clearance of abnormal or misfolded proteins is handled in concert by the ubiquitin proteasome system (UPS) and various autophagy mechanisms. While local administration of a UPS inhibitor in the substantia nigra has been shown to induce dopaminergic cell loss, it is still unclear if a similar single administration of an autophagy inhibitor in the substantia nigra of a healthy rat is sufficient to induce similar deficits.

**Methods:** A non specific inhibitor of the autophagy-lysosomal pathways (ALP) (ammonium chloride which can be dissolved in sterile saline), or the vehicle (sterile saline) were injected in the right substantia nigra of Sprague Dawley rats using the same coordinates as we routinely use in our 6OHDA studies. Behavioral evaluations (cylinder test and rotarod) were performed at baseline and 8 weeks after injection. MicroPET scans with a validated marker of the striatal DA terminals, 11C-dihydrotetrabenazine (DTBZ), were obtained 4-8 weeks post surgery in a subset of the animals. The animals were euthanized and the brain fixed in 4% paraformaldehyde for immunohistochemistry with TH and anti-inflammatory markers (ongoing). The DTBZ binding potential was estimated as the activity ratio between striatum and cerebellum minus 1 and the denervation severity as the ratio of the right (lesioned) to the left (intact) striatum.

**Results:** Preliminary results from in vivo microPET scanning revealed a significant decrease in the DTBZ binding potential in the striatum ipsilateral to the nigral injections. In this small subset (N=8), the denervation severity was minimal to moderate with the binding potential in the denervated side being 75 to 85% of the intact side. Preliminary post-mortem evaluation confirmed loss of TH immuno-reactivity in the injected side and increased presence of activated microglia around the injection side in the ALP inhibitor injected rats compared to controls. The unilaterally lesioned animals demonstrated increased asymmetry in the cylinder test and impaired motor function in the rotarod.

**Conclusions:** This is, to the best of our knowledge, the first study reporting the effect of a non specific autophagy inhibitor applied directly in the substantia nigra of a rat on the dopaminergic nigral system. Ammonium chloride was chosen because it is a non specific inhibitor and easily dissolved in saline. Further studies using specific inhibitors of chaperone-mediated, macro and micro-autophagy at various doses need to be performed to confirm this findings, dose-dependence and determine if decreased activity of all 3 autophagy systems is required for a toxic effect and pinpoint mechanisms. However our finding demonstrates a new mechanism for neurodegeneration and a possible lead for development of new neuroprotective therapies.
LBA 18

10-year follow-up of the German multicenter study on pallidal neurostimulation for generalized or segmental dystonia

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Objective: To evaluate clinical efficacy and safety of pallidal neurostimulation in patients with isolated generalized or segmental dystonia prospectively followed for 10 years within the framework of a controlled multicenter trial.

Background: Pallidal neurostimulation is a safe and efficacious treatment for severe isolated dystonia but long-term results from controlled clinical trials are still missing.

Methods: In the parent trial 40 patients were randomized to either sham- or neurostimulation for a period of 3 months and thereafter all patients were effectively stimulated for 6 months; 38 of these 40 patients agreed to annual follow-up visits for a period of up to five years. The study was amended to a 10 years follow-up, which was attended by 31 patients. Follow-up assessment included BFMDRS motor and disability score, SF36, BDI, BAI and GCI.

Results: An intention to treat and a per protocol analysis, revealed a sustained and significant improvement of the BFMDR motor score after 10 years compared to preoperative baseline but no significant change compared to 6 months and 5 years follow-up. On average the motor score had decreased by 48.0% at 6 months, 64.5% at 5 years and 53.4% at 10 years (per protocol analysis) but individual outcomes were variable. In the intention to treat population 27 patients were classified as responders (>25% improvement) with mean improvement of -65.2 + 21.4% (-31.5 to -100%) compared to preoperative baseline and 13 as non-responders with a mean change of 8.5 + 27.3% (range -21.0 to 60.0%) in motor BFMDRS after 10 years. Further, sustained improvement was also found for non-motor parameters such as BDI, BAI, SF-36.

Conclusions: On a group level, the efficacy of pallidal neurostimulation is sustained over 10 years after surgery in patients with generalized and segmental dystonia. The majority of patients (67.5%) showed a large and consistent response to chronic neurostimulation but about one third of patients has no or limited response on the long term. The individual outcomes require more detailed analysis of contributing factors such as lead location, stimulation parameters, adverse effects and variable disease progression in different types of dystonia.

LBA 19

Early and Late Onset Parkinson's Disease: two different entities?

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Objective: We aimed at investigating whether the neurovascular status differs in EOPD from PD and healthy subjects.

Background: Parkinson's Disease (PD) is the second most common neurodegenerative disease typically age-related. However, the 10% of subjects has an anticipated onset of the disease that is called Early Onset Parkinson’s disease(EOPD) (age of onset <45 yrs.).
**Methods:** Six participants with PD (3 males and 3 females, age 68 ± 9 yrs) and 5 EOPD patients (3 males and 2 females, age 42 ± 8 yrs) without known mutation involved in PD/EOPD underwent a Pulsed Ar-terial Spin Labeling (PASL) study of brain perfusion by 1.5 T MRI. We analyzed 10 representative Regions of Interest (ROI’s) involved in Parkinson’s disease. All the studied subjects took L-dopa before the MRI study.

**Results:** PD patients showed a significantly increased mean blood flow in the right centrum semiovale in comparison with age-matched normal controls (PD patients 29.22 ± 8.82 ml/100g/min; healthy subjects 18.27 ± 6.61 ml/100g/min; p=0.0371). The same result was found in the left centrum semiova-le (PD patients 40.89 ± 13.17 ml/100g/ min; healthy subjects 24.87± 6.96 ml/100g/ min; p=0.03). Conversely, EOPD patients didn’t show any significant difference in cerebral blood flow in comparison with the age matched healthy subjects. The comparison between EOPD and PD patients showed markedly lower blood flow in the right centrum semiovale in EOPD patients (EOPD patients 14.88 ±10.1 ml/100g/ min; PD patients 29.22 ±8.82 ml/100g/ min; p= 0.037) and left centrum semiovale (EOPD patients 15.19 ±11.59 ml/100g/ min; PD patients 40.89 ± 13.17 ml/100g/ min; p=0.007).

**Conclusions:** This is the first non invasive study evaluating the regional cerebral blood flow in patients affected by EOPD. EOPD separates from PD since brain perfusion shows different patterns in the two groups. These results could yield promising developments in the understanding of the basis of the neurodegeneration processes involved in Parkinson Disease.

**LBA 20**

Nicotinamide: A Key Player in the Developmental Origins of Parkinson’s disease?

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**Objective:** To investigate the role of vitamin B3 (nicotinamide) in the formation of midbrain dopamine neurons.

**Background:** The identification of nicotinamide as a morphogen points to a critical role for vitamin B3, in addition to its metabolite N-methyl-nicotinamide during development in influencing cell fate specification. There is growing evidence to suggest that nicotinamide levels must be tightly regulated to prevent neural defects caused by either too little or too much of this vitamin. With a normal diet, levels of nicotinamide are tightly regulated; however, vitamin B3 deficiency leads to Pellagra, whose phenotype include a range of neurological syndromes, mainly cognitive, but including motor and non-motor features of Parkinsonism.

**Methods:** Monolayer mouse embryonic stem cell cultures (mESC; Sox1GFP knock in 46C cell line) were treated with nicotinamide for different durations at specific developmental stages on the pathway from stem cells to neurons. Immunocytochemistry/ fluorescence microscopy was performed to assess the expression of stem cell, neural progenitor (NP) and neuronal subtype markers. Morphometric analyses were also performed to assess the extent of maturation and neurite development.

**Results:** For the first time, we showed that nicotinamide is fundamental in driving stem cells towards a neural lineage and accelerating their development to yield higher numbers of neurons, specifically dopamine neurons. We have some preliminary evidence that this effect is dependent on the dose received; there is a peak effect at a specific concentration (10mM), with higher doses being toxic to stem cells (20mM). Importantly, nicotinamide was shown to accelerate the conversion process by reducing the proportion of proliferating cells – that is, nicotinamide regulates the proliferation-to-differentiation switch from NP cells to neurons during brain development. Finally, we found that nicotinamide alone is as effective in creating new dopamine neurons as complex mixtures of cell culture additives that have been used in previously published methods.

**Conclusions:** We believe that an optimal dose of nicotinamide is critical for brain development and when outside this range could influence whether dopamine neurons are at risk of damage/death. Future work may add information on if Parkinson’s develops later in life, as a result of lack of or excess of vitamin B3. Also, as stem cell based
therapies are increasingly considered for Parkinson’s disease, we are confident that nicotinamide will offer a simple, safe and cost-effective media supplement in protocols currently being developed toward clinical application.

**LBA 21**

**DPI-289, a novel delta opioid agonist / mu opioid antagonist, has potential to provide an L-DOPA-sparing approach in Parkinson’s disease**

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**Objective:** To evaluate the therapeutic potential of DPI-289 as an L-DOPA-sparing strategy in the MPTP-lesioned non-human primate model of Parkinson’s disease (PD).

**Background:** L-DOPA-induced dyskinesia (LID) remains a significant problem in the management of PD. Reducing L-DOPA dose can reduce dyskinesia but at the expense of anti-parkinsonian benefit. A therapy that could enhance L-DOPA actions without exacerbating dyskinesia would allow L-DOPA reduction to be implemented as a means to avoid the impact of LID. In rodent and non-human primate (NHP) models of PD, delta opioid receptor agonists have anti-parkinsonian actions while mu opioid antagonists can reduce the expression of LID. DPI-289 is a novel, small molecule drug with a combination of delta opioid agonist and mu opioid antagonist (DAMA) actions. We hypothesised that the combined actions of a DAMA would provide an enhancement of L-DOPA actions that were not associated with increased L-DOPA-induced dyskinesia.

**Methods:** Eight female cynomolgus macaques were rendered parkinsonian with MPTP. LID was established by repeated once daily L-DOPA therapy. The actions of DPI-289 (1-20mg/kg, p.o.) on motor activity, parkinsonism and dyskinesia, as monotherapy and in combination with L-DOPA were evaluated for 6 h after acute administration. For each animal, two doses of L-DOPA were defined, high (LDh) and low (LDl) so as to provide either a maximal anti-parkinsonian benefit (LDh, lasting approximately 3h, though typically compromised by dyskinesia) or a threshold anti-parkinsonian benefit (LDl, short duration though not typically associated with dyskinesia).

**Results:** As monotherapy, DPI-289 (10 and 20mg/kg) had significant, though incomplete, anti-parkinsonian actions lasting approximately 4 h. These benefits were not associated with dyskinesia. Thus, DPI-289 (20 mg/kg) decreased parkinsonism by 19% and increased activity by 67% (P<0.001 and P<0.05 respectively, both cumulated over the entire 0-6 h observation period cf. vehicle treatment.). In contrast, LDh alleviated parkinsonism, lasting for approximately 3 h. However, these benefits were accompanied by significant dyskinesia that was disabling in nature. LDh provided a 50% reduction in parkinsonism over 0-6 h (P<0.01) and 151% increase in activity (P<0.05). The combination of DPI-289 (20 mg/kg) and LDl provided anti-parkinsonian benefits greater than LDl alone without eliciting any significant dyskinesia. Thus, LDl alone provided only threshold anti-parkinsonian benefit that did not reach significance. However, the combination of LDl and DPI-289 decreased parkinsonism for up to 5 h (p<0.01 cf. vehicle alone), longer than either LDh, LDl or DPI-289 alone, with parkinsonism being reduced by 35% and activity increased by 90% (both P<0.05 cf. vehicle alone). Combination therapy resulted in no change in levels of dyskinesia compared to LDl alone. The actions of the L-DOPA/ DPI-289 combination were qualitatively distinct to those of high dose L-DOPA alone, being especially pronounced on postural and attentional deficits. No adverse effects of treatment were observed at any period during the study.

**Conclusions:** DPI-289, as monotherapy, had modest anti-parkinsonian effects in MPTP-lesioned NHPs, but significant synergistic prolonged effects without worsening dyskinesia in L-DOPA experienced MPTP-lesioned NHPs receiving threshold therapeutic doses of L-DOPA (LDl). This indicates that DPI-289 may have unique therapeutic value for L-DOPA experienced Parkinson’s Disease patients with dose limiting dyskinesia.

**LBA 22**

**The Substantia Nigra 7 Tesla MRI in patients with REM Behaviour Disorder: new evidences supporting the link with neurodegenerative diseases**

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Objective: To evaluate 7 Tesla MRI anatomy of the SN in patients with Rapid-eye-movement (REM) sleep behaviour disorder (RBD).

Background: Seven Tesla (7T) MRI of the Substantia Nigra (SN) by means of high resolution three-dimensional Susceptibility-Weighted imaging has been described and its pathological correlate well defined. The loss of normal SN aspect is able to distinguish Parkinson's Disease (PD) patients from healthy subjects (HS) on an individual basis with high accuracy. Patients with RBD can develop synucleinopathies as PD, Multiple System Atrophy and Lewy Body Dementia associated with substantia nigra dysfunction and the risk of conversion is greater in patients with trans-cranial sonography or SPECT evidence of SN and nigro-striatal involvement.

Methods: We enrolled 7 patients (5 M, 2 F, mean age 71.6 ys) with polysomnography-confirmed RBD (disease duration range 1-11 years) and a brain SPECT with 123I FP-CIT suggestive for dopaminergic nigrostriatal dysfunction. All patients were clinically evaluated to exclude the presence of parkinsonism. Ten healthy subjects (HS) and 10 PD patients age-matched were also enrolled. 7T 3D-Gradient multi-echo susceptibility weighted image targeted to the midbrain was obtained in all subjects. Images were rated by an expert neuroradiologist blinded as for the diagnosis. According to recent evidences, SN was defined normal if hyperintense laminar and oval shaped areas could be detected into the larger hypointense area, abnormal if the SN appeared as a homogeneous hypointense structure at least at one level on one side of the midbrain.

Results: Six out of 7 patients exhibited abnormal 7T-MRI SN. Three patients showed asymmetrical SN involvement, 3 showed bilateral symmetrical involvement. The patient with normal MRI had the shortest disease duration (1 year). All the PD patients were rated as abnormal, and all the HS as normal.

Conclusions: Our data, although on a small sample of patients, support the SN involvement in RBD and the possible neurodegenerative process at least in some RBD patients. These findings also suggest the use of SWI MRI as possible marker of neurodegeneration in patients with RBD, however longitudinal evaluation on a larger group of subjects even without nigrostriatal dysfunction will clarify the impact of 7T SN abnormality in predicting the “motor” conversion of RBD patients and the mutual relationship of nigral anatomical changes with dopamine transporter presynaptic availability.

Assessment of tau pathology in patients with corticobasal syndrome using 18F-THK5351 PET

Akio Kikuchi, Akio Kikuchi, Takaumi Hasegawa, Ryuichi Harada, Shoichi Watanuki, Yoshihito Funaki, Kotaro Hiraoka, Toru Baba, Naoto Sugeno, Ryuji Oshima, Shun Yoshida, Junpei Kobayashi, Michihiro Ezura, Michiko Kobayashi, Ohito Tano, Shunji Mugikura, Ren Iwata, Aiko Ishiki, Katsutoshi Furukawa, Hiroyuki Arai, Shozo Furumoto, Manabu Tashiro, Kazuhiko Yanai, Yukitsuka Kudo, Atsushi Takeda, Masashi Aoki
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Sendai, Miyagi, Japan

Objective: We aimed to determine whether 18F-THK5351 PET can visualize tau deposits in living brain lesions in patients with corticobasal syndrome (CBS).

Background: Noninvasive imaging of tau protein deposits is potentially useful for early diagnosis of tauopathies including CBS.

Methods: We evaluated in vitro binding of 3H-THK5351 in post-mortem brain tissues from a patient with corticobasal degeneration (CBD). In clinical PET studies, 18F-THK5351 retention in five patients with CBS was compared with that in eight age-matched normal controls.

Results: The 3H-THK5351 was able to bind to tau deposits in the postmortem brain with CBD. In clinical PET studies, five CBS patients showed significantly higher 18F-THK5351 retention in the bilateral precentral and
postcentral gyri, globus pallidus, and putamen than eight age-matched normal controls. Higher 18F-THK5351 retention was observed contralaterally to the predominant side of higher cortical dysfunctions and parkinsonism.

**Conclusions:** 18F-THK5351 PET demonstrated high tracer signals in sites susceptible to tau deposition in patients with CBS. 18F-THK5351 should be considered as a promising candidate radiotracer of in vivo tau deposits in CBS.

**LBA 24**

**Drug re-positioning for Parkinson's disease dementia**

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*King's College London*  
*London, United Kingdom*

**Objective:** Cognitive impairment is a common fate in Parkinson's disease (PD), with risk of dementia increasing with age and years with PD (Buter et al., 2008). Currently, rivastigmine is the only licensed pharmacological therapy for Parkinson's disease dementia (PDD), and the need for new and more effective treatments for PDD is therefore imperative. Drug re-positioning offers an exciting and potentially valuable approach to drug development in PD/PDD. The process involves the identification of compounds which are already licensed for other therapeutic targets but which have mechanisms of action that indicate potential disease modification in PDD. In order to identify new potential therapeutics for PDD, we have utilised a bioinformatics approach to obtain a list of drugs and drug-like compounds which transcriptional profile is anti-correlated to transcriptional changes associated with PDD.

**Background:** The Broad institute's connectivity map project (CMAP) (Lamb, 2007) identified gene expression profiles for cultured human cells treated with a wide spectrum of drug-like compounds. By comparing these profiles to transcriptional changes associated with disease states, one can obtain a functional connection between drugs, genes and disease. Recently, a searchable platform-independent expression database (SPIED) extended the CMAP methodology to cover transcriptional data in the public domain (Williams, 2012). The use of CMAP and SPIED has allowed us to identify a list of clinically available drugs which show potential neuroprotective ability in PDD.

**Methods:** We have been utilising a human dopaminergic cell line (SH-SY5Y), to validate the neuroprotective ability of a selection of compounds identified by CMAP/SPIED in vitro. We have selected the top 50 transcriptional anti-correlates as potential PDD therapeutic drugs, as well as 10 correlates serving as negative controls. SH-SY5Y cells are treated with parkinsonian toxins MPP+ or 6-OHDA and exposed to varying concentrations (0.1 - 100µM) of the potential therapeutic drug. Vehicle and compound-alone controls are included in each experiment. Finally, cells are treated with cell viability PrestoBlue reagent and a quantitative fluorescence reading is measured.

**Results:** Thus far, 35 out of 41 tested compounds have proven neuroprotective at some concentration against MPP+ toxicity. A number of these compounds have also been tested against the parkinsonian agent 6-OHDA, though these experiments are still ongoing. The potential therapeutics identified include a series of antibiotics, anti-depressants, mTOR modulators and anti-diabetics. These classes of compounds have also been shown to be neuroprotective in other recent studies, further validating the results obtained.

**Conclusions:** This in vitro cell viability assay has identified a large number of positive hits, validating the use of CMAP and SPIED as tools to aid drug discovery for PDD. We aim to test the remaining compounds in vitro and select a number of candidates to proceed into in vivo studies using standard animal models of PD. In conclusion, validation of CMAP/SPIED bioinformatics studies using an in vitro based cell viability assay proved an efficient and fast method of identifying novel therapeutic prospects for PDD. Since the drugs tested already have established safety profiles, the time and cost required for taking these novel PDD therapeutics into clinical trials is greatly reduced.
Objective: To assess the efficacy of levodopa-carbidopa intestinal gel (LCIG, designated in the United States as carbidopa-levodopa enteral suspension [CLES]) on non-motor symptoms (NMS) and the safety of outpatient titration in a phase 3 study of LCIG in advanced Parkinson’s disease (PD) patients.

Background: LCIG, delivered via percutaneous gastrojejunostomy (PEG-J) and titrated in the inpatient setting, is reported to reduce motor fluctuations in advanced PD patients [ref1]. The effect of LCIG on NMS and the long-term safety of outpatient titration at 60-week follow-up have not been reported.

Methods: In this 60-week, open-label Phase 3 study, LCIG titration was initiated as a monotherapy in an outpatient setting following PEG-J placement. The change in NMS from baseline (BL) to Week 12 (primary outcome) and Week 60 was measured by the Non-Motor Symptom Scale (NMSS) total score; additional measures included NMSS domain scores, and normalized “off” time and “on” time without troublesome dyskinesia (TSD) as measured by a patient diary. Treatment extension was permitted for patients who completed their Week 60 visit before LCIG was commercially available. Adverse events (AE) were monitored.

Results: Of the 39 advanced PD patients enrolled, 28 completed the treatment. The mean total duration of LCIG infusion was 427 (189) days (n= 38). The mean NMSS total score and 6 of the NMSS domain scores were significantly reduced at Week 12 compared to BL, and these reductions were maintained at Week 60 with the exception of the urinary domain.[table1] There were accompanying improvements in normalized “off” time and “on” time without TSD at Week 12 that were also maintained at week 60.[figure 1] There were 37 (94.9%) patients with AEs and 8 (20.5%) with serious AEs; the most frequently reported AE was procedural pain (33.3%).[table 2] Five (12.8%) patients discontinued due to AE. There was one death, which was deemed unrelated to the therapeutic system.

Conclusions: LCIG treatment following outpatient titration led to reductions in NMS burden and motor fluctuations in advanced PD patients. The safety profile was consistent with previous studies that used inpatient titration and outpatient titration does not appear to pose additional risks [ref1].

References: 1. Fernandez et al. Mov Disord. 2014

Table 1: Mean Change from Baseline on the Non-Motor Symptom Scale Total Score and Domains

<table>
<thead>
<tr>
<th></th>
<th>BL (n=38) Mean (SD)</th>
<th>Week 12 (n=35) LS Mean (SE) Change from BL</th>
<th>P Value</th>
<th>Week 60 (n=28) LS Mean (SE) Change from BL</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMSS total scorea</td>
<td>48.3 (35.6)</td>
<td>-17.6 (3.6)</td>
<td>&lt;0.001</td>
<td>-11.8 (4.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>NMSS domainsb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascularb</td>
<td>1.4 (2.1)</td>
<td>-0.2 (0.4)</td>
<td>ns</td>
<td>0.5 (0.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Sleep/Fatigue</td>
<td>11.6 (9.2)</td>
<td>-6.0 (1.2)</td>
<td>&lt;0.001</td>
<td>-5.4 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mood/Cognition</td>
<td>4.1 (6.2)</td>
<td>0.0 (1.1)</td>
<td>ns</td>
<td>0.5 (1.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Perceptual problems/Hallucinations</td>
<td>1.9 (3.8)</td>
<td>-0.5 (0.4)</td>
<td>ns</td>
<td>0.4 (0.4)</td>
<td>ns</td>
</tr>
</tbody>
</table>
NMSS total score and NMSS domains were analyzed by a mixed-effect model for repeated measures using factors of study site, visit, and baseline and the baseline-by-visit interaction.

Including falls

The Miscellaneous domain includes questions on pain, change in the ability to taste and/or smell, weight change and excessive sweating.

BL = baseline; NMSS = non-motor symptom scale; SD = standard deviation; LS = least squares; SE = standard error; ns = not significant

Figure 1: Mean Change from Baseline in PD Diary Measures

Diary data were normalized to 16 waking hours and analyzed by a mixed-effect model for repeated measures using factors of study site, visit, and baseline and the baseline-by-visit interaction. Error bars indicate standard error. ***p<0.001; BL = baseline; TSD = troublesome dyskinesia

Table 2: Summary of Safety

<table>
<thead>
<tr>
<th>Safety</th>
<th>N (% of N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>37 (94.9)</td>
</tr>
<tr>
<td>Any Serious AE</td>
<td>8 (20.5)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>AEs occurring in &gt; 10% patients (N=39):</td>
<td></td>
</tr>
<tr>
<td>Procedural pain</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td>Stoma site infection</td>
<td>11 (28.2)</td>
</tr>
<tr>
<td>Stoma site pain</td>
<td>9 (23.1)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8 (20.5)</td>
</tr>
<tr>
<td>Stoma site erythema</td>
<td>8 (20.5)</td>
</tr>
<tr>
<td>Fall</td>
<td>7 (17.9)</td>
</tr>
</tbody>
</table>
Robust dopamine graft survival and extensive dopaminergic innervation does not obligate clinical recovery in a patient with Parkinson’s Disease

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Chicago, IL, USA; Sidney, Australia, Vancouver, British Columbia, Canada, Tampa, FL, USA, New York, NY, USA

Objective: To report a unique case in which a PD patient had robust dopamine graft survival and normalized putamenal dopaminergic reinnervation, but never displayed any functional recovery

Background: Dopaminergic cell replacement strategies have been proposed and employed to treat the motor features of Parkinson’s disease (PD). The goal has been robust graft survival and dopaminergic striatal reinnervation coupled with clinical improvement. This report documents a unique case that came to autopsy sixteen years following fetal nigral grafting.

Methods: This 55 year old female PD patient with tremor predominant PD and a good response to levodopa received bilateral solid grafts from 4 fetal mesencephalon aged 6.5-9 weeks post-conception placed into the post commissural putamen as part of our double blind NIH sponsored fetal transplant trial (Olanow et al., 2003). This patient was followed postoperatively for 31 months post-operatively in a blinded fashion and for an additional 12 years in an open label fashion. Fluorodopa positron emission tomography was also performed preoperatively and at 1 and 2 years post-grafting. Eight-years post-transplantation this patient received bilateral subthalamic nucleus deep brain stimulation to control severe dyskinesias. This patient died 16-years post-transplantation and the post-mortem interval was 6h.

Results: This patient never demonstrated any meaningful clinical benefit following grafting as determined by UPDRS in “off” (primary outcome measure) or “on” states or in any of the other secondary endpoints. Modest “off-medication” diphasic dyskinesias were observed. Robust increases in fluorodopa uptake was seen bilaterally in the putamen on PET. Post-mortem analyses confirmed the diagnosis of PD. Surviving grafts containing >300,000 TH positive grafted cells per side lead to and the densest and most extensive putaminal TH-ir fiber innervation reported in patients to date. About 25% of grafted cells stained positively for serine 129-phospho alpha synuclein.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight decreased</td>
<td>7 (17.9)</td>
</tr>
<tr>
<td>Urinary tract inflection</td>
<td>6 (15.4)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>5 (12.8)</td>
</tr>
<tr>
<td>Excessive granulation tissue</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>Stoma site irritation</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>Vitamin B6 Deficiency</td>
<td>4 (10.3)</td>
</tr>
</tbody>
</table>
subpopulation were positive for thioflavin S. Excessive melanin formation relative to the age of the cells was also observed.

**Conclusions:** Extensive dopaminergic graft viability and robust host innervation did not induce a short- or long-lasting positive clinical response in this patient and suggests that the goal of robust graft survival and striatal reinnervation is not always sufficient to translate into clinical benefit in PD.

**LBA 27**  
Baseline characteristics associated with therapeutic response to levodopa-carbidopa intestinal gel treatment for advanced Parkinson disease

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University of Alabama at Birmingham, Birmingham, Alabama, USA; University of Vermont College of Medicine, Burlington, Vermont, USA; Lund University, Lund, Sweden; AbbVie Inc., North Chicago, IL, USA; AbbVie Inc., North Chicago, IL, USA; AbbVie Inc., North Chicago, IL, USA, Birmingham, AL, USA

**Objective:** To identify baseline (BL) clinical characteristics associated with a therapeutic response to levodopa-carbidopa intestinal gel (LCIG, designated in the United States as carbidopa-levodopa enteral suspension [CLES]) in patients with advanced Parkinson disease (PD) during a 54-week, open-label phase 3 study.

**Background:** A previous report demonstrated that LCIG, administered via percutaneous gastrojejunostomy, reduced motor fluctuations in advanced PD patients [ref1], however the correlation between BL clinical characteristics and response to treatment was not examined.

**Methods:** Of the 354 patients enrolled, 307 patients had both BL and post-BL PD symptom diary data and were included in this newly available post-hoc analysis. Patients with a change from BL to final visit of at least 1 hr improvement in “Off” time were categorized as “Responders”; those with <1 hr improvement or worsening were “Non-Responders” [ref2]. BL demographics and disease characteristics were analyzed in the 2 subgroups. The correlations between BL characteristics and the change from BL in normalized “Off” time as well as “On” time with troublesome dyskinesia (TSD) were determined. Correlations with BL PD symptom scales were also examined.

**Results:** Out of the 307 patients, 272 (89%) were categorized as Responders and 35 (11%) were Non-Responders [table1]. Baseline characteristics were remarkably similar between Responders and Non-responders [table2]. No significant relationships were observed between change in “Off” time, or “On” time with TSD, and BL patient age, PD duration, or BMI [table2]. Baseline UPDRS Score did not differ between the 2 subgroups, but a higher BL Total UPDRS score was associated with a greater reduction in “Off” time ($r = -0.156; P = 0.009$). Adverse events were common and mostly mild to moderate in severity in this patient population as previously described [ref1].

**Conclusions:** LCIG treatment led to an improvement in “Off” by at least 1 hour in 89% of advanced PD patients. Notably, Responders to LCIG were observed independent of the range of BL demographics and clinical characteristics and a higher UPDRS was associated with a greater response to treatment.


**Table 1: Responder Classification**

<table>
<thead>
<tr>
<th>Change from BL in “Off” time</th>
<th>n (% of N=307)</th>
<th>Responder Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deteriorated</td>
<td>16 (5.2%)</td>
<td>Non-Responder</td>
</tr>
<tr>
<td>Improved by &lt; 1 hour</td>
<td>19 (6.2%)</td>
<td>Non-Responder</td>
</tr>
<tr>
<td>Improved between 1 and 2 hours</td>
<td>27 (8.8%)</td>
<td>Responder</td>
</tr>
<tr>
<td>Improved ≥ 2 hours</td>
<td>245 (79.8%)</td>
<td>Responder</td>
</tr>
</tbody>
</table>

BL = baseline
Table 2: Baseline Patient Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>BL. Characteristics</th>
<th>Responder (N=272)</th>
<th>Non-Responder (N=35)</th>
<th>Correlation with Change in PD Diary Assessments</th>
<th>Change in “Off” Time (r (P Value))</th>
<th>Change in “On” Time with TSD (r (P Value))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>64.1 (9.0)</td>
<td>64.0 (9.5)</td>
<td>0.015 (0.794)</td>
<td>0.003 (0.958)</td>
<td></td>
</tr>
<tr>
<td>&lt; 65, n(%)</td>
<td>133 (88)</td>
<td>18 (12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65, n(%)</td>
<td>139 (89)</td>
<td>17 (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n(%)</td>
<td>115 (88)</td>
<td>15 (12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>157 (89)</td>
<td>20 (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.0 (4.6)</td>
<td>23.4 (4.2)</td>
<td>-0.105 (0.068)</td>
<td>0.010 (0.867)</td>
<td></td>
</tr>
<tr>
<td>&lt; 25, n(%)</td>
<td>146 (85)</td>
<td>25 (15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 25, n(%)</td>
<td>126 (93)</td>
<td>10 (7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD duration (years), mean (SD)</td>
<td>12.3 (5.6)</td>
<td>12.6 (5.3)</td>
<td>0.088 (0.123)</td>
<td>-0.021 (0.715)</td>
<td></td>
</tr>
<tr>
<td>&lt; 10, n(%)</td>
<td>107 (91)</td>
<td>11 (9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10, n(%)</td>
<td>165 (87)</td>
<td>24 (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS Total Score, mean (SD)</td>
<td>48.9 (18.6)</td>
<td>45.0 (22.4)</td>
<td>-0.156 (0.009)**</td>
<td>0.103 (0.086)</td>
<td></td>
</tr>
</tbody>
</table>

Asterisks indicate statistical significance compared to baseline in a paired t test at the \( P<0.01 \) (***) level. BL = baseline; BMI = body mass index; TSD = troublesome dyskinesia; PD = Parkinson’s disease; UPDRS = Unified Parkinson’s Disease Rating Scale.

**LBA 28**

Treatment of restless legs syndrome in iron deficient non-anemic patients - a randomized, placebo-controlled trial using a single dose of iv ferric carboxymaltose

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(1) Göttingen, Kassel, Germany; (2) Munich, Germany; (3) Marburg, Germany; (4) Glattbrugg, Switzerland

**Objective:** To investigate the efficacy and safety of iv ferric carboxymaltose (FCM) as an early treatment of restless legs syndrome (RLS) in patients with low serum ferritin and/or low transferrin saturation (TSAT) and normal hemoglobin concentrations for the first time in a large randomized controlled trial in Europe.

**Background:** Compromised brain iron status is a major factor in the pathophysiology of RLS. It is of debate, however, how to adequately assess brain iron status and if RLS patients should be treated according to their serum ferritin levels before starting any pharmacological therapy. Study results with different iron formulations varied and did not provide clear evidence about which RLS patients might benefit most from iron treatment.

**Methods:** In a prospective, 12-week, patient- and assessor-blind, placebo-controlled, randomized, multicenter phase 4 study, 110 patients with moderate to severe RLS and serum ferritin <75 µg/L (if ≥75 µg/L but <300 µg/L, patients with a TSAT <20% could be included) were randomized to a single iv dose of FCM (1000 mg iron) or placebo. Primary efficacy outcome was the mean change in RLS symptom severity score from baseline to week 4 measured by International Restless Legs Severity Rating Scale (IRLS). Secondary measures included quality of life (QoL) and responder rates (IRLS sum score) defined as the proportion of patients with A) ≥50% improvement over time or B) an improvement ≥6 points at any time during treatment period.
Results: All 110 randomized patients (mean 54.1 [SD 15.8] years of age, 81.8% female; 49.1% previously receiving dopaminergic treatment) were included in the full analysis set (FAS; FCM n=59, placebo n=51). Mean IRLS sum score at baseline was 25.9 (SD 5.7) for FCM and 26.0 (SD 5.8) for placebo. Least squares mean change after 4 weeks (LOCF) was -7.7 (SE 1.2) for FCM and -5.2 (SE 1.3) for placebo with a treatment difference of -2.5 (95% CI -5.93, 1.02; p=0.163) and was not significantly different. At week 12 a significant difference to placebo was reached in favor of FCM in IRLS sum score (-4.66 [95% CI -8.59, -0.73]; p=0.021; Figure 1) and Clinical Global Impression severity of illness score (-0.7 [95% CI -1.25, -0.15]; p=0.013). There were significantly more responders at study end among FCM patients (A: 37.3% vs. 19.6% for placebo; p=0.042), in particular with an improvement ≥6 points at any time during treatment (B: 72.9% vs. 47.1%, p=0.006). Significant improvements compared to placebo were also observed for daytime tiredness and most of the QoL dimensions. No correlation between serum ferritin and FCM efficacy was detected.

Figure 1. Changes in IRLS sum score from baseline in both treatment arms.

Conclusions: Although the primary efficacy endpoint at week 4 was not met, significant treatment differences at end of study in favor of FCM indicate that a single 1000 mg dose of FCM can provide significant clinical improvements of RLS symptoms after 12 weeks in iron deficient non-anemic patients without correlation to serum ferritin values.

LBA 29
Heart rate variability in LRRK2-associated Parkinson’s Disease

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Toronto, Ontario, Canada

Objective: To determine whether heart rate variability (HRV) is altered in LRRK2-associated Parkinson’s Disease (LRRK2-PD).

Background: HRV is reduced in idiopathic PD (iPD), indicating cardiac autonomic dysfunction likely resulting from synucleinopathy in the peripheral autonomic nervous system. Very little is known about HRV in LRRK2-associated PD.

Methods: 7-min resting EKGs were obtained from 20 participants with LRRK2-PD (G2019S), 26 participants with iPD and 32 healthy controls (HC). EKGs were tagged and manually cleaned using ecgpuwave and wave programs respectively (Physionet). 5-min cleaned traces were imported into Kubios (v2.1) to derive standard time domain (SDNN, RMSSD) and low- and high-frequency domain (LF, HF, LF/HF) HRV parameters. We used multiple linear regression to compare HRV values between groups, adjusting for age, gender, heart rate and disease duration (for LRRK2-PD vs iPD).
**Results:** Age was significantly different across the 3 groups (mean age: iPD 64.2, LRRK2-PD 63.6, HC 59.0 yr). Disease duration in LRRK2-PD was significantly longer than in the iPD group (mean duration: LRRK2-PD 11.5, iPD 6.2 yr P<0.01); however, UPDRS-III was similar (mean UPDRS-III: LRRK2-PD 20.3, iPD 21.3), suggestive of a similar stage of disease progression. As expected, HRV was reduced in iPD vs controls (Table 1). In contrast, individuals with LRRK2-PD were not statistically different from controls in any HRV parameter measured. Furthermore, all parameter estimates were higher in LRRK2-PD compared with iPD, however results were not statistically significant.

**Conclusions:** HRV in LRRK2-PD may differ from iPD. Higher LF (an index of sympathetic and vagal influence) in LRRK2-PD compared to iPD is consistent with imaging studies that have suggested a sparing of cardiac sympathetic innervation in LRRK2-PD. Future studies, combining imaging and other peripheral biomarkers (e.g., skin biopsy) and in larger numbers of subjects (particularly given the known variability of CNS neuropathology in LRRK2-PD) will be required to confirm and extend these findings. These findings add to a growing literature supporting clinical and pathologic differences between LRRK2-PD and iPD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>p Value</th>
<th>Parameter</th>
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Table 1. Linear regression results of log HRV parameters (SDNN, RMSSD, LF, HF, LF/HF). Effects were adjusted for gender, age and mean heart rate. LRRK2-PD vs iPD was additionally adjusted for disease duration.

**LBA 30**
**A Single Ascending Dose Study of the Tau-Directed Monoclonal Antibody BMS-986168**

Giridhar Tirucherai, Michael Ahlijanian, Jane Crowell, Gerry Kolaitis, Sandra Skudalski, Matthew Medlock (Covance Clinical Pharmacology Services), Irfan Qureshi, Cliff Bechtold, Michael Grundman (Global R&D Partners, LLC)
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Lawrenceville, NJ, USA

**Objective:** To evaluate the safety, tolerability, and pharmacokinetics (PK) of BMS-986168 as well as the pharmacodynamic (PD) effects of BMS-986168 on extracellular tau (eTau) after a single intravenous (IV) infusion of BMS-986168 in healthy subjects.

**Background:** BMS-986168 is a humanized monoclonal antibody that recognizes human eTau. In a transgenic mouse tauopathy model, the murine analog of BMS-986168 slowed the progression of locomotor impairment, limited the spread of tau pathology and lowered interstitial and free cerebrospinal fluid (CSF) mouse eTau. In non-human primates, BMS-986168 reduced CSF eTau in a dose-dependent fashion following IV bolus infusion of escalating single doses. Based on the preclinical data, BMS-986168 is expected to prevent transmission of tau pathology by binding and reducing free eTau in human brain interstitial fluid and CSF.

**Methods:** The study was a randomized, double blind, placebo controlled single ascending dose trial. Healthy subjects (age: 21-65) in 6 ascending dose cohorts (21mg, 70mg, 210mg, 700mg, 2100mg and 4200mg of BMS-986168) comprised of 8 subjects per cohort were administered a single IV infusion of BMS-986168 (6 subjects) or placebo (2 subjects). Safety assessments, and serum and CSF samples (including 4 lumbar punctures) were collected over 12 weeks. Pharmacokinetic parameters (in serum and CSF) and pharmacodynamic measures (CSF concentrations of free eTau) and corresponding change and percent change from baseline were evaluated.
**Results:** Increases in peak (Cmax) and exposure (AUC[INF]) of BMS-986168 in serum appeared to be dose proportional. The terminal elimination half-life of BMS-986168 was approximately 25 days. CSF concentrations of BMS-986168 increased with dose and appeared dose-proportional. CSF-to-serum ratio of BMS-986168 was approximately 0.2% and similar across the dose range. Most adverse events were mild. There were no serious adverse events or discontinuations due to adverse events. The extent and duration of suppression of eTau increased with dose. Following single doses of BMS-986168, suppression of CSF eTau at 28 days ranged from 65% to 96% at doses ranging from 70mg to 4200mg.

**Conclusions:** The ability of BMS-986168 to robustly suppress CSF concentrations of free eTau in preclinical studies and in this phase 1 study suggests that BMS-986168 has potential utility for the treatment of human tauopathies. Single doses of BMS-986168 administration were safe and well tolerated at doses up to 4200mg. An ongoing study is evaluating multiple doses of BMS-986168 in patients with progressive supranuclear palsy.

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### LBA 31

**In vivo imaging of neuromelanin in Parkinson’s disease using 18F-AV-1451 PET**

*Allan Hansen, Tatyana Fedorova, Peter Parbo, Karen Ostergaard, David J Brooks & Per Borghammer*

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**Aarhus, Denmark**

**Objective:** To examine the radioligand 18F-AV-1451’s off-target neuromelanin binding ability as an investigative tool in Parkinson’s disease.

**Background:** The radiotracer 18F-AV-1451 (18F-T807) primarily binds to paired helical filaments of tau protein but has also been shown to bind to neuromelanin in the midbrain, and may therefore be a measure of the pigmented dopaminergic neuronal count in the substantia nigra. Neuromelanin in the substantia nigra has long been known to increase with age, but decrease in Parkinson’s disease. At disease onset, nigral dopamine neuron loss has been estimated to be around 30% from post-mortem data, while putamen dopamine terminal loss is estimated to be around 50-70%. We investigated the utility of 18F-AV-1451 PET to visualize the concentration of nigral neuromelanin in Parkinson’s disease and correlated the findings to dopamine transporter density, measured by 123I-FP-CIT SPECT.

**Methods:** 17 patients with idiopathic Parkinson’s disease and 16 age- and sex-matched control subjects had 18F-AV-1451 PET on a Siemens High-Resolution Research Tomograph. A subset of twelve patients with Parkinson’s disease also received a standardized 123I-FP-CIT SPECT scan at our imaging facility.

**Results:** Visually, many Parkinson’s disease patients showed apparent decreased 18F-AV-1451 signal in the midbrain. On average, patients showed a 30% mean decrease in total nigral 18F-AV-1451 volume of distribution compared with controls (p=0.004), but a large overlap of the individual ranges was seen. We found no significant correlation between symptom dominant side and contralateral nigral volume of distribution. Also, there was no correlation between nigral 18F-AV-1451 volume of distribution and age or time since diagnosis. In the 12 patients who also had a 123I-FP-CIT scan, the mean putamen dopamine transporter signal was decreased by 55% and the mean 18F-AV-1451 substantia nigra volume of distribution was decreased by 33% after a median disease duration of 4.7 years (range 0.5-12.4 years).

**Conclusions:** 18F-AV-1451 PET may be the first radiotracer to reflect the loss of pigmented neurons in the substantia nigra of parkinsonian patients. The magnitude of the nigral signal loss was smaller than the decrease in putamen dopamine transporter signal measured by dopamine transporter SPECT, in accordance with the post-mortem literature.

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### LBA 32

**A Phase 2a study of standard administration versus semicontinuous intraoral administration of levodopa/carbidopa in patients with advanced Parkinson’s disease**

*Fabrizio Stocchi, Ephraim Heller, Laura Vacca, Ephraim Heller, Adam Heller, Paola Grassini, Miriam Casali, Fabiana Radicati, Chiara Fossati, Paola Stirpe, C. Warren Olanow*
Objective: We investigated whether a noninvasive, continuous, intraoral delivery of levodopa/carbidopa (LCD) would safely reduce variability in plasma levodopa concentrations and reduce OFF time in fluctuating PD patients versus standard, intermittent oral LCD tablets.

Background: Continuous administration of LCD via duodenal infusion dramatically reduces motor fluctuations but requires surgical implantation of a PEG tube. We investigated whether a noninvasive, continuous, intraoral delivery of LCD would safely reduce variability in plasma levodopa concentrations and reduce OFF time in fluctuating PD patients.

Methods: We assessed the safety, tolerability, plasma pharmacokinetics and efficacy of intermittent LCD oral administration vs. semi-continuous intraoral administration of LCD in patients with fluctuating Parkinson’s disease (PD). The trial was an open-label, single-center study of 18 PD patients who experienced ON-OFF fluctuation. Standard intermittent oral LCD tablets were compared with the same total doses of LCD suspension delivered into the mouth every 5–10 minutes over 8 hours. The primary endpoint was the variability of the levodopa concentrations. Efficacy was measured by a neurologist-based assessment of motor state performed at 30-minute intervals over 8 hours.

Results: Continuous intraoral administration of a LCD suspension over the course of 8 hours was associated with a significant reduction (p < 0.001) in the variability of plasma levodopa concentrations as measured by both fluctuation index and linearity. During the 8-hour observation period, OFF time was reduced by 43% (from 2.20±0.3 to 1.26±0.22 hours; p < 0.001). Off time was reduced in 15 patients, remained the same in 3 patients, and was not increased in any patient. There was no significant increase in ON time with troublesome dyskinesia. The procedure was well tolerated and there were no treatment-related adverse events.

Conclusions: Continuous intraoral administration of a LCD suspension significantly reduced the plasma levodopa variability and reduced OFF time as compared to standard intermittent LCD tablet therapy. These results suggest that continuous intraoral LCD administration may provide a safe, convenient, noninvasive approach for reducing OFF time without increasing troublesome dyskinesia in patients with motor fluctuations.

LBA 33
PINK1 selectively accumulates at mitochondria-associated membranes during mitophagy and promotes ER-mitochondria tethering and autophagosome formation

Vania Gelmetti, Enza Maria Valente, Liliana Torosantucci, Elettra Sara Marini, Alessandra Romagnoli, Martina Di Rienzo, Giuseppe Arena, Domenico Vignone, Gian Maria Fimia, Enza Maria Valente
IRCCS Casa Sollievo della Sofferenza, CSS-Mendel Institute; National Institute for Infectious Diseases "Lazzaro Spallanzani" IRCCS, Section of Neurosciences, Dept. of Medicine and Surgery, University of Salerno
Rome and Salerno, Italy

Objective: To characterize a novel function of PINK1, a neuroprotective protein mutated in autosomal recessive Parkinson Disease, in promoting autophagosome biogenesis at the ER-mitochondria interface.

Background: Mitophagy is a highly specialized process to remove dysfunctional mitochondria through the autophagy pathway. PINK1 has been implicated in the activation of mitophagy by selectively accumulating on depolarized mitochondria, and promoting PARK2/Parkin translocation to them. While these steps have been well characterized, less is known about the process and site of autophagosome formation during mitophagy. A previous study reported that, in starvation-induced autophagy, the proautophagic protein BECN1/Beclin1 (which we previously showed to interact with PINK1) relocates at specific regions of contact between the endoplasmic reticulum (ER) and mitochondria called mitochondria-associated membranes (MAM), from which the autophagosome originates.

Methods: For mitophagy: fluorescence microscopy to visualize mitochondrial morphology, mass, and functional state, quantification of mitochondrial DNA; for autophagosome formation: fluorescence microscopy and
biochemical assay to monitor the activation of different autophagy markers (LC3 and DFCP1); for ER-mitochondria contact sites: confocal imaging in cells expressing ER-GFP and Mito-red constructs; for localization of proteins at MAM: subcellular fractionation and western blotting; for protein-protein interaction: co-immunoprecipitation; for apoptosis: western blotting and FACS.

**Results:** We showed that, also in conditions of mitophagy, BECN1 is recruited to MAM to form omegasomes, that represent autophagosome precursors. Intriguingly, endogenous PINK1 selectively and strongly accumulated at MAM, where it promoted the enhancement of ER-mitochondria contact sites, the translocation of BECN1 and the formation of autophagosomes. PARK2 was also enhanced at MAM following mitophagic stimuli. However, while PARK2 and BECN1 were dispensable for each other’s translocation at MAM, both proteins required PINK1, suggesting a novel, essential role for PINK1 in regulating mitophagy.

**Conclusions:** MAM have been recently implicated in many key cellular events, such as modulation of mitochondrial calcium levels, mitochondrial dynamics, and apoptosis; moreover, other PD-related proteins, such as alpha-synuclein and DJ-1, were recently found to locate to these specialized domains. In this light, the observed marked accumulation of PINK1 at MAM may well explain other neuroprotective activities of this eclectic protein.

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**LBA 34**

**Study of subthalamic motor cortical connectivity and its application for deep brain stimulation**

*Rebeca Conde, Antonio Gutierrez, Isabel Sastre, Carlos Botella*
*Hospital Universitari i Politecnic La Fe*
*Valencia, Spain*

**Objective:** The objective is to describe the subthalamic patterns connectivity with DTI_MRI analysis and make a correlation study of DTI patterns with hyperdirect pathway with MER and clinical effect of DBS therapy.

**Background:** The modulator role of premotor and motor cortex is the basis for deep brain stimulation. Identification of the motor part of the subthalamic nucleus as part of the pre-surgical workup.

**Methods:** Analyze 30 Parkinson patient for bilateral subthalamic DBS surgery and 165 MER. Stereotactic procedure was made with Leksell frame or nexion-frame, and planning with Neuronavigation Steath-Station S7 or IPlan 6. Alpha-omega software micrguided system for MER. 3T preoperative MRI T1, T2, slice 0.8 mm (625 images), 3D CT scan co-register (stealthstation S7), 4 Sequential intraoperative O-arm (MER and DBS), Postoperative CT scan, DTI MRI DTI 3T Philips 32 gradient overplus ON rel 2.5. Analysis DTI stealthviz. Parameter FA0.20 ADC 0.10 Seed 1.0 MPR5.0. Post-analysis DTI Amira system: microscope module. UPDRS III previous and one year after the surgery.

**Results:** We could study the level of segregation of the subthalamic motor part, which is relevant for the planning of STN DBS procedures. There is an intrasubthalamic connection between premotor and motor tracks. Dorso-lateral region of subthalamic nucleus has the main density of beta-oscillations. This region has also the main density of motor and premotor points of connectivity in probabilistic DTI images. So we think this validated both techniques. These studies let us preoperative and intraoperative define motor part of subthalamus, our target for DBS. We observe a correlation with motor recruitment and better clinical results in patients with DBS sets near motor connectivity points.

**Conclusions:** 1. MRI-DTI allow to study subthalamic connectivity. This let us preoperative identify motor region of subthalamus, our target for surgery. 2. We defined intrasubthalamic axis created with premotor and motor connection. This axis is in dorso-lateral region, and another inferior near nigra. 3. We get beta oscillation in dorso-lateral region, and also in inferior region near nigra. 4. Both of them, tractography and MER register are in dorso-lateral region of sub thalamus. 5. Patients with bilateral lead implant on motor connectivity region and beta-oscillations improve more than 60% on UPDRS III. We don’t get differences about clinical results between general anesthetic and local anesthetic, neither in beta oscillation register. DBS surgery could be made under general anesthetic to improve comfort for patients.
Skin sebum production is abnormal in Parkinson’s disease- a potential biomarker?

Diana Angelika Olszewska*, Siona Ni Raghallaigh*, Allan McCarthy 1, Owen Ross 3, Emer M Fallon 1, Frank Powell 4, Tim Lynch 1

1. Department of Neurology at the Dublin Neurological Institute at the Mater Misericordiae University Hospital, Dublin 7, 2. Department of Dermatology, AMNCH, Tallaght, Dublin 24, 3. Mayo Clinic, Jacksonville, Florida, USA, 4. Department of Dermatology, UCD Charles Institute of Dermatology, University College Dublin, Belfield, Dublin 4, Dublin, Ireland

* authors contributed equally

Objective: To measure the sebum levels, pH and hydration of facial skin in patients with Parkinson’s disease (PD) and to determine any relationship between skin findings and type or severity of neurological disease.

Background: Skin changes are a recognized feature of some patients with PD. The relationship between the skin changes in PD has not been analysed in depth. Hypotheses include abnormal dopaminergic control, parasympathetic hyperactivity, hormonal control and pooling of sebum due to immobility. Quantitative changes in sebum and its possible relationship to disease subtype, genetic markers or severity have not been evaluated using modern methodology.

Methods: We studied 55 PD patients and 57 age-and sex-matched controls with normal facial skin and without family history of neurodegeneration. We screened for known PD genes and recorded the Unified Parkinson’s disease Rating Scale (UPDRS) on the day of skin analysis. Skin examination was performed using standardized conditions (“on medication”, set skin preparation protocol, regulated room temperature and humidity, mid-morning sampling). A handheld device (Courage+Khazaka electronic GmbH), applied to the mid-glabellar region, was used to measure the sebum, hydration and pH.

Results: 35 PD patients were men. Mean age was 65 years with average disease duration of 10.7 years. 5 patients had Parkin mutations, 1 had LRRK2 mutation. 29 had tremor-predominant PD, 18 postural instability gait disorder (PIGD) and 8 mixed subtype. Mean sebum level (µg/cm2) was 127 +/- 58.8 in PD vs 88.2 +/- 65 in controls; p = 0.001. Mean sebum in PD males was 143 +/- 56 vs 116.6 +/- 62 in control males; p = 0.03. Mean sebum in PD females was 98.8 +/- 53.9 vs 42.9 +/- 39.6 in female controls; p =0.0002. Mean pH in the PD group was 5.04 +/- 0.53 vs 4.77 +/- 0.43 in controls; p = 0.002 (Fig. 1). There was no difference in skin surface hydration. The mean Unified Parkinson’s disease Rating Scale part III (UPDRS-III) in PD was 21.29 (range 4-46). Mean sebum in PD patients with UPDRS-III ≤ 32 (mild PD) was 119.8 +/- 57.3 vs 163.2 +/- 55.3 in patients with UPDRS-III > 32 (moderate PD); p = 0.042. Average sebum level was 114 +/- 61.3 in the tremor predominant PD vs 136.1 +/- 53.4 in combined PIGD and mixed subtypes, p =0.043. No statistically significant association was found between levodopa, dopamine agonists use and sebum production.

Conclusions: We found that PD patients (especially females) have higher skin surface sebum levels than control subjects, and levels are higher in those with moderate PD (higher UPDRS-III) than those with mild disease. In the presence of normal skin hydration and pH levels these surface sebum changes may reflect a hitherto unrecognized neurocutaneous link that merits further evaluation. Sebum production and analysis may offer a diagnostic marker or a biomarker for PD.

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<td>88.2 +/- 65</td>
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<td>Mean sebum level men</td>
<td>143 +/- 56</td>
<td>116.6 +/- 62</td>
<td>0.03</td>
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<tr>
<td>Mean sebum level</td>
<td>98.8 +/- 53.9</td>
<td>42.9 +/- 39.6</td>
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<tr>
<td>Mean sebum level</td>
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<td>Mean ph level</td>
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LBA 36
Tau pathology spreads into striatal allografts in Huntington’s disease patients

Giulia Cisbani, Francesca Cicchetti, Francesca Cicchetti,
Centre de Recherche du CHU de Québec (CHUQ)/Université Laval; University of South Florida
Quebec, BC, Canada

Objective: It has recently been reported that tau aggregates and neurofibrillary tangles, as seen in Alzheimer’s disease (AD), could be found in Huntington’s disease (HD) as well. This suggests that tau protein may contribute, along with mutant huntingtin protein (mHtt), to HD pathology. We therefore investigated whether tau pathology can spread from the diseased brain into striatal allografts placed in the brains of patients with HD who underwent this experimental approach with the hope to slow down the progression of their disease.

Methods: Immunohistochemical stainings were performed using four distinct antibodies against different forms of the phosphorylated protein: AT8 (phospho-PHF-tau pSer202+Thr205), CP13 (phospho tau-pSer202), AT180 (phospho-PHF-tau pThr231) as well as PHF-1 (phospho-PHF-tau pSer396+pSer404). The histological evaluation was carried out on 2 brains (from patients 1 and 7) of the initial 7 HD patient cohort in the open label study on fetal striatal allografting conducted at the University of South Florida. Patient 1 had 42 CAG repeats, while patient 7 had 53 CAG repeats. These two women were transplanted at 58 and 28 years of age respectively, and died 9 and 12 years post-transplantation of causes unrelated to surgery.

Results: Tau pathology was found within all of the transplants. AT8+ fibrillary tangles were found throughout the grafts. Similar results were obtained with the anti-CP13 antibody. The anti-AT180 antibody revealed the presence of more fragmented and punctuated tau+ inclusions. In all cases, the antibodies showed extracellular localization of phosphorylated tau; we did not observe tau+ neuronal inclusions in the grafted tissue.

Conclusions: We provide the first evidence that tau pathology can spread from the brain of a patient with HD into unrelated neural tissue placed within this milieu. This finding also suggests that tau protein, found in other types of neurodegenerative diseases, including AD, may spread through the nervous system via similar mechanisms. This finding adds further weight to the theory that many, if not all neurodegenerative disorders of the CNS, have a pathology that relies on protein spread regardless of their etiological cause.

LBA 37
Alterations of diffusion kurtosis and neurite density indices in deep grey matter and white matter in Parkinson’s disease

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Objective: To improve PD diagnosis or differentiate between the postural instability gait difficulty (PIGD) and the tremor dominant (TD) phenotypes.

Background: In Parkinson’s disease (PD), microstructural changes pathology occur in deep grey matter as well as white matter tracts. Such changes might be detected using diffusion kurtosis imaging (DKI) and neurite density imaging (NDI). However it is still unclear whether DKI and NDI can improve PD diagnosis or differentiate between the postural instability gait difficulty (PIGD) and the tremor dominant (TD) phenotypes.

Methods: In the present study we included 105 patients with PD and 44 healthy controls, which all underwent diffusion MRI of the brain as part of the prospective Swedish BioFINDER study. DKI analysis was performed using regions of interest in basal ganglia, thalamus, pons and midbrain and tractography of several white matter tracts.
Results: In PD, MD in the putamen was increased and fractional anisotropy (FA) mean kurtosis (MK) was decreased compared to controls (p < .05). These changes correlated negatively with motor speed, balance and cognitive function (p < .05) (Fig 1). MD in the putamen was increased in patients with the PIGD compared to the TD phenotype (p < .01). In the thalamus, MD was increased and FA was decreased (p < .05) in PD and correlated significantly with reduced motor speed and balance (p < .05) (Fig 1). Finally, MD in the superior longitudinal fasciculus (SLF) was increased in PD (p < .05) and correlated significantly with worsening of motor speed and balance (p < .05). However, only increased FA and MK in the putamen were specific for PD. The other changes were also observed in cases with PSP (N=10) and/or MSA (n=11).

Conclusions: The present results indicate microstructural changes in putamen, thalamus, and SLF in PD, which are associated with worse disease severity. The changes are not sufficiently specific to improve the diagnostic work-up of PD, but longitudinal studies are needed to evaluate whether these measures can be used to track disease progression, e.g. in clinical trials.

LBA 38
Gait rather than cognition predicts cognitive decline in early Parkinson’s disease

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Newcastle-Upon-Tyne, UK

Objective: To predict cognitive decline in early Parkinson’s disease (PD) using discrete gait characteristics quantified at diagnosis and compare to prediction models using baseline cognition.
Background: Cognitive decline and dementia are significant in PD with major personal, social and economic impact. Identifying individuals most at risk of cognitive decline and dementia is vital to enable early or prodromal treatment, paving the way for progress in novel therapies and optimizing clinical management. Prognostic markers still remain an urgent unmet need. While no single marker is likely to satisfy all requirements, discrete gait characteristics have shown promise as prognostic markers of cognitive decline and dementia in older adults.

Methods: 119 idiopathic PD participants were recruited at diagnosis for the ICICLE-Gait study (a sub-study of ICICLE) and assessed at; baseline, 18 and 36 months. Participants walked for two minutes around a circuit. Gait was quantified using a 7m instrumented walkway from which 16 gait characteristics were derived according to a model representing five independent domains: pace, variability, rhythm, asymmetry and postural control. A comprehensive cognitive battery assessed global cognition, attention, fluctuating attention, executive function, working memory, visual memory and visuospatial ability. Linear mixed effect modelling was used to i) quantify change in cognition over 36 months, ii) predict change in cognition from gait characteristics at diagnosis and iii) predict change in cognition from baseline Montreal cognitive assessment (MoCA). All models were determined using backward elimination to adjust for correct covariates including age, education, gender, depression and levodopa equivalent dose (LEDD). Log-likelihood tests were used to compare the fit of models.

Results: Significant deterioration in cognition over 36 months was evident for attention, fluctuating attention, executive function and visual memory. Variability predicted decline in attention (p=.04). Pace, variability, rhythm and postural control predicted decline in fluctuating attention (p).

Conclusions: This is the first study to demonstrate that discrete gait characteristics at diagnosis predict cognitive decline in early PD. Discrete gait characteristics may provide low cost clinical markers for risk detection and could make an important contribution to prognostic models of dementia risk.

LBA 39
Restless legs syndrome associated with functional movement disorders: a pilot study

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Prague, Czech Republic

Objective: To assess the frequency of restless legs syndrome (RLS) in a heterogeneous group of patients with functional movement disorders (FMD).

Background: RLS is often under-recognized condition. Due to varied descriptions of broad and unusual sensations it could mimic functional sensory symptoms in FMD patients. RLS is diagnosed by self-reported symptoms and can be confirmed using actigraphic assessment of periodic limb movements (PLM) which are present in 85-95% of RLS patients.

Methods: Seventy-four patients (62 females, mean [SD] age 44.0 [13.5] years) with FMD participated in the study. Presence of sensory symptoms, organic comorbidities and use of antidepressants (AD) were recorded from medical reports and detailed interviews. All patients were administered a validated 3-question RLS screening form. Duration and family history of RLS were recorded from positive screened patients (RLS+). All RLS+ patients underwent actigraphy from both big toes for 3 consecutive nights at home. The threshold of PLM index=7.6 in at least 1 night was used as cutoff for PLM positivity (PLM+). Comorbidity index was calculated as a sum of diabetes, hypertension, myocardial infarction, obesity, stroke, cancer, renal disease, anemia, depression, thyreopathy, and migraine. Effect of age, comorbidities and use of AD on frequency of RLS+ and PLM+ was analyzed.

Results: Sensory symptoms were reported in 58 (78.4%) FMD patients. Thirty-nine (52.7%) patients screened positive for RLS (95% CI 41.3%-64.1%). Family history of RLS was present in 6 patients (8.1%). In 20 patients (27.0%) RLS occurred after FMD onset. PLM was found in 74.4% of RLS+ patients (95% CI 60.7%-88.1%). RLS+ patients were older (mean [SD] age 48.5 [10.7] vs. 39.0 [14.6] years, p<0.01), however no age difference was found
between the PLM+ and PLM- group. No difference between any tested groups was found for comorbidity index and use of AD.

**Conclusions:** In our FMD patients, questionnaire-based RLS frequency was higher than the frequency in general population (52.7% vs. 5-10%) with rather low false-positive rate according to actigraphic confirmation of PLM. Similarly to previous findings, increased age may represent a risk factor for RLS in FMD. Detailed clinical evaluation along with objective assessment of PLM may help differentiate RLS from functional sensory symptoms and effectively treat this condition in FMD patients.

**LBA 40**

**Family with mutation in the GIGYF2 (PARK11) gene with complex dystonia-parkinsonism phenotype**

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1 - Neurology Clinic, CCS, Faculty of Medicine, University of Belgrade, Serbia 2 – Institute of Mental Health, Belgrade, Serbia 3 - Institute for Human Genetics, Faculty of Medicine, University of Belgrade, Serbia 4 -Clinic for Endocrinology, Diabetes and Metabolic Diseases, CCS, Faculty of Medicine, University of Belgrade, Serbia. 5- Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia

**Objective:** Mutations in the Grb10-interacting GYF protein 2 (GIGYF2) gene, within the PARK11 locus, have been nominated as a cause of Parkinson’s disease. Majority of replication studies conducted in different populations, failed to confirm the pathogenicity of these mutations in PD. In recent animal study heterozygous disruption of gigyf2 gene resulted with motor dysfunction other then parkinsonism and with histopathological evidence of neurodegeneration in brainstem and cerebellum but not in substantia nigra.

**Background:** The aim of this study was to elucidate the genetic cause underlying disease in a family with autosomal-dominant, late onset dystonia, mild parkinsonism and psychiatric features.

**Methods:** Four affected members, and one unaffected member of the same family were subjected to sequencing using TruSight One Sequencing Panel, created by Illumina for the simultaneous sequencing of the exon regions of 4,813 clinically relevant genes.

**Results:** We have identified a novel missense variant, c.2129G>T (p.G710V) in the GIGYF2 gene in all affected family members. The clinical presentation consisted of focal to segmental dystonia without generalization and mild parkinsonism with limited response to levodopa therapy. Significant psychiatric comorbidity was found, ranging from depression and generalized anxiety disorders to psychosis.

**Conclusions:** Our results suggested that mutations in the GIGYF2 gene might induce a phenotype other than classical Parkinson's disease and should be considered in patients with adult-onset dystonia-parkinsonism syndrome.

**LBA 41**

**Spinocerebellar Ataxias types 3 and 10 - Relation between the onset or worsening of the Ataxia with the gestational period and postpartum**

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**Objective:** To assess female patients with types 3 and 10 ataxias and verify if the symptoms begun or worsened during pregnancy or postpartum period.

**Background:** The Spinocerebellar Ataxias (SCA) is a heterogeneous and complex group of neurodegenerative disorders, with dominant autosomal inheritance, characterized by the progressive degeneration of the cerebellum and its afferent and efferent connections. More than 40 subtypes have already been described with a molecular genetic
basis. The type 3 SCA is the most commonly found on the world, specially among patients with Portuguese-Azorean ancestry, while type 10 SCA represents a rarer form with an Amerindian origin. As already published in the article “Symptom onset of spinocerebellar ataxia type 10 in pregnancy and puerperium” (Teive et al 2011), three asymptomatic patients from the same family have developed type 10 SCA during puerperium. This discovery opened a discussion if this form of ataxia is triggered by factors involved in pregnancy and puerperium.

**Methods:** 40 patients with confirmed genetic diagnosis and age of onset between 15 and 45 years were interviewed (22 SCA3 and 18 SCA10). The objective of the interviews was to assess if the symptoms started or had worsened during pregnancy or postpartum period.

**Results:** 66.7% of the SCA10 patients reported that the symptoms started and/or intensified on the last three months of the pregnancy or on the postpartum period, while only 4.5% percent of the SCA3 patients reported the same condition (p<0.0001).

**Conclusions:** The type 10 SCA appears to have a strong connection with hormonal factors involved in pregnancy, seeing as two thirds of the women in fertile age reported advent and/or significant aggravation of the ataxia symptoms on the last trimester of pregnancy or during postpartum period.

**LBA 42**

**Altered functional connectivity in patients with blepharospasm/Meige’s syndrome**

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**Objective:** To investigate functional connectivity (FC) in patients with blepharospasm/Meige’s syndrome in comparison to healthy controls using resting-state functional magnetic resonance imaging (fMRI) before and after treatment with botulinum toxin (BTX).

**Background:** Blepharospasm is a focal dystonia that is characterized by involuntary eyelid spasms. When associated with perioral dystonia, it is classified as Meige’s syndrome. Only two resting state studies on blepharospasm have been published with inconsistent results.

**Methods:** Resting-state fMRI was acquired in 13 patients with blepharospasm, in some cases accompanied by mild oromandibular dystonia, before and 4 weeks after periocular BTX-treatment as well as in 13 gender- and age-matched healthy controls. Simultaneous facial electromyography (EMG) was applied in order to control for involuntary facial movements. A region of interest (ROI)-based analysis of FC was performed using the CONN toolbox.

**Results:** Compared to healthy controls, patients before BTX-treatment showed reduced FC of the caudatum to primary sensorimotor, somatosensory association and visual cortices as well as between the putamen and the supramarginal gyrus. Cingular ROIs showed lower FC with primary sensorimotor and premotor cortices and the supramarginal gyrus, premotor cortices with primary somatosensory cortices, postcentral ROIs with temporoparietal, cingular and cerebellar regions and the somatosensory association cortex. FC of cerebellar ROIs to somatosensory and visual association cortices was reduced, FC of thalamic to cerebellar regions was increased. The pattern changed after BTX-treatment: FC was reduced in patients between caudatum and prefrontal cortex, between pallidum and cerebellum as well as between cingular ROIs and the inferior parietal cortex. FC was also reduced between postcentral/cerebellar ROIs and supramarginal regions. We found increased FC between thalamus and orbitofrontal areas and between cerebellar ROIs and secondary visual cortices.

**Conclusions:** Patients with blepharospasm and Meige’s syndrome show a widespread pattern of altered functional connectivity at rest including basal ganglia, cerebellar, primary/secondary sensorimotor and visual areas, which can be partially modulated by BTX therapy.
**LBA 43**

**Validation of a new ELISA for detection of α-Synuclein in cerebrospinal fluid**

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**Objective:** We developed and validated a new, independent assay for detecting total α-Synuclein in cerebrospinal fluid.

**Background:** α-Synuclein aggregation and deposition is the pathological hallmark of several neurodegenerative diseases. However, α-Synuclein’s potential as a diagnostic or prognostic biomarker is still under investigation.

**Methods:** We developed an ELISA with commercially available antibodies based on electrochemiluminescence technology. The assay protocol is straightforward with short incubation steps and requires only 25ul cerebrospinal fluid. We validated this assay for precision, parallelism, dilution linearity, specificity, and spike recovery. We also compared it to the newly validated α-Synuclein assay from BioLegend by analyzing 50 cerebrospinal fluid samples with both assays independently.

**Results:** The new assay quantifies α-Synuclein in cerebrospinal fluid with a lower limit of detection of 36.3pg/ml. The assay showed excellent linearity over a wide concentration range, had no cross-reaction with other synucleins and the results of spike recovery, dilution linearity and parallelism were well within accepted limits set by the recently published guidelines for validation of immunological methods. We found a strong correlation between the two assays.

**Conclusions:** We have developed and validated a new ELISA assay that is based on freely available components to quantify total α-Synuclein in small amounts of cerebrospinal fluid. It was developed as an additional, independent method to aid in the evaluation of α-Synuclein as a biomarker in neurodegenerative diseases. It convinces with high performance and convenient assay protocol.

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**LBA 44**

**Translational models of apathy: A novel paradigm assessing motivation in Huntington’s disease patients and R6/1 Huntington’s mice**

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**Objective:** Development of effective therapies for apathy in neurodegenerative disease relies on improved translational models of this symptom. We present the first example of a translational touchscreen paradigm assessing apathy in a rodent model of Huntington’s disease (HD) and human HD patients.

**Background:** Apathy is pervasive in neurodegenerative disease, but little progress has been made to identify its pathophysiology and uncover novel therapeutic targets. Progress has been hampered by a lack of accurate assessment tools to evaluate apathy. Therefore, development of a translational model sensitive to apathy in both rodents and humans is of immense theoretical and clinical interest.

**Methods:** Progressive ratio (PR) schedules measure motivation as a ‘breakpoint’ is derived where subjects cease responding to receive a reward that becomes progressively smaller and requires greater effort as the task progresses. To assess apathy in rodents we developed a novel touchscreen version of the PR task, which was validated against dopamine manipulations in C57Bl/6 mice [1]. In the current study, 29 wild type and 22 transgenic mice expressing exon 1 of the human HD gene (R6/1 mice) were assessed on the PR task. Measures of generalised locomotor activity were also taken. For the human arm, we developed a computerised PR paradigm that was standardised on
300 healthy volunteers [2]. A cohort of 23 HD patients and 14 age-matched controls were evaluated on the PR task and on questionnaires assessing apathy.

**Results:** Relative to wild type mice, R6/1 mice had significantly lower breakpoints (p<.001), consistent with impaired motivation. Critically, the mouse strains did not differ on locomotor measures, confirming motor impairment does not account for the reduced motivation in the R6/1 group. Human HD patients had significantly lower breakpoints than controls (p<.001, d = 1.9). Performance on the PR task was strongly correlated with clinical assessment of apathy (r=-.55, p<.001), supporting PR breakpoint as a valid indicator of apathy symptomatology.

**Conclusions:** In a rodent model of HD and in HD patients, we show motivational deficits on a novel translational paradigm. Effects in the mice were not explained by generalised motor dysfunction, and effects in the humans were related to clinical levels of apathy. This translational paradigm provides a vital platform to explore apathy across different conditions and to identify and validate pharmacological treatments.


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**LBA 45**

**striatal dopamine receptor and transporter alterations induced by accumulation of pathological alpha synuclein in a rat model of Parkinson’s disease**

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**Objective:** The aim is to study the status of the pre and post-synaptic dopamine system in a rat model of early Parkinson’s disease (PD), which is based on the overexpression of alpha-synuclein (asyn) using local intranigal injections of viral vectors.

**Background:** PD is characterised by progressive degeneration of dopaminergic neurons in the substantia nigra (SN) and loss of striatal dopaminergic terminals. The pathological hallmark of PD is the presence of Lewy bodies and Lewy neurites, which contain aggregated asyn. We have recently shown that the overexpression of asyn using recombinant adeno-associated virus (rAAV) vectors leads to pathological asyn aggregation and results in dysfunction of the striatal dopaminergic terminals revealed by in vivo positron emission tomography imaging. However, no loss of dopaminergic neurons in the SN was observed by immunohistochemistry, thus, providing a novel model of early Parkinson’s disease (PD) in need of additional validation.

**Methods:** Rats were injected with rAAV pseudotype 2/6 encoding human wild-type asyn or enhanced green fluorescent protein (eGFP) in the right SN. Motor performance was assessed with the cylinder test ten weeks after the injections. At twelve weeks, rats were decapitated and autoradiography was performed on the brain tissue with the following radioligands: [3H]-DTBZ, a tracer of the vesicular monoamine transporter 2 (VMAT2); [3H]-GBR12935, a tracer of the dopamine transporter (DAT); and [3H]-Raclopride, a tracer of dopamine 2/3 (D2/3) receptors.

**Results:** Rats injected with rAAV-asyn exhibited motor defects absent in the rAAV-GFP group. Tracer binding in the rAAV-asyn animals showed a significant decline in [3H]DTBZ and [3H]GBR12935 binding, and increase in [3H]Raclopride binding in the ipsilateral vs. contralateral striatum compared to the rAAV-GFP group.

**Conclusions:** Reduced VMAT2 and DAT and increased D2 receptor expression together with asyn deposition and motor impairments replicate the pathology observed in PD patients. These changes, in the absence of cell death, make this asyn model relevant to study treatments in early PD, when there is a greater chance to modify the disease course.
Effects of donepezil on the prognosis of Parkinson’s disease with severe hyposmia - a multicenter randomized double-blind placebo-controlled trial (DASH-PD study)

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Objective: To study the effect of donepezil on the prognosis of Parkinson disease.

Background: Parkinson’s disease dementia (PDD) greatly contribute to the poor prognosis of Parkinson’s disease. Although cholinesterase inhibitors including donepezil are effective for the treatment of PDD, the average life-expectancy of patients who developed PDD remains relatively short. Thus an early therapeutic intervention that can prevent the onset of PDD may enable to improve the long-term prognosis of Parkinson’s disease substantially. Our previous study showed that olfactory dysfunction could be a predictive indicator of the development of PDD. In this trial, we investigated whether early administration of donepezil to patients with severe olfactory dysfunction can reduce risk for the subsequent development of PDD.

Methods: This is a multi-center, randomized, double-blind, parallel group, placebo-controlled trial in patients with Parkinson’s disease, who have severe hyposmia but not yet developed PDD. 200 patients will be randomly allocated in a 1:1 ratio either to receive 5mg of donepezil or placebo, in addition to standard therapy for Parkinson’s disease. Patients will be followed up every 6 months until the onset of PDD or for a maximum of 4 years (208 weeks). Primary endpoint is the onset of PDD, which is measured by the Mini-Mental State Examination and the Clinical Dementia Rating (CDR) stage. Secondary endpoint is cognitive impairment, which is measured by the Addenbrooke’s Cognitive Examination-Revised score and the CDR stage. Statistical analysis will be made to evaluate whether donepezil has a favorable effect on the risk of developing PDD. The study is registered at UMIN Clinical Trials Registry (UMIN000009958).

Results: Two hundred-four cases were enrolled to the study from March 2013 to April 2014. By March 2016, 41 cases were dropped out and 7 cases were reached to the endpoint. At present, other 156 cases are followed. No serious adverse events have not been reported.

Conclusions: The mean-observation period is 1.5 years at present and 5mg of donepezil can be safely administrated to cases with PD.

Exploratory analysis of the relationship between domain-specific cognitive impairments and regional cortical atrophy in Parkinson’s disease

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Objective: To establish the main cognitive domains affected in Parkinson’s disease with mild cognitive impairment (PD-MCI), and find correlations between these and regional cortical atrophy, which can act as a potential biomarker for cognitive impairment in PD.

Background: PD-MCI is thought to be characterized mainly by attentional-executive dysfunction (1) although amnestic and visuospatial deficits can be seen with disease progression. The common neuropsychological tests used to assess PD-MCI demonstrate substantial overlap in their demands on different cognitive domains and therefore lack specificity. Previous imaging studies using such neuropsychological tests to look for neuroanatomical correlates of PD-MCI may therefore in turn lack specificity in their findings (2). We avoided these confounds by using factor analysis to obtain more empirically derived cognitive domain profiles. We then correlated these cognitive factors
with volumetric neuroimaging data to determine the specific patterns of cortical atrophy associated with deficits in each cognitive domain.

**Methods:** Patients (n=23) diagnosed with PD-MCI, but not meeting diagnostic criteria for PD dementia, underwent an extensive battery of neuropsychological tests. Factor analysis was used to derive empirically driven cognitive domains and to obtain factor scores for each cognitive domain for each patient. All patients underwent multi-echo quantitative brain MRI in 1mm3 spatial resolution at 3.0 Tesla. FreeSurfer image analysis suite was used to evaluate regional cortical thicknesses for each patient and then to correlate these with the cognitive domain factor scores using a general linear model.

**Results:** The factor analysis extracted five cognitive factors, which could broadly relate to ‘Attention’, ‘Executive function’, ‘Language’, ‘Memory’ and ‘Visuoperceptual’ domains. Impairments in these domains are known to be associated with disease progression in PD (3). The ‘Attention’ factor accounted for the most variance in the dataset. The general linear model found significant (p<0.01) correlations between impairments in each of the cognitive factors and specific changes in cortical thickness. The 'Attention' factor showed a significant correlation with bilateral cortical atrophy in the superior temporal lobes (p<0.001). The 'Executive function' factor correlated with several clusters of cortical atrophy in the precuneus and cuneus bilaterally (p<0.01).

**Conclusions:** Our findings confirm that impairments in attention and executive function characterize the initial cognitive decline associated with PD. Deficits in these cognitive domains correlated strongly with regional cortical atrophy in the precuneus, cuneus and superior temporal lobes, suggesting that atrophy in these specific brain regions represents the neuroanatomical correlate of early cognitive decline in PD. Application of the same techniques as those used here to a larger cohort could determine the viability of measuring atrophy in these specific areas as a biomarker for PD-MCI.

**LBA 48**

**Writer’s cramp patients had normal rapid adaptation to rotation yet abnormal movement execution**

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**Objective:** We aimed to confirm that writer’s cramp (WC) patients had abnormal motor adaptation and to describe the related cortical and subcortical networks.

**Background:** Patients with WC have abnormal sensorimotor coupling and altered eye blink conditioning suggesting that sensorimotor adaptation may be abnormal. When tested to rotation adaptation WC patients had a normal rate of learning yet an abnormal washing-out (1). Adaptation of walking parameters was also found abnormal in WC patients (2).

**Methods:** We applied functional imaging in 16 WC patients and 19 matched controls (HV) using 3T MRI while, using a joystick in their right hand, participants moved a cursor on a screen to reach straight five targets arrayed radially in a half circle. There were 3 conditions: direct coupling between the joystick and the cursor, 25° clockwise rotation, -30° anticlockwise rotation. In each of the 3 sets of 135 movements the conditions were alternated every 15 movements. With such a task we explored the early phase of the adaptation (3). Patients were scored for dystonia using the Burke Fahn Marsden scale and the Writer’s Cramp Impairment Scale (WCIS) developed at HMCS, NINDS, NIH (Bethesda, USA).

**Results:** Behavioral data Compared to HV patients had - abnormal movement features for movements without and with imposed rotation with: (i) longer time to target (GROUP: P

**Conclusions:** Movement execution differed between HV and WC patients with longer trajectories even in the simplest movements. WC patients had a normal rate of early adaptation. Adaptation to rotation and force-field had also been found normal in patients with cervical dystonia (4). During sequence learning WC patients had similar performances as HV (5, 6) yet demonstrated less activation in a network including posterior parietal cortex, SMA,
putamen and cerebellum. Underactivation during adaptation or sequence learning might be not related to the learning process per se yet to a general disorganization of movements.

1 Hubsch et al Brain 2013
2 Hoffland et al Cerebellum 2014
3 Krakauer et al J Neurophysiol. 2004
4 Sadnicka et al Cerebellum 2014
5 Zeuner et al Brain and Behavior, 2015
6 Wu et al 2010 J Neurol Neurosurg Psychiatry 201

**LBA 49**

**Surgical Coverage of the Putamen in Parkinson’s disease with AAV2-AADC using MRI-Guided Convective Delivery**

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**Objective:** To determine the volume of the putamen surgically covered with adeno-associated-virus serotype 2 encoding aromatic L-amino acid decarboxylase (AAV2-AADC), using real time MRI-guided convection-enhanced delivery technique, in an ongoing open label, phase 1b, dose escalation trial.

**Background:** AAV2-AADC gene therapy has the potential to enhance and prolong the response to levodopa in advanced Parkinson’s Disease (PD) and is being evaluated in an ongoing dose escalation trial. Prior gene therapy trials in PD with AADC and other transgenes have used convective delivery, but were unable to visualize the infusion or determine the distribution in the putamen. MRI guided delivery allows for accurate cannula placement and real-time adjustment to maximize anatomical coverage. We estimate that ≥30% coverage of the putamen is necessary to adequately test the clinical effect of a given concentration and volume of gene therapy on motor function and response to levodopa.

**Methods:** Eight PD subjects with refractory motor fluctuations received vector at a concentration of 8.3e11 vector genomes/ml. Five subjects in cohort 1 received up to 450 microliters/putamen and 3 subjects in cohort 2 received up to 900 microliters/putamen. Vector was co-infused with gadoteridol to visualize distribution, using bilateral skull-mounted MRI compatible devices and canulas.

**Results:** Participants in cohort 1 received the full infusion of 450 microliters/putamen, bilaterally and achieved an average coverage of 21% (range 17-25%) of the volume of the putamen. Participants in cohort 2 received between 752-900 microliters/putamen and achieved an average coverage of 33% (range 25-38%). Infusions could be stopped before the maximum of 900 microliters/putamen was reached based on real time visualization of the infusion and evolving coverage of the putamen. The ratio between volume of distribution and volume infused was <3:1. Infusions were well tolerated.

**Conclusions:** Infusion volumes of 752-900 microliters/putamen and real-time MRI guidance resulted in coverage of over 30%, which is estimated to be 5 fold greater coverage of the putamen than achieved in previous gene therapy trials. Advances in anatomical coverage may reduce the likelihood of adverse effects and increase the likelihood of clinical benefit by minimizing off target coverage and maximizing target coverage.

**LBA 50**

**Treadmill exercise improves motor deficits and regulates expression of striatal GLT-1 and AMPA receptor subunits in 6-OHDA-induced Parkinson’s rats**

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Objective: To investigate the plastic effects of treadmill exercise on expression of striatal glutamate transporter 1 (GLT-1) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor subunits (AMPARs, GluR1 and GluR2/3).

Background: After striatal dopamine depletion, excessive glutamatergic inputs from cortex and thalamus induced striatal hyperexcitability. AMPARs are responsible for the majority of fast excitatory neurotransmission and GLT-1 is important for glutamate elimination, both of them mediate long term exercise-dependent processes that alter synaptic strength. An underlying mechanism of exercise-induced improvement may relate to expression of AMPARs and GLT-1.

Methods: All male SD rats were randomly divided into four groups, namely, control group (Control, n = 10), control with exercise group (Control + Ex, n = 10), PD group (PD, n = 22) and PD with exercise group (PD + Ex, n = 28). Twenty-four hours after injection of 6-OHDA into the right medial forebrain bundle, rats in exercise groups were trained to exercise on a treadmill (11 m/min, 30 min/d, 5 days/week, and 4 weeks). All rats were received cylinder test at 28 days and apomorphine was used to test all rats at 14 and 28 days after 6-OHDA injection. Western blot and immunohistochemical technique were used to assess striatal AMPARs and GLT-1 expression.

Results: The net number of APO-induced rotations in the PD + Ex group significantly decreased 2 and 4 weeks after the surgery (118 ± 10.8 and 226.7 ± 16.2 turns/30min) compared with the PD group (148 ± 18.3 and 282.8 ± 32 turns/30min), P < 0.01 at 2 and 4 weeks after surgery. Cylinder test results indicated that the asymmetry of forelimb was markedly improved after exercise compared with PD group (P < 0.05). Compared with PD, treadmill exercise increased GluR2/3 subunit and GLT-1 expression (P < 0.05), with no significant effect on GluR1 (P > 0.05).

Conclusions: Our findings indicate that the improved motor performance after moderate treadmill exercise is accompanied by an increase in both GluR2/3 subunit and GLT-1 protein expression, which could facilitate the attenuation of glutamate-mediated hyperexcitability.

LBA 51
The regulating effects of A2AR/D2DR in the exercise intervention to PD basal ganglia dysfunction

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Objective: To reveal the related neurobiological mechanisms, we investigate the role of striatal adenosine A2A receptor(A2AR) and dopamine D2 receptor(D2DR) in exercise intervention to improve the PD motion behavior dysfunction and movement disorders.

Background: Parkinson’s disease is a common neurodegenerative disorder that is often associated with movement disorders. Exercise training is widely used for neurorehabilitation of PD. As G protein-coupled receptors, A2AR–D2DR heteromers, which are most probably localized in the dendritic spines of the striatopallidal GABAergic neurons, where they are in a position to modulate glutamatergic neurotransmission. The discovery of A2AR–D2DR heteromers gives a frame for the well-known antagonistic interaction between both receptors, which is the bases for a new therapeutic approach for neuropsychiatric disorders, such as Parkinson’s disease and schizophrenia.

Methods: Clean level male SD rats were randomly divided into Control group(n=24), Control+Ex group(n=24), PD group(n=32), PD+Ex group(n=32). PD model of rats received microinjections of 6-hydroxydopamine bilaterally into the right medial forebrain bundle. At 24h after 6-OHDA injection, the animals in the exercise group were forced to run on a treadmill exercise for 4 weeks. The exercise behavior function of PD rats was evaluated by Rotarod test. We investigated the localization of A2AR and D2DR and alternations in their expression in neurons of striatal using double-label immunofluorescence, and real-time fluorescence quantification and polymerase chain reaction (Real-time PCR) in rats.

Results: Compared with control group, PD model rats decreased significantly in the duration of rotarod exercise, exercise can significantly improve the motor function of PD rats, and there is an obvious dose-response relationship. The expression of D2DR in striatum of rat PD model significantly reduced ,and the expression of A2AR was
significantly up-regulated. Exercise intervention can significantly improve the abnormal expression of A2AR and D2DR in PD rats.

**Conclusions:** Exercise intervention can effectively improve the behavior function and movement disorder of PD model rats, striatal A2AR and D2DR may mediate this process. The possible mechanism may be related with exercise neuroprotective effect regulated the expression of striatal A2AR and D2DR, inhibiting the excessive activation of the basal ganglia indirect pathways, improve the dysfunction state of basal ganglia in PD.

**LBA 52**
High expression of α-synuclein in damaged mitochondria with PLA2G6 dysfunction

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**Objective:** To clarify the role of α-synuclein (αSyn) in neuronal membrane remodeling in the neurons with PLA2G6 deficiency.

**Background:** The physiological function of αSyn has recently become known. αSyn binds to lipid membranes, especially to membranes with high curvature like synaptic vesicles and mitochondria. The N-terminus of αSyn lies along the surface of the membrane, where it senses lipid-packing defects and leads to membrane remodeling and stabilization. Previously, we reported PLA2G6-knockout (KO) mice, which demonstrate marked mitochondrial membrane degeneration.

**Methods:** We analyzed the expression of αSyn in neurons with a dysfunction of PLA2G6, which is indispensable for membrane remodeling. In immunohistochemistry, αSyn/phosphorylated-αSyn (PaSyn) distribution and neurodegeneration were quantitatively estimated in PLA2G6-knockout (KO) mice. We also pathologically assessed the relationship between αSyn deposits and mitochondria in brain tissue from patients with PLA2G6-associated neurodegeneration (PLAN, n=1) and Parkinson’s disease (PD, n=7), and quantitatively examined Lewy bodies and neurons.

**Results:** The expression αSyn was high in PLA2G6-KO mice before onset of motor symptoms. Strong PaSyn expression was also observed in neuronal granule, which never seen in wild-type mice. The granules were mitochondrial outer membrane protein (TOM20)-positive. Ultramicroscopy revealed that PaSyn-positive granules were localized to mitochondria with degenerated membranes. In PLAN neurons, small PaSyn-positive inclusions with a TOM20-positive edge were frequently observed and clustered into LBs. The surfaces of most LBs were TOM20-positive in PLAN and TOM20-negative in PD brains. The neuronal number was preserved both in KO mice and in PLAN and the proportion of LB-bearing neurons was high in PLAN.

**Conclusions:** The high proportion of LB-bearing neurons suggest long-term survival of LB-bearing neurons in PLAN. As PaSyn-loading abnormal mitochondria did not lead to neuronal death in KO mice, the strong affinity of αSyn/PaSyn for damaged mitochondrial membranes in LBs may promote membrane stabilization of mitochondria and the low toxicity of LBs in PLAN.

**LBA 53**
Improving postural stability in early Parkinson’s disease by enhancing somatosensory integration through exercise

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**Objective:** The objective of this study was to explore whether postural instability in Parkinson's Disease can improve through imposed use of focusing attention on somatosensory input when exercising balance.

**Background:** Postural instability (PI) in Parkinson’s Disease (PD) can be due to deficits in the cerebral integration of somatosensory information with visual and vestibular input. Hypotheses state that persons with PD can benefit
from exercise-induced neuroplasticity. This led to researching whether PI in PD can improve through imposed focusing of attention on somatosensory input when performing balance exercises in persons with early PD (ePD).

**Methods:** Subjects with ePD (n=28) were randomized into two groups exposed to the same training program focusing attention to somatosensory input. (INSERT Fig exercise around here) Assessments were made before intervention, after intervention, and at 5-month follow-up. Clinical outcome measures of the Berg Balance Scale (BBS), Timed Up and Go, Timed Up and Go – cognition, BDL Balance Scale (BDL), 10 m walk and the Modified Eight of Balance were analyzed with nonparametric statistics and compared to age and sex matched controls to establish sensitive outcome measures.

**Results:** After intervention, the ePD group improved significantly in BDL (p=0.009), BBS (p=0.013) and 10 m walk (p=0.024). These effects remained at follow-up, except for the 10 m walk. (INSERT Fig boxplot around here) The only test showing a difference in performance between controls and ePD at inclusion was the BDL.
Conclusions: An exercise program with focus on somatosensory integration for maintaining balance in ePD showed positive effects on several outcomes. This could be a sign of exercise-induced neuroplasticity, although the findings need further exploration.

LBA 54
18F-FDG PET Studies with freezing of gait in Parkinson’s disease

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Objective: In this retrospective study we investigate the cerebral glucose metabolism characteristics with freezing of gait in Parkinson’s disease. We hypothesized to detect the mechanism under freezing of gait by using 18F-FDG PET/CT and then provide guidance for the disease.

Background: Freezing of gait has become a common disorder in Parkinson’s disease, and the recognition is important for diagnosis and treatment.

Methods: Thirty-one PD patients (13 with FOG+ and 18 with FOG-) underwent 18F-FDG PET brain scans. Analysis the H&Y scale, the UPDRS-III score, MMSE, MOCA testing and the FOG score using Student t tests and Chi-square test. SPM8 was used to process the imaging data and two-sample t tests were used to analyze the changes in metabolism between two groups. Moreover, we use correlation analyze between the cognitive score and the FDG score.

Results: Compared with the PD-FOG-, the PD-FOG+ patients showed hypometabolism in the superior frontal gyrus (BA11), inferior frontal gyrus (BA10), caudate nucleus and putamen, midbrain, anterior cingulate, and the cerebellum. Compared the indivisual MOCA score between the PD-FOG+ and PD-FOG-, we found that visual space/executive function, naming, memory, language, abstract distinction had no statistical significance (P > 0.05), but the attention between the two groups was statistically significant. Then the Pearson correlation coefficient test between attention and freezing gait is negative, the correlation coefficient is -0.577. Moreover, the executive function correlation analysis found that visual space and FOGQ into negative correlation, the correlation coefficient is-0.417.

Conclusions: PD patients with FOG showed hypometabolism in the superior frontal gyrus (BA11), inferior frontal gyrus (BA10), caudate nucleus and putamen, midbrain, anterior cingulate and the cerebellum compared with PD-FOG- patients. Attention has close reality to freezing of gait, the worse the attention, the more serious the freezing gait clinical severity was. The worse the visual space/executive function was, the more serious the freezing of gait clinical syndrome was. Combine the metabolism changing with the cognitive region score may be helpful for the PD with FOG.

### Table 1: Demographic and clinical characteristics of the PD and control groups

<table>
<thead>
<tr>
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<th>PD-FOG+</th>
<th>PD-FOG-</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender(M/F)</td>
<td>6/7</td>
<td>10/8</td>
<td>0.61a</td>
</tr>
<tr>
<td>Age(years)</td>
<td>68.5±7.9</td>
<td>63.2±7.6</td>
<td>0.07b</td>
</tr>
<tr>
<td>Evolution(years)</td>
<td>3.7±2.0</td>
<td>3.7±2.0</td>
<td>0.97b</td>
</tr>
<tr>
<td>H&amp;Y</td>
<td>2.3±0.6</td>
<td>1.9±0.5</td>
<td>0.07b</td>
</tr>
<tr>
<td>UPDRS-III</td>
<td>37.5±10.2</td>
<td>32.3±14.5</td>
<td>0.28b</td>
</tr>
<tr>
<td>MMSE</td>
<td>20.4±5.1</td>
<td>22.2±4.6</td>
<td>0.32b</td>
</tr>
<tr>
<td>MOCA</td>
<td>14.9±4.9</td>
<td>18.8±5.5</td>
<td>0.05b</td>
</tr>
</tbody>
</table>

Age and clinical ratings are expressed as mean±standard deviation
H&Y: Hoehn and Yahr scale score;
UPDRS-III: motor portion of the Unified Parkinson’s Disease Rating Scale
Table 2: Anomalous areas of cerebral glucose metabolism in PD-FOG+ and the PD-FDG-

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>Coordinates&lt;sup&gt;a&lt;/sup&gt;</th>
<th>t</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reft Cerebrum // Frontal Lobe // Superior Frontal Gyrus</td>
<td>24 60 -22</td>
<td>3.02</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Left Cerebrum // Frontal Lobe // Superior Frontal Gyrus</td>
<td>-24 48 -22</td>
<td>3.06</td>
<td>&lt;0.005</td>
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<tr>
<td>Left Cerebrum // Frontal Lobe // Inferior Frontal Gyrus</td>
<td>-47 56 14</td>
<td>2.68</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Left Cerebrum // Frontal Lobe // Inferior Frontal Gyrus</td>
<td>-58 34 14</td>
<td>2.85</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Right Cerebrum // Sub-lobar // Caudate // Caudate body</td>
<td>14 10 14</td>
<td>2.97</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Right Cerebrum // Lentiform Nucleus // Putamen</td>
<td>23 4 14</td>
<td>2.85</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Left Cerebrum // Sub-lobar // Caudate // Caudate body</td>
<td>-15 2 16</td>
<td>2.64</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Left Cerebrum // Limbic Lobe // Parahippocampal Gyrus // Hippocampus</td>
<td>-19 -7 -16</td>
<td>2.68</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Left Brain stem // Midbrain</td>
<td>-8 -15 -16</td>
<td>2.78</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Left Cerebrum // Limbic Lobe // Anterior cingulate</td>
<td>-2 50 10</td>
<td>2.61</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Right Cerebrum // Limbic Lobe // Anterior cingulate</td>
<td>2 46 10</td>
<td>2.61</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Left Cerebrum // Frontal Lobe // Precentral gyrus</td>
<td>-22 -16 56</td>
<td>2.83</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Right Cerebrum // Frontal Lobe // Precentral gyrus</td>
<td>28 -16 62</td>
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</tr>
<tr>
<td>Left Cerebrum // Cerebellum Anterior Lobe</td>
<td>-52 -44 -36</td>
<td>3.94</td>
<td>&lt;0.005</td>
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<tr>
<td>Right Cerebellum // Cerebellum Anterior Lobe</td>
<td>50 -50 -36</td>
<td>2.69</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Left Cerebrum // Cerebellum Posterior Lobe // Pyramis</td>
<td>-7 -86 -36</td>
<td>2.63</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

<sup>a</sup>Montreal neurological Institute (MNI) standard space. BA = Brodman area.

Fig 1. Comparison of anomalous areas of metabolic change in PD-FOG+ groups versus PD-FOG-(P < 0.005 uncorrected; age as covariates). Yellow represents more hypometabolism than red.
Promotion of mitochondrial biogenesis by necdin protects dopaminergic neurons in experimental Parkinson’s disease

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Objective: This study was designed to assess dopaminergic neuronal protection provided by necdin, a potent PGC-1α stabilizer that promotes mitochondrial biogenesis.

Background: Dopaminergic neurons rely heavily on mitochondria for their function and survival. Mitochondrial dysfunction contributes to the pathogenesis of Parkinson’s disease. PGC-1α is a master regulator of mitochondrial biogenesis and function.

Methods: We examined the interaction between necdin and PGC-1α by co-immunoprecipitation assay. To examine whether necdin promotes mitochondrial biogenesis and function, we transferred the necdin gene into several neuronal cells using lentivirus vectors. We also exploited necdin-deficient mutant mice, recombinant adeno-associated viral (rAAV) vector-mediated gene transduction, and a well-validated and reproducible model of neurodegeneration, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridie (MPTP)-induced dopaminergic (DA) neurodegeneration model of Parkinson’s disease.

Results: Necdin strongly stabilizes PGC-1α by inhibiting its ubiquitin-dependent degradation. Forced expression of necdin enhances mitochondrial function in primary cortical neurons and human SH-SY5Y neuroblastoma cells to prevent mitochondrial respiratory chain inhibitor-induced degeneration. Moreover, overexpression of necdin in the substantia nigra in vivo of adult mice protects dopaminergic neurons against degeneration in experimental Parkinson’s disease.

Conclusions: Our data reveal that necdin, a PGC-1α stabilizer, is a molecule that promotes mitochondrial biogenesis and thereby can provide neuroprotection against mitochondrial damage and its associated
neurodegeneration. Furthermore, our study conveys important information on the regulatory mechanisms of mitochondria biogenesis in neurons that play a critical role in neurodegenerative diseases including Parkinson’s disease.

**LBA 56**  
**Oro-facial symptoms in Parkinson’s disease as predictor of disease progression: data from a longitudinal Swedish cohort**

Örjan Skogar, Johan Lökk,  
Karolinska Institute / FUTURUM  
Stockholm, Sweden

**Objective:** To determine whether the appearance and severity of oro-facial symptoms can be used as a predictor of disease progression in Idiopathic Parkinson’s Disease (IPD).

**Background:** One of the most distinctive clinical features in IPD is hypomimia. Oro-facial symptoms are common both as onset symptoms and as late markers for complication of the disease. A main challenge is to predict the expected progression of the disease.

**Methods:** Data were consecutively collected from routine care visits of IPD patients at an outpatient department of a referral hospital in southern Sweden, Jönköping. In this study, we recruited patients who fulfilled the clinical diagnosis of IPD according to the UK Brain Bank Parkinson’s Disease Criteria. Data were collected from a specially designed, computerized “Parkinson Register” consisting of data on baseline symptomatology, Unified Parkinson's Disease Rating Scale (UPDRS), medications and baseline characteristics during each visit. Scores on different oro-facial features were merged together to create a new severity indicator. Patients were followed for an average of 4.2 (SD=2.7) yrs ranging between >1 to 12 years.

A)
Mean age and duration of disease were 64.7 (SD=9.9) yrs and 6.6 (SD=5.5) yrs at the time of registration. Hypomimia, affected speech, drooling and impaired swallowing were present in 37.3%/91.6 %, 14.1 %/65.5 %, 11.7 %/55.3 % and 10.2%/34.5% at baseline/follow-up, respectively. IPD patients with more severe oro-facial symptoms at baseline had a shorter median time to develop into a worse motoric status showed by UPDRS-Part II>10 [3rd tertile=0.8 yr (SE=0.6), 2nd tertile=8.0 yr (SE=1.3), 1st tertile=8.5 yr (SE=1.4); p28 [3rd tertile=4.7 (SE=2.2) yr, 2nd tertile=6.2 (SE=0.9) yr, 1st tertile=7.8 (SE=1.0) yr; p=0.014].

Conclusions: Prospective, consecutive registrations of IPD-related orofacial symptoms were shown to have a predictive value regarding disease progression. If disease- and symptom-specific registrations would be implemented in ordinary routine care on a nation-based manner, increased knowledge of disease progression, prognosis, and effects of treatments in PD could be of clinical value.

Figure 2. Survival curve to progress into the more than median value of the maximum UPDRS scores during the follow-up in patients with idiopathic Parkinson’s disease with different severities of orofacial symptoms at baseline:

A) UPDRS-Part I: 1st tertile [median survival time=6.2 yr (SE=0.5)], 2nd tertile [median survival time=5.5 yr (SE=0.9)], 3rd tertile [median survival time=4.5 yr (SE=2.1)] (Breslow p-value=0.067)

B) UPDRS-Part II: 1st tertile [median survival time=8.5 yr (SE=1.4)], 2nd tertile [median survival time=8.0 yr (SE=1.3)], 3rd tertile [median survival time=0.8 yr (SE=0.6)] (Breslow p-value<0.001)

C) UPDRS-Part III: 1st tertile [median survival time=7.8 yr (SE=1.0)], 2nd tertile [median survival time=6.2 yr (SE=0.9)], 3rd tertile [median survival time=4.7 yr (SE=2.2)] (Breslow p-value=0.014)
Objective: to determine the effects of Levodopa/carbidopa intestinal gel (LCIG) infusion on axial symptoms of patients affected by advanced Parkinson’s disease (PD) versus OFF medication and ON best medical treatment conditions (ON-bmt).

Background: PD is complicated in advanced stages by gait and balance disorders, which enhance the disability, morbidity, mortality and care giver burden. Those disorders could be difficult to characterized and treat. In our experience, PD patients may benefit from LCIG, consistent as previously reported in literature.

Methods: We performed a prospective observational open-label study: 15 idiopathic advanced PD patients with axial symptoms, subjectively and objectively FOG unresponsive to best available combinations of oral therapies, were enrolled. The motor status were study with UPDRS and H&Y stages: Berg Balance Scale (BBS), Tinetti balance and gait scale and Gait and Falls questionnaire (G&F-Q), FOG questionnaire (FOGQ), new FOG questionnaire (N-FOGQ) for objective and subjective evaluations were choose. At the same time accelerometric gait analysis were performed along two ad hoc walking path, characterized by freezing triggers. The protocol evaluations were performed at the baseline in OFF and ON condition and after 12 months stable LCIG infusion. Cognitive impairment at baseline and at follow-up were tested too.

Results: The whole gait protocol was accomplished by 66.7% of patients. An improvement trend in UPDRS III, BBS score, Tinetti scale was detected from ON-bmt to LCIG. Subjective evaluation made by questionnaires confirmed this data. The accelerometer analysis reported a reduction of performance time in both paths, but with no statistical significance.

Conclusions: this study reports preliminary, but interesting data of the potential benefits of LCIG infusion on PD axial disorders. Matter of next research should be the extension of the sample, longer follow-up with multi-centric protocol and enhancement of objective instrumental gait and balance analysis.

LBA 58
Novel structural congeners of a known phosphodiesterase type-IV inhibitor against experimental Parkinson's disease

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Cell Biology and Physiology Division of CSIR-Indian Institute of Chemical Biology, Organic and Medicinal Chemistry Division of CSIR-Indian Institute of Chemical Biology
Kolkata, West Bengal, India

Objective: To examine whether novel congeners of irsogladine, a phosphodiesterase type 4 inhibitor are potential antiparkinsonian molecules, employing cellular and animal models of Parkinson’s disease (PD).

Background: Degeneration of substantia nigra pars compacta (SNpc) dopaminergic neurons of the midbrain causes loss of control of motor functions as seen in PD due to decreased dopamine levels in the striatum. Dopaminergic receptor signalling employs cyclic adenosine monophosphate (cAMP) as a secondary messenger, levels of which are regulated by cAMP degrading phosphodiesterase (PDE). PDE’s belong to a family of enzymes with 11 types and multiple subtypes therein; they have varying substrate specificities, tissue and cellular distribution making them potential specific therapeutic targets in multiple neurologic disorders. We hypothesize that inhibiting PDE would elevate cAMP levels countering dopamine deficit effects in animal models of the disease, and therefore PDE could be an ideal therapeutic target for PD.

Methods: The parkinsonian neurotoxin, 1-methyl 4-phenylpyridinium (MPP+) treated differentiated SH-SY5Y neurons and PD patient derived cybrid neurons were employed in the investigation of therapeutic potential of newly synthesized irsogladine derivatives. We investigated neuronal death and mitochondrial dysfunctions as indicators of PD pathology. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mouse model was employed for assessing neuromotor behavioural dysfunctions (akinesia, catalepsy, swim, pole, open field and rotarod tests with ANY-maze software), altered striatal biogenic amine metabolism (as measured by HPLC-electrochemistry), and survival of dopaminergic neurons of SNpc (by tyrosine hydroxylase immunohistochemistry). PDE activity was estimated by radiometric assay.
**Results:** We found the 6-aryl substituted 1,3,5-triazine-2,4 diamine (irsogladine) to be active against MPTP-induced experimental parkinsonism in terms of motor function, nigral neuronal protection and probable increase in cAMP from striatal phosphodiesterase inhibition. Changing of halogens (chlorine, bromine) or shifting their position (2,5 and 2,4) or changing their number (dichloro, monobromo) did not lead to loss of anti-parkinsonian activity. However replacement of the aryl group at the 6th position of the triazine diamine with a methyl group resulted in loss of antiparkinsonian activity indicating the aryl moiety is essential for the activity.

**Conclusions:** Our results suggest strong therapeutic potential of novel structural congeners of irsogladine in Parkinson's disease.

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**2016 MDS STUDY GROUP ABSTRACTS**

**SG 1**

**Objectives of the MDS rare movement disorders study group**


**Objective:** There is a need to unify diagnostic criteria, develop a comprehensive approach regarding educational and practical challenges in diagnosis, treatment, and outcome measures and to disseminate knowledge about rare diseases.

**Background:** While the World Health Organization (WHO) does not endorse a single definition for orphan or rare diseases, this group of diseases may be defined as “any disease or condition that affects fewer than 200,000 persons or about 1 in 1,500 people disease”. With recent advances in genetics and other diagnostic techniques there is an increasing number of rare diseases being identified, many of which manifest as movement disorders.

**Methods:** We intend to achieve our main objectives by (1) characterizing the clinical signs and symptoms suggestive of rare disorders; (2) designing a practical movement-based classification; and (3) creating an international database to include epidemiological, demographic, genetic and therapeutic approaches; and (4) establishing a prospective cohort study to identify novel rare diseases.

**Results:** The Rare Movement Disorder Study Group (RMDSG) has been endorsed by Officers of the International Parkinson and The Movement Disorder Society on September 1, 2015. A systematic review was conducted to find a universally applicable definition of “rare diseases”. The RMDSG concluded that “rare diseases” was a more appropriate term than “orphan disease” as the latter is considered politically inappropriate. There is an ongoing strategic plan for the RMDSG to increase education about rare diseases.

**Conclusions:** The RMDSG is bringing together an international team of researchers, patient groups and health professionals to help improve diagnostic and therapeutic options for the growing number of rare diseases and increase education and awareness programs regarding these disorders.

**SG 2**

**Magnetic resonance imaging and pyramidal impairment in Huntington disease**

A. Sanguinetti, S. Lescano, M. Cesarini, J. Etcheverry, E. Gatto (Buenos Aires, Argentina)

**Objective:** To identify structural involvement of the corticospinal pathway in Huntington disease (HD) with clinical upper motor neuron signs using diffusion tensor imaging (DTI).

**Background:** Although, HD is characterized by a selective degeneration of striatal neurons, several studies suggest a corticospinal tract involvement. A marked loss of pyramidal neurons in the primary motor cortex has been related
to motor dysfunction. However, only scarce information is available about the presence of pyramidal motor signs in patients with HD.

**Methods:** This observational study was approved by institutional review board. Six HD patients from our data base with upper motor neuron signs (excluding potential spinal or other unrelated HD causes) composed the sample. We used Diffusion Tensor Imaging (DTI) to investigate corticospinal tract.

**Results:** 6 HD patients (1 man, 5 women) composed the sample, mean age at onset 35 years old; mean diseases duration 6.83 years; mean nCAG expanded allele 46.5. Pyramidal signs included Hoffman and Babinski signs, hyperreflexia and clonus. DTI failed to identify corticospinal tract impairment in this population.

**Conclusions:** In our patients we failed to identify abnormalities in corticospinal tract with DTI. This results should be taken cautiously due to the small sample size. A study with a larger sample of patients is ongoing to confirm this preliminair findings.

SG 3

Pan American multiple system atrophy (PANMSA) consortium database

*M. Cesarini, A. Sanguinetti, J. Etcheverry, E. Mosto, I. Litvan, E.M. Gatto (Buenos Aires, Argentina)*

**Objective:** To create a database coordinating individual MSA study groups of the Pan American region with the required standards by the Global MSA Registry, as previously suggested by the MDS MSA study Group.

**Background:** Multiple system atrophy (MSA) is a rare sporadic progressive neurological disorder with an estimated prevalence of 4 in every 100,000 people. The low prevalence rate prevents individual research sites from studying sufficient number of patients. We previously, conducted a retrospective, observational, cross-sectional Pan-American multicentre cohort study of MSA. Here we propose a prospective study.

**Methods:** A system with web domain easy to use was developed to gather information on MSA. The site has a restricted access for site investigators who participate in the project and will collect de-identified information to protect patient confidentiality. The site has a dynamic architecture. It will collect epidemiologic and demographic data; premotor symptoms, a detailed neurologic examination findings to provide the phenotype, clinical classification (possible, probable), presentations including motor and non motor symptoms and signs; psychiatric and sleep disturbances; Hoehn and Yahr scale and total MDS UMSARS scores; pharmacological and non-pharmacological treatment of sexual dysfunction, urinarly and orthostatic hypotension, sleep, cognitive, psychiatric as well Parkinsonian syndrome and associated complications. Ancillary, information will include Brain MRI findings, neuropsychological tests as well as the first degree family data.

**Results:** The example trial pilot of database is available at link http://www.panmsa.com.

**Conclusions:** The PANMSA database will allow users of South, Central and North America, to collect data that will determine clinical epidemiological and demographic data that will lead to a more focused research or clinical efforts. The PANMSA patient database will also improve collaborative research opportunities with the Global MSA Registry.

SG 4

Diffusion tensor imaging (DTI) within the primate caudate nucleus marks dopaminergic (DA) and serotonergic (5-HT) lesions

*S. Thobois, E. Météreau, M. Beaudoin-Gobert, S. Duperrier, L. Tremblay, V. Sgambato-Faure (Bron, France)*

**Objective:** To determine the best diffusion tensor imaging markers of dopaminergic and serotonergic lesions in the non-human primate.

**Background:** DTI has received particular interest to highlight early markers of neurodegeneration. In Parkinsonian patients, correlations have been evidenced between the motor symptomatology and the alteration of diffusional
parameters within the substantia nigra where DA cell bodies are lost. However, neurodegenerative processes can also involve the 5-HT system and Parkinsonian patients may exhibit different lesion profiles according to the variety of motor and non-motor symptoms expressed.

**Methods:** DA and 5-HT lesions were modelled in monkeys by sequential use of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and MDMA (3,4-methylene-dioxy-methamphetamine; better known as ecstasy). We confronted longitudinal measures of mean diffusivity (MD) and fractional anisotropy (FA) with severity of Parkinsonism, PET imaging analyses and post-mortem fibers quantification.

**Results:** The MPTP-induced lesion was associated to increases of MD in target structures notably within the caudate nucleus, ventral striatum, and the anterior cingulate cortex. These DTI variations discriminated the moderately and severely lesioned monkeys and reflected profound alterations of DA and/or 5-HT fibers. MD increase within the anterior cingulate cortex also correlated with nigral cell bodies loss and severity of Parkinsonism, while MD increase within the caudate correlated with [18F]DOPA caudate uptake. Interestingly also, these DTI alterations were reduced by the compensatory sprouting taking place in moderately lesioned monkeys. The MDMA-induced lesion caused an opposite pattern of DTI alterations with an increased FA within basal ganglia, the one within the caudate nucleus correlating with the Parkinsonian score. Here again, DTI variations reflected profound alterations of 5-HT fibers. Finally, the confrontation of DTI measures within key structures discriminated between single (MPTP) and double (MPTP/MDMA) lesioned monkeys.

**Conclusions:** Taken together, these results demonstrate that DTI within the caudate nucleus characterize both severity and specificity of lesions. They further highlight DTI measures within this brain region as key markers to reveal specific patterns of lesion in Parkinsonian patients.

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**SG 5**

Cerebrospinal fluid biomarkers in Parkinson’s disease and associated cognitive impairment


**Objective:** Our aim is to assess CSF levels of amyloid-β1-42 (Aβ1-42), T-Tau, threonine-181 phosphorilated tau (P-Tau) and α-synuclein (α-syn) as well as different ratios of these proteins as potential biomarkers for PD and cognitive impairment.

**Background:** There is a need for biological markers of PD as well as for the detection of early dementia in this disease. Despite several studies, no CSF biomarker has been yet validated.

**Methods:** 40 non-demented PD patients and 40 controls underwent lumbar puncture, and a comprehensive clinical and neuropsychological evaluation. According to their cognitive state patients were classified as cognitively normal (PDCN) (n=15) or with PD mild cognitive impairment (PD-MCI) (MDS-task force diagnostic criteria) (n=22). CSF levels of Aβ 1-42, T-Tau, P-Tau, and α-syn were measured by ELISA commercial kits.

**Results:** PD patients were on average older than controls (71.08 ± 6.28 vs. 68.21 ± 5.04; p=0.028). Adjusting for age, Aβ 1-42 levels (736.80 ± 239.15 vs. 1009.56 ± 487.43 pg/mL; p=0.048) were lower in PD patients than in controls and α-syn (877.62 ± 289.51 and 1188.36 ± 399.78 pg/mL; p=0.068) levels showed a trend towards significance (lower levels in the former). Although T-Tau and P-Tau did not differ, PD patients showed higher ratios T-Tau/α-synuclein (p=0.001), P-Tau/α-synuclein (p<0.001), T-Tau/Aβ+α-synuclein (p=0.020), and P-Tau/Aβ+α-synuclein (p=0.001) than controls. A ROC analysis showed an area under the curve for the P-Tau/α-synuclein ratio of 0.811 (95% confidence interval: 0.713-0.910; p<0.001) for differentiating PD from controls. No differences in the proteins assessed or in their ratios were observed in the comparison between PDCN and PD-MCI. However, the T-Tau/Aβ ratio (r=−0.450; p=0.018) and the T-Tau/Aβ+α-synuclein ratio (R=−0.433; p=0.008) negatively correlated with the memory z score in PD patients.
Conclusions: The CSF study of the P-Tau/α-synuclein ratio might be useful as a biomarker in the diagnosis of PD. In addition, high T-Tau/Aβ and T-Tau/Aβ+α-synuclein ratios might also be useful in the early detection of cognitive deficits in PD, in particular in memory decline.

SG 6
Cytokines in CSF and plasma as potential biomarkers for PD cognitive impairment


Objective: To assess CSF and plasmatic levels of cytokines as potential biomarkers of PD and PD mild cognitive impairment (PD-MCI).

Background: Neuroinflammation may play a role in the pathogenesis of PD. Cytokine levels are increased and microglia is activated in several cerebral areas of PD patients. In addition, cognitive impairment has been associated with inflammation, as IL-6, IL-1, and IL-1β CSF levels are increased in PD-MCI patients.

Methods: 40 PD patients and 40 controls underwent clinical and neuropsychological evaluation (at least two test for each cognitive domain) and lumbar puncture. According to their cognitive state patients were classified as cognitively normal (PDCN) (n=15) or with PD-MCI (n=22). CSF levels of IL-1β, IL-2, IL-6, IFNγ, and TNF-α were measured using multiplex technology. Cytokines with detectable levels in CSF (IL-6 and TNF-α) were individually assessed in plasma using commercial ELISA kits (R&D Systems, Minneapolis, MN, USA).

Results: Concentration of IL-1β, IL-2, and IFNγ in CSF were below the detection threshold in all the subjects. Levels of IL-6 did not differ between patients and controls (0.617 ± 0.30 vs. 0.531 ± 0.22 pg/mL; p=0.346). Adjusting for age, TNF-α levels were higher in patients than in controls (0.4013 ± 0.158 vs. 0.3078 ± 0.124 pg/mL; p=0.021. In plasma, IL-6 levels were not different between groups (2.294 ± 2.66 vs. 1.917 ± 1.27 pg/mL; p=0.742) and TNF-α levels were under the detection threshold. There was no difference in CSF IL-6 and TNF-α levels and plasmatic IL-6 levels between PDCN and PD-MCI patients. In contrast, IL-6 plasmatic levels negatively correlated with the composite z score of attention and working memory (r=-0.378; p=0.009), executive function (r=-0.359; p=0.016), language (r=-0.553; p<0.001), global cognition z score (r=-0.411; p=0.005), MMSE (r=-0.383; p=0.01), and MOCA (r=-0.429; p=0.003). After adjusting for age, only correlation with language remained significant (corrected p=0.009).

Conclusions: In PD patients, CSF levels of TNF-α are elevated and plasmatic levels of IL-6 negatively correlated with cognitive outcome in language. As decline in semantic fluency has been associated with progression to dementia, plasma IL-6 could deserve further studies as potential biomarker of cognitive dysfunction in PD.

SG 7
Altered connectivity within the cerebello-thalamo-cortical network in essential tremor: A resting state fMRI study

V. Nicoletti, I. Pesaresi, S. Fabbri, S. Giannoni, U. Bonuccelli, M. Cosottini, R. Ceravolo (Pisa, Italy)

Objective: To evaluate the tremor network in Essential Tremor(ET) patients in rest conditions with respect to Healthy Controls(HC).

Background: Pathophysiology of ET is poorly understood. Neuroimaging, neurophysiological evidences suggested the involvement of cerebello-thalamo-cortical network.

Methods: 23 possible/probable ET patients and 23 matched HC underwent a 3T-MRI with acquisition of a resting state sequence. Connectivity was investigated using a seed-based regression analyses approach. Regions of interest were identified from a between-group activation map obtained in a previous task-related fMRI study. They were located in left primary motor cortex(M1), supplementary motor area(SMA), somatosensory cortex, thalamus and
right cerebellum hemisphere. Statistical correlation maps obtained for each seed and each subject were registered to MNI. Between group differences were evaluated using FSL Fixed Effect with correction for multiple comparisons.

**Results:** ET patients showed compared to HC: reduced connectivity of left M1 both with premotor cortex, SMA and somatosensory areas and with cerebellum; decreased connectivity between cerebellar hemispheres each other; increased connectivity between somatosensory cortex and parietal areas as well as primary motor, premotor cortex, supplementary motor area and also increased connectivity between right cerebellar lobule VI and thalamus and left putamen. In ET SMA were more connected to premotor cortex whereas it was hypoconnected with parietal regions, precentral cortex and left putamen and globus pallidus(GP); thalamus revealed higher connectivity with cerebellum and left caudate and less connectivity with right GP.

**Conclusions:** The altered connectivity within the cortical sensory-motor network in ET could be due to alterations in cortical integrative processing. The decreased connectivity of cerebral cortex with cerebellum as well as the decreased connectivity within the cerebellum in ET patients is consistent with recent findings showing altered connection of motor network between cerebellum and cerebral cortex. The increased connectivity between cerebellum and thalamus and the complex alteration of connectivity between BG and thalamus are congruent with the crucial role of both cerebellum and thalamus in tremor generation. Thus the oscillatory activity in ET might be due to a dynamic entrainment of several mutually linked cortico-subcortical drivers.

**SG 8**

**Diagnostic reliability of clinical symptoms in patients with incomplete manifestation of the triad of Parkinsonism compared to 18F-DOPA PET-CT MRI imaging**


**Objective:** To describe the diagnostic reliability of the triad of clinical symptoms compared to the uptake of 18 F-DOPA PET-CT fusion MRI scan. To compare the match between the visual and quantitative interpretation of the 18 F-DOPA uptake in putamen and caudate.

**Background:** The differential diagnosis of Parkinson’s disease in cases of incomplete manifestation of the triad of bradykinesia (B), rigidity (R) and tremor (T) includes essential/dystonic tremor and Parkinsonism unrelated to striatal dopaminergic deficiency.

**Methods:** Patients who presented incomplete/atypical presentation of the clinical triad (2/2 or 3/3 and/or unresponsive to dopaminergic therapy) underwent 18F-DOPA PET-CT fusion MRI scan. Neurologists examined the patients and ranked the clinical suspicion, masked to the 18F-DOPA PET-CT results.

**Results:** There were 14 patients, mean age= 62 ys old (41–79); male/female=9/5; mean symptoms duration=3.6 y (1–10), clinical triad: TR=3, TBR=9, BR=1, TB=1. Out of 14 patients with clinical suspicion of Parkinsonism, 6 had dopaminergic deficit in 18F-DOPA PET-CT (42.86%). 2/2 clinical symptoms were not associated with low putaminal uptake, as opposed to 3/3 symptoms in which 6/9 patients presented reduced putaminal uptake (67%). The correlation between low 18F-DOPA putaminal uptake and higher UPDRS scores was stronger than in caudate (p=0.05). Higher UPDRS scores were associated with reduced putaminal uptake in correlation coefficients (-0.63 (right), -0.73 (left)). There was no association in caudate (-0.27 (right) -0.50 (left)). In the visual analysis, 8 patients had low putaminal uptake and 7 were confirmed by the quantitative analysis, while 6 had normal uptake confirmed by quantitative analysis (13/14 correctly diagnosed).

**Conclusions:** This exploratory analysis showed that 2/2 symptoms were not associated with a decrease in putaminal uptake, while 3/3 symptoms showed low putaminal uptake in 67% of cases. Higher UPDRS scores were more frequently associated with a decrease in putaminal uptake. Accuracy for detection of 18F-DOPA uptake was similar for visual and quantitative analysis.
**SG 9**  
*Cerebellar GABA-A receptor activity is inversely correlated with gait speed in Parkinson’s disease*


**Objective:** To investigate the relationship between regional cerebral expression of benzodiazepine receptors and gait speed in Parkinson’s disease (PD).

**Background:** Flumazenil is a short-acting intravenously administered gamma-aminobutyric acid (GABA-A) antagonist which has shown to rapidly improve motor impairments in PD. Based upon current basal ganglion models in PD, flumazenil could normalize neuronal signaling at several different locations but little is known about the relationship between regional cerebral benzodiazepine receptor expression and gait speed in PD. We have previously shown that gait speed is a correlate of cortical cholinergic activity in PD.

**Methods:** PD patients \( N=16 \) (15M; 67.9 ± 4.9 years old; 10.6 ± 4.4 years motor disease duration, HY range 2-3, mean MMSE score 28.5 ± 2.1 and mean UPDRS motor score of 29.1 ± 11.4) underwent \([^{11}C]\)flumazenil GABA-A receptor and \([^{11}C]\)PMP (acetylcholinesterase) brain PET scanning and clinical assessment. Gait speed was assessed as the time needed to walk a 8.5 meter pathway in the dopaminergic “off” state.

**Results:** Stepwise regression analysis was used to best predict regional cerebral correlates of gait speed using cortical, caudate nucleus, putamen, thalamic and cerebellar flumazenil binding estimates using a 0.15 significance model entry level. The overall model was significant \( (R^2=0.35) \) with only cerebellar receptor activity as the single predictor in the model \( (F=7.57, P=0.016) \). Cerebellar receptor activity and gait speed correlation findings remained significant after adjustment for cortical cholinergic activity.

**Conclusions:** Cerebellar GABA-A receptor expression is inversely correlated with gait speed in PD independent from cortical cholinergic status. Findings may augur novel non-dopaminergic approaches to treating gait difficulties in PD.

**SG 10**  
*Anosmia predicts development of more severe motor symptoms including freezing of gait and impaired balance at 2 year follow-up in PD*

*N.I. Bohnen, J. Haugen, V. Kotagal, K.A. Frey, R.L. Albin, M.L.T.M. Muller (Ann Arbor, MI, USA)*

**Objective:** To investigate the relationship between baseline anosmia and 2-yr interval development of motor impairments in Parkinson’s disease (PD).

**Background:** More severe olfactory deficits have been associated with akinetic-rigid motor symptoms in PD. Presence of anosmia may potentially predict development of motor disability in PD.

**Methods:** PD patients, \( n=32 \) (F8; 67.3±6.8 (54-88) years old; 6.9±4.6 (1-18) years motor disease duration, HY range 1-3, mean MOCA score 25.8±3.4 (15-30) and mean MDS-UPDRS motor score of 30.5±12.8 (11-62) underwent olfactory assessment using the 40-item University of Pennsylvania Smell Identification test (UPSIT) and clinical motor testing. MDS-UPDRS motor assessment was performed in the dopaminergic “off” state. MDS-UPDRS examination was repeated 2 years later.

**Results:** The mean UPSIT score was 16.7±8.3 (range 0-36) with 7 scoring in the anosmic range (UPSIT 10 or less) at baseline with most of the remainder subjects in the hyposmia range. There were 11 patients who developed a balance-disabled status (HY 3 or higher) at 2-yr follow-up including 6 out of 7 anosmic subjects (85.7%). Presence of baseline anosmia was a significant predictor of balance-disabled status \( (2=10.4, P=0.0012) \). Anosmia was also a significant predictor of freezing of gait at follow-up \( (2=6.2, P=0.01) \). Repeat measures mixed linear modeling showed significant between-subjects \( (F=4.63=0.04) \) and within-subjects effects for the MDS-UPDRS motor scores: time \( (F=8.44, P=0.0071) \) and interaction term between time and the anosmia \( (F=5.69, P=0.02) \).
Conclusions: Presence of anosmia in relatively mild stage disease may predict more severe motor decline, including impaired balance and freezing of gait, in PD. Early appearance of anosmia may potentially represent limbocentral Lewy pathology spreading preferentially to balance and gait associated areas.

SG 11
Participation in cognitively-stimulating activities and computer use are associated with better cognitive performance in Parkinson’s disease independent from nigrostriatal dopaminergic and cortical cholinergic degenerations

J.L.B. Bohnen, M.L.T.M. Muller, J.D.J. Haugen, N.I. Bohnen (Ann Arbor, MI, USA)

Objective: To investigate the relationship between times spent with cognitively stimulating activities and cognitive functions in Parkinson’s disease (PD) while accounting for the degree of primary neurodegenerations.

Background: There is accumulating evidence that frequent participations in cognitively stimulating activities are beneficial to brain health among subjects at risk of dementia. No prior studies have investigated similar associations in PD.

Methods: PD patients [N=48 (40M); 69.4±7.4 years old; 8.4±4.2 years motor disease duration and mean MMSE score 28.4 ± 1.9 underwent [C-11]DTBZ PET imaging to assess nigrostriatal denervation, and completed the CHAMPS questionnaire and neuropsychological testing. CHAMPS questions 1-6, 8, 11-13 & 17-18 were summed, which include activities such volunteering, visiting friends, computer use, crafts, attending a concert, reading, playing cards or a musical instrument. [C-11]PMP cholinergic PET was also performed in 42 patients.

Results: Mean duration of participation in cognitively stimulating activities was 23.2±12.5 (range 6-44 hr), including computer use (4.4±2.4, range 0-6 hr). Bivariate correlations between global cognitive z-score and duration of cognitive hobbies and computer were R=0.50, P=0.0005 and R=0.52, P=0.0002, respectively. Multiple regression analysis using the global cognitive function z-score as outcome variable demonstrated significant regressor effect for duration of weekly participation in cognitive stimulating activities (F=12.2, P=0.0013) while accounting for effects of caudate nucleus dopaminergic (F=0.25, ns), cortical cholinergic activity (F=0.74, ns), education (F=1.43, ns), age (F=4.7, P=0.036) and duration of disease (F=0.02, ns; total model: F=4.15, P=0.003). Post-hoc analysis limited to duration of weekly computer use showed similar regression with higher cognitive scores (F=14.1, P=0.0006; total model: F=4.60, P=0.0015).

Conclusions: Engagement in cognitive activities, including computer use, is associated with better cognitive abilities in PD independent from nigrostriatal dopaminergic and cortical cholinergic degenerations. Findings may imply that participation in cognitively stimulating activities may help to promote cognitive preservation in PD.

SG 12
Motor rigidity selectively associates with impaired odor identification in Parkinson’s disease

J.D. Haugen, M.L.T.M. Muller, V. Kotagal, K.A. Frey, R.L. Albin, N.I. Bohnen (Ann Arbor, MI, USA)

Objective: To investigate the relationship between impairments of the cardinal motor symptoms and odor identification deficits in Parkinson’s disease (PD).

Background: Although hyposmia has been shown to correlate with striatal dopaminergic losses in PD, previous studies have shown no or limited motor correlates with hyposmia. The variable and limited association between these variables may be explained by specific rather than global motor correlates of hyposmia.

Methods: PD patients, n=151 (F39; 65.9±7.7 (50-86) years old; 6.1±4.4 (0.5-20) years motor disease duration, HY range 1-5, and mean MOCA score 23.9±2.6 (15-30) underwent clinical testing. Olfactory function was assessed using the 40-item University of Pennsylvania Smell Identification test (UPSIT). MDS-UPDRS motor assessment was performed in the dopaminergic “off” state. Subscores for the cardinal motor symptoms (tremor, rigidity, axial and distal bradykinesia) were calculated.
Results: The mean UPSIT score was 16.3±8.2 (range 0-36) and the mean MDS-UPDRS motor score was 32.6±14.1 (8-72). Bivariate correlation analysis between the UPSIT and total MDS-UPDRS motor scores was significant (R=-0.23, P=0.0054). Stepwise regression analysis using the UPSIT as outcome parameters and the four rank-normalized MDS-UPDRS motor sub-scores showed a significant model with rigidity (F=10.32, P=0.0016) as the only significant motor parameter in the model (F=9.7, P=0.0022). Multiple regression analysis using the rank-normalized rigidity scores as outcome parameter and UPSIT, age and duration of motor disease as regressors yielded a significant total model (F=4.83, P=0.0031) with significant regressor effects for UPSIT scores (F=8.87, P=0.004), duration (F=3.91, P<0.05) but not for age (F=1.19, ns).

Conclusions: Rigidity but not the other cardinal motor impairments associates with impaired odor identification in PD. The selective association between motor rigidity and hyposmia in PD may reflect a partially shared neural network underlying these symptoms. Findings may agree with recent observations of a mesolimbic-striatal loop that is part of a larger neural network underlying rigidity in PD.

SG 13
Impaired color discrimination selectively associates with postural instability and gait difficulties in Parkinson’s disease

J.D. Haugen, M.L.T.M. Muller, N.I. Bohnen (Ann Arbor, MI, USA)

Objective: To investigate the relationship between impairments of the cardinal motor impairments and color discrimination deficits in Parkinson’s disease (PD).

Background: Previous studies have shown that impaired color discrimination functions reflect cognitive deficits in PD, in particular executive and visuospatial deficits. Such cognitive deficits may also contribute to postural instability gait difficulties (PIGD) motor features in PD.

Methods: PD patients, n=55 (F14; 67.2±7.3 (54-86) years old; 7.4±5.3 (0.5-20) years motor disease duration) tested color discrimination using the Farnsworth-Munsell 100 Hue Test (FMT). MDS-UPDRS motor and gait assessment was performed in the dopaminergic “off” state. Subscores for the cardinal motor symptoms (tremor, rigidity, PIGD and distal bradykinesia) were calculated. 8.5-meter walking time and timed up and go test (TUG) were also assessed.

Results: The mean FMT total error score was 101.2±88.8 (range 4-428). There was a significant inverse correlation between performance on the FMT and MOCA cognitive scores (R=-0.39, P=0.003). There was also a significant correlation between the FMT and total MDS-UPDRS motor scores (R=0.31, P=0.02). Stepwise regression analysis using the FMT as the outcome parameter and the four rank-normalized MDS-UPDRS motor sub-scores showed a significant model with PIGD features (F=5.73, P=0.02) as the only significant motor parameter in the model. Multiple regression analysis using the rank-normalized PIGD scores as the outcome parameter and FMT, age and duration of motor disease as regressors yielded a significant total model (F=4.17, P=0.01) with significant effects for FMT scores (F=5.14, P=0.028), duration (F=4.34, P=0.05) but not age (F=1.54, ns). There were also significant correlations between performance on the FMT and the rank-normalized timed gait (R=0.37, P=0.0065) and TUG tests (R=0.47, P=0.0003). Multiple regression analysis using the rank-normalized TUG as outcome parameter showed significant predictor effects for FMT (F=14.35, P=0.0004), age (F=5.43, P=0.023) but not for duration of disease (F=1.82, ns; total model F=8.04, P=0.0002).

Conclusions: Impaired color discrimination selectively associates with PIGD motor features in PD. Findings may reflect a shared pathophysiology between impaired color discrimination, cognitive impairment and axial motor symptoms in PD.

SG 14
Substantia nigra \(\alpha4\beta2\) nicotinic cholinergic receptor expression correlates with tremor in Parkinson’s disease

M. Muller, R. Albin, N. Bohnen (Ann Arbor, MI, USA)
Objective: To investigate the relationship between tremor and α4β2 nicotinic cholinergic receptor (nAChR) expression in brain regions associated with tremor in Parkinson’s disease (PD), including the substantia nigra, putamen, thalamus, premotor cortex, cerebellar hemisphere and vermis.

Background: Anticholinergic agents are effective against tremor in many PD patients. Cholinergic system changes may play a role in the pathophysiology of PD tremor.

Methods: PD patients (N=19) [7 Female; 67.7±8.3 (52-88) years old; 5.9±3.4 (1-16) years motor disease duration, HY stages 2-3, MOCA score 27.6±2.2 (22-30); MDS-UPDRS motor score 43.7±15.4 (20.5-74)] underwent [18F]flubatine α4β2 nicotinic receptor PET imaging. MDS-UPDRS motor assessment was performed in the dopaminergic “off” state. Tremor severity was based on the MDS-UPDRS sub-scores for tremor.

Results: The mean MDS-UPDRS tremor sub-score was 8.5±4.6 (range 1-19.5). Stepwise linear regression with tremor score as the dependent variable showed a significant (F=6.5, p=0.021) positive association between α4β2 nAChR expression in substantia nigra and MDS-UPDRS tremor sub score (β=0.526, t=2.55, p=0.021). There was no significant association of tremor with MDS-UPDRS total motor score and disease duration or α4β2 nAChR expression in putamen, thalamus, premotor cortex, cerebellar hemisphere and vermis.

Conclusions: Increased α4β2 nAChR expression in the substantia nigra correlates with increased tremor in Parkinson’s disease. This finding may reflect changes in expression of α4β2 nAChRs by nigral neurons or by presynaptic pedunculopontine cholinergic afferent terminals. These results suggest that PD tremor is mediated by altered cholinergic signaling in the nigra.

Motor-related brain changes associated with acute administration of trihexyphenidyl in patients with cervical dystonia


Objective: The goal of the current study was to assess task-related brain activity in patients with cervical dystonia (CD) using functional magnetic resonance imaging (fMRI) with and without a single-dose administration of trihexyphenidyl.

Background: CD is the most common type of primary dystonia, and is characterized by involuntary neck muscle contractions that cause abnormal movements of the neck and head. Currently, there is no FDA approved oral medication for CD. Anticholinergic agents such as trihexyphenidyl are sometimes used. As yet, no study has investigated how anticholinergics modulate brain activity in CD.

Methods: A grip force production task known to extensively engage motor brain networks was performed in a 3T MRI scanner by 16 patients with idiopathic CD, and 16 age- and gender-matched healthy individuals. CD patients were scanned twice, off-medication, and on average two hours after a single-dose (2 mg) administration of trihexyphenidyl. Control subjects did not receive the medication, and were therefore only scanned once.

Results: Off-medication, CD patients had reduced motor-related activity compared to healthy individuals in the contralateral primary motor and somatosensory cortices, middle frontal gyrus, and insula, and increased activity in the ipsilateral pre-supplementary motor area, superior parietal lobule, and contralateral lobules V, I-IV of the cerebellum. Administration of trihexyphenidyl to CD patients was associated with an increase in the motor-related activity of the primary somatosensory cortex, bilaterally, and contralateral middle frontal gyrus as compared to the off-medication state.

Conclusions: These results suggest a baseline disruption of somatosensory processing in CD that can be modulated acutely by administration of trihexyphenidyl.
In-vivo free-water imaging and functional connectivity in a knock-in mouse model of DYT1 dystonia

J.C. DeSimone, M. Febo, P. Shukla, E. Ofori, L.M. Colon-Perez, Y. Li, D.E. Vaillancourt (Gainesville, FL, USA)

Objective: To examine in-vivo functional connectivity and free-water diffusion imaging in dystonic mutant Tor1a knock-in (DYT1) and wild-type (WT) control mice. We test the hypothesis that striatal and sensory circuits are functionally and structurally abnormal in the DYT1 mouse model.

Background: Human DYT1 dystonia is characterized by sustained and involuntary muscle contractions resulting in twisting, repetitive movements and disabling posture. DYT1 is an inherited movement disorder caused by a trinucleotide (ΔGAG) deletion encoding a glutamic acid residue in the TorsinA protein. In the in-vivo DYT1 mouse model, a reduction in dopamine receptor binding results in impaired cortico-striatal inhibitory control and long-term depression deficit. Previous imaging studies have shown that the DYT1 mouse model is associated with increased metabolic activity in the cerebellar vermis in-vivo, and reduced structural integrity of the fiber tracts linking cerebellum and cortex ex-vivo. To our knowledge, no previous research has examined both functional connectivity and free-water of DYT1 dystonia in-vivo.

Methods: We used in-vivo resting-state functional and diffusion MRI at 11 Tesla to examine functional connectivity and extracellular free-water differences in 20 DYT1 and 19 WT mice. Temporally correlated blood oxygenation level dependent signal fluctuations and functional connectivity were examined using an independent component analysis, whereas a bi-tensor diffusion analysis model was employed to evaluate free-water diffusion imaging.

Results: DYT1 mice exhibited increased functional connectivity in the right striatum, right thalamus, and right somatosensory cortex – and increased free-water in the right striatum and cerebellar vermis compared to WT. A support vector machine classification algorithm that combined functional connectivity and free-water values in a training cohort of 15 DYT1 and 15 WT mice rendered a classification accuracy of approximately 98%, and 8 of 9 mice were accurately classified in an independent cohort.

Conclusions: DYT1 mice evidenced increased functional connectivity in the striatum, thalamus, and somatosensory cortex, and elevated free-water in the striatum and cerebellum. These effects were robust in the classification algorithm in a large cohort of mice. Thus, it is clear that mutant torsinA impairs the cortical, striatal, and cerebellar regions in living mice.

Mild cognitive impairment is linked with white matter degeneration in the cortico-subcortical tracts in patients with Parkinson’s disease


Objective: Evaluate the correlation between brain tractography changes in patients with Parkinson’s disease (PD) with and without mild cognitive impairment (MCI).

Background: Up to 40% of PD patients have MCI early in the disease and PD patients with MCI (PD-MCI) have a higher risk of developing dementia compared to those with normal cognition (PD-NC). Finding an early marker for MCI in PD would help in reducing the potential of developing dementia in the event that neuroprotective and neurorestorative therapy becomes available.

Methods: 39 non-demented patients with PD and 16 healthy volunteers (HV) underwent a neuropsychological assessment and analyses of DWI data. Regions of interest were drawn using ITKSnap. Fiber tract analyses were performed using FiberNavigator and we studied the white matter parameters between cortical and subcortical structures.
**Results:** Patients with PD and normal cognition (PD-NC) had increased tract count compared with HV between the caudate nucleus (CAU) and the ipsilateral primary motor area (M1), while PD-MCI patients had a decrease in tract count compared with both groups and it was statistically significant with PD-NC (p=0.04). Other parameters revealed increased radial diffusivity (RD) and mean diffusivity (MD) in PD-NC vs. HV and in PD-MCI vs. PD-NC and HV. Increased RD is thought to reflect de/dys-myelination while increased MD has been associated with diminished membrane density. Similar patterns were observed between CAU and ipsilateral dorsolateral prefrontal cortex, supplementary motor area (SMA) and premotor cortices. Additionally, tractography analyses between CAU and ipsilateral SMA showed a pattern of increased axial diffusivity (AD) in PD-NC vs. HV, and a decreased AD in PD-MCI vs. PD-NC. Decreased AD was suggested to reflect axonal injury while increased AD might reflect brain maturation or compensation.

**Conclusions:** Our data reveal a significant increase in tract counts in PD-NC compared to HV and a significant decrease of this parameter in PD-MCI patients. This effect might reflect a compensational effect in PD-NC patients, which allows them to preserve the normal cognitive function. These results might serve as a marker for identifying the availability of compensational resources and for earlier prediction of the evolution of cognitive decline in PD.

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**SG 18**

Fall prediction in Parkinson’s disease based on motor dual-tasking: Evidence from the prospective MODEP study

*S. Heinzel, M. Maechtel, S.E. Hasmann, M.A. Hobert, T. Heger, D. Berg, W. Maetzler (Tuebingen, Germany)*

**Objective:** To evaluate the predictive value of dual-task performance for future falls in patients with Parkinson’s disease (PD).

**Background:** Falls entail very severe health-related consequences in patients with Parkinson’s disease (PD). Cognitive impairment including dual-tasking deficits have been shown to contribute to an increased risk of falling in PD. However, specific types of motor-cognitive dual-tasking deficits that precede falls in PD are still unclear.

**Methods:** Walking speed during a concurrent box-checking or serial 7s subtraction task were assessed twice a year in 40 PD patients over a mean (±S.D.) observation period of 2.8±1.0 years. During this period, 14 patients reported a fall (4 excluded fallers already reported falls at baseline). Dual-task costs (DTC) 4.2±2.2 months before the first reported fall were compared to DTC of 22 patients who never reported falls. ROC analyses and logistic regressions accounting for DTC, UPDRS-III and disease duration were calculated to classify and predict fallers.

**Results:** Walking/box-checking dual-tasking, but not walking/subtracting, predicted fallers. Higher DTC for walking while box-checking in fallers (p=.029), but no significant difference for box-checking while walking (p=.178; combined motor DTC, p=.022) compared to non-fallers were observed. Fallers and non-fallers were classified based on combined motor DTC (area under curve: 0.75; 95% confidence interval, CI: .60-.91) with 71.4% sensitivity (95% CI: 41.9%-91.6%) and 77.3% specificity (54.6%-92.2%), which significantly predicted future fallers (p=.023). Here, an increase in combined motor DTC by 20.4%-points, which corresponds to the mean difference between fallers and non-fallers, was associated with a 2.6 (1.1-6.0) times higher odds to be a future faller.

**Conclusions:** The simultaneous performance of two motor tasks is a valuable predictor of falls in PD. Falls in PD may be prevented by avoiding dual task situations as well as by specific motor dual-task training. These findings and their clinical and therapeutic relevance need to be further validated with various motor-motor dual-tasks in early stage PD patients.

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**SG 19**

Visual vs. automated analysis of [123I]FP-CIT SPECT scans in patients with Parkinsonism

*E. Mäkinen, J. Joutsa, J. Johansson, M. Mäki, M. Seppänen, V. Kaasinen (Turku, Finland)*

**Objective:** To investigate the differences between visual and automated analyses of brain dopamine transporter (DAT) SPECT scans.
**Background:** Clinical evaluation of DAT SPECT scans typically relies on visual evaluation of striatal tracer binding in combination with an automated semiquantitative region-of-interest (ROI) –based method. The interpretation of the result is complicated in cases that show disagreement between the two methods on the borderline of abnormality. The prevalence and clinical characteristics of these cases are unknown.

**Methods:** Automated ROI analyses (BRASS software) and independent visual evaluations by two experienced nuclear medicine physicians, blinded to automated ratings, were performed for 120 Parkinsonism patients scanned with [123I]FP-CIT SPECT. The scans were selected to represent the large range of tracer binding and they were evenly distributed across ages and genders. Agreement between visual and automated analyses was investigated with Cohen’s kappa. Cases with discrepant results were identified and the clinical characteristics of these patients were studied in detail.

**Results:** Inter-rater agreement between the visual evaluations was excellent (κ=0.81) and the agreement between visual and automated analyses was good (κ=0.66 and κ=0.72). However, twelve patients (10%) showed discrepancy between the two methods. Nine were visually evaluated as abnormal while automated analysis categorized them as normal, and vice versa in three cases. Patients with discrepant findings had 17.6% lower mean striatal tracer binding compared to normal scans (p=0.003) and 62.7% higher binding compared to abnormal scans (p<0.0001). These patients were older compared to patients with non-discrepant normal findings (72.6 vs. 62.4 years, p=0.023) and after a clinical follow-up of 4.5 years, none of them developed neurodegenerative dopaminergic Parkinsonism (one case was lost to follow-up).

**Conclusions:** Clinical DAT SPECT scans show discrepancy between visual and automated analyses in 10% of cases. The disagreement is mostly due to visual evaluations interpreted as abnormal without tracer binding reductions in the ROI analysis. The majority of the patients with discrepant analyses are older patients. Importantly, patients with discrepant imaging findings do not seem to develop degenerative Parkinsonism syndromes.

### Clinical characteristics of the cases that showed discrepant findings between visual and automated analyses.

<table>
<thead>
<tr>
<th>Discrepancy</th>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical reason for imaging</th>
<th>Symptom duration and predominant side of motor symptoms</th>
<th>Current diagnosis</th>
<th>Cognitive defect</th>
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</thead>
<tbody>
<tr>
<td>Brass normal, visual abnormal</td>
<td>1</td>
<td>59</td>
<td>M</td>
<td>Suspected Parkinsonism plus sdr</td>
<td>2 years, Left side</td>
<td>Alzheimer’s disease</td>
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<td></td>
<td>2</td>
<td>70</td>
<td>F</td>
<td>Re-evaluation of PD diagnosis</td>
<td>11 years, Right side</td>
<td>Undetermined Parkinsonism</td>
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<td>3</td>
<td>73</td>
<td>F</td>
<td>Differential diagnosis between PD and DIP</td>
<td>0.5 years, Right side</td>
<td>DIP (Risperidone 2 mg/day)</td>
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</tr>
<tr>
<td></td>
<td>4</td>
<td>80</td>
<td>F</td>
<td>Differential diagnosis between PD and DIP</td>
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<td>DIP (Prochlorperazine, dose unknown)</td>
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</tr>
<tr>
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<td>5</td>
<td>84</td>
<td>F</td>
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<td>DIP (Perfenazine 8 mg/day)</td>
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<td>Age</td>
<td>Sex</td>
<td>Diagnosis</td>
<td>Duration</td>
<td>Symmetry</td>
<td>Disease Etiology</td>
<td>Notes</td>
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<td>6</td>
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<td>F</td>
<td>PD vs DIP</td>
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<td>DIP (Risperidone, dose unknown)</td>
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<td>Essential tremor</td>
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<td>Re-evaluation of PD diagnosis</td>
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<td>No</td>
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<tr>
<td>9</td>
<td>80</td>
<td>M</td>
<td>Unclear Parkinsonian sdr</td>
<td>1 year</td>
<td>Right side</td>
<td>Vascular Parkinsonism</td>
<td>Yes</td>
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<td><strong>Brass abnormal, visual normal</strong></td>
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<tr>
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<td>M</td>
<td>Unclear Parkinsonian sdr</td>
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<td>Cervical degenerative disease</td>
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<td>M</td>
<td>Differential diagnosis between PD and ET</td>
<td>10 years</td>
<td>Right side</td>
<td>Essential tremor</td>
<td>No</td>
</tr>
</tbody>
</table>

Current diagnosis after a minimum of 4.5 years of clinical follow-up. Cognitive defect at the time of imaging or within 5 years after imaging. DIP=drug-induced Parkinsonism.

**SG 20**

**Long-term incidence of Parkinson’s disease in rural areas of Finland**

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**Objective:** To investigate possible long-term changes in the incidence of Parkinson’s disease (PD) in rural regions.

**Background:** Living in rural areas has long been suspected to increase the risk of PD. Rural living, agricultural occupation or well water drinking are possible proxies to a common nominator, such as pesticide exposure that could trigger PD pathogenesis via mitochondrial damage. During recent years, a global process of urbanization has paralleled a reallocation of labor from agriculture to other sectors and a large decrease in pesticide use. We hypothesized that these changes have decreased PD incidence in rural areas.

**Methods:** We compared annual age-standardized PD incidences of 317 urban and rural regions in Finland from an 18-year period (1997 to 2014). The total annual population in the analysis was 5.2-5.5 million with 26 731 new cases of PD. Regions were classified as rural or urban using population-based (<15 000 vs. >30 000) and production-based (<5% vs. >5% of work force in primary production) categorization. Annual regional PD incidences were derived from the Finnish National Prescription Register. Age-standardized incidence rates for each region and year were calculated using the EU standard population as reference.

**Results:** Age-adjusted incidence of PD was higher in rural areas over the entire study period (rural 33.2 vs. urban 30.9 per 100 000 person-years; incidence rate ratio=1.08, p<0.0001). The incidence increased in both rural and urban areas over 18 years, but there were no significant differences in the slopes (p=0.28) indicating no regional differences in the trend in IRs. The results were essentially the same using production-based classification of regions.
**Conclusions:** The current age-adjusted risk of PD in Finnish rural areas remains higher compared to urban areas and the incidence is on the rise in all regions. Rural-to-urban incidence rate ratio has not decreased. Either the specific rural risk factors have remained constant, the gradual reduction in incidence is too slow to be detected in 18 years, or the process is associated with a long latency period.

**SG 21**

**MRI-supported diagnosis of multiple system atrophy: Implications for clinical trials**

*F. Krismer, G.K. Wenning, S. Bajaj, M. Schocke, C. Scherfler, W. Poewe, K. Seppi (Innsbruck, Austria)*

**Objective:** To assess whether MSA-specific MRI changes predict a more rapid clinical decline in a cohort of patients with a clinical diagnosis of MSA.

**Background:** It is currently unknown whether patients with clinically suspected MSA and MR features consistent with MSA differ in their progression from those patients who do not have MSA-specific MR changes.

**Methods:** 22 MSA patients who participated in previous prospective natural history studies and had a MR scan soon after their first clinic visit were followed for at least 48 months at our outpatient clinic. 12-month clinical progression was determined using the UMSARS. The following baseline MR abnormalities were assessed: putaminal, pontine, cerebellar and middle cerebellar peduncle atrophy, a putaminal hyperintense rim, putaminal signal hypointensity, and the hot cross bun sign. MR abnormalities were graded on a 4-point likert scale with increasing severity (no, mild, moderate, severe abnormality). Patients were stratified into two subgroups: (1) Patients with MR features consistent with MSA (MR-positive) and (2) patients without evidence of MSA-specific structural MR changes (MR-negative). MR-positivity was defined by the presence of at least one MR abnormality graded moderate or of more than two minor MR abnormalities. Clinical progression between the two groups were compared using an ANCOVA model which was corrected for baseline UMSARS score, age, gender and disease duration.

**Results:** 17 of 22 patients (77%) showed MR abnormalities consistent with MSA. There were no significant differences between the two groups in age, gender, disease duration at baseline visit or baseline UMSARS scores. Disease progression was significantly different between the two groups with MR-positive patients showing a more rapid clinical decline (UMSARS total mean difference MR-positive vs. MR-negative group: 21.7 [95% CI 16.4 – 27.1] vs. 9.3 [95% CI -1.0 – 19.6], F = 4.9, p = 0.041)

**Conclusions:** The presence of MR abnormalities has a significant impact on disease progression irrespective of clinical diagnosis, disease duration or baseline disease severity in MSA patients. This observation should be considered for the planning of future clinical trials.

**SG 22**

**Dorsolateral nigral hyperintensity on 3.0 tesla susceptibility-weighted imaging in idiopathic rapid eye movement sleep behaviour disorder**

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**Objective:** To assess the loss of dorsolateral nigral hypersensitivity (DNH), which seems to correspond to nigrosome-1, using susceptibility-weighted imaging (SWI) at 3.0 Tesla (T) in subjects with idiopathic REM sleep behaviour disorder (IRBD).

**Background:** RBD is a parasomnia characterized by lack of muscular atonia during REM sleep associated with dream-enacting behaviour and unpleasant dreams. Prospective cohort studies of subjects with IRBD have shown that a majority go on to develop an alpha-synuclein-related neurodegenerative disease. These findings suggest that a proportion of subjects with IRBD could represent patients in a pre-motor stage of Parkinson’s disease (PD). Recently, several groups have reported a novel MRI marker for PD based on the loss of DNH using iron-sensitive MRI including SWI at 3.0 and 7.0 Tesla.
**Methods:** 15 IRBD patients were studied with 3T MRI. In order to compare DNH status (present or absent) between subjects with IRBD, healthy controls (HC) and PD we used imaging data of our recently published cohort of 104 PD subjects and 42 HC. 19 randomly selected subjects from our previous study (10 HC and 9 PD patients) were added to the analysis set of MR images of IRBD subjects and DNH raters were kept blind to diagnostic categories. Unilateral absence of DNH was classified as abnormal. The main per-protocol analysis to assess differences of DNH loss between groups was performed excluding scans of insufficient quality for reliable assessment.

**Results:** Ten out of 13 (77%) IRBD patients showed loss of DNH, which was distinct from HC (corrected p<0.001) but similar to patients with PD (corrected p=0.27). Overall, one of 35 controls (3%) and 83 of 90 (92%) patients with PD patients showed loss of DNH.

**Conclusions:** In this study we found that 77% of IRBD patients showed loss of DNH, which is distinct from HC but similar to patients with PD. In PD this imaging finding has been linked to loss of dopaminergic cells in the Nigrosome 1 area of the substantia nigra (SN), corresponding to a calbindin-negative subregion in the healthy SN pars compacta. This finding not only further supports the role of IRBD as a biomarker for prodromal PD but also raises the possibility that absent DNH on MR SWI might be a diagnostic tool to identify those IRBD subjects in whom there is ongoing synuclein pathology in the SN.

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**Effects of age and gender on brainstem MR-planimetry**

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**Objective:** To evaluate age and gender effects on brainstem MR-planimetric measures. (1,2).

**Background:** Brainstem planimetry has been successfully applied to differentiate Progressive Supranuclear Palsy (PSP) from Parkinson’s disease (PD), Multiple-System-Atrophy (MSA) and healthy controls (HC). It has been suggested that ageing might influence the brainstem midbrain-to-pontine-area-ratio (M/PA).

**Methods:** MR planimetry was performed in 97 HC (mean age 62.8 years; SD 10.9 years; female-to-male-ratio = 49:48) on a 1.5T scanner to assess midsagittal midbrain area, midsagittal pontine area, mean middle cerebellar peduncles (MCP) diameter, mean superior cerebellar peduncle (SCP) diameter, as well as midsagittal midbrain diameter (acc. QS) (2) and pontine diameter (acc. QS) (2). From these parameters, the MR-Parkinson-Index (MRPI) (1), midbrain-to-pons area ratio (M/PA) (1) as well as the midbrain-to-pontine-diameter-ratio (M/Pd) (2) were calculated. Planimetric measures were performed on an imaging database program (IMPAX EE). Gender-related differences of all MR-planimetric measurements as well as of the MRPI, M/PA and M/Pd were calculated using ANCOVAs entering gender as factor and age as covariate. Due to the multiple comparisons, p-values of < 0.01 were considered statistically significant.

**Results:** ANCOVA models revealed no significant gender-effects on any variable. However, ANCOVA models revealed significant age-effects on midbrain diameter (p < 0.0001; F 18.708), on the MRPI (p=0.513; F 0.431), the M/Pd (p < 0.0001; F 12.385) and the M/PA (p < 0.0001; F 24.764) when including all study participants. However, when including only the population aged 50 to 80, there was no significant age-effect on neither variable.

**Conclusions:** While there are no significant gender-effects on any brainstem MR planimetric measures, our data suggest significant age-effects on the midbrain diameter, midbrain-to-pontine-diameter-ratio (M/Pd), and midbrain-to-pons area ratio (M/PA). However, when applying MR-planimetric measures to controls aged 50 to 80, no age-effects on these brainstem MR planimetric measures were observed. This age-group is relevant for the differential diagnosis of neurodegenerative Parkinsonism, thus suggesting that there is no need for age specific-cut offs for these brainstem MR planimetric measures. (1) Hussl A et al. Mov Disord. 2010;25(14):2444-9. (2) Massey LA et al. Neurology. 2013;80(20):1856-61.
The effect of STN-DBS on movement initiation control is modulated by the noradrenergic system: Evidence of an interaction from a combined pharmacological/DBS/EEG study

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Objective: Assessing the role of the noradrenergic system underlying the effect of subthalamic nucleus stimulation (STN-DBS) on akinesia.

Background: Slowness in movement initiation, associated with akinesia, is a cardinal symptom of Parkinson’s disease. It has recently been revisited as a possible executive rather than a purely motor dysfunction (Favre et al., 2013). Patients would be locked into an inappropriate mode of proactive inhibitory control of movement initiation. Standard dopamine based medication does not fully alleviate this disorder, only STN-DBS would be efficient to release inhibition, at the expense of increased impulsivity. Recently, the effect of STN-DBS on movement initiation latency was found to be modulated by the noradrenergic (NA) system (Albares et al., 2015). But direct evidence of NA-dependent STN-DBS-induced brain activity changes is still missing.

Methods: Eighteen PD patients under STN-DBS were enrolled in a placebo-controlled study and tested in a reaction time task investigating movement initiation latency. This pharmacological protocol crossed NA manipulation (by means of Clonidine, an α-2A adrenergic agonist or Placebo) and STN-DBS manipulation (ON or OFF). EEG recordings were conducted using advanced methods for filtering out stimulation artifacts and unmixing/localizing neural sources.

Results: Under placebo, STN-DBS improved movement initiation latency (ON vs. OFF DBS). This behavioural effect was associated with a reduction of proactive tonic alpha power (a marker of neural inhibition) within the SMA. Under Clonidine, the positive effect of STN-DBS vanished. This behavioural effect was associated with an increase in tonic alpha power within the SMA.

Conclusions: These results support the hypothesis according to which clonidine counteracts the positive effect of STN-DBS that consists in restoring control of proactive inhibition over movement initiation. The opposite patterns of DBS-induced changes in alpha power observed under Clonidine and Placebo in the SMA strongly suggest that the inhibitory control of movement initiation is dysfunctional in the pathological state, restored under STN-DBS, and back to dysfunctional under combined STN-DBS/Clonidine. These results provide the first direct neural-based evidence in humans of NA-dependent STN-DBS-efficiency.

Functional connectivity underpinnings of fatigue in “drug-naïve” patients with Parkinson’s disease

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Objective: Using resting-state functional MRI, we investigated the functional correlates of fatigue in a cohort of “drug-naïve” patients with PD.

Background: Fatigue is a common problem in Parkinson’s disease (PD) either in the early or later stage of the disease.

Methods: MRI at 3Tesla was collected in 40 patients with PD, 20 with and 20 without fatigue and 20 matched healthy controls. The presence and the severity of fatigue was defined based on the 16-item Parkinson fatigue scale. Single-subject and group-level independent component analysis was used to investigate functional connectivity differences within the major resting state networks between patients sub-groups and healthy controls. In addition, we used voxel-based morphometry to test whether between-group functional changes were related to structural differences.

Results: Distressing fatigue was associated with a decreased connectivity in the supplementary motor area within the sensorimotor network and an increased connectivity in the prefrontal and posterior cingulate cortices within the default mode network (p<0.05 corrected). Fatigue severity was correlated with both sensorimotor and default mode
networks connectivity changes. Voxel-based morphometry analysis did not reveal any significant volume
differences between all patients with PD and healthy controls and between patients with PD with and without fatigue
(p<0.05; FWE).

Conclusions: Our findings revealed that primary PD-related fatigue is associated with an altered default mode
network and sensorimotor network connectivity in drug naive patients. We hypothesize that these divergent motor
and cognitive networks connectivity changes and their adaptive or maladaptive functional outcome may play a
prominent role in the pathophysiology of fatigue in PD.

SG 26
PET imaging of tau pathology in progressive supranuclear palsy

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Objective: This study aimed to determine whether there is an increase in [18F]-AV-1451 uptake in the brains of
progressive supranuclear palsy (PSP) patients compared to Parkinson’s disease (PD) patients and healthy controls
(HC).

Background: PSP is a rare form of parkinsonism that differs neuropathologically from other Parkinsonian
disorders; however, there is often an overlap of clinical symptoms, especially in the early stages of PSP. While PD,
Lewy body dementia, and multiple system atrophy are classified as synucleinopathies, PSP is a tauopathy due to the
aggregation of pathological tau in the brain. [18F]-AV-1451 (also known as [18F]-T807) is a positron emission
tomography (PET) radiotracer that binds to paired helical filaments (PHF) of tau in Alzheimer’s disease (AD), as
shown previously in clinical studies. We investigated whether [18F]-AV-1451 could be used as biomarker for the
diagnosis and disease progression monitoring in PSP.

Methods: A total of 11 patients (5 PSP: age 74.0±5.65, 3 female; and 6 PD: age 63.7±9.61, 3 female) and 8 age-
matched HC (age 63.3±9.11, 8 female) were recruited. An anatomical MRI and a 90-minute PET scan, using [18F]-
AV-1451, were acquired from all participants. The standardized uptake value ratio (SUVR) from 30 to 60 minutes
post-injection was calculated in each region of interest (ROI) with the cerebellum, as well as the corpus callosum as
reference regions. ROIs were selected based on cortical and subcortical brain regions previously reported to present
with tau pathology in PSP. A nonparametric Kruskal–Wallis test was employed to check for differences in SUVR
between the three groups.

Results: Differences in age and gender across groups were not significant. There were no significant increases of
[18F]-AV-1451 SUVR in PSP compared to PD and HC in any of the tested cortical and subcortical ROIs. These
results were reliable when analyzed using the two different reference regions (i.e. cerebellum and corpus callosum).

Conclusions: No differences in SUVR could be detected in any of our PSP patients compared to controls. Any
uptake in tracer could have
been potential off target binding. Our preliminary results suggest that using SUVR on [18F]-AV-1451 images may
not be an appropriate marker for abnormal tau deposition in PSP.

SG 27
The relationship between the cognitive phenotype and 5-HT2A receptor in PD with visual hallucinations

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Objective: The aim of this study was to investigate the relationship between cognitive phenotype and 5-HT2A
receptor availability in PD patients with visual hallucinations (VH).

Background: There is growing evidence indicating that the serotonergic system may be involved in cognitive
processing and in the development of VH. Studies investigating the relationship between cognitive/behavior
phenotype and level of 5-HT2A receptor availability in PD with VH are lacking.
Methods: In total, 19 PD patients (8 PD without VH and 11 PD with VH) and 10 age-matched healthy controls participated and completed the full neuropsychological test battery testing visuospatial, executive, memory/language, and frontal function. PET scan using [18F]setoperone, 5-HT2A antagonist radioligand, was acquired in the PD patients. The parametric binding potential (BP) map of [18F]setoperone were calculated with the simplified reference tissue model using the cerebellum as a reference after the frame-based motion correction in each participants. Group analysis and psychometric correlation analysis were done with BP images and z-transformed cognitive measurements using SPM 8.

Results: We found significant decline of processing speed and visuo-perceptual function in PD with VH compared with age matched controls. Performance levels of these functions were not significantly different from PD without VH. Comparison between PD with, and without, VH disclosed several brain regions with BP differences in [18F]setoperone. PD with VH group appears to be reliant on decreased BP in the right insula, bilateral dorsolateral prefrontal cortex, right orbitofrontal cortex, right middle temporal gyrus and right fusiform gyrus. Subsequent correlation analysis revealed, within the top-down information processing network, a significant positive correlation between Visual Object, Space Perception battery, Facial Recognition Test and the level of BP; within the bottom-up information processing network, the Rey Complex Figure Test score and Judgement of Line Orientation Test score showed a negative correlation with the level of BP.

Conclusions: The changes observed in this study imply a relationship between bottom-up/top-down cognitive information processing and 5-HT2A receptor function in PD patient with VH.

SG 28
Unilateral subthalamotomy in Parkinson’s disease: Cognitive and neuropsychiatric effects and correlation with lesion size

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Objective: To assess cognitive and neuropsychiatric effects of unilateral subthalamotomy in Parkinson’s disease (PD) and their correlation with lesion size.

Background: Surgery for treatment of PD motor signs is effective, but its precise consequence in non-motor domains still remains controversial. Prior studies investigated lesion effects from bilateral subthalamotomy but yet no information on STN unilateral lesions is at hand.

Methods: Fourteen PD patients (5 right, 9 left subthalamotomy) were evaluated pre and post surgery while ON medication. The mean post-surgery evaluation was 6 months. In addition to motor assessments, cognitive evaluations (MMSE, FAB, DRS, verbal fluency, executive function, learning), quality of life and neuropsychiatric assessments (apathy, depression, anxiety, mania, hypo- and hyperdopaminergic states, impulsivity) and volume of lesions from MRI were obtained.

Results: After surgery, as expected significant motor improvement was observed. Subthalamotomy improved general cognitive status, but left lesions reduced verbal fluency compared to before surgery. Anxiety, depression and quality of life scores were significantly improved after surgery. However, specific hyper-emotionality was present after surgery. Moreover, right subthalamotomy led to disinhibition which was associated with larger volume lesions, as shown by correlations with post-surgery MRI.

Conclusions: Right and left subthalamotomy produced beneficial effects on quality of life, general cognitive status and mood in PD. However, right subthalamotomy increased disinhibition associated with larger lesions size and left subthalamotomy induced deficits in verbal fluency. Overall, unilateral subthalamotomy is an effective treatment for motor symptoms and non-motor signs of PD, but right subthalamotomy may carry greater risk of adverse neuropsychiatric effects.
Brain mechanisms underlying visual processing in Parkinson’s disease

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Objective: We used fMRI and a visual cognitive task to study brain mechanisms underlying visual processing at different cognitive loads in patients with PD and PD with mild cognitive impairment (PD_MCI) as compared with healthy controls (HC).

Background: Visual processing deficits can be found in PD_MCI.

Methods: Altogether, 95 subjects (55 HC, 16 PD and 24 PD_MCI) performed a visual object matching task in a 3T MR scanner. The task consisted of pairs of conventional view images, unconventional view (spatially rotated) images, and a control task. Participants pressed a YES button if the second object of the paired images was the same as the first object (regardless of spatial orientation) or a NO button if they were different. The number of correct answers was an outcome measure. The effect of stimulation was computed using a general linear model implemented in SPM12. T statistic maps were computed to assess the effects of activation with respect to task conditions. A one-way ANOVA was used to assess the differences across groups followed by post-hoc t-tests. Group results were assessed using cluster level inference at p (FWE) < 0.05 at a height threshold of p (uncor) < 0.001. For group classification we used an ROC analysis.

Results: We found significant differences between groups only for the unconventional view task condition. The post-hoc analysis revealed that PD_MCI differed from HC (p=0.011). Based on behavioral results we evaluated our fMRI data using the unconventional vs. conventional condition contrast only. ANOVA revealed significant differences in the anterior cingulate cortex (ACC, p=0.013) and in the superior parietal lobule (SPL, p=0.017). Using a post-hoc t-test we found that PD_MCI and HC groups differed in activation of ACC (decreased in PD_MCI) while PD_MCI as compared to PD showed significantly decreased activation of both ACC (p=0.047) and SPL (p=0.004). ROC analysis of fMRI contrast in SPL distinguished PD_MCI from PD with 87.5% sensitivity and 86.98% specificity, AUC=0.94 (0.86-1.00).

Conclusions: Results of fMRI analysis using a visual object matching task with unconventional vs. conventional view contrasts revealed differences between PD_MCI and PD primarily in a component of the dorsal visual pathway implicated in mental rotation (SPL). ROC analysis of fMRI data distinguished PD_MCI from PD with > 85% sensitivity and specificity Our fMRI paradigm could be used as a biomarker for PD_MCI diagnosis.

Speech prosody impairment predicts cognitive decline in Parkinson’s disease

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Objective: We assessed whether baseline speech prosodic parameters, alone or in combination with other predominantly non-dopaminergic symptoms may predict global cognitive decline as measured by the Addenbrooke’s cognitive examination (ACE-R) and/or worsening of cognitive status as assessed by a detailed neuropsychological examination.

Background: Impairment of speech prosody is characteristic for PD and does not respond well to dopaminergic treatment.

Methods: Fifty consecutive non-depressed PD patients underwent clinical and cognitive testing, and perceptual and acoustic voice analysis at baseline and at the two-year follow-up. Influence of speech and other clinical parameters on worsening of the ACE-R and of the cognitive status was analyzed using linear and logistic regression.

Results: The cognitive status (classified as normal cognition, mild cognitive impairment and dementia) deteriorated in 25% of patients during the follow-up. The multivariate linear regression model consisted of the variation in range of the fundamental voice frequency (F0VR) and the REM sleep Behavioral Disorder Screening Questionnaire...
These parameters explained 37.2% of the variability of the change in ACE-R. The most significant predictors in the univariate logistic regression were the speech index of rhythmicity (SPIR; \( p=0.012 \)), faciokinesis (\( p=0.049 \)), disease duration (\( p=0.019 \)), and the RBDSQ (\( p=0.032 \)). The multivariate regression analysis revealed that combining faciokinesis with RBDSQ led to 81.8% accuracy in predicting a change in cognitive status. The SPIR alone predicted a cognitive status change with 73.2% accuracy.

**Conclusions:** Impairment of speech prosody and faciokinesis together with symptoms of RBD predict rapid cognitive decline and worsening of PD cognitive status during a two-year period.

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**SG 31**

**Diffusion tensor imaging biomarkers of nigrostriatal neurodegeneration in early Parkinson’s disease**

*J.A. Pineda-Pardo, G. Foffani, J.A. Obeso (Móstoles, Spain)*

**Objective:** Identify magnetic resonance imaging (MRI) biomarkers of nigrostriatal neurodegeneration in early-stage drug-naïve Parkinson’s disease (PD).

**Background:** Diffusion tensor imaging (DTI) is an MRI technique that seems appealing for developing early biomarkers of nigrostriatal neurodegeneration in PD, but current findings are controversial. We hypothesize that a pathophysiologically-relevant source of variability could be the presence of left-right asymmetries in the dysfunction of the nigrostriatal system, previously observed with single-photon emission computed tomography (SPECT). These asymmetries are often neglected by pooling patients based on the most affected side of the body, without stratifying right-onset vs left-onset patients.

**Methods:** The sample in this study is the open cohort of the Parkinson Progression Marker Initiative (PPMI) [3], specifically 128 PD patients at baseline and 49 healthy controls, all right-handed. T1 images were normalized to a MNI template using ANTS, and the inverse transformation was applied to the Keuken atlas [4] in order to create substantia nigra (SN) and striatum native masks. DTI datasets were pre-processed using FSL, and scalar DTI images were estimated and co-registered to the T1 images using a linear affine transformation. DTI measures included fractional anisotropy (FA), and mean (MD), radial (RD) and axial diffusivity (AD). Average values of these measures were extracted in SN and striatum masks. Patients were stratified based on the most affected side of the body: right-onset (n=75) vs. left-onset (n=53).

**Results:** The right-onset PD group displayed lower FA than healthy controls in the left SN, and higher FA in the left striatum. Lower FA in the SN might reflect a reduction of axonal integrity, while higher FA in the striatum might represent pruning in the complex arborisation of this structure. Conversely, the left-onset PD group displayed no differences in FA compared with healthy controls, either in right SN or striatum. Instead, this group displayed lower MD and RD than healthy controls in the right striatum.

**Conclusions:** These results corroborate the left hemispheric predominance of nigrostriatal dysfunction in PD, previously observed with SPECT, [2] and suggest DTI measures as promising biomarkers for both striatal and nigral neurodegeneration.

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**SG 32**

**A proposed Parkinson’s disease neuropsychological battery (PNB)**

*L.L. van Wanrooij, J. Hoogland, J.G. Goldman, G. Stebbins, G.J. Geurtsen, D. Weintraub (Amsterdam, Netherlands)*

**Objective:** To propose a neuropsychological battery for assessing cognitive abilities in Parkinson’s disease (PD) that also fulfills proposed MDS diagnostic criteria for PD mild cognitive impairment (PD-MCI).

**Background:** Cognitive deficits are increasingly recognized in PD as being both common and detrimentally affecting quality of life. To diagnose PD-MCI by MDS Level II criteria, a detailed neuropsychological assessment is the gold standard. However, many different tests are used by different studies, which limits comparability of results.
Therefore, having a research-informed Parkinson’s Neuropsychological Battery (PNB) would be desirable for pooling data across sites and for use in research trials.

**Methods:** Neuropsychological test data from 22 centers participating in the MDS PD-MCI Validation Study Group were analyzed. Neuropsychological tests administered in at least two countries were selected (N=28). Z-scores based on published norms were determined. The main outcome was the discriminative ability of tests to separate non-demented PD patients from Healthy Controls (HC). The discriminative ability, expressed by effect sizes, was determined in two ways: (1) the average z-score for each test was compared between PD patients and the theoretical population mean of zero and then ranked, and (2) z-scores were compared between PD patients and HCs for those centers with a HC population. Moreover, regression techniques (least absolute shrinkage and selection operator [LASSO]) were used to analyze the z-scores based on published norms as well as the z-scores based on de HCs. By combining these different statistical methods tests were ranked on sensitivity to detect cognitive impairment in non-demented PD patients.

**Results:** Twenty-eight tests were analyzed of which 7 in the Attention and Working Memory domain, 6 in the Memory, 7 in the Executive Functioning, 3 in the Language and 5 in the Visuospatial/Visuoconstructive domain. Data from 22 centers were included, containing 3,434 non-demented PD patients and 1225 HCs. Analyses are ongoing and will be completed in time to present at the upcoming MDS meeting.

**Conclusions:** We expect to be able to propose a comprehensive PNB based on our research findings. A subsequent step will be to analyze the sensitivity of the PNB tests to detect cognitive decline using longitudinal data.

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**SG 33**

**Imaging correlates of hypodipsia in progressive supranuclear palsy**


**Objective:** Aims of the present study were
- to confirm hypodipsia as a characteristic feature of PSP and
- to offer hypothesis on the pathological substrate for hypodipsia in PSP patients.

**Background:** Progressive supranuclear palsy (PSP) may be difficult to distinguish from other Parkinsonian syndromes, particularly from Parkinson’s disease (PD). However, these syndromes differ both in their prognosis as well as in their therapy. A previous study proposed hypodipsia (reduced thirst) as a useful parameter to discriminate between PSP and PD [Stamelou et al., 2011].

**Methods:** In patients with a probable clinical diagnosis of PSP (N=8), and PD (N=9), and in healthy controls (HC, N=11), we provoked thirst with a 3% NaCl-infusion at a rate of 11.4 ml/kg body weight/hour for 50 min. The level of thirst was assessed with a standardized thirst questionnaire scaled from 0 to 8 (0=no thirst, 8=maximal thirst) every 5 minutes. At the end of the study, the volume of water each subject drank until satiation was recorded. Serum-osmolality and ADH levels were assessed before and after the infusion period. A functional brain imaging paradigm was carried out in a 3T-MRI scanner, during which the subjects looked at ten consecutive blocks of either thirst stimulating images (e.g. drinking people) or neutral images (e.g. empty streets, plants). To assess the level of thirst these images provoked, subjects were asked to press one of eight buttons (1=no thirst, 8=maximal thirst) after each activation block. A resting-state MRI (rsMRI) for network analysis before and after NaCl-infusion was also performed.

**Results:** PSP patients reported less thirst than PD patients and HC (2-way ANOVA, P<0.001). After the test, PSP patients drank significantly less water to satiation than PD patients and HC (ANOVA, P<0.05). No significant differences in ADH levels and serum osmolality among PSP, PD, and HC were found. Several brain areas were significantly less activated in PSP and PD patients compared to HC, particularly the left putamen and the precuneus bilaterally. Analyses of rsMRI are underway.

**Conclusions:** Based on the fMRI findings, we propose that the expectation- and the reward-system associated with the putamen and the precuneus may be impaired in both, PSP and PD. Analysis of changes in pre- and post-infusion rsMRI will provide further insights into changes associated with hypodipsia in PSP.
Correlation of clinical and pathological data in Progressive Supranuclear Palsy

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Objective: In the present study we attempted to determine whether the initial clinical presentation of Progressive Supranuclear Palsy (PSP) is associated with demographic data or specific histopathological features.

Background: PSP belongs to the group of neurodegenerative diseases with tau-positive inclusions. In addition to the classical Richardson Syndrome (RS) phenotype with early onset of falls and of supranuclear gaze palsy (SNGP), PSP exhibits broad clinical heterogeneity including features of frontotemporal lobar degeneration (PSP-FTLD), corticobasal syndrome (PSP-CBS) and Parkinson’s disease (PSP-P).

Methods: We analyzed standardized clinical data and histopathological features of 101 clinically well-characterized and autopsy-confirmed PSP cases. Patients were classified into clinical subgroups on the basis of their initial clinical presentation.

Results: PSP-RS cases represented the largest clinical subgroup followed by PSP-FTLD and PSP-CBS. In addition, we identified a subgroup which was characterized by predominant postural instability and unusually late onset of SNGP - PSP-PI. PSP-P cases exhibited a longer than average disease duration of 11 years. Regarding clinical presentation, falls and cognitive decline occurred late in PSP-P patients, SNGP occurred late in PSP-PI and in PSP-FTLD and Parkinsonian features occurred late in PSP-FTLD and PSP-PI. Furthermore, patients with PSP-P and PSP-PI developed dysarthria and dysphagia at a remarkably late stage of their illness. All PSP cases displayed widespread histopathological changes in virtually all brain regions analyzed. Most prominent neuronal tau deposits were located in the striatum, limbic system, subthalamic nucleus and midbrain, in line with the most distinct neurodegenerative changes. Additional differences were found in several core regions: PSP-PI and PSP-P revealed severe neurodegenerative changes in the substantia nigra and oculomotor nucleus, whereas more tau-positive neuronal cell inclusions were seen in the temporal cortices of PSP-PI, PSP-FTLD and PSP-CBS and in the pallidum in PSP-P and PSP-CBS.

Conclusions: PSP-P cases represent the subgroup with the longest disease duration. PSP-P and PSP-PI cases had the longest latency to the onset of disabling symptoms such as dysarthria and dysphagia. The sequence of clinical milestones varied interindividually, but eventually all PSP cases developed all core symptoms and did not significantly differ in their age at death. The heterogeneity in the distribution of pathological changes may reflect the involvement of different functional networks. In the future, functional brain imaging and new positron emission tomography tau ligands hold considerable promise to gain a deeper insight into the spread of the disease during lifetime.

MDS-Clinical Diagnostic Criteria for Progressive Supranuclear Palsy (PSP)

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Objective: To provide an evidence-based revision of the clinical diagnostic criteria for PSP.
**Background:** PSP is a neuropathologically defined disease entity. Clinical diagnosis remains a challenge. The NINDS-SPSP criteria for the clinical diagnosis of PSP (Litvan et al., Neurology 1996; 46:922-930) are widely accepted because of their high specificity. However, their sensitivity is limited for patients early in the clinical course and for phenotypic PSP variants other than Richardson’s syndrome that have been described recently.

**Methods:** We inquired the PubMed, Cochrane, Medline, PSYCInfo databases for original research articles, systematic reviews and meta-analyses, published in English language from 1996 to 2015, using postmortem diagnosis or the NINDS-SPSP criteria as the diagnostic standard. Published evidence was evaluated as proposed by the Scottish Intercollegiate Guidelines Network. Secondly, standardized clinical data were extracted from charts of patients with pathologically diagnosed PSP (N=198), CBD (N=50), MSA-P (N=51), PD (N=51), and FTLD (N=64). On this basis, criteria were drafted, optimized in two modified Delphi evaluations, and submitted to a structured discussion and consensus procedure during a 1.5 day in-person meeting.

**Results:** From N=5894 identified articles, N=469 met the inclusion standards. We identified the functional domains of ocular motor dysfunction, postural instability, akinesia-rigidity, and cognitive dysfunction as clinical predictors of PSP. Within these domains, distinct clinical features provide varying levels of predictive values. Specific combinations of these do provide different degrees of diagnostic certainty (probable > possible > oligosymptomatic). Defined imaging findings support the diagnosis. Defined clinical, imaging, laboratory and genetic findings help to rule out alternative diagnoses.

**Conclusions:** In summary, we propose new criteria for the early, sensitive and specific clinical diagnosis of PSP on the basis of currently available evidence, to be validated in prospective clinico-pathological studies.

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Long term recordings of subthalamic oscillatory activity in patients with Parkinson’s disease


Increased cerebrospinal fluid lactate levels in Parkinson’s disease: Is it a proof of mitochondrial inefficiency?

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Detailed proteomic analysis of early PD brain highlights altered expression of mitochondrial proteins as an important event in sporadic PD


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J. De Pauw, R. Mercelis, A. Hallemans, S. Michiels, S. Truijen, P. Cras, W. De Hertogh (Antwerp, Belgium)

1641 Clinical characteristics and natural history of oromandibular dystonia
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