

MDS Study Groups

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Genotype-phenotype correlations in 104 Uzbekish families with Spinocerebellar ataxias

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Objective: Spinocerebellar ataxias are neurodegenerative disorders involving the cerebellum and its connections. There are more than 30 distinct subtypes, 16 of which are associated with an identified gene. The aim of the current study was to evaluate a large group of patients from 104 Uzbekish families with spinocerebellar ataxias.

Background: The background of the current study was to evaluate a large group of patients from 104 Uzbekish families with spinocerebellar ataxias.

Methods: We studied 150 patients from 104 families with spinocerebellar ataxias who had received molecular genetic testing for spinocerebellar ataxia types 1, 2, 3, 6, 7, 8, 10, 12, 17, and dentatorubral-pallidoluysian atrophy. A statistical analysis of the results was performed using basic descriptive statistics and the correlation coefficient (r), Student's t-test, chi-square test, and Yates' correction. The statistical significance level was established for p-values <0.05.

Results: The results show that the most common subtype was spinocerebellar ataxia 3, which was followed by spinocerebellar ataxia 10. Moreover, the comparison between patients with spinocerebellar ataxia 3, spinocerebellar ataxia 10, and other types of spinocerebellar ataxia revealed distinct clinical features for each type. In patients with spinocerebellar ataxia 3, the phenotype was highly pleomorphic, although the most common signs of disease included cerebellar ataxia (CA), ophthalmoplegia, diplopia, eyelid retraction, facial fasciculation, pyramidal signs, and peripheral neuropathy. In patients with spinocerebellar ataxia 10, the phenotype was also rather distinct and consisted of pure cerebellar ataxia and abnormal saccadic eye movement as well as ocular dysmetria. Patients with spinocerebellar ataxias 2 and 7 presented highly suggestive features of cerebellar ataxia, including slow saccadic ocular movements and areflexia in spinocerebellar ataxia 2 and visual loss in spinocerebellar ataxia 7.

Conclusions: Spinocerebellar ataxia 3 was the most common subtype examined, followed by spinocerebellar ataxia 10. Patients with spinocerebellar ataxia 2 and 7 demonstrated highly suggestive features, whereas the phenotype of spinocerebellar ataxia 3 patients was highly pleomorphic and spinocerebellar ataxia 10 patients exhibited pure cerebellar ataxia. Epilepsy was absent in all of the patients with spinocerebellar ataxia 10 in this series.

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MSA Preliminary Panamerican Report

M. Cesarini, E. Gatto, J. Etcheverry, G. Da Prat, N. Gonzalez Rojas, H. Teive, M. Rodriguez, J. Ziliani, M. Miranda, P. Chana, F. Cardoso, A. Cardozo, C. Uribe Roca, I. Amorin, L. Abaroa, c. Cosentino, Y. Nuñez, A. Lescano, E. Dieguez, A. Alleva, I. Litvan, G. Wenning (La Plata, Argentina)

Objective: To report the results of the PAN American MSA (PANMSA) database

Background: Multiple system atrophy (MSA) is a rare neurodegenerative disease and coordinated efforts are required to improve understanding, diagnosis, and treatment. Recently, Walsh RR et al. published some recommendations for Global MSA research including the creation of a unified dataset for MSA and implementation of a global international registry. In an attempt to reduce the knowledge gap in our region in 2014 we reported the preliminary data from PANMSA cohort.1 Two years later we implemented, a system

with web domain database with a restricted access for site investigators to collect de-identified information to protect patient confidentiality.²

Methods: Demographic and clinical data from MSA patients were collected until March 2018 and included in the new encrypted database. Inclusion criteria required: >21 years old individuals fulfilling clinical diagnosis of MSA on the basis of the current consensus criteria for the disease (revised criteria for clinical diagnosis of MSA, 2008) and ancillary neuroimaging. Exclusion criteria required: patients with any other causes of Parkinsonism.

Results: 72 patients met criteria. The sample consisted of 61 Hispanic Latinos, 1 Amerindian and 10 non Hispanic white. 54% probable MSA-P, 16.6% probable MSA-C, 15.7% possible MSA-P 13.8% possible MSA-C. 55.5% were women. The mean age at start of symptoms is 58.4 years and. The mean years of diseases duration is 4.6. The mean UMSARS II score 48.6 points, H&Y between 2.5-4 involve more than 63 patients, 93% present with orthostatic hypotension. Premotor symptoms were identified as depression 69.4%, hyposmia 30.6%. Autonomic dysfunction occurred in 84%,(constipation 84%, orthostatism 93%, urogenital dysfunction 91.7%) Sleep disorders: RLS 15%, insomnia 50%, RBD 56.9%. Cognitive impairment 40%, and neuropsychiatric disorders like Hallucinations 9.7%. AS expected falls were frequent 91.7%, but were relatively infrequent Camptocormia 8.3%and severe anterocollis 31.9%. Benefit with L-dopa was reported in 30.6%, lasting 2.3 years. Urinary incontinence was present in 46.6%. MRI is available in 69 cases. The most frequent findings in MSA-P were Putaminal atrophy 13.8% and Putaminal rib 8.3%.

Conclusions: Despite the larger race mixture in PAN American region, our cohort data are in accordance with other study. On the other hand, this sample included few Amerindian representation, future studies should include a larger representation.

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Cortical and brainstem neurodegeneration associate with the clinical severity in spinocerebellar ataxia patients

D. Tamuli, M. Kaur, S. Kumaran, A. Jaryal, A. Srivastava, K. Deepak (New Delhi, India)

Objective: The aim of the study was to know the association of degree of atrophy in brain areas with clinical severity in SCA patients.

Background: Spinocerebellar ataxia (SCA) is a progressive neurodegenerative disorder with prominent clinical heterogeneity amongst the subtypes. Clinical manifestations include gait imbalance, ophthalmoplegia, dysarthria, pyramidal and extrapyramidal signs. This clinical diversity is the result of unstable trinucleotide

(CAG) repeat expansion especially in SCA type 1, 2 and 3 patients. This could be indicative of a differential neuronal loss in the SCA subtypes thus culminating into a differential clinical profile.

Methods: Clinical severity was assessed by International Cooperative Ataxia Rating Scale (ICARS) in the genetically proven SCA (n = 49, age = 34 ± 9.4 yrs) patients. Then MRI was performed by using a 3T scanner (Philips, Achieva) to obtain 3D T1-weighted scans of the whole brain and analysed by FreeSurfer (version 5.3) software in the same SCA patients. MRI parameters used in T1-weighted scans were: Voxel size = 0.6×0.6×1, FOV = 240×240×180 and flip angle = 8°. Based on the distribution of data, Pearson's correlation (for parametric data) and Spearman's rank correlation (for nonparametric data) analyses were done between brain areas and ICARS score of SCA patients.

Results: In SCA patients, ICARS showed a significant inverse correlation with cortical thickness of left rostral middle frontal (r = -0.382, p = 0.007), left caudal middle frontal (r = -0.324, p = 0.023), left medial orbitofrontal (r = -0.351, p = 0.013), left middle temporal (r = -0.324, p = 0.023), right middle temporal (r = -0.292, p = 0.042) and right entorhinal (r = -0.286, p = 0.046). Furthermore, the subcortical volume of midbrain (r = -0.472, p = 0.001), pons (r = -0.523, p = <0.001), medulla (r = -0.462, p = 0.001) and the total brainstem (r = -0.534, p = <0.001) were significantly associated with clinical severity in SCA patients.

Conclusions: We have found a significant correlation between the degree of atrophy in certain cortical and subcortical areas (known to be involved in regulation of motor movements) and the clinical severity score in SCA patients.

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The clinical value of SPECT in identifying dystonic muscles of patients with cervical dystonia

L. Jin, L. Feng, I. Djibo, S. Chen, F. Teng, B. Li, H. Ma (Shanghai, China)

Objective: The aim of this study is to compare the efficacy of selecting target muscles for botulinum toxin injection by abnormal movement pattern and by SPECT combined with abnormal movement pattern.

Background: Cervical dystonia (CD) is caused by involuntary and excessive contraction of cervical muscles which leads to abnormal movement and posture. Botulinum toxin injection has become the first line treatment for CD, the critical step which decides the treatment efficacy is to accurately identify dystonic muscles. At present, dystonic muscles are selected by patients' abnormal movement pattern. However, most patients have a combination of various patterns, and the same pattern may be caused by contraction of different muscles. SPECT imaging uses 99mTc-MIBI as a contrast agent, which can reveal abnormal contraction of the muscle. However, SPECT has not been reported to guide the treatment of CD.

Methods: Forty patients with idiopathic CD were enrolled. These patients had not received botulinum toxin injection for last 3 months. The first group: dystonic muscles were screened based on cervical dystonia pattern (n1=20). The second group: we analyzed cervical muscles with increased uptake of 99mTc-MIBI in cervical SPECT, the SPECT results combined with cervical dystonia pattern were used to determine dystonic muscles (n2=20). SPSS20.0 software was used to compare the results between the two groups after botulinum toxin injection. The TWSTRS score reduction rate and Tsui score reduction rate at the second week, the first month, the third month and the sixth month were compared.

Results: The number of botulinum toxin reinjection in 6 months was significantly higher in the first group than in the second group (13: 4). The interval between the first and the second injection of the second group was significantly longer than the first group (p < 0.05). There was no significant difference between TWSTRS score reduction rate and Tsui score reduction rate in the second week and the first month after treatment, p > 0.05. At the third month, TWSTRS score reduction rate and Tsui score reduction rate of the second group was significantly higher than the first group, p < 0.05. At the 6th month, although the number of follow-up in was decreased in both groups because of repeat injection (n1 = 5: n2 = 14), the TWSTRS reduction rate and the Tsui reduction rate in the second group were significantly higher than the first group, P < 0.05.

Conclusions: SPECT imaging can more accurately select the dystonic muscles and thus greatly improve the efficiency and remission rate of botulinum toxin treatment.

Altered putamen and cerebellum connectivity between different subtypes of Parkinson's disease

B. Shen, L. Zhang (Nanjing, China)

Objective: we investigate the functional connectivity (FC) patterns of the putamen between different subtypes of PD) and healthy controls, and explore its clinical significance.

Background: Impairment of the basal ganglia-thalamo-cortical circuit causes motor symptoms of Parkinson's disease(PD).

Methods: 16 tremor dominant (TD) PD patients, 23 postural instability and gait difficulty dominant PD patients and 31 healthy controls, were scanned with resting-state functional magnetic resonance imaging. A voxel-wise FC analysis was performed by computing the temporal correlation between the bilateral putamen and the other voxels within the whole brain. Correlation analysis was performed between the FC strength and motor symptoms.

Results: Compared with PIGD dominant group, TD dominant group showed increased FC between bilateral putamen and right cerebellum lobules VI, cerebellum crus I. While compared with healthy controls, tremor dominant PD patients showed increased FC between left putamen and bilateral cerebellum crus I, right cerebellum lobules VI, right thalamus, left paracentral lobule, right inferior occipital lobule, cerebellar vermis, fusiform gyrus, left supplementary motor area. Increased FC between right putamen and right cerebellum crus I, right cerebellum lobules VI, right thalamus, bilateral paracentral lobule, right inferior occipital lobule, right inferior temporal gyrus, bilateral supplementary motor area and left sensorimotor cortex were also shown in TD patients, . PIGD dominant group showed increased FC between right putamen and right thalamus compared with healthy controls. The FC strength between the left putamen and right cerebellum lobules VI showed positive correlation with tremor scores in TD dominant group. The FC strength between right putamen and left sensorimotor cortex showed negative correlation with PIGD scores. While in PIGD dominant group, the FC strength between left putamen and right thalamus showed negative correlation with TD scores.

Conclusions: The altered connectivity of basal ganglia-cortical circuit in PD patients was related to PIGD symptoms, Compared to PIGD patients, motor and cognitive impairment declined slowly in TD patients, Which may be related to the increased functional connectivity between basal ganglia and cerebellum.

References: [1] O'Reilly J X, Beckmann C F, Tomassini V, Ramnani N, Johansen-Berg H. Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity[J]. *Cereb Cortex*,2010,20(4):953-965. [2] Bostan A C, Dum R P, Strick P L. Cerebellar networks with the cerebral cortex and basal ganglia[J]. *Trends Cogn Sci*,2013,17(5):241-254.

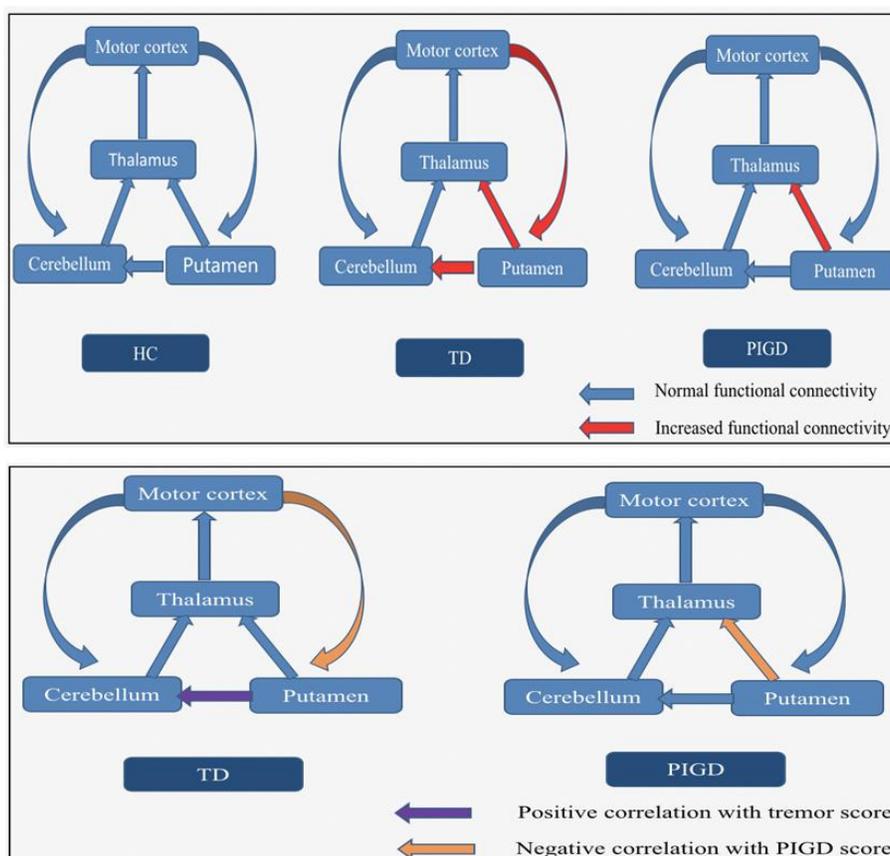


FIG. 1 (1444)

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Semi-automated segmentation and quantification of the substantia nigra depigmentation in Parkinson's disease - a multicentre case control MRI study in 284 participants

Y. Xing, S. Schwarz, A. Martin-Bastida, L. Parkes, H. Abdul-Sapuan, S. Naidu, M. Silverdale, D. Grosset, P. Piccini, D. Burn, N. Bajaj, N. Pavese, D. Auer (Nottingham, United Kingdom)

Objective: To provide a semi-automated segmentation and quantification method of the changes in the substantia nigra (SN) in Parkinson's disease (PD) using neuromelanin (NM)-sensitive MRI in a large multi-centre dataset (Parkinson's MR imaging repository: PaMIR).

Background: Previous studies investigating small groups of patients (<30) consistently showed reduced NM-related signal in the SN [1-2], which may have the potential to serve as a diagnostic imaging marker of PD. Hence, evidence of this via large-scale multi-centre studies is needed. In addition, manual segmentation of SN is time-consuming and therefore a faster and reliable segmentation method is desirable.

Methods: Participants from five sites (n= 192 PD [66.0±8.9 years; 130 males] and 92 healthy controls (HC) [64.2± 9.9 years; 34 males] underwent NM-MRI at 3T and MDS-UPDRS as part of the multimodal PaMIR study. A user-friendly interface was designed to automatically divide the SN into anterior "aNM-SN" and posterior "pNM-SN", once a region containing the whole SN (wNM-SN) is determined manually. It also automatically computes 1) the suprathreshold hyperintense volume of the NM-rich region following a previously published approach to correct for sequence- and platform-dependent differences (Figure 1) [1] and 2) the contrast to noise ratios (CNR) of aNM-SN, pNM-SN and wNM-SN vs. background signal. Non-parametric tests were used for between-group comparisons controlled for the midbrain volume, sex, and age.

Results: We found significant loss of NM-rich volume and contrast in PD vs. HC as markers of depigmentation (Figure 2). Additionally, both metrics in pNM-SN were lower than aNM-SN in line with an anterior-posterior pigmentation gradient in PD. [figure1] [figure2]

Conclusions: Our results provide further evidence of NM volume and contrast abnormalities in PD, reflecting pigmented cell loss in the SN and indicate the validity of the current semi-automated SN segmentation and quantification approach. This paves the way for the assessment of using volumetric and contrast measures of the SN as a potential multi-site diagnostic and severity marker in our large-scale NM study. Our ongoing work focuses on quality assurance, interrater reliability and using the follow-up data to clarify the role of NM-sensitive MRI in tracking the progression of disease.

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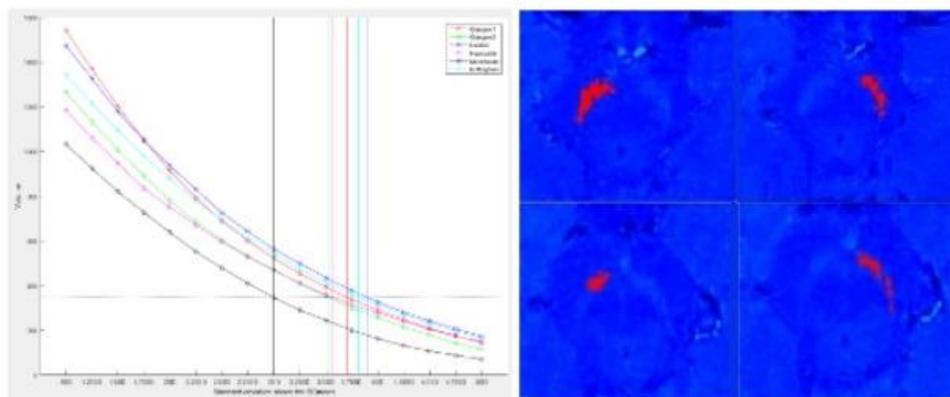


Figure1: Adjustment to account for MR sequence and scanner-dependent (illustrated in different colors) NM signal intensity [1]. The values (vertical lines) of standard deviations above mean background signal intensity were used as thresholds to define the NM-rich area in SN (colors: sites). Examples of the NM-rich areas in the SN of HC (1st row) and PD (2nd row) are illustrated using our semi-automatic segmentation approach.

FIG. 1 (1471)

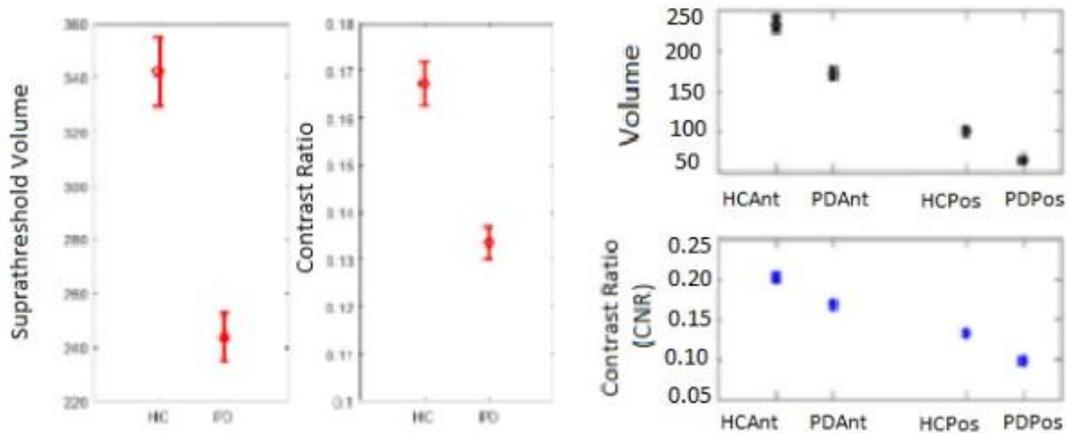


Figure 2: Significant volume and contrast differences of the MRI-derived neuromelanin-rich area in whole SN (left), anterior and posterior SN (right) in PD and HC across all sites (mean±standard error of the mean). All the p values <0.001.

FIG. 2 (1471)

MDS Study Group: Non-Motor PD Study Group (NM-PD)

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Beneficial nonmotor effects of subthalamic and pallidal DBS in Parkinson's disease

H. Dafsari, M. dosSantos Ghilardi, V. Visser-Vandewalle, A. Rizos, K. Ashkan, M. Silverdale, J. Evans, R. Martinez, R. Cury, M. Barbe, G. Fink, A. Antonini, K. Ray-Chaudhuri, P. Martinez-Martin, E. Fonoff, L. Timmermann (Cologne, Germany)

Objective: To investigate nonmotor effects of bilateral subthalamic (STN) and pallidal (GPi) deep brain stimulation (DBS) in Parkinson's disease (PD).

Background: Bilateral STN-DBS as well as bilateral GPi-DBS improves quality of life and motor symptoms in PD. Beneficial non-motor effects have been reported for STN-DBS, whereas few studies have investigated a wide range of NMS in patients with PD undergoing GPi-DBS. Therefore, we conducted a comparative investigation of non-motor effects for these two DBS targets. We hypothesized that (1) GPi-DBS has beneficial effects on NMS and (2) STN-DBS and GPi-DBS have distinct non-motor effect profiles.

Methods: In this prospective, observational, multicenter study including 60 PD patients undergoing bilateral STN-DBS (n=40) or GPi-DBS (n=20), we examined PDQuestionnaire (PDQ), Nonmotor Symptom Scale (NMSS), Unified PD Rating Scale-activities of daily living, -motor impairment, -complications (UPDRS-II, -III, -IV), Hoehn&Yahr, Schwab&England Scale, and levodopa equivalent daily dose (LEDD) preoperatively and at 6 months follow-up. Intra-group changes from baseline to follow-up were analyzed with Wilcoxon signed-rank or paired t-test, if parametric tests were applicable, and corrected for multiple comparisons. Differences between STN-DBS and GPi-DBS were explored with Mann-Whitney-U or unpaired t-tests. Analyses were performed before and after propensity score matching which balanced out demographic and preoperative clinical characteristics. Strength of clinical changes was assessed with effect size.

Results: In both groups, PDQ, UPDRS-II, -IV, Schwab&England Scale, and NMSS improved significantly from baseline to follow-up. STN-DBS was significantly better for LEDD reduction, GPi-DBS

for UPDRS-IV improvement. While NMSS total score outcomes were similar, explorative NMSS domain analyses resulted in distinct profiles. Both targets improved sleep/fatigue and mood/cognition, but only STN-DBS improved the miscellaneous (pain/olfaction) and attention/memory and only GPi-DBS cardiovascular and sexual function domains.

Conclusions: To our knowledge, this is the first study to report distinct patterns of beneficial nonmotor effects of STN-DBS and GPi-DBS in PD patients. This study highlights the importance of comprehensive assessments of NMS to tailor the choice of DBS target to patients' individual motor and nonmotor profiles.

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Non-motor outcomes of subthalamic DBS in PD depend on the location of volume of activated tissue

JN. Petry-Schmelzer, H. Dafsari, M. Krause, T. Dembek, A. Keyoumars, A. Rizos, M. Silverdale, J. Evans, M. Barbe, G. Fink, P. Martinez-Martin, V. Visser-Vandewalle, A. Antonini, L. Timmermann, K. Ray-Chaudhuri (Cologne, Germany)

Objective: To investigate the impact of stimulation location on non-motor symptoms (NMS) in PD patients with DBS in the subthalamic nucleus (STN) via an analysis of volumes of activated tissue (VAT).

Background: STN-DBS improves non-motor and motor symptoms. In a recent study, we showed that NMS improvement is higher with a more anterior, ventral and medial position of the active contact, whereas motor symptoms improve more with a more posterior and lateral position of the active contact. However, investigating only electrode locations neglects the spatial extent of electrical stimulation, which also depends on the stimulation parameters. We thus conducted an investigation into the spatial distribution of NMS improvement in the STN using VATs.

Methods: Clinical data was collected from an ongoing prospective, open-label, multicenter study (Cologne, London, Manchester) including 92 patients with bilateral STN-DBS. The following scales were collected at preoperative baseline (MedON) and on follow-up (FU) six months after surgery (MedON/StimON): SCOPA-motor examination (SCOPA-motor), -activities of daily living (ADL), NMSScale (NMSS), NMSQuestionnaire (NMSQ), Hospital Anxiety and Depression Scale-anxiety and depression subscales (HADS-A/-D). Wilcoxon signed-rank test was used to test for significant changes between baseline and follow-up and Bonferroni-correction was applied for multiple comparisons. Individual VATs, based on the stimulation parameters used in clinical setting, were calculated in MNI space (ICBM 2009b) as described elsewhere (1). To analyse the relationship between VATs and change scores, we employed probabilistic stimulation maps and projected them on the DISTAL-Atlas (2).

Results: All outcomes, besides HADS-D, improved significantly at FU. Probabilistic stimulation maps showed higher improvement of NMS for stimulation localized in the limbic and associative STN, whereas motor symptoms improved more for stimulation localized in the motor STN.

Conclusions: Our preliminary results support the finding that the non-motor outcome after DBS may depend on the location of neurostimulation. DBS in non-motor STN subregions was associated with bigger improvement of NMS. The underlying mechanisms and clinical relevance of our results should be investigated in future studies.

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The International Parkinson and Movement Disorder Society Non-Motor Scale (MDS-NMS) for Parkinson's Disease: Preliminary results from an international validation

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Objective: To provide an update on the ongoing international validation programme of an expanded, refined and improved scale for the assessment of non-motor symptoms (NMS) in Parkinson's disease (PD), the MDS-NMS, sponsored by the International Parkinson and Movement Disorders Society (IPMDS).

Background: The PD NMS scale (NMSS) was developed in 2006 and remains the only dedicated composite scale to assess NMS in PD. As it needed updating, a project to revise and update the NMSS, now called the MDS-NMS, was commissioned by the IPMDS. The MDS-NMS has already undergone cognitive pre-testing and a final version of MDS-NMS was developed. It includes 13 domains with 52 items total, each item scoring for frequency (0 to 4) and severity (0 to 4), which are multiplied to obtain the item score (0 to 16). The domain scores result from sum of the item scores within each domain. Additionally, the scale includes an optional section for evaluating non-motor fluctuations (NMFs) for 8 domains.

Methods: In this cross-sectional, open, multicentre international validation study, we report clinical data from administration of the MDS-NMS. Acceptability, internal consistency, reliability, construct validity and precision in 400 non-demented PD patients (MoCA score >20) is ongoing. Test-retest reliability, assessed after two weeks (average) as well as inter-rater reliability are reported in 100 patients. NMS are also assessed with existing measures, as are motor symptoms and global severity of PD.

Results: 347 patients, 58.8% male, mean age 68.7 yrs (35-93), median H&Y 2 (1-5), mean duration of disease 7.2 yrs (0-30). Mean and median scores for the 13 domains and for NMFs for 8 domains are listed [Table 1]. Standardised domain scores (% of maximum possible score), and % of patients experiencing any problems in each domain are illustrated [Figure 1]. The most frequently reported problems were found in domains "Others" (including loss of sense of smell) (83.3%) "Sleep/wakefulness" (79.3%), "Cognition" (75.5%), and "Urinary" (64.8%). The greatest average severity of symptoms were found in "Urinary" (mean 13.8%), "Others" (13.3%), "Sexual" (12.9%) and "Pain" (10.2%).

Conclusions: Interim results suggest the MDS-NMS may perform well as an outcome measure in clinical trials and epidemiological studies to assess the wide range of NMS that occur in PD.

TABLE 1 (1807)

Domain	Mean score	Min	Max	Maximum possible score	SD	Median
A. Depression	4.5	0	72	80	9.3	1
B. Anxiety	4.7	0	54	64	7.6	2
C. Apathy	3.2	0	34	48	6.2	0
D. Psychosis	1.3	0	48	64	4.6	0
E. ICD and related	0.7	0	12	64	1.9	0
F. Cognition	8.2	0	66	96	11.4	4
G. Orthostasis	1.9	0	18	32	3.7	0
H. Urinary	6.6	0	48	48	9.9	2
I. Sexual	3.5	0	32	32	7.2	0
J. Gastrointestinal	5.4	0	47	64	8.0	2
K. Sleep /wakefulness	9.0	0	76	96	10.6	5
L. Pain	6.5	0	53	64	9.4	3
M. Others	10.7	0	56	80	12.2	6
Non-Motor Fluctuations	4.1	0	32	32	5.2	1

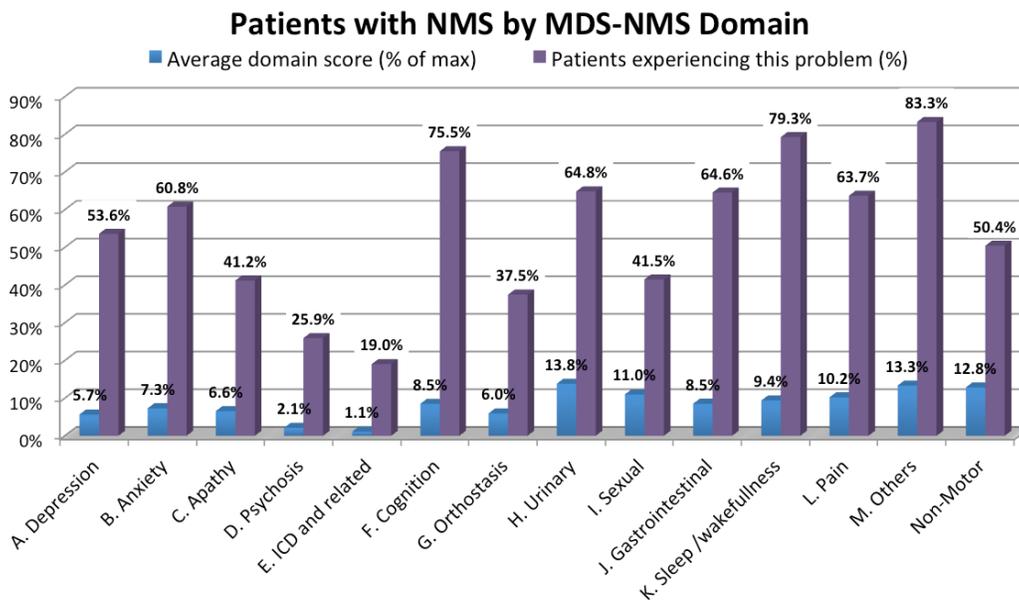


FIG. 1 (1807)

**MDS Study Group:
Progressive Supranuclear Palsy (PSP)**

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Evolution of diagnostic certainty and PSP-predominance types in 187 pathologically confirmed PSP patients

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Objective: To examine the evolution of diagnostic certainty and clinical predominance types as defined by the movement disorder society (MDS) criteria for the clinical diagnosis of PSP (Höglinger et al, 2017) during the course of disease in autopsy-confirmed patients with PSP.

Background: Three degrees of diagnostic certainty ("suggestive of" = s.o., "possible", or "probable"), and definition of clinical predominance types (PSP-RS, PSP-PGF, PSP-P, PSP-F, PSP-OM, PSP-SL, PSP-CBS, PSP-PI) were implemented into the new clinical diagnostic criteria for PSP (MDS criteria for the clinical diagnosis of PSP, Höglinger et al, 2017). The evolution of diagnostic certainty and predominance types over the course of disease in PSP patients according to the MDS-criteria has not been studied so far. However, this is relevant for further understanding the natural history and clinical spectrum of PSP.

Methods: Features relevant for the diagnosis of PSP according to the MDS-diagnostic criteria were collected in 187 autopsy-confirmed PSP patients by chart review. Diagnostic certainty and PSP-predominance types according to the MDS-diagnostic criteria were determined for each patient and each year.

Results: According to the MDS-PSP diagnostic criteria, 62% (n=115) of patients had a clinical diagnosis of PSP in the first year of disease, as opposed to 14% (n=26) according to the NINDS SPSP criteria, and 98% (n=183) at final record, as opposed to 79% (n=147) according to the NINDS/SPSP criteria. A diagnosis of s.o. PSP was present in 44% (n=83) of patients in the first year. Of these, 77% (n=64) had a diagnosis of "probable" PSP at final record. In the first year of disease, the variability of predominance types was greatest, and PSP-RS represented only 11% of patients. At final record, 56% patients had a PSP-RS predominance type.

Conclusions: The conversion of s.o. PSP into possible and probable PSP in 72% of the cases shows that the concept of s.o. PSP indeed allows identification of PSP patients at a very early clinical stage. Furthermore, our data suggest that many initially variant PSP presentations converge to a PSP-RS phenotype during the course of the disease.

References: MDS criteria for the clinical diagnosis of PSP, Höglinger et al, 2017.

LBA 04

Clinical, pathological and genetic determinants of benign PSP

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Objective: To identify clinical, pathological, and genetic determinants of survival in PSP. This study involved 186 autopsy-confirmed PSP cases which were recruited from eight brain banks.

Background: Demographic and clinical information was retrospectively reviewed. Symptoms were analysed with respect to their potential association with long (≥ 10 years) and medium or short survival (< 5 years and 5-10 years). Central histopathological analysis and harmonization of staining protocols has been performed. PSP-specific brain lesions were analysed in 36 brain regions and compared between different survival groups. In addition, the survival groups have also been stratified by known SNPs risk allele carrier status.

Method: This study involved 186 autopsy-confirmed PSP cases which were recruited from eight brain banks. Demographic and clinical information was retrospectively reviewed. Symptoms were analysed with respect to their potential association with long (≥ 10 years) and medium or short survival (< 5 years and 5-10 years). Central histopathological analysis and harmonization of staining protocols has been performed. PSP-specific brain lesions were analysed in 36 brain regions and compared between different survival groups. In addition, the survival groups have also been stratified by known SNPs risk allele carrier status.

Results: Of 186 PSP patients with sufficient clinical data, 24 % had a long disease duration of ≥ 10 years (mean: 13.8 [10 – 27] years), while similar percentage of patients (21.5 %) were found to have progressive clinical course of < 5 years (mean: 3.3 [1-4] years). The analysis of timeline and evolution of main clinical milestones revealed different pattern in long duration PSP, compared with both groups of medium and short less survival. The latter groups presented with identical evolution of symptoms. The presence or absence of oculomotor signs in the first 3 years from disease onset was the main predictor of short (< 5 years) or long (≥ 10 years) survival, respectively. Neurodegenerative changes and neuronal tau lesions were most prominent in infratentorial regions, while glial tau lesions showed the opposite pattern with highest density in cortical and subcortical regions. The crucial differences between survival groups were found in the rates of glial tau lesions in cortical, subcortical and infratentorial regions. There was no difference in SNPs risk allele carrier status.

Conclusion: Herein, we described a benign form of PSP with distinctive clinical and pathological patterns. The absence of supranuclear gaze palsy and abnormal saccades in the first 3 years from onset were independent predictors of long duration PSP (≥ 10 years). Our observations suggest that glial pathology plays a crucial role in determining survival in PSP.

**MDS Study Group:
Rare Movement Disorders (RMD)**

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An international survey of stiff person spectrum disorders: Exploring the clinical spectrum and unmet needs

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Objective: To build a platform in order to investigate the clinical spectrum of stiff person syndrome and related disorders, and to explore possible gaps in management and areas for further research.

Background: Stiff person syndrome and related disorders (stiff person spectrum disorders, SPSD) are a very rare group of autoimmune movement disorders with an estimated prevalence of 1/1 000 000. Whereas the classical variant is associated with GAD-antibodies and manifests with predominant lumbar stiffness, the clinical and serological spectrum has broadened to include a wider range of phenotypes and antibodies.

Methods: The survey started in 03/2018 and is conducted amongst the members of the MDS rare movement disorders study group.

Results: The survey is ongoing and at the time of abstract submission we report the first preliminary results. So far, 16 patients from 3 centres (UK, Argentina, Spain) were included (9 female) with a follow up time of 10 years on average (range 2-28). Median age of onset was 52.5yrs (range 29-68). Most patients (68,8%) had focal stiffness at onset and manifested with (painful) cramps (62.5%), axial stiffness (56,3%). Cerebellar signs (nystagmus, ataxia) or bulbar involvement occurred in 18.8%, respectively. 12.5% of patients displayed myoclonus at presentation, whereas prominent autonomic signs or epilepsy were rare (6,3% and none). Most of the patients harboured GAD-antibodies (93.8%), and concomitant autoimmunity was frequent (56.3%). Two cases were possibly paraneoplastic, as neurological symptoms occurred in close temporal relationship with cancers (oral squamous cell carcinoma, nasopharyngeal). Treatment approaches and outcomes were similar across the different centres. All but 1 patient received immunotherapy, most frequently intravenous immunoglobulins (87.5%) and plasma exchange (43,8%). Other immunotherapies used were steroids and rituximab (12.5% each), and azathioprine (6.3%). In 50%, a combination of at least two immunotherapy approaches was required. With treatment, half of the cases improved and a third remained stable.

Conclusions: This is the first international multicentre SPSD study with prospective data collection by movement disorder experts. Further plans include expanding this cohort and, using a health services approach, identifying unmet needs in SPSD and areas for further research.

**MDS Study Group:
Validation of Mild Cognitive Impairment in Parkinson's Disease (MCI)**

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The possible neuroprotective potential of galantamine along with soya-lecithin and hydroxychloroquine against ICV-STZ induced cognitive dysfunction in rats

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Objective: The present study investigates the possible neuroprotective potential of galantamine with soya-lecithin and HCQ against intracerebroventricular streptozotocin (ICV-STZ) induced memory impairment in a rat model of sporadic dementia of Alzheimer's type

Background: Galantamine an acetylcholinesterase (AChEs) inhibitor used for the symptomatic treatment of Alzheimer's disease. Soya-lecithin is a good source of choline improves cognitive performance. Hydroxychloroquine (HCQ) an antimalarial drug with an anti-inflammatory property.

Methods: Animals received single bilateral ICV injections of STZ (3 mg/kg). Drugs galantamine (2 mg/kg), soya-lecithin (100 & 200 mg/kg), HCQ (25 & 50 mg/kg) and their combination was administered for a period of 21 days. Various neurobehavioral parameters, followed by biochemical (oxidative stress markers), AChEs level, molecular (TNF- α level), mitochondrial respiratory enzyme complexes (I-IV), neurotransmitter levels and histopathological (H&E staining) evaluations.

Results: ICV-STZ administration significantly impaired cognitive performance indicated by MWM test, increased oxidative stress (raised lipid peroxidation, nitrite concentration, reduced glutathione, catalase activity), AChEs level, increased TNF- α level, decrease neurotransmitter levels, mitochondrial dysfunction and histopathological alterations as compared to sham treatment. Chronic treatment with galantamine (2 mg/kg), soya-lecithin (100 & 200 mg/kg), HCQ (25 & 50 mg/kg) significantly improved cognitive performance in MWM test, reduced AChEs activity, neuroinflammation, oxidative damage, TNF- α level, restored mitochondrial respiratory enzyme complex (I-IV) activities and histopathological alterations as compared to ICV-STZ treated animals. Further, combinations of soya-lecithin (100 & 200 mg/kg) and HCQ (25 & 50 mg/kg) with galantamine (2 mg/kg) and soya-lecithin (100 & 200 mg/kg) and HCQ (25 & 50 mg/kg) combination suggests the modulation of the neuroprotective potential as compared to their effect alone in ICV-STZ treated animals. Further, the present study suggests the combination potential of soya-lecithin (100 & 200 mg/kg) and HCQ (25 & 50 mg/kg) with galantamine (2 mg/kg) and it was found that galantamine (2 mg/kg) significantly modulate the neuroprotective potential of soya-lecithin (100 & 200 mg/kg) and HCQ (25 & 50 mg/kg) combination in ICV-STZ treated rats as compared to their effect alone.

Conclusions: The present study suggests that co-administration of galantamine with soya-lecithin and HCQ significantly improves cognitive performance in ICV-STZ treated rats as compared to their effect alone.

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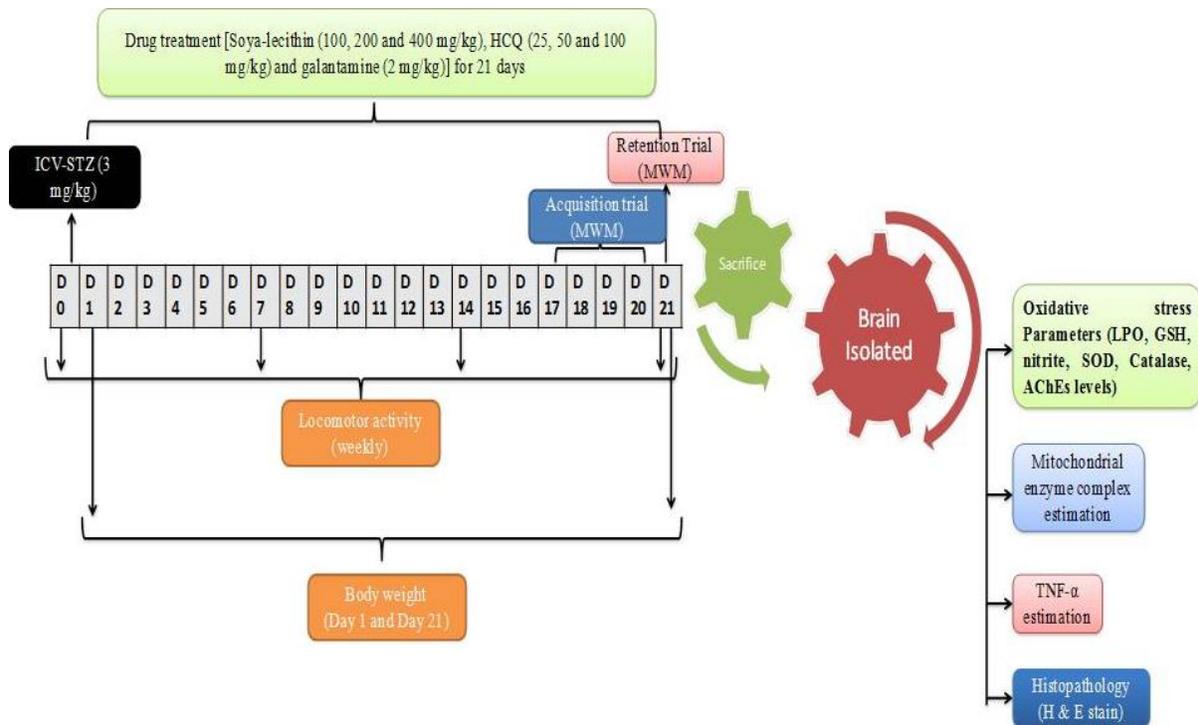


FIG. 1 (64) Experimental protocol design (ICV-STZ: intracerebroventricular streptozotocin; MWM; Morris water maze; IAL: initial acquired latency; RL retention latency; LPO: lipid peroxidase; GSH: reduced glutathione; SOD: superoxide dismutase; AChEs: acetylcholinesterase; TNF: Tumor necrosis factor; H&E: hematoxylin & eosin stain).

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After Deep Brain Stimulation Surgery for Parkinson's Disease risk Factors for Postoperative Delirium *F. Rakhimov, G. Rakhimbaeva (Tashkent, Uzbekistan)*

Objective: The aim of this study was to investigate the incidence of and risk factors for postoperative delirium (POD) after deep brain stimulation (DBS) surgery in patients with Parkinson's disease (PD).

Background: The background of this study was to investigate the incidence of and risk factors for postoperative delirium (POD) after deep brain stimulation (DBS) surgery in patients with Parkinson's disease (PD)

Methods: We analyzed the preoperative T1-weighted magnetic resonance imaging data of 71 PD patients who underwent DBS surgery. Multiple regression analysis was done with age, l-dopa equivalent daily dose, laterality of the surgery, target regions, number of electrode trajectories tried, grey matter (GM) volume, and white matter (WM) volume as explanatory variables and the duration (number of days) of POD as the response variable. In addition, regional brain atrophy associated with POD was investigated by means of voxel-based morphometry.

Results: Excluding patients with outliers, 61 patients were included in the analyses. POD had occurred in 26 (42.6%) of the 61 patients. Age and total WM volume were shown by multiple regression analysis to correlate significantly with the duration of POD ($p < 0.05$ and < 0.01 , respectively). WM was significantly reduced in the temporal stem, and the reduction in volume correlated significantly with the duration of POD ($p < 0.001$). GM atrophy was not associated with POD.

Conclusions: We found that age and WM atrophy in the temporal stem are factors predictive of POD after DBS surgery. In aged patients with temporal stem atrophy, surgical procedures and postoperative management should be carefully explored to reduce the risk of postoperative delirium.

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PLG restores the balance of autophagy and apoptosis by increasing BCL2 phosphorylation in rotenone-induced Parkinson disease models

J. Liu, H. Yang (Beijing, China)

Objective: Parkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease and there are few treatments currently available. The present study investigated the protective effects of PLG in rotenone-induced PD cell and mouse models.

Background: Apoptosis and macroautophagy/autophagy play critical roles in PD pathogenesis; as such, modulating their balance is a potential treatment strategy. BCL2 (B cell leukemia/lymphoma 2) is a key molecule regulating this balance. PLG is an alkaloid extracted from Piper longum L. that has anti-inflammatory and anticancer effects. Our previous study concerned PLG has protective effects in PD models involve inhibiting mitochondrial dysfunction and apoptosis, although the underlying mechanism is unknown.

Methods: C57BL mice were orally administered rotenone and PLG, motor behavior was evaluated with the rotarod and pole tests. The number of dopaminergic neurons was measured by immunohistochemistry. In cell models, cell viability and cytotoxicity were measured by MTT and LDH assay, and mitochondrial function was evaluated with JC-1 and Calcein AM assay. The interaction of BCL2 and BAX or BECN1 was measured by co-immunoprecipitation to evaluate apoptosis or autophagy.

Results: We found that PLG administration (2 and 4 mg/kg) for 4 weeks attenuated motor deficits in mice and prevented the loss of dopaminergic neurons in the substantia nigra induced by oral administration of rotenone (10 mg/kg) for 6 weeks. PLG improved cell viability and enhanced mitochondrial function in primary neurons and SK-N-SH cells. These protective effects were exerted by inducing BCL2 phosphorylation at Ser70 via MAPK8 activation, which resulted in the dissociation of BCL2 and BECN1 and the stabilization of the BCL2 and BAX heterodimer, consequently enhancing autophagy and inhibiting apoptosis.

Conclusions: Our results demonstrate that PLG exerts therapeutic effects in a rotenone-induced PD models, and restoring the balance between apoptosis and autophagy by targeting BCL2 may be an effective treatment for PD.

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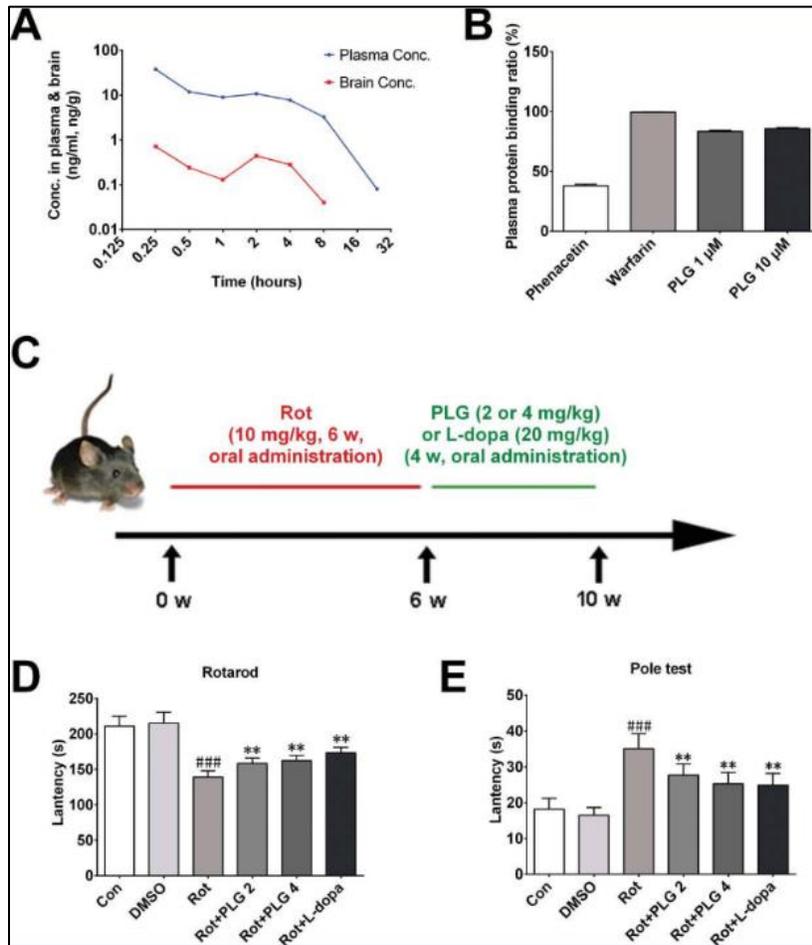


FIG. 1 (405)

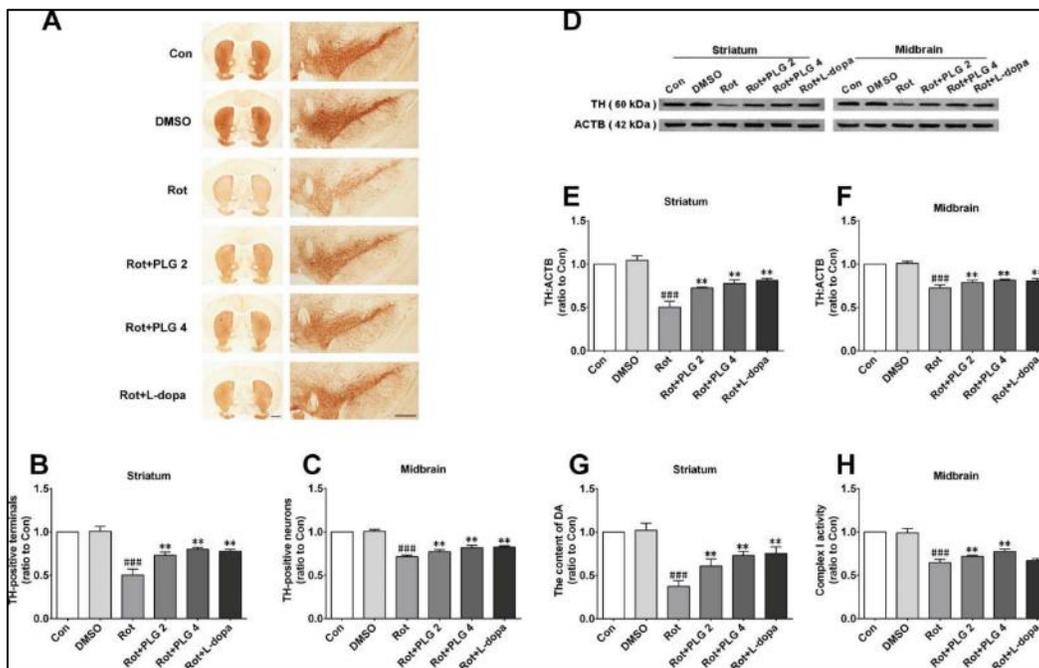


FIG. 2 (405)

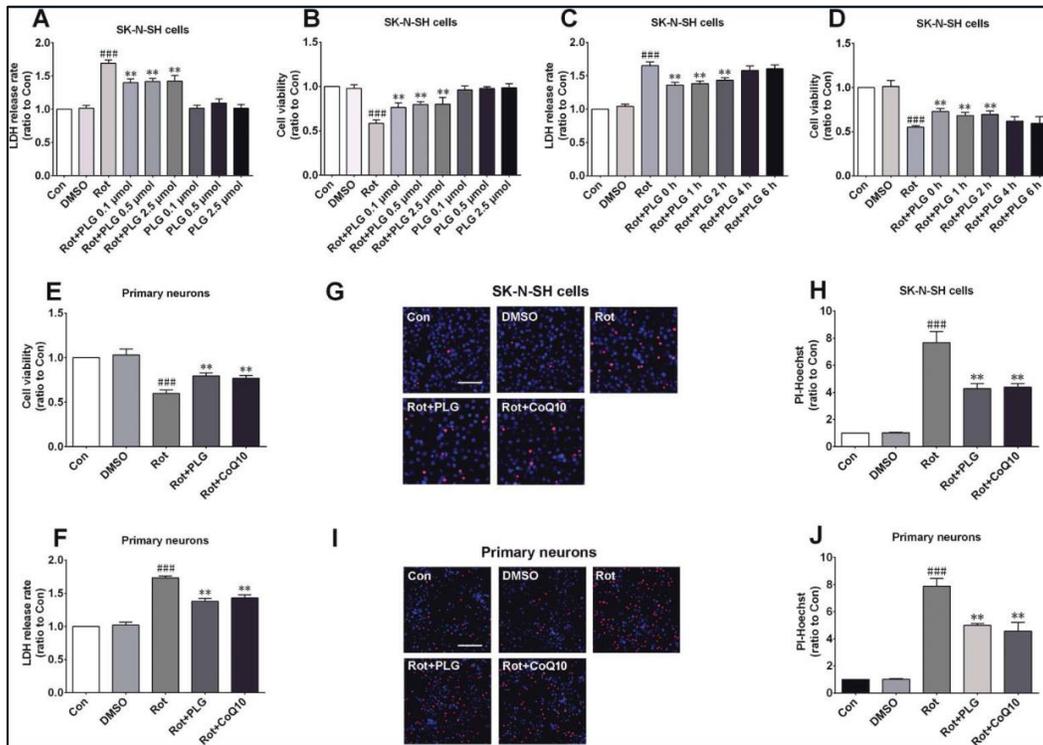


FIG. 3 (405)

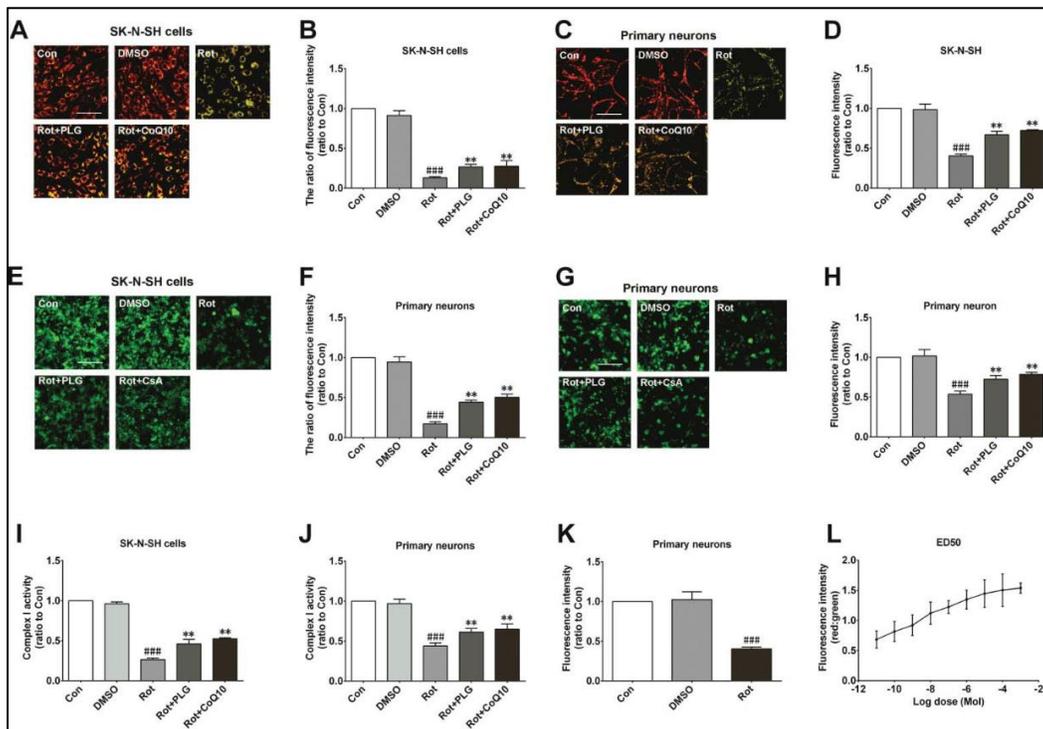


FIG. 4 (405)

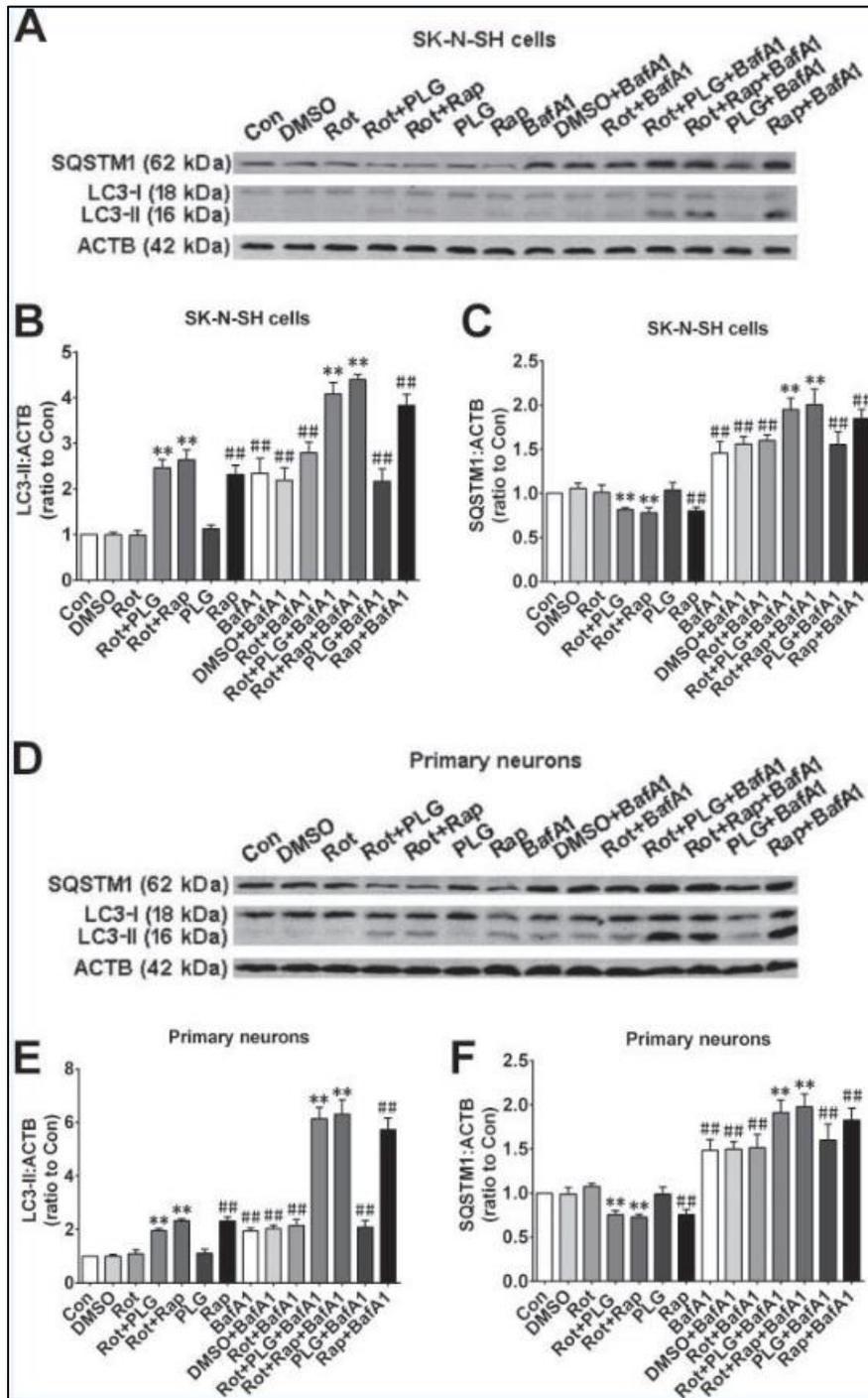


FIG. 5 (405)

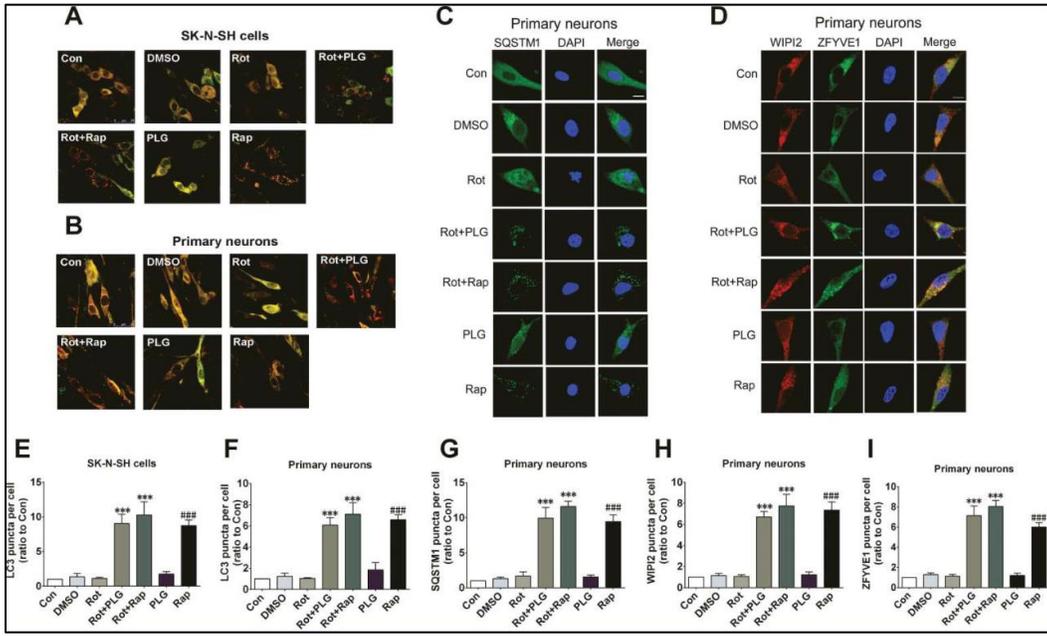


FIG. 6 (405)

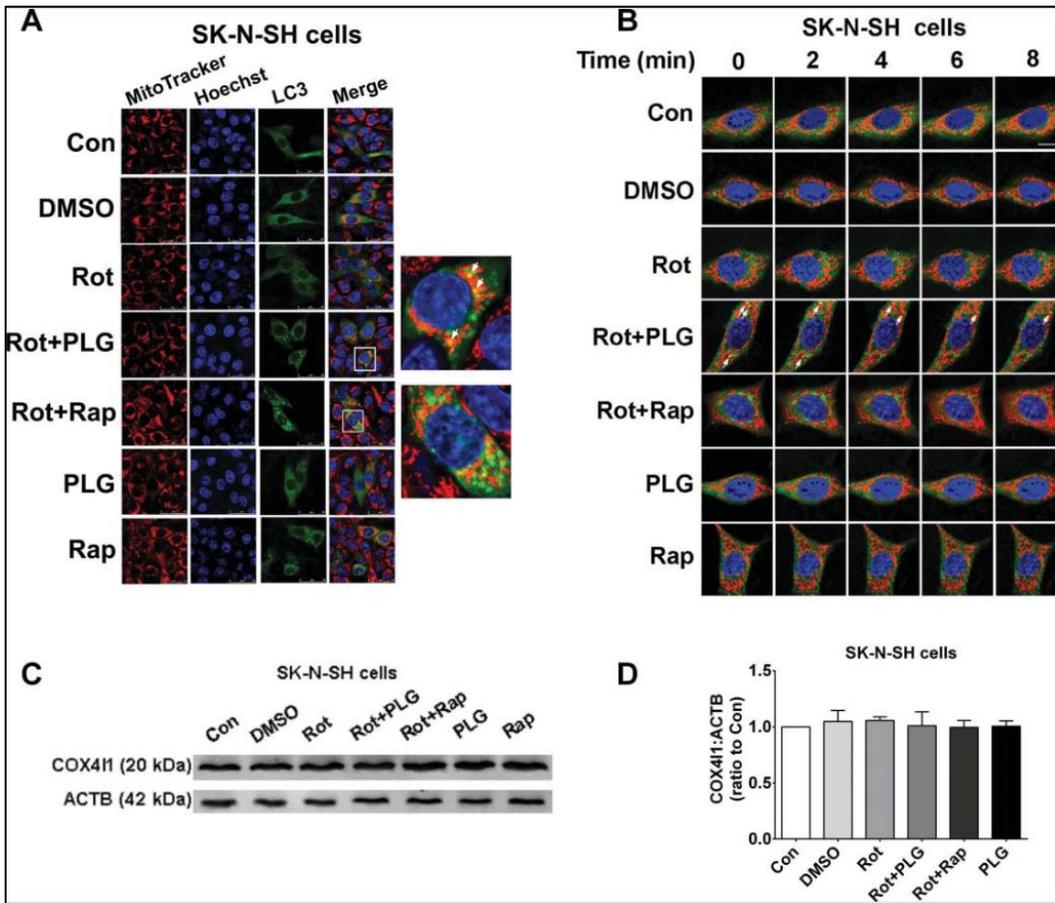


FIG. 7 (405)

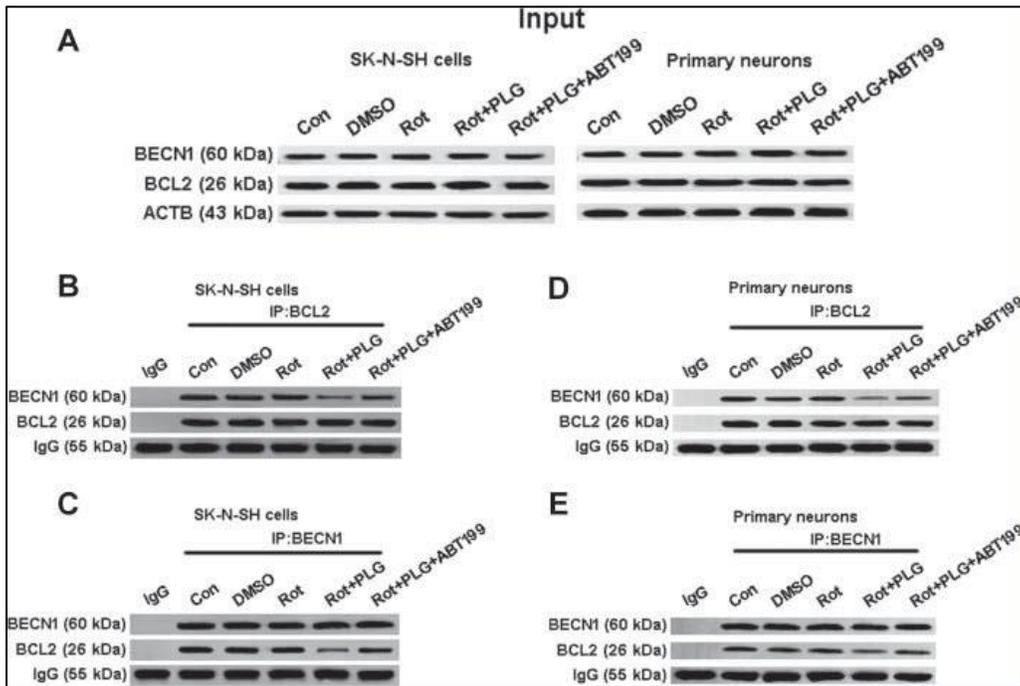


FIG. 8 (405)

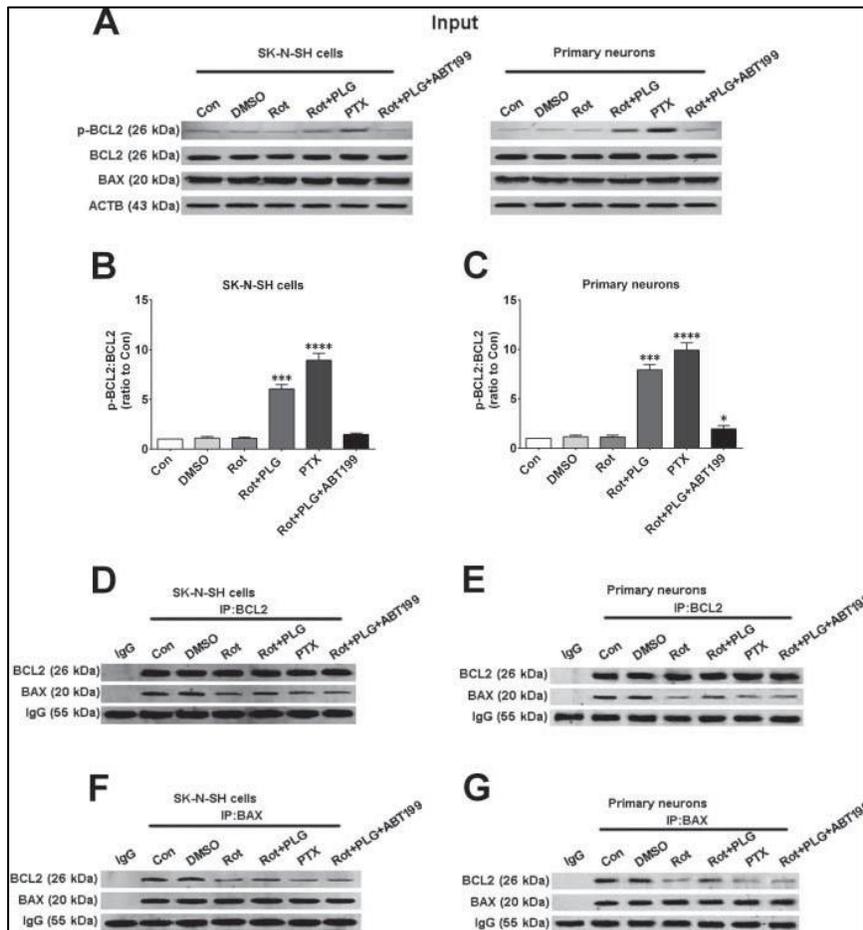


FIG. 9 (405)

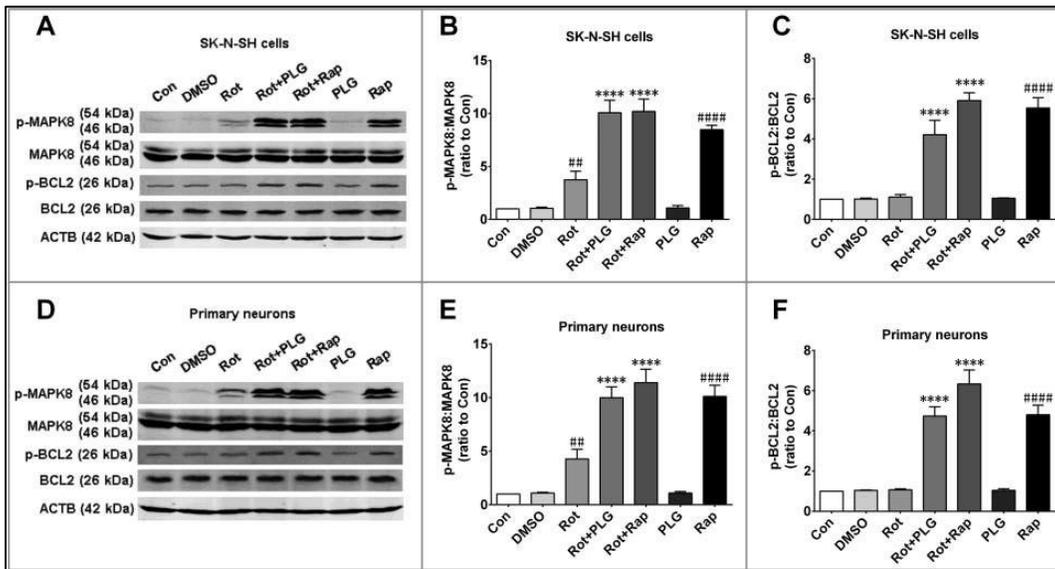


FIG. 10 (405)

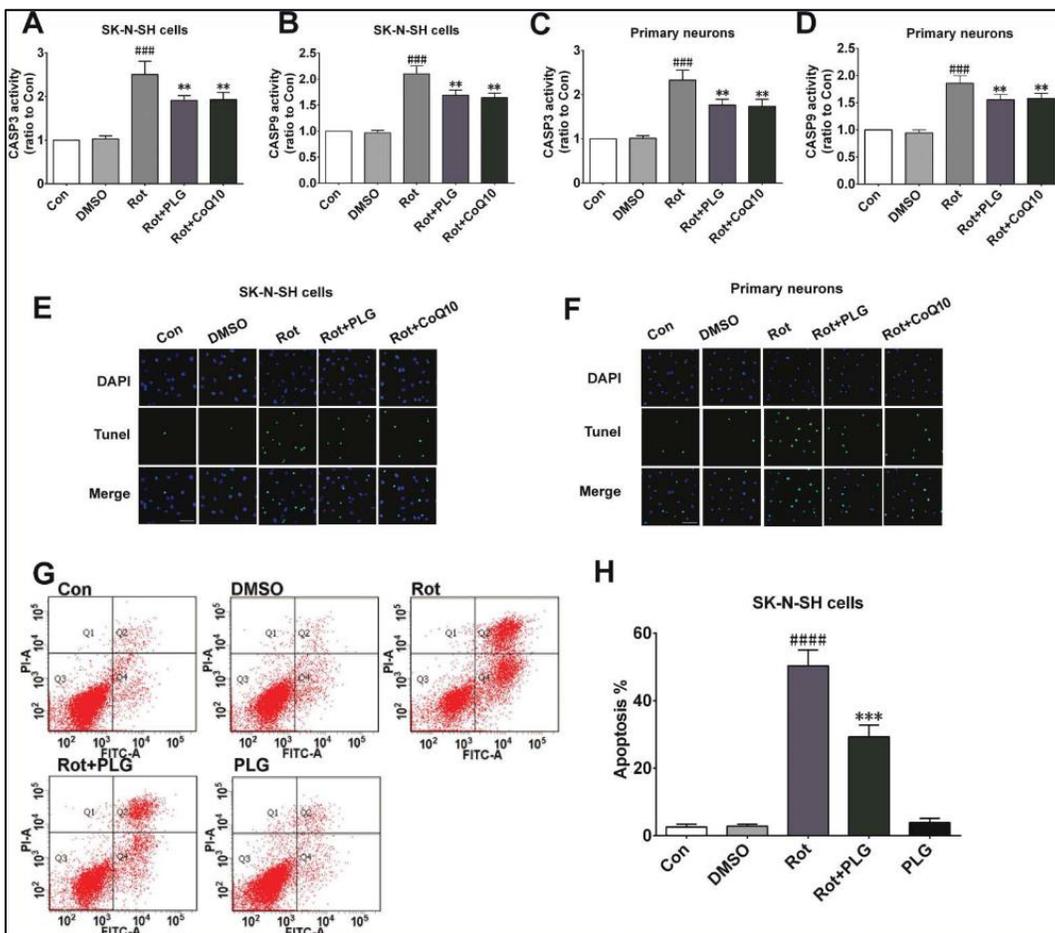


FIG. 11 (405)

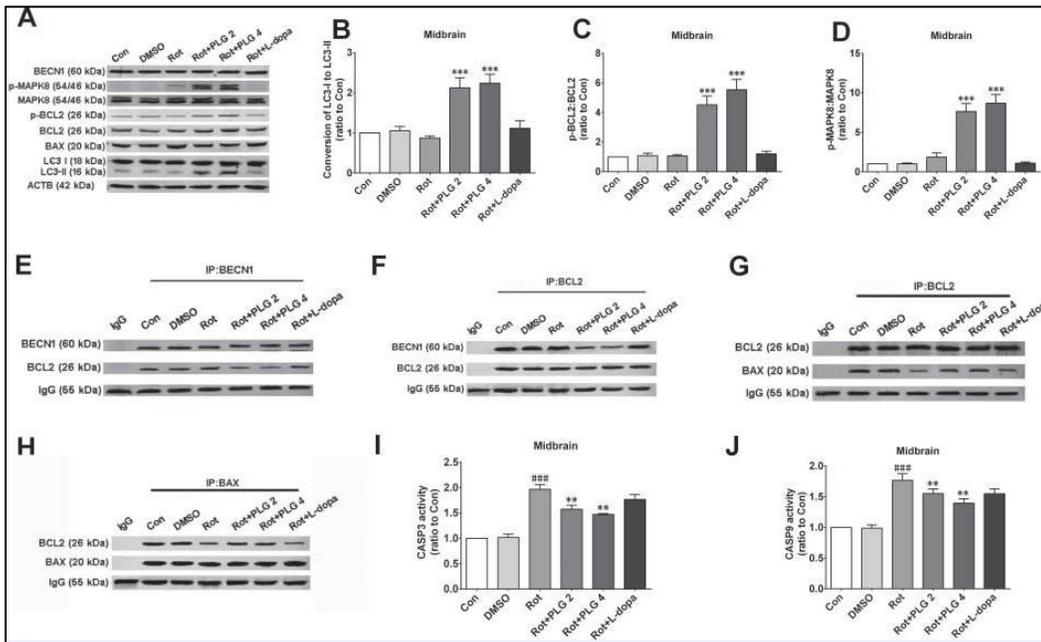


FIG. 12 (405)

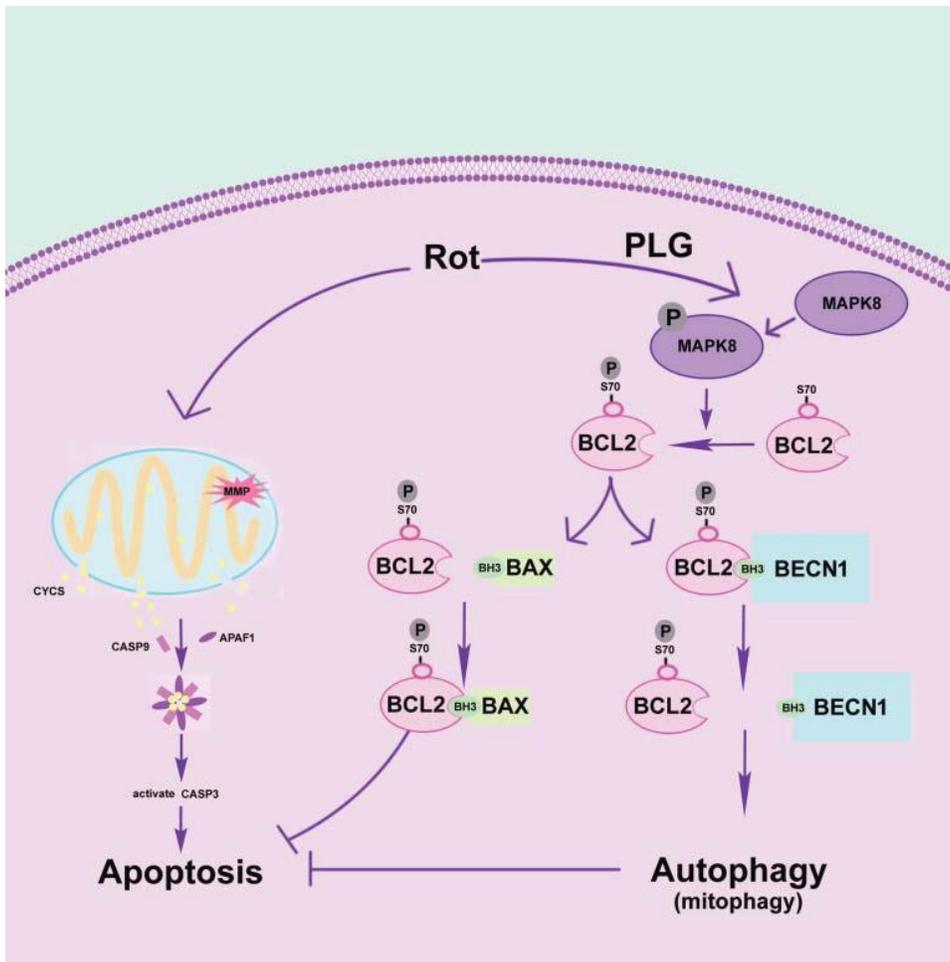


FIG. 13 (405)

Research on nearinfrared brain function imaging for Freezing of Gait in Parkinson's Disease
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Objective: In the study, fNIRS technique was used to study the activation level and activation mode of prefrontal cerebral cortex for patients with FOG under cognitive processing, in order to analyze the correlation between the severity of FOG and the prefrontal cortex function and to explore the pathophysiology of PD with FOG. To provide a theoretical basis for the diagnosis, intervention and treatment of PD with FOG, to help patients establish confidence, improve symptoms and improve quality of life.

Background: fNIRS is a real-time brain function monitoring, with its portability, noninvasive, high temporal resolution, low cost and other unique advantages are widely used in the field of cognitive neuroscience. The pathophysiology of FOG remains obscure and some research suggests that cognitive impairment plays a key role in the occurrence of FOG.

Methods: The patients were divided into two groups: parkinson's disease with freezing of gait (PD-FOG+) and parkinson's disease without freezing of gait (PD-FOG-) according to the clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank and FOG questionnaire. Patients were assessed using the Hoehn and Yahr scale (H&Y), motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) in the "off" (minimum of 12h without anti-parkinsonian medication). All patients underwent MMSE, HAMD and FAB testing. The VFT was used as a stimulus task, recording group words or idioms, and the 52-channel fNIRS system was used to perform signal acquisition when the patient performed the VFT task. The activation of the prefrontal cortex was compared between the two groups.

Results: ① When the VFT task was performed, the number of words or idioms set out in the PD-FOG+ group was significantly less than that of the PD-FOG- group, and the FOG questionnaire was negatively correlated with the VFT result. ② For the PD-FOG+ group the activation area of the prefrontal cortex was lesser than that of lower. ③ The mean oxygen hemoglobin concentrations in the left ventrolateral prefrontal cortex of PD-FOG+ group were significantly lower than the PD-FOG- group, and the severity of the FOG was negatively correlated with the mean oxygen hemoglobin concentration.

Conclusions: In PD-FOG+ patients, executive function is impaired, cognitive flexibility, inhibition, memory, language use ability decreased significantly. There is a specific pattern of structure and/or functional impairment in the left ventrolateral prefrontal cortex of PD with FOG patients, so when the need for selection, memory, reaction inhibition and other more complex cognitive activities can not be effectively recruited to solve the problem. Suggesting that executive dysfunction and FOG may have a common neuropathological mechanism in the ventrolateral prefrontal cortex and the specific model brain network damage of the ventrolateral prefrontal cortex is closely related to the occurrence of FOG.

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LBA 11

Predictive Validity of Level I PD-MCI Criteria, using Global Cognitive Screeners, for PDD

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Objective: PD-MCI can be used as a descriptive entity for clinical and research purposes and the PD-MCI criteria need to be validated. The objective is to assess the predictive validity of Level I MDS PD-MCI criteria, using global cognitive screeners, for PDD.

Background: Our analyses regarding Level II2 and Level I3 showed a contribution of PD-MCI to the hazard of PDD amongst other clinical variables. The predictive value of global cognitive screeners still needs to be evaluated and compared to Level I and II.

Method: This retrospective study combined 4 large datasets. Conversion to PDD was the primary outcome. A Cox model was used to evaluate whether Level I PD-MCI based on a global cognitive screener at baseline adds to the risk of PDD as estimated by age, gender, level of education, disease duration, UPDRS-III, and depression. Either the MMSE (cut-off of

Results: Follow-up data on 467 PD patients were available. The mean age was 68.7 years (SD 8.8), median duration since PD symptom onset was 4.0 years (IQR 2.0-8.0), and median UPDRS-III total score was 20 (IQR 13-28). A total of 69 patients developed PDD during follow-up (14.3%). Preliminary analyses indicate a clear contribution of MMSE and MoCA scores to the hazard of PDD, i.e. MMSE/MoCA scores below the cut-off resulted in significantly higher hazard ratios. Additional analyses, the comparison of the current analyses to Level I and II, will still be performed and will be presented at the congress.

Conclusion: N/A