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ACCADEMIA ITALIANA PER LO STUDIO DELLA MALATTIA DI PARKINSON
E I DISORDINI DEL MOVIMENTO



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Comunicazioni Orali



C1

3T MRI findings of multiple system atrophy with laryngeal stridor

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Objective: To assess different 3T brain magnetic resonance imaging (bMRI) features in two case series of multiple system atrophy (MSA) patients with or without laryngeal stridor.

Background: MSA is a neurodegenerative disease with autonomic dysfunction, often leading to severe breathing disorders like stridor. The linkage of this sign with bMRI findings has not yet been well identified. Neuropathological studies demonstrated neuronal depletion in brainstem networks. A few distinct bMRI patterns were described on T2-weighted images in MSA: supratentorial (atrophy/hypointensity of posterior putamen and slit-like putaminal hyperintensity) and infratentorial ("hot cross bun sign", atrophy/hyperintensity of the middle cerebellar peduncles, atrophy of pons and cerebellum).

Methods: We undertook a retrospective study of 60 MSA patients (45 MSA-P and 15 MSA-C) admitted to our center. We separately examined patients with (group 1, 14 MSA-P and 5 MSA-C) and without stridor (group 2, 31 MSA-P and 10 MSA-C), considering their different 3T bMRI features. Video-polysomnography revealed stridor in 19 (32%) patients. The 3T MRI protocol consisted of axial ponto-bulbar T1/T2-weighted acquisitions (at 2 mm slice thickness) normalized for mean sagittal intracranial area, resulting in a quantitative index for ponto-bulbar atrophy.

Results: Compared to group 2, group 1 has less supratentorial/putaminal (56% vs 67%) and more infratentorial (50% vs 36%) bMRI alterations, in particular more frequent pontine (50% vs 28%) and cerebellar (50% vs 31%) atrophy, and middle cerebellar peduncles alterations (38% vs 14%). 3T MRI analysis demonstrates a higher pontine (18% more) and bulbar (10% more) atrophy in group 1.

Conclusions: MSA with stridor may be a partly different form associated to a more diffuse and important infratentorial neuronal loss, in particular in the brainstem, regardless of the clinical subtype. A higher ponto-bulbar atrophy is significantly related to the stridor development since early stages.

C2

Differential induction of dyskinesia and inflammatory responses by intermittent versus continuous L-Dopa delivery in the 6-OHDA model of Parkinson's disease and in PD patients

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Neuroinflammation is associated with L-Dopa treatment in Parkinson's disease, suggesting a role in dyskinesia (LID). However, it is unclear whether the increased inflammatory response is an intrinsic feature of L-Dopa or is specifically associated with L-Dopa dyskinetic outcome. Inflammatory responses induced by dyskinetic pulsatile or non-dyskinetic continuous L-Dopa were compared in 6-OHDA-lesioned rats and Parkinsonian patients. Rats were chronically treated with pulsatile L-Dopa (DOPAp, 6 mg/kg/day for 15 days), or continuous L-Dopa via subcutaneous osmotic minipumps (DOPAc 12 mg/kg/day for 15 days), or DOPAp followed by DOPAc. In a separate experiment rats received one peripheral dose of LPS (2 mg/kg) 24 hrs before DOPAp. AIMs were evaluated during L-Dopa treatments as a correlate of dyskinesia. Two groups of advanced Parkinsonian patients were examined, being either on standard oral L-DOPA treatment and experiencing troublesome dyskinesia, or on L-Dopa-carbidopa intrajejunal infusion, displaying stabilized motor responses with low dyskinesia. Dyskinesia was assessed by UPDRS scale items 32, 33, 34. Confocal analysis of OX-42, TNF-alpha, iNOS and GFAP immunoreactivity (IR) was performed in the rat striatum. Serum was collected from rats and parkinsonian patients for TNF-alpha analysis.

Increased OX-42, iNOS, GFAP IR in microglia, and TNF-alpha IR in both microglia and neurons, were found in dyskinetic rats receiving DOPAp. In contrast, none of the inflammatory markers was altered in non dyskinetic rats receiving DOPAc. Rats rendered dyskinetic by DOPAp before DOPAc, did not develop dyskinesia during continuous infusion, displayed striatal microgliosis but TNF-alpha was unaltered. LPS pre-treatment increased amplitude of AIMs induced by DOPAp, and exacerbated microgliosis and TNF-alpha IR. In all L-Dopa treated rats and in parkinsonian patients receiving oral or intrajejunal L-Dopa, serum TNF-alpha was in the normal range, with a significant increase found in patients under oral L-Dopa. Results suggest an involvement of neuroinflammation in LID development, showing a specific increase of the pro-inflammatory cytokine TNF-alpha in microglia of dyskinetic rats.

C3

Volition and action control in Parkinson's disease patients with impulsive-compulsive behaviour disorders

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Objective: We aimed to explore different aspects of action control, assessing reward-related behaviour, inhibition (externally and internally triggered) and sense of agency in Parkinson's disease (PD) patients, with and without impulsive-compulsive behaviours (ICB) compared to a group of healthy subjects.

Background: Pathophysiology of ICB in PD is poorly understood. Most previous research focussed on reward-related processing in the brain. However, other aspects of volitional control of action may be important in the pathophysiology of ICB, such as sense of agency for action and action inhibition.

Methods: Thirty-eight PD patients (19 with and 19 without ICB) and 19 healthy subjects (HS) were included in the study. Subjects underwent a short test battery covering key components of voluntary action, including: Intentional Binding task which measures experience of agency; the Marble task, which measures the sequential balance between action and inhibition in intentional self-control; Stop signal reaction time which measures capacity for reactive inhibition; Balloon Analog Risk Task which measures reward sensitivity by titrating reward against risk.

Results: When comparing the degree of binding effects among groups, one way ANOVA showed a significant main effect of group for action binding ($p=0.004$, $F=6.27$). Post hoc analysis revealed that PD-ICB showed significantly stronger action binding than HS ($p=0.004$), and than PD-no-ICB ($p=0.04$). There was no difference between PD-no-ICB and HS.

A significant difference between PD-no-ICB and HC was detected in quantile SSRT ($p=0.008$).

No other significant differences were found among groups in the other tasks.

Conclusions: PD patients with ICB have abnormal performance on a task of action binding compared to PD patients without ICB and healthy subjects. They appear to have a weak experience of their own volitional actions. They had no deficit on tasks evaluating externally and internally triggered inhibitory control, or in reward-based decision-making. Thus, we conclude that PD patients with ICB have a deficit in action representation at the cognitive/experiential level. This result opens new perspective on the pathophysiological basis of ICB deficits, and on the future therapeutic management of them.

C4

Involvement of Cerebello-Thalamo-Cortical circuit in patients with rest tremor and normal dopaminergic scans (SWEDD)

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Introduction: The term SWEDD (Scans-Without-Evidence-of-Dopaminergic-Deficit) indicates patients with a clinical suspicion of PD but normal dopaminergic scans. Although several diseases may have this clinical-radiological phenotype, many patients with SWEDD present asymmetric rest tremor resembling parkinsonian tremor. In fact, current available studies on such a specific population suggest a dystonic origin of this tremor [1]. Dysfunctions in the Cerebello-Thalamo-Cortical (CTC) circuit are involved in the pathogenesis of tremor in PD, but also of numerous other movement disorders [2,3,4].

Objectives: To provide a neurophysiological characterization of the CTC circuit in tremulous patients with SWEDD.

Methods: By using TMS (Transcranial Magnetic Stimulation), we investigated the connectivity and the plasticity of the CTC circuit in 12 tremulous patients with SWEDD, compared to 9 healthy controls (CTL), 8 patients with PD and 8 patients with adult-onset isolated dystonia (DYT). Specifically, we studied the effects of a single cerebellar magnetic pulse over the excitability of the contralateral primary motor cortex (M1) tested with MEPs (cerebellar-Inhibition or CBI protocol), in two different conditions: at rest and during arm extension. In addition, we measured the effects of cerebellar continuous-Theta-Burst-Stimulation (cTBS) on the contralateral MEPs amplitude.

Results: Patients with SWEDD have a deficient cerebellar-inhibition of the contralateral M1 at rest but not in arm extension; in both these conditions they result different from PD but not from DYT. Cerebellar cTBS induced the expected long-lasting cortical inhibition of MEPs amplitude in patients with SWEDD, but not in PD and DYT.

Conclusions: Patients with SWEDD showed a singular mild impairment of CTC circuit, resulting in the deficient cerebellar inhibition at rest but not in arm extension, in the presence of normal CTC plasticity. Such physiological properties of the CTC circuits differ from PD and DYT, suggesting a distinct involvement of the pathway in the pathophysiology of these disorders.

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C5

The role of deep brain stimulation in Parkinson related postural abnormalities

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Introduction: Parkinson's disease (PD) is often characterized by postural abnormalities related to abnormal trunk flexion. Deep brain stimulation (DBS) is recently gaining popularity in the treatment of PD-related postural abnormalities with encouraging but still conflicting data.

Objective: To evaluate the efficacy of subthalamic DBS (STN-DBS) in PD patients with relevant postural abnormalities poorly responsive to dopaminergic therapy.

Methods: We analyzed data on postural abnormalities before surgery and after 1-year of stimulation of all STN-DBS treated patients at our Center. Patients with a presurgical score ≥ 2 in UPDRS-III item-28 ("posture") in "On-condition" (after a challenge levodopa dose) were considered. Changes in item-28 scores between baseline (before surgery) and follow-up (1 year after surgery) were analyzed.

Results: Twenty-nine patients had a presurgical "On-condition" score ≥ 2 in UPDRS item-28 and were considered in this study. Comparing the average item-28 score in "On-condition" before surgery and after 1 year of STN-DBS in Med-On/Stim-On, a significant improvement was observed ($p:0,001$), with 75,9% patients improving, 10,3% maintaining and 13,8% worsening their UPDRS "posture" score. Evaluating the effect of stimulation alone (presurgical Med-Off vs. Med-Off/Stim-On), a significant improvement was observed in 24/29 patients. Comparing presurgical item-28 score in "Med-On" with the follow-up score in Med-Off/Stim-On, 16 patients showed an improvement. Dividing the patients in two subgroups, trunk flexion improving and trunk flexion not improving (TFI and TFNI, respectively), no significant differences were observed in terms of pre and post-DBS Levodopa Equivalent Daily Dose (LEDD). 18/22 TFI patients received dopamine-agonist at baseline and 4 of them discontinued it after surgery, while 5/7 TFNI subjects received dopamine-agonist at baseline and no one discontinued it after surgery.

Conclusions: The limited understanding of the pathophysiological underpinnings reflects the difficulties in the treatment of postural abnormalities in PD. These results suggest a positive effect of STN-DBS in the improvement of postural abnormalities in parkinsonian patients.

C6

Resting-state functional connectivity predates impulse control disorders in “drug-naïve” patients with PD

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Background: Impulse control disorders (ICDs) are common in Parkinson's disease (PD) generally thought to be related with dopamine replacement therapy, demographic and other clinical risk factors [1]. Previous studies have shown an impaired corticostriatal and limbic regions connectivity in patients with ICD [2,3].

Objectives: Using resting-state (RS) functional MRI, we retrospectively investigated the functional correlates of ICD symptoms, at baseline, in a cohort of “drug-naïve” patients with PD which successively developed ICD at follow up (ICD +) compared with patients without ICD (ICD -).

Methods: Baseline 3Tesla MRI images of 20 “drug-naïve” PD patients, 10 ICD + and 10 ICD -, and 10 matched healthy controls (HCs) were analyzed. The presence and the severity of ICDs at six months follow up was defined based on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating 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 HCs. In addition, we used voxel-based morphometry to test whether between-group functional changes were related to structural differences.

Results: At baseline, a decreased connectivity within the default mode and the right fronto-parietal networks and an increased connectivity within the salience network were detected when ICD + were compared with ICD- patients. Voxel-based morphometry analysis did not reveal any significant volume differences between all patients with PD and HCs and between ICD + and ICD - groups. ($p < 0.05$; FWE).

Conclusions: Our findings demonstrated, for the first time, that an abnormal RS connectivity within default mode, fronto-parietal and salience networks characterizes “drug naïve” patients who will eventually develop ICD while on dopaminergic treatment. We hypothesize that these divergent cognitive and limbic networks connectivity changes at baseline could represent an additional risk factor of incident ICD in a sub group of “drug naïve” patients with PD.

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C7

Different neuronal firing patterns in subterritories of the subthalamic nucleus in Parkinson's disease

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Background: Deep brain stimulation of the subthalamic nucleus (STN-DBS) is an established treatment for advanced Parkinson's disease (PD). The STN is functionally divided into different subterritories: sensorimotor, limbic, and associative domain, located in its dorsolateral (dSTN), ventral (vSTN) and medial part, respectively. The precise targeting of sensorimotor STN is crucial for stimulation efficacy and it's achieved with intraoperative micro-electrode recordings (MER) analysis. However, a different functional activity across STN subterritories is still controversial.

Objective: We characterized the electrophysiological activity of STN subterritories in PD patients as anatomically defined on fused CT/MRI images or by the recording tract itself.

Methods: We analyzed stable recordings from MER of 31 PD patients undergoing STN-DBS. Each recording was assigned to dSTN or vSTN by means of an anatomically based method and, with an a priori tri-segmented partition of the recording itself. We computed: (i) the inter-spike interval (ISI); (ii) ISI-characteristics; (iii) mean firing rate (MFR); (iv) discharge patterns and, (v) mean burst rate (MBR) of each detected single unit activity.

Results: We showed a different MBR between dSTN and vSTN (1.51 ± 0.18 vs. 1.76 ± 0.22 , Wilcoxon ranksum test, $p < 0.05$) with anatomically based method. We also described a trend in difference of MFR between dSTN and vSTN (12.78 vs. 15.05 Hz, Wilcoxon ranksum test, $p = 0.053$). Results were not resembled with the a priori tripartite method, despite similar ISI and ISI-characteristics.

Conclusion: Our results suggest that the different functions of STN subterritories are encoded in specific burst signaling, which is not necessarily reflected in different discharge rates.

C8

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Introduction: Neuromelanin is a byproduct of dopamine and noradrenaline metabolism and is thought to protect neurons from oxidative stress and has paramagnetic properties resulting in high signal on specific T1-weighted MRI.

Objectives: The purpose of this study was to investigate whether the signal intensity of the substantia nigra pars compacta (SNc) and locus coeruleus (LC) on neuromelanin-sensitive magnetic resonance imaging (MRI) can discriminate early-stage parkinsonism and whether volume loss increases in parallel with disease severity and duration.

Methods: 31 PD patients and 9 healthy controls (HC) underwent high-resolution T1-weighted MRI with magnetization transfer effect at 3T. All patients were evaluated and scanned in 'OFF' phase. Disease severity was evaluated by Hoehn and Yahr (H&Y), motor evaluation was performed using the Unified Parkinson's Disease Rating Scale (UPDRS III), cognitive evaluation by Addenbrooke's cognitive examination (ACE-R) and Montreal Cognitive Assessment (MoCA).

Results: The T1 hyperintense area in the SNc was substantially smaller in PD patients than in HC (p: 0.0001). No significant differences were found for the T1 hyperintense area in the LC (p:0.321). Spearman's test showed significant correlations between SNc area and disease duration (r: 0.432, p: 0.015), H&Y (r: 0.486, p: 0.006), UPDRS III (r: 0.500, p: 0.004), and the subitems bradykinesia (r: 0.507, p: 0.004) and rigidity (r: 0.422, p: 0.018). Significant correlations were also observed between SNc area of the most affected side and disease duration (r: 0.432, p: 0.14), UPDRS III (r: 0.437, p: 0.014) H&Y (r: 0.486, p: 0.006). No significant correlations were found for LC area.

Conclusions: MRI neuromelanin-sensitive images were able to detect significant changes in the SN area in PD patients. Our findings suggest that neuromelanin decrease is directly related with disease severity and duration. Neuromelanin MRI may be considered a biomarker of nigral degeneration in patients with PD.

C9

Dopamine receptor genes polymorphisms: a risk factor for developing dyskinesia in Parkinson's disease

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Introduction: Dyskinesia represent one of the most frequent motor complications of advanced Parkinson's disease (PD) and are strictly related to Levodopa (LD) therapy. While female sex, earlier disease onset and longer disease duration are well established risk factors, preliminary evidence suggests that also dopamine receptor gene (DRD) single nucleotide polymorphisms (SNPs) could be involved in dyskinesia development.

Objective: To establish whether DRD SNPs influence dyskinesia development in PD.

Methods: We enrolled 72 PD patients, equally divided in two groups, defined by the presence/absence of dyskinesia, and matched for age, disease duration, total daily LD and therapy duration. The following SNPs were analyzed: DRD1 (rs4532, rs686), DRD5 (rs6283), DRD2 (rs1800497, rs6277), DRD3 (rs6280, rs1800828), DRD4 (rs747302, 7 48-base pair) and compared using Chi2 test.

Results: We found that frequencies of haplotype G at DRD2 rs1800497 ($p = 0.03$), A at DRD3 rs6280 ($p = 0.05$) and G at DRD3 rs1800828 ($p = 0.01$) were significantly increased in dyskinetic compared to non-dyskinetic PD patients.

Discussion: Our data show that DRD2 and DRD3 variations increase the risk of dyskinesia in PD. Such findings are confirmatory for rs6280, while they represent the first report for rs1800497 and rs1800828. Furthermore, SNPs rs1800497 and rs6280 have been previously shown to increase the risk of developing PD, but also psychiatric conditions (schizophrenia, ADHD, bipolar disorder, akathisia, alcohol abuse and smoking habit).

C10

Single-subject FDG PET patterns and cognitive dysfunctions in Parkinson's disease

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Introduction: Cognitive dysfunction is common in Parkinson's disease (PD) patients and variably progress during the disease course. Recently, a statistical parametric mapping (SPM) standardized procedure [1] defined the [18]FDG-PET hypometabolism pattern of Alzheimer's disease (AD), dementia with Lewy bodies (DLB), corticobasal syndrome (CBS) and frontotemporal dementia (FTD). Single subject FDG-PET patterns have never been evaluated in large series of PD patients.

Objective: To evaluate the single-subject perfusion patterns in PD patients and their relationship with cognitive dysfunction and progression during five years of follow-up.

Methods: Consecutive non demented PD patients underwent FDG-PET imaging and an extensive motor and cognitive assessment. The single subject FDG-PET pattern [1] was evaluated blind to clinical diagnosis. All patients underwent a five-years clinical follow-up in order to re-evaluate the clinical progression.

Results: Fifty-four PD patients with normal cognition (n=37) and PD-MCI (n=17) entered the study. Blind FDG-PET classification allowed the identification of atypical brain metabolic patterns in 25 PD subjects (46%). The study recognized DLB-like (n=12), AD-like (n=6) CBS-like (n=5), FTD-like (n=2) metabolic patterns, reflecting specific cognitive impairment at a single-subject level. More patients with atypical FDG patterns (15 out of 25) progressed to cognitive impairment or dementia during clinical follow-up compared with subjects with the typical FDG PD-pattern (2 out of 29, p=0.001). However, they did not develop any specific clinical feature leading to a diagnosis of atypical parkinsonisms.

Conclusions: Cognitive dysfunction in PD is heterogeneous and often associated with "atypical" single-subject FDG-PET pattern that also reflects deficits in specific cognitive domains. This FDG PET technique might identify PD patients with higher risk of progression to dementia.

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C11

Amyloid deposition at baseline and gray matter atrophy progression in probable dementia with Lewy bodies

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Introduction: More than 50% of patients with DLB show Amyloid-beta (A β) deposition as measured with C11-Pittsburgh-compound-B (PiB) binding on PET. The association of A β deposition, with the progression of structural brain changes in patients with DLB is unknown.

Objectives: We investigated the longitudinal rates of GM atrophy and their association with baseline A β deposition in a cohort of patients with a clinical diagnosis of probable dementia with Lewy bodies (DLB).

Methods: Patients with probable DLB (n=19), who were consecutively recruited to the Mayo Clinic Alzheimer's Disease Research Center, underwent PiB-PET and MRI examinations at baseline. A second MRI was performed after a mean (SD) follow-up period of 2.5(1.2) years. Regional GM loss was determined on a high resolution 3D-T1 MRI with the Tensor Based Morphometry-Symmetric Normalization. Linear regression was performed between both global and regional baseline PiB standard unit value ratio (SUVR) and longitudinal change in regional GM volumes from an in-house modified anatomically atlas adjusting for age.

Results: DLB patients had a mean (SD) PiB SUVR of 1.53 (0.36). Higher regional and global PiB SUVR was associated with greater GM loss in the medial temporal lobe, caudate, putamen, posterior cingulate cortex and occipital cortex, after adjusting for age (p=<0.05).

Conclusions: A β deposition at baseline is associated with faster GM atrophy particularly in regions associated with AD-related neurodegeneration in patients with probable DLB. In addition, increased rates of atrophy in the corpus striatum may suggest a potential interaction of A β deposition with Lewy body disease.

C12

Pain-motor integration in the primary motor cortex in Parkinson's disease

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Introduction: Although chronic pain is a common non-motor symptom in Parkinson's Disease (PD) [1], the possible influence of chronic pain on parkinsonian motor features in PD has been never investigated experimentally so far.

Objective: We have recently designed a new transcranial magnetic stimulation (TMS) technique in healthy subjects (HS) to induce long-term (LTP)-like plasticity in the primary motor cortex (M1), through pain-motor integration processes [2].

Methods: This protocol combines the nociceptive system activation achieved by laser evoked potentials (LEPs), and M1 activation through TMS, in a laser-paired associative stimulation design (Laser-PAS). In HS, Laser-PAS at interstimulus interval (ISI) of 50ms (Laser-PAS50) induces long-term changes in motor evoked potential (MEP) amplitudes reflecting M1 LTP-like plasticity, arising from pain-motor integration processes.

Results: In this study, we found, differently from HS, reduced responses to Laser-PAS50 in PD patients, with and without chronic pain. When we compared responses to Laser-PAS50 in patients with and without chronic pain, we found similar abnormalities in the two patients' subgroups. When we compared however, patients referring chronic pain in the right upper limb (the body region investigated with Laser-PAS50) with those referring pain in other body regions, we found prominent changes in the former compared to the latter. Finally, when we compared patients off and on dopaminergic therapy, we found similar responses in these patients, regardless of the presence of chronic pain.

Conclusions: We conclude that in PD, chronic pain further degrades the response to Laser-PAS50 through mechanisms of abnormal pain-motor integration.

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Poster



P1

Freezing of gait in Dementia with Lewy bodies: a single-centre prevalence study

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Introduction: Freezing of gait (FoG) is a severe gait disorder commonly attributed to Parkinson's disease (PD), however it is frequently observed in patients with parkinsonisms. So far there are few published data on the frequency and characteristics of FoG in atypical parkinsonisms, even more so in the Dementia with Lewy bodies (DLB). Objective: To assess the prevalence of FoG in DLB subjects.

Methods: We have retrospectively analysed the prevalence of FoG in 30 patients (14 men and 16 women) with a clinical diagnosis of probable DLB. The presence or absence of FoG and its severity was assessed from the clinical charts of patients at our Movement Disorders Center with a median follow-up of 4 years; the assessment of FoG was based on patient history and clinical examination through the 14 item of UPDRS II and we have further subclassified patients with $FoG \geq 1$ and patients with $FoG \geq 2$.

Results: At the first visit (median 2,1 years after symptom onset) 17 (60,7%) patients had $FoG \geq 1$ and 8 (28,5%) patients had $FoG \geq 2$. FoG showed a great frequency also at the follow-up, so that at the fourth visit (approximately 4 years after the first visit) 91,6% of the 12 patients still available had $FoG \geq 1$ and 66,6% had $FoG \geq 2$.

Conclusions: This is the first study to investigate FoG in a population of DLB patients confirming that the occurrence of FoG is frequent even early in the course of disease and suggesting that studies of FoG could aid in the early diagnosis of DLB with respect to PD. The increased prevalence of FoG with the disease progression could also reflect a poor response to dopaminergic therapy, despite a very good documented benefit from levodopa on the parkinsonism in the majority of our DLB patients.

P2

Levodopa and neuropathy risk in patients with Parkinson disease: effect of COMT inhibition.

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Objective: Our purpose was to determine whether the use of catechol-O-methyltransferase-inhibitors (ICOMT) can reduce the risk of developing levodopa (LD)-induced neuropathy in Parkinson's disease (PD) patients.

Methods: A multicentre study of 197 PD patients was performed. 144 were exposed to LD for more than three years (LELD group); 53 simultaneously assumed Entacapone for at least eighteen months (LELD_ICOMT group).

Results: The prevalence of neuropathy in LELED patients was 19.4% whereas it was 5.7% in LELED_ICOMT group with a significant difference ($p=0.025$). In LELED_ICOMT cohort the daily LD dose and serum Vitamin B12 levels were significantly higher ($p<0.0001$), the serum Homocysteine levels were significantly lower ($p=0.001$) compared to LELED group.

Conclusion: Our results suggest that ICOMT could have a protective effect on the development of LD-induced neuropathy. Their action probably occurs through the metabolic rebalancing of the one-carbon-pathway cycle and is independent of the PD duration and severity and the duration of LD intake.

P3

Diagnostic approach to dysphagia in parkinsonism: a comparative analysis of bedside test, fiberoptic endoscopic evaluation of swallowing and electromyographic evaluation of swallowing

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Background: Though dysphagia is a common and disabling symptom in parkinsonism, precise diagnostic and therapeutic guidelines are lacking.

Aim: In order to optimize the diagnostic workup for dysphagia in parkinsonism, in this study we evaluated and compared the sensitivity and accuracy of three different methods of investigation of dysphagia: clinical approach by using “bed-side test”, fiberoptic endoscopic evaluation of swallowing (FEES) and electromyography (EMG) of swallowing.

Methods: We enrolled 46 patients: 19 patients with Parkinson’s disease, 12 with atypical parkinsonism in observation, 10 patients with Multiple System Atrophy, 3 with Progressive Supranuclear Palsy and 2 with Levy Body Dementia. All subjects underwent a multidisciplinary assessment that included all three methods studied. These techniques were compared with each other and, ultimately, with a final comprehensive evaluation, called “gold standard”, performed by a neurologist with expertise in rehabilitation who analysed all the data for assessing severity of dysphagia.

Results: The data obtained showed excellent correlation between the three diagnostic methods as regards the level of dysphagia severity. Statistical differences were observed between clinical evaluation and FEES regarding mild dysphagia and between “bed-side test” and EMG for severe dysphagia. With respect to the “gold standard”, FEES shows the higher specificity and diagnostic accuracy, compared with the other techniques, for all three levels of severity of dysphagia.

Conclusions: These findings suggest that the clinical evaluation of dysphagia is important also in the early phases of disease. As the disease worsens, it is appropriate to implement a diagnostic approach that also includes FEES and EMG, in order to collect all the necessary qualitative and quantitative data for devising a useful and effective rehabilitation program.

P4

Intracortical inhibition within the S1 and temporal discrimination in cervical dystonia

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Introduction: The somatosensory temporal discrimination threshold (STDT) has been suggested as an endophenotype of dystonia. Recent evidence in healthy subjects (HS) support the role of S1 intracortical inhibition abnormalities in driving STDT.

Here we aimed to explore cortical measures of inhibition within the S1 and their correlations with STDT in dystonia.

Methods: Twenty-one consecutive patients (13 F, mean age 62.3±8.8) with idiopathic isolated cervical dystonia and 21 age-matched HC were recruited. We performed: STDT on the index finger of the dominant hand, somatosensory evoked potentials (SEPs) recording of the N20 and P14 components, paired pulses SEPs at different interstimulus intervals (ISI 5-20 and 40 ms) and double SEPs (digital nerves on the dominant I and II fingers). We evaluated high frequency oscillations (HFOs) from the underlying N20, early (e-HFO) and late (l-HFO) area.

Results: Patients had significantly reduced values of STDT. Patients had decreased SEPs suppression evaluated with paired pulses (at every ISI) and with double pulses. HFOs area as well was decreased in the group of patients. There was a strong correlation between the STDT values and the PP N20 SEPs at ISI of 5 ms and between STDT and l-HFO area. This held true when repeating the correlation analysis in two groups separately.

Discussion: STDT performances correlate with neurophysiological measurements dependent on local inhibitory system within the S1 both in dystonic patients and in HC. Abnormal local inhibition within the S1 might be the endophenotypic landmark of dystonia, which by itself is necessary but not sufficient in order to develop dystonia.

P5

Mirror visual feedback to improve bradykinesia in Parkinson disease

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Background: Mirror visual feedback (MVF), has been successfully used in unilateral pain disorders rehabilitation and to promote motor recovery in post ictus patients. It has been shown that MVF during a motor skill training is able to improve performance of the trained and the untrained hands and enhances excitability of both primary motor cortices (M1). Bradykinesia is one of the main features of Parkinson's disease (PD), it consists in reduced movement speed and it is often asymmetrical.

Aim: The aim of the present study was to evaluate whether MVF may improve bradykinesia of the more affected hand in patients with PD.

Methods: 12 PD patients and 12 age-matched healthy controls performed for 10 minutes a finger sequence, receiving MVF of the more affected/ non-dominant hand. M1 excitability was assessed in both the trained and deluded hemispheres by means of transcranial magnetic stimulation (TMS), before and after MVF training. All participants performed a finger sequence at their spontaneous pace before and after MVF training.

Results: Cortical excitability of both M1s enhanced after the MVF training in both groups ($p < 0.01$). Movement speed increased in both groups after MVF training ($p = 0.01$), in the trained as in the untrained hand. Further, when we correlated the amount of fatigue, measured with PFS-16 scale, and the movement speed increase induced by MVF training, we found a significant negative correlation for the trained hand (the higher the fatigability, the lower the movement speed increase) whereas no significant correlation was found for the untrained hand.

Conclusions: Our data indicate that MVF is able to (i) increase movement speed of the trained and untrained hands and (ii) induce plasticity in both the trained and deluded M1s in PD patients. Further, we found that fatigue can impact behavioural improvement in the trained hand, but not in the untrained one.

P6

The semeiology of orbicularis oculi spasms as a prognostic factor for spread of focal blepharospasm?

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Background: Blepharospasm (BSP) is an adult-onset focal dystonia characterized by brief or prolonged involuntary symmetric spasms of the orbicularis oculi (OO) muscle leading to incomplete or complete rim closure. Aim of the study to verify whether differences in the clinical phenomenology of the muscle spasms reflects differences in severity and prognosis.

Materials and methods: Eighty-nine outpatients with primary BSP underwent a standardized interview assessing relevant clinical variables. A standardized videotape was also taken and analyzed by trained neurologists to identify the pattern of muscle spasms. A cluster analysis was performed to identify different BSP phenotypes.

Results: Cluster analysis identified three groups of BSP patients: 1) patients with prolonged spasms inducing incomplete rim closure who could also have brief and/or prolonged spasm leading to complete rim closure; 2) patients with prolonged spasms and complete rim closure who could also have brief spasms with complete rim closure; 3) patients with only brief spasms with complete rim closure. The three groups did not differ for age, sex, disease duration, age of onset, ocular symptoms, geste antagoniste, apraxia of eyelid opening, family history of dystonia. However patients from group 2 reported a significantly greater frequency of dystonia spread in comparison versus group 1 and group 3 patients (80% vs 40% vs 34%, $p < 0.035$).

Conclusions: This study provides new information about the possible use of the semeiology of orbicularis oculi spasms as a prognostic factor. Our finding suggests the need of a longitudinal study verifying whether the phenomenology of orbicularis oculi spasms can predict spread of dystonia.

P7

Efficacy and safety in the long-term treatment with botulinum toxin A for cervical dystonia

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Introduction: Botulinum toxin is considered a first line therapy for cervical dystonia; while short-term efficacy and safety is well known in the short-term, only few papers addressed these issues in the long-term [1,2].

Aims: To present the long-term outcome of patients with primary cervical dystonia (PCD) treated with abobotulinumtoxinA and onabotulinumtoxinA, focusing on safety and efficacy.

Methods: Consecutive patients with PCD receiving at least six injections with abobotulinumtoxinA and onabotulinumtoxinA were included. Clinical and demographic data were collected. Safety was assessed on the basis of patients' self-reports. Efficacy was assessed by recording duration of benefit, disease severity measured by Tsui scale, pain intensity with Visual Analog Scale (VAS), clinical global improvement (CGA) in a six-point scale (0: no efficacy; 6=remission of dystonia).

Results: 85 patients with PCD were included, encompassing 2169 treatments (onabotulinumtoxinA in 1365, abobotulinumtoxinA in 804). Mean dose injected was 701 ± 288 U for abobotulinumtoxinA and 185 ± 83 U for onabotulinumtoxinA. Mean duration of clinical improvement was higher for abobotulinumtoxinA than onabotulinumtoxinA: 93 ± 32 days and 89 ± 32 days, respectively ($p=0.008$). Mean VAS before and 4 weeks after injection was 4 ± 2 and 2 ± 2 , respectively. Mean Tsui scale before and 4 weeks after treatment was 6 ± 2 and 4 ± 2 , respectively. Mean CGA for all the sessions was 4 ± 1 . Side effects occurred in 441 out of 2169 injections, but were severe in 13 treatments. Doses of onabotulinumtoxinA and abobotulinumtoxinA significantly increased along time until treatment number 20, remaining stable thereafter.

Conclusions: Up to 21 years of repeated treatments, a good effect was observed in 86.2 % of injections. The two serotypes are both effective and safe in treating PCD; efficacy is long lasting. Injections with abobotulinumtoxinA showed a slight but significantly higher duration of benefit.

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P8

The use of Mirabegron in the treatment of overactive bladder in patients affected by Parkinson's disease

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In patients with Parkinson's disease (PD), overactive bladder (OAB) has a higher prevalence due to their older age and the impact of urinary symptoms may be more pronounced due to the increased burden of concomitant chronic comorbidities. Mirabegron is a specific agonist of β_3 -adrenoceptors in the human detrusor, stimulation of which leads to active relaxation of the detrusor in the storage phase.

Aim of the study: to evaluate the efficacy and tolerability of Mirabegron in PD patients with OAB and different comorbidities.

19 PD patients who experienced intolerable side effects to a previous treatment with antimuscarinics, were included. Baseline evaluation: 3- day voiding diary, uroflowmetry and VAS to score the bother of urinary symptoms on Quality of Life. Patients started assuming Mirabegron 50 mg once daily. Patients were evaluated at 1, 3 and 6 months follow up with the 3- day voiding diary, uroflowmetry and VAS. Side effects during treatment were also noted.

Ten males and 9 female were enrolled; mean age: 76 ± 4.2 yrs. All patients presented with urgency and urgency urinary incontinence (UUI); mean daily frequency of urgency and UUI: 9.7 ± 3.6 and 4.2 ± 2.1 , respectively. At 3 months follow up, 6 (30%) patients stopped Mirabegron, due to: lack of efficacy (4 patients) and the cost of the drug (2 patients). In the remaining 16 patients, mean daily frequency of urinary urgency episodes and of UUI were reduced to 6.2 ± 2.9 and 3.1 ± 1.3 , respectively. The mean VAS score improved from 3.8 ± 0.9 to 6.6 ± 1.7 . We did not observe intolerable side effects. At the 6 mos follow up these results persisted in 13 patients.

The results of this study represent the first observation on the efficacy and tolerability of Mirabegron in PD patients with refractory overactive bladder. About 70% of PD patients continued to assume Mirabegron at the 6 month follow up, with an improvement of OAB symptoms. The lack of intolerable side effects with Mirabegron can be considered the more relevant aspect of this kind of treatment.

P9

Low cerebrospinal fluid 3,4-dihydroxyphenylacetic acid and 3,4-dihydroxyphenylglycol levels are biomarkers of parkinsonian disorders

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Introduction: Low CSF levels of 3,4-dihydroxyphenylacetic acid (DOPAC) and 3,4-dihydroxyphenylglycol (DHPG), the main respective neuronal metabolites of dopamine and norepinephrine, are biomarkers of the alpha-synucleinopathies Parkinson's disease (PD) and multiple system atrophy. Whether non-synucleinopathic forms of parkinsonism also involve low CSF DOPAC and DHPG levels has been unknown.

Objectives: In the present study we extend previous results using controls and a cohort of patients with non-synucleinopathic neurodegenerative disorders: progressive supranuclear palsy (PSP), Alzheimer's disease (AD) who were not on any medications or had a washout from dopaminergic or noradrenergic medications.

Methods: We enrolled patients with PD, AD, PSP, and controls after obtaining informed consent. CSF samples were obtained by lumbar puncture between 8 and 9 AM after a fasted overnight. Dopamine agonists were stopped at least 2 days beforehand. Levodopa/Carbidopa or levodopa/benserazide were held overnight. Patients discontinued MAO-B inhibitors for at least a few weeks before hospitalization. Entacapone was held during the 2 days of hospitalization. The first 4 mL of CSF were used for routine analyses. The next 1.5-2 mL was aliquoted into 200 µL aliquots in which 4 µL of 0.01M perchloric acid was added. The samples were frozen until shipped to the NIH in dry ice. Analysis was done on CSF data where DOPA level was less than 1000 pg/mL.

Results: Data were collected in 131 subjects: 41 PD, 50 AD, 14 PSP, and 26 controls. CSF DOPAC in PD and PSP was lower than in AD ($p=0.01$ and $p=0.003$ respectively) or controls ($p=0.03$ and $p=0.007$ respectively). CSF DHPG was also lower in PD ($p=0.008$) and PSP ($p=0.03$) than in controls.

Conclusion: Low CSF DOPAC and DHPG seem to provide specific biomarkers of parkinsonism regardless of the underlying mechanism. Further investigation on a larger cohort of patients with different clinical subtypes is a matter for future research.

P10

Descending pain modulation is abnormal in cervical dystonia

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Introduction: Pain affects up to 70% of patients with Cervical Dystonia (CD), but its underlying mechanisms are largely unknown. Previous reports showed that nociceptive pathway function, as assessed by laser-evoked potentials (LEP), is normal in CD. However, the role of the 'diffuse noxious inhibitory controls' (DNIC) in CD patients has not been explored.

Objectives: To explore the DNIC system in CD.

Methods: We recruited 8 CD patients (6M/4F; mean age: 58.8±16.3) and 8 gender- and age-matched healthy controls (HC). Patients rated their maximum pain on an NRS scale ranging from 0 to 10, whereas HC were pain-free. Patients were further stratified into two subgroups: 1) with no significant pain (NP-CD; NRS<4); and 2) with significant pain (P-CD; NRS≥4). Latency and amplitude of the N2/P2 component of LEP were measured at baseline (T0), during (T1) and after 10 minutes (T2) the application of a heterotopic noxious stimulation (HTNS).

Results: At T0, there were no differences between groups as to both N2/P2 latency and amplitude. During the HTNS (T1), N2/P2 amplitude significantly decreased in HC (within-group p<0.001), but not in CD (between group diff. at T1 p<0.001). The lack of N2/P2 amplitude reduction during HTNS was observed in both P-CD and NP-CD and did not correlate with NRS pain scores, but with disease duration (p<0.01).

Conclusions: Our results suggest that the DNIC system is altered in CD, regardless of the clinical presence of pain. This abnormality might therefore explain why CD patients are prone to develop pain. Our findings would also imply that additional factors are required for pain to develop clinically. Additionally, we showed that DNIC abnormalities correlate with disease duration suggesting it might be a potential bio-marker of CD.

P11

Re-emergent tremor in Parkinson's Disease: epidemiological and clinical features

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Introduction: In 1999, Jankovic described 12 patients with Parkinson's Disease (PD) with resting tremor showing a tremor which appeared after a variable delay while maintaining the upper limbs outstretched [1]. The authors defined this tremor as "re-emergent tremor" (RET). So far, no studies have assessed the prevalence of RET in PD and it is still unclear whether PD patients with RET may represent a distinct PD clinical subtype.

Objective: To evaluate the prevalence and the clinical features of RET in a large sample of consecutive patients with PD and to compare the demographic and clinical features of PD patients with and without RET.

Methods: We consecutively enrolled 210 patients with PD. We collected PD patients' demographic and clinical data. The severity of the disease was assessed by means of MDS - Unified Parkinson's Disease Rating Scale. We assessed the presence of different types of tremor in each patient, including RET, resting tremor and action tremor. RET was defined as a tremor that appears in the outstretched upper limbs after at least 1 second while maintaining the posture. Latency and severity of RET was evaluated and we also investigated possible relationship with demographic and clinical features.

Results: RET was present in 42/210 patients. The mean latency of RET was 7.20 ± 6.5 seconds. The mean severity was 2.5 ± 1.9 . By comparing patients with and without RET, we found that the two groups showed similar demographic features. Patients with RET showed less severe speech and gait disorder, upper limbs and global bradykinesia in comparison with patients without RET. Similar results were also present comparing patients with RET with patients with resting tremor associated with action tremor and without tremor.

Conclusions: Twenty percent of patients with PD showed RET. PD patients with RET have a less severe disease.

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P12

Use of inertial sensors to quantitatively assess the levels of physical activity in individuals with Parkinson's disease after 5 weeks of intensive rehabilitation.

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Background: Individuals with Parkinson's disease (PD) generally exhibit reduced physical activity (PA) levels and increased time spent in sedentary behavior when compared with healthy subjects despite the fact that PA has been shown effective in attenuating their motor symptoms. We recently demonstrated that after 5-weeks of supervised rehabilitation treatment individuals with PD reported clinically meaningful changes in gait velocity and improved on most spatio-temporal gait parameters. However, it still remains unclear whether the PA levels are maintained over time.

Objective: To quantitatively assess patterns of PA in individuals with mild to moderate PD after 5 weeks of intensive rehabilitation and 12 weeks of home-based unsupervised activity during which participants performed a set of exercises suggested by their therapists.

Methods: Twenty-one adults with PD (age 65.7±15.9, H&Y 2.0±0.5) were provided with ActiGraph wGT3X-BT accelerometer, which was positioned on a wrist and held for one week. PA patterns were calculated from raw accelerometric data according to cut points specific for PD and then compared with those of a control-group age- and gender-matched.

Results: No significant differences between individuals with PD and controls were found as regards time spent in sedentary (43.62% vs. 49.46%), light (22.42% vs. 19.07%) moderate (25.17% vs. 20.68%) and moderate-to-vigorous activity (8.01% vs. 10.80%). Similarly, even when the walking velocity was used as PA indicator, no differences were found in terms of time spent in walking at low (< 1.04 m/s, 73.5% vs. 73.6%) and moderate speed (1.05-1.30 m/s, 26.5% vs. 26.4%).

Conclusions: The results show that good levels of physical activity are maintained after several months from the rehabilitative treatment. The use of wearable sensors may be of great clinical utility as it allows to accurately monitoring the long-term effects of rehabilitation on people with PD during daily life activities.

P13

Predictive value of ¹²³I-FP-CIT-SPECT on surgical outcome in idiopathic adult chronic hydrocephalus: a pilot study

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Introduction: Idiopathic adult chronic hydrocephalus (IACH) is a complex syndrome characterized by ventricular dilation accompanied by a progressive triad of a gait disturbance, cognitive impairment and incontinence. IACH can be also associated with extrapyramidal signs.

Objective: The aim of our study was to evaluate if dopaminergic nigro-striatal dysfunction might impact the clinical outcome after surgery.

Methods: Twenty cases of IACH (diagnosed according to the International Clinical and Radiological guidelines for IACH) with a parkinsonian syndrome consisting of ≥ 1 sign between resting tremor, bradykinesia and rigidity (scored by Unified Parkinson's Disease Rating Scale, UPDRS-III) were included. All patients underwent [¹²³I]FP-CIT SPECT and had a 6-weeks trial with levodopa. Eighteen patients underwent ventriculoperitoneal shunt and two endoscopic third ventriculostomy. Preoperatively and postoperatively (after 3 and 6 months) motor, urinary and cognitive functions were assessed by the Japanese normal pressure hydrocephalus grading scale – revised (JNPHGSR), and the Mini-Mental State Examination (MMSE).

Results: Ten patients showed a reduced striatal uptake (IACH-p), while the other ten had a normal one (IACH-n). The two groups did not show significant differences with respect to age, disease duration, clinical motor presentations and UPDRS-III. A levodopa partial positive response was more frequently observed in the IACH-p than in IACH-n. IACH-n showed, at both 3 and 6 months after surgery, a significant improvement compared to IACH-p in MMSE, JNPHGSR, walking and urinary functions.

Conclusions: Our preliminary findings suggest that the detection of dopaminergic nigro-striatal dysfunction, due to either concomitant degeneration or mechanic interferences, in IACH with parkinsonism, could predict the negative clinical outcome after surgery, however a larger study is warranted.

P14

Early stridor onset predicts survival in Multiple System Atrophy

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Introduction: Multiple System Atrophy (MSA) is a progressive neurodegenerative disorder with a mean survival ranging from 6.2 to 10 years. Various clinical factors have been reported as predictive of shortened survival, among these stridor has been identified as a negative prognostic indicator in one study but not confirmed in others.

Objective: To evaluate the predictive value of stridor and of its latency of onset in a cohort of MSA patients referred to a tertiary centre.

Methods: We retrospectively identified all patients with a final clinical diagnosis of MSA referred to our Department between 1991 and 2015 and evaluated at least once a year during the disease course. Stridor was defined as present when confirmed by a whole night video-polysomnography and categorized as early if presenting within 3 years of disease onset. Survival data were defined based on time to death from the disease onset and calculated using Kaplan-Meier curves. Predictors were identified in a univariate and multivariable COX regression analysis.

Results: A total of 136 MSA patients were included (88 males; 68 MSA with predominant Parkinsonism), 113 were deceased at the time of data collection. On Kaplan-Meier curve the median duration of illness was 7.84 years. Stridor was diagnosed in 42 patients, 22 of these presented an early stridor onset. The overall survival did not differ between patients with and without stridor ($p=0.3467$), while the risk of death in patients with early stridor onset was higher compared to those developing this symptom later ($p=0.0209$). In the stridor subgroup, the multivariable model retained the early stridor onset as unfavourable predictor of survival (Hazard Ratio=3.21, $p=0.006$).

Conclusions: The study showed that the overall survival did not differ between MSA patients with and without stridor, however we demonstrated for the first time that early stridor onset is an independent predictor for shorter survival.

P15

The effect of L-Dopa/Carbidopa intestinal gel assessed with neurophysiological techniques in Parkinson's disease

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Introduction: L-Dopa /Carbidopa intestinal gel (LCIG) infusion allows stable and smooth L-Dopa plasmatic levels in Parkinson's disease (PD) patients, reproducing the physiological continuous dopaminergic receptor stimulation. PD motor and non-motor impairment, such as bradykinesia and somatosensory temporal discrimination (assessed by somatosensory temporal discrimination threshold - STDT), shared dopaminergic depletion as an underlying pathophysiological mechanism. To date, however, neurophysiological studies demonstrated that immediate-release of oral L-Dopa do not normalize all bradykinesia and STDT features.

Objective: As long as LCIG provides a more suitable model to investigate the role of the dopaminergic system in the pathophysiology of PD, we assessed the effects of LCIG on bradykinesia and somatosensory abnormalities in PD.

Methods: We studied 11 advanced PD patients in therapy with LCIG and 11 age-matched healthy subjects, as a control group. Bradykinesia was measured by kinematic recording of finger tapping task, and sensory abnormalities were evaluated through STDT. All patients were studied in OFF and ON phase, in two different experimental sessions.

Results: PD patients were highly bradykinetic and hypokinetic, with no progressive reduction in amplitude and speed during finger tapping. STDT values were higher in patients than in healthy subjects. LCIG did not change finger tapping kinematics but it improved STDT values in patients.

Conclusion: The study provides novel information on motor and sensory abnormalities, as assessed by neurophysiologic techniques, in advanced PD patients. LCIG is able to improve sensory deficits, thus indicating that they mainly reflect functional abnormalities due to dopaminergic denervation. The lack of LCIG effects on finger tapping likely indicates that motor abnormalities in advanced PD mainly reflects the anatomically brain damage.

P16

Blinking in early Parkinson's disease

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Background: Clinical and experimental studies in patients with Parkinson's disease document numerous facial motor abnormalities, including abnormalities of voluntary, spontaneous and reflex blinking, but no studies have objectively assessed blinking abnormalities in the early stage of the disease.

Methods: We enrolled 10 patients diagnosed as having clinically Parkinson's disease and 10 healthy age- and gender-matched controls. Participants were asked to blink voluntarily as fast as possible; spontaneous blinking was recorded during two 60 seconds epochs during which the subjects were instructed to look straight ahead. Reflex blinking was evoked by supraorbital-nerve electrical stimulation and the blink reflex recovery cycle was tested with a paired-pulse technique. Blinking was recorded with a 3D optoelectronic motion system equipped with dedicated software for data analysis.

Results: During voluntary blinking, the closing and opening phases and the inter-phase pause duration between the closing and opening phases had similar duration in patients and in healthy controls. The peak velocities of the closing and opening phases were also similar in the two groups. Similarly, no difference was found in the spontaneous blinking rate and in the blink reflex recovery cycle between patients and healthy controls.

Conclusions: The kinematic analysis of blinking features provides a further characterization of early PD patients. The lack of voluntary, spontaneous and reflex blinking abnormalities in early PD suggests that the facial motor control systems may be involved in the more advanced stages of the disease.

P17

**MMSE and MoCA in Parkinson's disease and Dementia with Lewy bodies:
a multicenter 1-year follow-up study**

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Introduction: The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are the most commonly used scales to test cognitive impairment in Lewy body disease (LBD), but there is no consensus on which is best suited to assess cognition in clinical practice and most sensitive to cognitive decline.

Methods: Retrospective cohort study of 265 LBD patients [Parkinson's disease (PD) without dementia (PDnD, N=197), PD with dementia (PDD, N=40), and dementia with Lewy bodies (DLB N=28)] from an international consortium who completed both the MMSE and MoCA at baseline and 1-year follow-up (N=153). Percentage of relative standard deviation (RSD%) at baseline was the measure of inter-individual variance, and estimation of change (Cohen's *d*) over time was calculated.

Results: RSD% for the MoCA (21%) was greater than for the MMSE (13%) ($p=0.03$) in the whole group. This difference was significant only in PDnD (11% vs. 5%, $p<0.01$), but not in PDD (30% vs. 19%, $p=0.37$) or DLB (15% vs. 14%, $p=0.78$). In contrast, the 1- year estimation of change did not differ between the two tests in any of the groups Cohen's effect <0.20 in each (group)

Conclusion: MMSE and MoCA are equal in measuring the rate of cognitive changes over time in LBD. However, in non-demented PD (PDnD), the MoCA is a better measure of cognitive status as it lacks both ceiling and floor effects.

P18

Functional connectome organization is altered in PD patients with mild cognitive impairment

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Background: Investigation of the brain wiring architecture is a powerful approach in the examination of the pathogenic mechanisms of neurodegenerative disease.

Objective: To investigate the functional brain connectome organization in patients with Parkinson's disease (PD) with mild cognitive impairment (MCI).

Methods: 54 PD-MCI patients, 54 demographically matched PD patients with no cognitive impairment (PD-ncog), and 41 healthy controls underwent resting state functional MRI (fMRI). Graph theory analysis was used to measure the global topological properties of functional brain networks in patients and controls. Differences in regional functional networks among groups were investigated using Network-Based Statistic (NBS).

Results: PD-ncog patients did not show altered global graph theory measures and regional functional connections relative to controls. PD-MCI patients had lower mean network degree, connection density, and global efficiency as well as higher path length compared to controls and PD-ncog cases. NBS analysis revealed that, relative to healthy subjects, PD-MCI patients showed a large network of reduced functional connectivity that included basal ganglia and the majority of fronto-temporo-parietal areas with the most significant being the precentral, postcentral, superior and inferior frontal, and superior temporal gyri, anterior and posterior cingulate cortices, and supramarginal gyri and insula bilaterally.

Conclusions: The topological properties of brain networks are altered in PD patients with cognitive deficits, suggesting a loss of efficiency of long-distance functional connections. The pattern of these alterations and their anatomical distribution suggest that they might reflect the neuropathological substrate underlying PD-related cognitive impairment. Assessing functional brain network abnormalities in PD patients with cognitive impairment could improve our understanding of the relationship between PD pathology and cognitive deficits.

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P19

Structural brain connectome and cognitive impairment in Parkinson's disease

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Objectives: To investigate structural brain connectome in Parkinson's disease (PD) patients with (PD-MCI) and without mild cognitive impairment (PD-ncog).

Materials and Methods: We enrolled 170 PD patients (116 PD-ncog; and 54 PD-MCI), and 41 healthy controls. Fifty-four PD-ncog, matched with PD-MCI for demographical features (matched PD-ncog), were selected for the group comparison. Individual structural brain connectome was reconstructed using deterministic diffusion tensor tractography and its integrity was measured in terms of fractional anisotropy (FA) and mean diffusivity (MD). Network based statistic was used to assess structural connectivity differences among groups. In PD patients, structural network alterations were correlated with neuropsychological scores.

Results: PD-MCI patients showed network alterations compared to both controls and PD-ncog. Relative to controls, PD-MCI showed a large basal ganglia/frontoparietal network with decreased fractional anisotropy (FA) in the right hemisphere and a subnetwork with increased mean diffusivity (MD) involving similar regions, bilaterally. Compared to PD-ncog, PD-MCI showed a network with decreased FA including basal ganglia and fronto-temporo-parietal regions, bilaterally. Similar findings were obtained adjusting for motor disability. FA of connections linking basal ganglia, fronto-temporo-parietal, and fronto-occipital regions correlated with visuospatial and executive scores, while correlations between MD networks and neuropsychological performances were more widespread. PD-ncog patients did not show network alterations relative to healthy controls and PD-MCI patients.

Conclusions: A disruption of structural connections between brain areas forming a network contributes to determine an altered information integration and organization and thus cognitive deficits in patients with PD. Our results provide novel information concerning the structural substrates of MCI in PD and may offer markers of cognitive deterioration in these patients.

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P20

Cortical thinning associated with mild cognitive impairment in Parkinson's disease

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Background: Parkinson's disease (PD) is often associated to cognitive deficits. Cortical thickness analysis might be a valid instrument to investigate gray matter loss.

Objectives: To investigate patterns of cortical thinning associated with mild cognitive impairment (MCI) in a large sample of Parkinson's disease (PD) patients and to explore relationships with cognitive deficits.

Materials and Methods: We studied 108 PD patients (54 without cognitive impairment [PD-ncog], and 54 with MCI [PD-MCI]), and 41 healthy controls. All subjects underwent structural magnetic resonance imaging (MRI) and clinical and neuropsychological evaluation. The cortical thickness analysis was performed using Freesurfer and data were compared among groups. In PD patients, thickness measures of the brain areas that were significantly different between groups were correlated with neuropsychological measures.

Results: Compared to PD-ncog and healthy controls, PD-MCI showed cortical thinning of superior temporal sulcus, inferior parietal, middle and superior temporal gyri bilaterally, as well as left frontal pole and supramarginal gyrus. Bilateral precentral gyri and left entorhinal cortex and superior frontal gyrus as well as right inferior frontal gyrus revealed reduced thickness only when PD-MCI were compared to controls. When compared to PD-ncog, PD-MCI showed additional cortical thinning of the postcentral gyri bilaterally. PD-ncog did not show differences relative to controls. Lower scores on global cognition tasks were associated with widespread cortical thinning. Cortical thinning of fronto-temporo-parietal regions was correlated to lower executive and visual spatial scores.

Discussion: Our results demonstrate that MCI in PD has a neuroanatomical substrate of cortical thinning which correlates with performance in neuropsychological evaluation test involving executive functions and visual spatial abilities. The atrophy pattern identified in this study might be used as a surrogate marker of cognitive impairment in nondemented PD

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P21

The cerebral structural and functional signatures of impulse control disorder in Parkinson's disease

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Introduction: Impulse control disorder (ICD) is characterized by recurring and compulsive behaviours, frequently observed in patients with Parkinson's disease (PD). Compared with PD no-ICD, PD-ICD patients showed more severe psychiatric symptomatology and cerebral structural alterations in the meso-cortico-limbic circuit. However, in the comparison between the two groups of PD, few studies have taken into account the clinical impairment of PD, thus, multiple factors may have affected patient differences.

Objective: To assess cortical thickness (CT) measures, white matter (WM) microstructural damage, and resting state (RS) functional connectivity alterations in PD-ICD compared with controls and PD no-ICD cases matched for disease stage and duration, motor impairment, and cognitive status.

Methods: 85 PD patients (35 PD-ICD) and 50 controls. All subjects underwent 3D T1-weighted, diffusion tensor (DT), and RS-functional MRI (RS-fMRI). CT measures were assessed using surface-based morphometry. DT metrics were explored using region-of-interest-based and tractography approaches. RS-fMRI data were analyzed using a model free approach.

Results: Compared with controls, both PD patient groups showed a pattern of brain structural alterations involving basal ganglia, pyramidal and associative systems. Compared with PD no-ICD, PD-ICD patients showed reduced CT of the left precentral and superior frontal gyri, and motor and extramotor (limbic) WM tract involvement. Furthermore, compared with controls, both patient groups had an increased functional connectivity within the visual-network. Additionally, PD no-ICD patients showed increased functional connectivity of bilateral precentral and postcentral gyri within the sensorimotor network compared to both controls and PD-ICD cases.

Conclusion: Relative to PD no-ICD, PD-ICD patients are characterized by a more severe involvement of frontal, meso-limbic and motor circuits. Furthermore, in PD-ICD, the lack of increased functional connectivity within the sensorimotor-network together with their cortical thinning in the same regions, suggest a greater disconnection among these systems in this condition.

P22

Suicide in Parkinson's disease: an open question on a complex and poorly explored phenomenon. A systematic literature review.

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Despite high rates of neuropsychiatric symptoms in idiopathic Parkinson's disease (PD), suicidal thoughts and behaviors have traditionally been regarded as less common relative to the general population. Recent reports of an increased suicide risk associated with subthalamic nucleus deep-brain stimulation (DBS) and levodopa-carbidopa intestinal gel (LCIG) in advanced PD call attention to the need for systematic investigation of risk factors related to suicidal and death ideation. Taking a cue from a recently observed case of suicide in PD patient under LCIG therapy, we conducted a structured search using PubMed and included publications from 1972 to 2015 to provide an overview of the current data concerning suicidal behavior in PD. The possible role of the dopamine agonist withdrawal syndrome (DAWS) in PD patients under LCIG and previously treated with DA has gained much attention in the scientific literature. However, the pathophysiology of suicide is extremely complex and evidence of DAWS being directly or indirectly associated with suicidal behavior remains meagre. Herein we report a patient with advanced PD who committed suicide 2 years after onset with LCIG despite fair to excellent motor improvements. In our case DAWS cannot be considered a precipitating factor. In a condition of advanced PD, dopaminergic drugs may be responsible of a over-thinking and hyper self-awareness states that has been linked to suicide. Moreover, over-thinking shares some similarities with impulse control disorders and increased impulsiveness was probably a major factor in suicidal behavior of some of patients after DBS. We speculated that improvement in motor condition with effective treatment (be it DBS or LCIG) and possibly increased impulsivity or agitated-dysphoric state (as observed in patients with bipolar disorder) allowed the patient to commit suicide. It become apparent that much attention should be paid concerning a potentially increased of suicidal ideation and affective alterations.

P23

Facial emotion recognition in Parkinson's disease de novo patients

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Background: Parkinson's disease (PD) has been frequently associated with facial emotion recognition impairment. Specifically, emotional processing has been widely studied in patients with PD and several studies have shown specific impairments in patients' capacity to recognize emotions from facial cues. These deficits may be related to a dysfunction of the ventral striatum and subthalamic nucleus which have connections with other brain regions, including the orbitofrontal cortex, the amygdala and the putamen. Despite these deficits in explicit emotion recognition and categorization there were no studies on the implicit attentional processing of emotional stimuli.

Aim of the study is to assess whether and to what extent PD patients are impaired in attentional allocation toward facial expression.

Methods: We assessed 16 elderly controls and 16 PD de novo patients (9 males and 7 female, mean age 64 years, mean Hoehn-Yahr stage 1.5, mean UPDRS III score 9/108), in a dot-probe task. During the dot-probe task, participants are asked to stare at a fixation cross on the center of the screen. Two faces, one of which is neutral and one of which is an emotional face (fearful, disgusted and happy) appear randomly on either side of the screen. The faces were presented for 500ms, then a dot is presented in the location of one former stimulus (emotional or neutral face). Participants are instructed to indicate the location of this dot as quickly as possible, either via keyboard. Reaction times (RTs) were collected and used to compute scores.

Results: PD patients had no attentional facilitation for fearful faces. This may indicate a very early deficit in processing of fearful faces, maybe related to the dopaminergic impairment. Furthermore our data indicate that PD patients have difficulties in disengage attention toward happy facial expression, because they are slower than controls to remove positive facial expression from Working Memory.

P24

Creativity in Parkinson's disease

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Background: Parkinson's disease (PD) is a neurological disorder characterized by reduced flexibility, conceptualization, and visuospatial abilities. Creative problem solving typically requires divergent thinking, a thought process used to generate ideas by exploring many possible solutions, and flexibility restructuring and manipulating problem information. Although creative thinking requires a combination of these abilities, several reports described enhanced artistic creativity in PD patients treated with dopaminergic agents [1].

Objective: We aimed to assess creativity in PD.

Methods: We recruited 11 patients with PD (aged 49–77 years; education 5-18 years; H&Y 1-4) treated with dopamine agonists and/or levodopa and 11 healthy controls (HC) (aged 60–87 years; education 5-13 years). Creativity was assessed with The Test of Divergent Thinking (TCD). TCD, providing an overall Total Score and 5 Factor scores: Fluidity, Flexibility, Originality, Elaboration and Title.

We used One-way between-subjects ANOVA to compare two groups and the Spearman test to evaluate whether there was a correlation between creativity and L-Dopa dosage.

Results: We found significant differences between the groups in TCD total score [(mean±SD) PD: 64.92±21.23 vs HC: 56.64±5.48, $p = 0.03$] and in Originality factor (PD:21.33±8.37 vs HC: 15.64±3.64, $p = 0.008$). There were no significant correlations between creativity as indexed by TCD (Total Score, Originality) and L-Dopa dosage ($p > 0.05$).

Conclusion: Our study suggests that PD patients enhanced creativity as compared to neurologically healthy controls. PD patients seem to be more flexible and, through creative thinking, they generated an original solution that resulting in an original and valuable artist production. We speculate that dopaminergic agents can induce a reduction of latent inhibition and enhancement of novelty-seeking behavior, resulting in widening of the associative network and enriched divergent thinking.

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P25

Mild cognitive impairment in Parkinson's and Alzheimer's Diseases show different relationships between cortical resting state EEG rhythms and global cognitive function

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Introduction: Parkinson's (PD) and Alzheimer's (AD) diseases are two neurodegenerative disorders affecting cognitive functions including attention-executive, episodic memory, etc. [1]. Furthermore, abnormalities of resting state theta (4-8 Hz) and low-frequency alpha (8-10.5 Hz) electroencephalographic (EEG) rhythms characterized AD and PD groups, respectively, in the stages of dementia [2] and mild cognitive impairment (MCI; [3]).

Objective: Test the hypothesis that global cognitive status of AD and PD subjects with MCI is related to the abnormalities of theta (4-8 Hz) and low-frequency alpha (8-10.5 Hz), respectively.

Methods: Resting state eyes-closed EEG rhythms were recorded in 24 ADMCI, 24 PDMCI, and 24 control healthy (Nold) subjects. Age, gender, and education were matched across the three groups. Mini Mental State Evaluation (MMSE) score was matched between the ADMCI and PDMCI groups. Cortical EEG sources were estimated by eLORETA freeware in the following frequency bands: delta (2-4 Hz), theta (4-8 Hz), alpha1 (8-10.5 Hz), alpha2 (10.5-13 Hz), beta1 (13-20 Hz), beta2 (20-30 Hz), and gamma (30-40 Hz). Activity in the whole cortex at delta, theta, and alpha1 was correlated with MMSE score in the ADMCI and the PDMCI group, separately (Spearman test, $p < 0.05$).

Results: Compared to the Nold group, the global theta sources were higher in activity in the PDMCI group, while the activity of global alpha sources was lower in the ADMCI group. The MMSE score correlated negatively with global theta sources in the PDMCI (but not ADMCI) group ($p < 0.05$), and correlated positively with global alpha1 sources in the ADMCI (but not PDMCI) group ($p < 0.05$).

Conclusions: These results suggest that PD and AD may differently affect cortical neural synchronization oscillatory mechanisms generating EEG rhythms in quiet wakefulness as a correlate of the cortical arousal. The regulation of cortical arousal would impact on global cognitive function in PD and AD patients with MCI.

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P26

Gait initiation in response to emotion-inducing pictures in Parkinson's disease

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Objective: To investigate gait initiation in response to emotion inducing pictures in subjects with Parkinson's disease (PD).

Background: Novel pathophysiological models have linked gait disturbances in PD to the dysfunction in brain circuits involved in emotion and cognition rather than motor control. In healthy, it has been directly demonstrated that emotion stimuli influence the initiation and execution of voluntary stepping. Particularly, participants made forward or backward steps on a force plate in response to the valence of visual stimuli [1]. The authors showed that unpleasant images selectively caused an initial freezing response.

Methods: Thirteen patients with PD and 12 age and gender-matched healthy controls were recruited for this study. In the affect- congruent condition participants made forward (approach) steps in response to pleasant visual stimuli whereas they made backward (avoidance) steps in response to unpleasant visual stimuli. In the affect-incongruent condition, this mapping was reversed. The experiments were made in two separate days and the order was randomized. Reaction time and step size were recorded by means of a sensorized mat (GaitRite).

Results: Results revealed significant effects of emotion on the step parameters. Unpleasant images caused an increase in reaction time in both groups of subjects ($p < 0.01$), whereas in PD only unpleasant images caused also a reduction in the step size ($p < 0.05$). These effects were not influenced by the congruency of the task.

Conclusions: The results confirmed that affect, especially negative emotions, and voluntary stepping are coupled. In patients with PD the valence of emotional stimuli influenced not only step preparation (reaction time), but also step execution (step size) supporting the theory on the role of the non-motor systems (e.g., limbic system) in the pathophysiological mechanisms of gait disturbances.

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P27

White matter connectome in patients with genetic dystonia

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Introduction: Primary dystonia (DYT) has traditionally been attributed to basal ganglia dysfunction. Recent studies expanded this picture suggesting primary DYT as a circuit disorder.

Objective: This study investigated structural neural pathways in clinically manifesting and non-manifesting individuals with several DYT genotypes using a network approach.

Methods: We studied 9 asymptomatic mutation carriers (4 DYT1, 4 DYT6, 1 DYT10), 26 symptomatic mutation carriers (7 DYT1, 7 DYT6, 9 DYT5, 1 DYT18, 1 DYT10, 1 DYT25) and 37 healthy controls. Subjects underwent 3D T1-weighted and diffusion tensor (DT) MRI. The human macroscale connectome was constructed from DT MRI. Tissue segmentation was performed on T1-weighted images using Freesurfer. The affected structural connections in DYT samples were investigated using Network-Based Statistic ($p < 0.01$, 10.000 permutations).

Results: Compared to healthy controls, asymptomatic mutation carriers showed a basal ganglia/frontal subnetwork characterized by decreased fractional anisotropy and increased mean diffusivity (MD) including the left putamen, precentral gyrus, middle and superior frontal gyri, middle temporal and insula. Clinically manifesting DYT mutation carriers showed an altered subnetwork characterized by increased MD connecting left putamen, middle and superior frontal gyri, orbitofrontal cortex, middle temporal, insula, and right anterior cingulate cortex. No differences were found between symptomatic and asymptomatic DYT subjects. A trend toward a greater disconnection was observed in symptomatic DYT1 and DYT6 subjects.

Conclusions: Our findings suggest that structural brain abnormalities in both clinically manifesting and non-manifesting DYT mutation carriers are distributed at a network level, beyond the basal ganglia/sensorimotor cortex regions. The identified subnetworks include dorsal frontal, insular and temporal cortices along with the basal ganglia and primary motor cortex. Studying of asymptomatic mutation carriers offered the possibility of identifying genotype-related trait characteristics without the confound of clinical symptoms. We conclude that analyzing the affected structural subnetworks may provide new insights into understanding DYT generation.

P28

Longitudinal Clinical and Brain MRI Changes in Multiple System Atrophy

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Introduction: Multiple System Atrophy (MSA) is a rare and rapidly progressive neurodegenerative disorder. The predominant clinical feature (parkinsonism [MSA-p] vs cerebellar ataxia). Longitudinal studies focused on clinical and MRI changes in MSA are still missing.

Objective: To assess clinical, cognitive, and neuroimaging brain changes in patients with MSA-p.

Methods: We enrolled 25 MSA-p patients and 21 matched healthy controls. Patients underwent clinical and neuropsychological evaluations and MRI scan at baseline and after a mean follow-up (FU) of 1.1 years. At baseline, MRI was obtained from controls. Changes in cortical thickness and diffusion tensor (DT)-MRI metrics of white matter (WM) tracts were assessed in MSA-p patients.

Results: During follow up, MSA-p patients showed a worsening of motor impairment, cognitive deficits and behavioural changes. At baseline, MRI study did not detect significant cortical and WM abnormalities in MSA-p patients compared with controls. After 1 year, MSA-p patients showed only a subtle, focal thinning of the frontotemporal cortices. Conversely, they showed significant, severe WM changes involving the corpus callosum, and frontotemporal and frontoparietal connections bilaterally (anterior>posterior). No longitudinal changes were observed in the infratentorial regions. In MSA-p, the progressive involvement of corpus callosum, external capsule, and long-range associative WM pathways bilaterally was associated with the worsening of cognitive deficits and behavioral changes.

Conclusions: This is the first longitudinal, multimodal MRI study of MSAP patients. In MSA-p patients, the progression of WM microstructural damage is prominent compared to cortical damage and may explain the worsening of cognitive and behavioural symptoms. DT-MRI has the potential to offer promising biomarkers for monitoring MSA-p and predicting the clinical evolution.

P29

Modeling trajectories of brain damage in Progressive Supranuclear Palsy: a longitudinal multimodal MRI study

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Introduction: Progressive Supranuclear Palsy syndrome (PSPs) is a rapidly progressive neurodegenerative disease. In PSPs a linear decline in frontal volume and the midbrain area, correlated to clinical decline, has been shown. However, no studies have explored white matter (WM) longitudinal changes in PSPs yet.

Objective: To study longitudinally clinical, cognitive, and neuroimaging changes in PSPs patients.

Methods: We enrolled 21 patients with Richardson's syndrome (PSP-RS) and 10 with PSP-parkinsonism (PSP-P). Patients underwent clinical and neuropsychological evaluations and MRI scan at baseline and after a mean 1.4 year follow-up (FU). Diffusion tensor (DT) metrics of WM tracts were assessed in both PSPs groups. Cortical thickness changes were investigated in PSP-RS patients. At baseline, 35 healthy controls underwent MRI.

Results: Both PSPs groups manifested significant motor and cognitive decline (PSP-RS > PSP-P). Apathy worsened in both groups, while depression and behavioral changes in PSP-RS only. At study entry, PSP-RS patients presented focal thinning of frontotemporal and cingulate cortices bilaterally, compared to controls. Over time, these areas and insular cortices showed a progression of thinning. PSP-RS patients exhibited baseline WM damage in midbrain, superior cerebellar peduncles, corpus callosum and main long-range tracts. At FU, damage progressed in corpus callosum, frontotemporal/-parietal connections, but not in infratentorial WM, and correlated with the worsening of disability and cognitive/behavioral dysfunction. At baseline, PSP-P patients had WM damage in the anterior corpus callosum, external capsule, corona radiata, and superior longitudinal fasciculus bilaterally, compared to controls; these same regions showed a subtle progression of damage during FU.

Conclusions: In PSPs patients, the progression of WM microstructural damage is prominent compared to cortical damage and it is related to the worsening of clinical symptoms. DT MRI offers useful biomarkers to monitor the progression of PSPs disease.

P30

Structural organization of the brain connectome in patients with psychogenic dystonia

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Introduction: Psychogenic dystonia (pDYT) is a controversial diagnosis. The neurobiological basis of psychogenic movement disorders remains poorly understood. It is increasingly recognized that disturbances of brain function do underlie the occurrence of these disorders.

Objective: Using diffusion tensor (DT) MRI, this study investigates the structural organization of the brain connectome in patients with pDYT.

Methods: The study involved 31 pDYT patients and 36 age- and sex-matched healthy controls. All subjects underwent 3D-T1 weighted and DT MRI. The structural connectome was reconstructed based on brain parcellation and whole brain DT MRI tractography. The affected structural connections in patients relative to controls were investigated using Network-Based Statistic ($p < 0.01$, 10.000 permutations).

Results: Compared to controls, pDYT patients showed a large brainstem/basal ganglia/frontal network (or principal connected component) with decreased fractional anisotropy (FA) and increased mean diffusivity including the brainstem, left thalamus, putamen, pallidum, pre- and post-central gyri, right caudate, and anterior cingulate and middle/superior frontal cortex bilaterally. The principal connected component included also some nodes in the posterior brain regions. Smaller secondary networks with reduced FA were found in the right hemisphere connecting the right pre- and post-central gyri to the thalamus and middle frontal areas. In pDYT patients, affected connections between the right thalamus and putamen and the right thalamus and precentral gyrus correlated with the total phenomenology subscore of the Psychogenic Movement Disorder (PMD) scale.

Conclusions: This study points toward a structural disconnection of the brainstem/basal ganglia/frontal brain networks in patients with pDYT. Altered structural connections between basal ganglia and primary sensorimotor cortex are associated with the severity and duration of the disease. Future longitudinal studies are warranted to clarify whether these abnormalities reflect a primary disease process in these networks or are secondary effects of the disorder.

P31

Structural and functional brain network alterations in psychogenic dystonia

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Introduction: Psychogenic movement disorders are a diagnostic and therapeutic challenge for clinicians.

Objective: The aim of this study is to explore the brain structural and functional MRI abnormalities in psychogenic dystonia patients.

Methods: This study included a large series of 31 psychogenic dystonia patients and 36 age- and sex-matched healthy controls. Subjects underwent 3D T1-weighted, diffusion tensor (DT) MRI, and resting state functional MRI (fMRI). Cortical thickness measures and subcortical grey matter nuclei volumes were analyzed using surface-based morphometry. Tract-based spatial statistics was applied to compare DT MRI metrics between groups. Resting state fMRI was analyzed using a model free approach investigating the main sensorimotor and cognitive brain networks.

Results: Compared to controls, psychogenic dystonia patients showed reduced volume of the right thalamus and caudate bilaterally, and thinning of precentral and frontoparietal cortices, bilaterally. They also showed a distributed pattern of decreased fractional anisotropy and increased mean diffusivity including the main motor and cognitive white matter tracts. Compared to controls, psychogenic dystonia patients showed a decreased functional connectivity of the right basal ganglia, insula and dorsolateral prefrontal cortex in the striatal-frontal network and of the precuneus in the default mode network.

Conclusions: This study shows that psychogenic dystonia is characterized by a structural and functional breakdown of motor and extramotor brain networks. Neuroimaging may improve our understanding of the functional and anatomical substrates of this condition and ultimately help developing new therapeutic strategies. Future studies comparing psychogenic dystonia with genetic dystonia patients may help to elucidate the primary or secondary nature of these abnormalities.

P32

The anatomical basis of genetic dystonia: a multimodal MRI study

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Introduction: The vast majority of dystonia (DYT) genotypes follow an autosomal dominant inheritance pattern with reduced penetrance but the mechanisms underlying disease development remain unclear.

Objective: The aim of this study is to investigate structural and functional alterations in asymptomatic and symptomatic DYT mutation carriers.

Methods: 9 asymptomatic DYT mutation carriers, 26 symptomatic DYT mutation carriers and 37 healthy subjects underwent 3D T1-weighted, diffusion tensor (DT) and resting state (RS) fMRI to study cortical thickness, white matter (WM) tracts damage, and functional network alterations.

Results: Compared to controls and asymptomatic DYT mutation carriers cases, symptomatic carriers showed cortical thinning of motor and frontal areas, bilaterally. Compared to controls, asymptomatic carriers showed increased mean (MD) and radial diffusivity (radD) and decreased fractional anisotropy (FA) of the main motor tracts, while symptomatic DYT mutation carriers showed decreased FA of the WM close to the right premotor cortex and a more widespread increase of MD, axial diffusivity, and radD involving the main motor and associative tracts. No DT MRI differences were observed between symptomatic and asymptomatic subjects. Compared to controls, symptomatic carriers showed reduced functional connectivity of insula and basal ganglia, and asymptomatic carriers cases a reduced connectivity of the fronto-insular areas.

Conclusions: Brain network alterations in asymptomatic carriers support the hypothesis that these changes are causative rather than an effect of the disorder. The analysis of the DT MRI eigenvalues, revealing a different pattern of abnormalities in symptomatic DYT mutation carriers and asymptomatic carriers, may gain insight into the possible determinants of penetrance. Whether different DYT mutations are associated with specific network changes remains to be tested in larger subject groups.

P33

Clinical features and functional imaging in seven cases of corticobasal syndrome.

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Background: Corticobasal syndrome (CBS) is a clinical phenotype characterized by a variable association of symptoms and signs both motor (asymmetric parkinsonism, alien limb phenomena, dystonia, myoclonus) and cognitive (dysexecutive syndrome, behavioural changes, memory impairment, cortical sensory loss, non-fluent aphasia). CBS is associated with different neuropathologies. In the clinical practice, antemortem diagnosis of underlying pathology in CBS is challenging, but may be improved by combining clinical and imaging findings.

Objective: To describe clinical presentation, clinical assessment, imaging findings and follow-up in a small cohort of patients with CBS.

Methods: We collected 7 patients with clinical diagnosis of CBS. All patients underwent clinical examination by neurologists expert in movement disorders, and scored using Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr (H&Y) stage. All patients underwent brain magnetic resonance imaging (MRI), 123I-Ioflupane single photon emission computed tomography (FP-CIT SPECT) and cerebral 18F-fluorodeoxyglucose positron emission tomography (FDG-PET).

Results: At clinical presentation, 6 patients had bradykinesia and rigidity; among them, 4 had an evident prevalence of side, 2 had also tremor (primarily postural), and 3 associated cognitive symptoms. One patient had an onset characterized exclusively by cognitive impairment. Apraxia was detected in 6 patients, 3 of which had a clear alien limb syndrome. 5 patients developed early cognitive decline, primarily involving executive functions. FP-CIT SPECT shown reduced uptake of the tracer both in putamen and in caudate nuclei. FDG-PET imaging demonstrated asymmetrical glucose metabolic reductions prevalent in cortical (frontal and parietal) and sub-cortical (striata and thalami) regions of one hemisphere, contralateral to the most affected side.

Conclusions: Clinical presentation of CBS is variable, but an accurate clinical and neuropsychological assessment may detect in the early stage of the disease the presence of asymmetric parkinsonism associated with dysexecutive syndrome and apraxia. FP-CIT SPECT and FDG-PET neuroimaging may represent a valid diagnostic support.

P34

Exploring the brainstem functions in cervical dystonia

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Introduction: Dysfunction of the inhibitory components along the motor system has been reported in patients with cervical dystonia (CD). We investigated the brainstem involvement, combining a multimodal reflex study to evaluate the segmental and suprasegmental functions in this condition.

Methods: 14 patients with CD and 14 sex- and age-matched healthy controls (HC) were recruited. The blink reflex (BR) including its recovery cycle (BRRC), trigemino-cervical reflex (TCR), and sternocleidomastoid exteroceptive reflex (SER) were recorded in all subjects. Demographical and clinical features were collected for all patients, including severity, pain, tremor and sensory trick.

Results: The polysynaptic component of the BR is prolonged in patients with CD compared to HC (iR2 32,86 vs 38,06 ms, cR2 33,04 vs 40,23 p < 0.001). BRRC is impaired at 100 ms (0,20 vs 0,40, p = 0.009) and 200 ms (0,27 vs 0,42, p = 0.038) intervals in CD. The P19/N31 component of the TCR is abnormal in all patients (p < 0.001). The SER was present in 31% of patients compared to HC (p < 0.001). Loss of inhibition at BRRC is correlated with history of disease (r = 0,672, p = 0.008), as well as clinical severity and the polysynaptic component of the BR (r = 0.713, p = 0.004).

Conclusions: We found either segmental than suprasegmental brainstem networks dysfunction in patients with CD. Loss of the suprasegmental inhibitory control is significantly correlated with duration of disease.

P35

An investigation of cerebrovascular lesions in dementia with Lewy bodies compared to Alzheimer's disease

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Introduction: Cerebrovascular lesions such as brain infarcts and white matter hyperintensities (WMH) on MRI are common in Alzheimer's disease (AD) dementia, but less is known about their frequency and impact on dementia with Lewy bodies (DLB). Furthermore, the pathophysiology of WMH is poorly understood, with potential contribution from both vascular and neurodegenerative pathologies.

Objectives: To assess the frequency and distribution of WMH and cerebral infarcts on MRI in patients with DLB and in a reference cohort of AD dementia patients, compared to a population based cohort of CN subjects. Our second objective was to gain some insight into the mechanisms underlying WMH by investigating its associations with the disease severity and the clinical features of patients with DLB.

Methods: White matter hyperintensities (WMH) and infarcts on MRI were assessed in consecutive DLB (n=81) and AD dementia (n=240) patients and compared to age and sex matched cognitively normal subjects (CN) from a population-based cohort.

Results: DLB had higher WMH volume compared to CN and WMH volume was higher in the occipital and posterior periventricular regions in DLB, compared to AD. Higher WMH volume was associated with history of cardiovascular disease and diabetes but not with clinical disease severity in DLB. Frequency of infarcts in DLB was not different from the matched CN and AD dementia.

Conclusions: In DLB, WMH volume is higher than AD and CN and has a greater posterior brain involvement. Its association with the history of cardiovascular disease and diabetes but not with the core clinical features of DLB suggests that vascular disease is influencing higher WMH volumes in patients with DLB.

P36

Anti-GAD antibodies: a possible link between corticobasal syndrome and Stiff Person Syndrome?

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A 62 year-old woman came to our attention because of different episodes of falls without loss of consciousness associated to dizziness and nausea started at the age of 53. After one of these falls, she complained of her left hand fingers being “stiff”, a condition that progressively worsened over years. Subsequently she described the acute onset of blurring of vision with diplopia in the left sight. An ORL visit revealed a rotator nystagmus in both eyes. She performed a cerebral MRI without evidence of focal lesions. Since she developed a mild plastic hypertone in the left upper limb and absence of pendular movement on the left side she performed a DAT-Scan in 2008 without evidence of striatal degeneration. Ropirinol was started but disrupted because of episodes of syncope and lack of clinical benefit. While hospitalized in our Neurology Department in 2010 a dystonic trait of the left hand with the hyperextension of the fingers, an ataxic gait and dysmetria of the upper left limb were noted. In the hypothesis of a spinocerebellar ataxia (SCA) she was tested for SCA 3-6-17 but no alterations were found. Levodopa therapy was started (300 mg per day) without a clear benefit. Because of her medical history of a thyroid goit, vitiligo and hives, several immunological tests were performed revealing a higher titer of antiGAD antibodies (up to 6908 UI/mL) and antiGM1 antibodies (962 UM). She started corticosteroid, followed by endovenous immunoglobulins and azathioprine without clinical benefit. Over the years she performed several neuroimaging studies, with evidence of cerebellar atrophy without supratentorial lesions, a cerebral PET (2013) showing hypometabolism of left cerebellar cortex, PEM and SSEP that were normal. The patient has recently completed the second endovenous Ig therapy without an important clinical improvement. The last AntiGAD antibodies determination revealed a decreased titer (65 UI/mL).

P37

Cognitive profile and presenting symptoms in Lewy body dementia.

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Objective: The study aim is to outline the Lewy body dementia (DLB) phenotypes as presenting symptoms and its correlation with cognitive profiles and clinical evolution of disease.

Background: DLB is the second most common cause of dementia in the elderly. DLB is clinically and pathologically related to Parkinson's disease (PD) and PD dementia, and the three disorders can be viewed as existing on a spectrum of Lewy body disease. Sleep disturbances as REM and NREM parasomnia are mostly represented in early DLB as in advanced phases of disease. The pattern of neuropsychological deficits seen in DLB is different to those of Alzheimer disease, with less marked memory impairment and more severe impairments of visuo-spatial, attentional and frontal-executive functions.

Methods: Seventy-one out patients with DLB have been collected from 2011 since 2014 among patients referring to the Parkinson's Disease and Movement Disorders Unit, Sleep Medicine Unit and Alzheimer Unit at the IRCCS C. Mondino National Institute of Neurology Foundation in Pavia, Italy. All the patients underwent to neurological and neuropsychological assessment.

Results: We divided the patients in three groups on the basis of presenting symptoms: twenty-four patients referred psychiatric/behavioural symptoms (that include REM behaviour disorders, confusional arousal, visual hallucinations, delirium and depression) as presenting symptom (group 1- G1); thirty-five patients referred parkinsonism (group 2-G2); twelve patients referred cognitive impairment (group 3- G3). The three groups differed in impairment of amnesic domain: 40% of G1 patients show amnesic impairment, 41% in G2 and 66% in G3. The G3 patients show a shorter disease duration than G1 and G2 patients.

Conclusion: The presenting features of DLB can be broadly placed in three categories: psychiatric/behavioural symptoms, parkinsonism and cognitive impairment. The presenting symptoms don't configure a different phenotype of disease. The patient that initially present cognitive impairment have earlier diagnosis and show, at the moment of diagnosis, more cognitive impairment in amnesic domain than the patients that initially present with non cognitive symptoms.

P38

Venlafaxine-induced akathisia: case report and review of the literature

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Background: Venlafaxine is a serotonin (5HT) reuptake inhibitor bicyclic antidepressant that also impairs the reuptake of norepinephrine (NE) and dopamine [1]. Here we report a case of severe akathisia after the initiation of venlafaxine.

Case presentation: A 58 years old lady presented a depressive disorder since 2008, treated with, imipramine, mirtazapine, valproate, and citalopram, all tapered off early in 2014 for her explicit will. In November 2014, for a relapse she was started on venlafaxine 37.5 mg. After 24 hours from the increase to 75 mg, the patient began to experience a severe inner restlessness. At admission to our clinic, in December 2014, she was restless, fidgety. She scored 8/9 on BARS [2].

Brain imaging, blood exams, cardiologic and Huntington's disease screening were negative. Venlafaxine-induced akathisia was diagnosed. After venlafaxine discontinuation, akathisia resolved in 2 weeks. She is to date taking sertraline 100mg daily, without adverse events.

Discussion: Only four cases of venlafaxine-induced akathisia have been reported to date [1;3-5]. Our case has the lowest dosage inducing akathisia in an adult women without comorbid conditions. The mechanisms of anti-depressive drugs related akathisia is complex. Since the mesocortico- limbic dopamine(DA)-ergic pathway projecting from the ventral tegmental area (VTA) to the prefrontal cortex is involved in akathisia [6], a serotonin increase, induced by venlafaxine, may produce an inhibition of dopaminergic transmission. Acting NA similarly to 5HT in reducing VTA DA-output, the selective impairment of NA and 5HT uptake might lead to a synergic negative effect on DA-ergic transmission.

This might also explain akathisia outbreaking under an SNRI drug such as venlafaxine, with no hyperkinetic disorder with a more selective SSRI such as sertraline.

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P39

Clinical and pharmacokinetics study to evaluate the therapeutic equivalence and bioequivalence of Levodopa Benserazide generic formulation (Teva Italia) versus the originator (Madopar®)

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Background: A number of generic preparations of Levodopa/Carbidopa and levodopa/benserazide preparations are available but bioequivalence and therapeutic bioequivalence studies with levodopa generics on the market in Italy are not available. Levodopa preparations differs from the “originator” for bioavailability or having different pharmacokinetic characteristics and may induce unpredictable OFF periods and worsening of dyskinesia. Increasing knowledge on generics characteristics and patients' clinical response to these drugs may be useful to optimize their use and increase doctors and patients confidence in generics.

Objectives: The primary objective of this study was to demonstrate the non-inferiority in improving motor symptoms measured by the Unified Parkinson's Disease Rating Scale (UPDRS) part III and bioequivalence in the primary pharmacokinetic (PK) parameter (total Area Under the Curve) of the generic levodopa/benserazide compared with originator.

Methods: The trial was an experimental two-centers, randomized, double-blind, two-sequence, non-inferiority cross-over study. This study enrolled 43 out-patients with a diagnosis of idiopathic Parkinson's disease, receiving stable dosages of Levodopa/Benserazide. The total duration of the trial was approximately 8 weeks for patient divided in two maintenance periods of 4 weeks each. A pharmacokinetic study with a fixed dose (100+25 mg) was performed in a sub-population of 14 subjects.

Results: The treatment with the generic drug was not inferior to treatment with the originator (95% confidence interval between -2,21 : 0,11). No statistically significant difference was found with respect to AUC_{0-t} (paired t-test P=0.69) and other PK parameters.

P40

A Phase 2A study of standard administration versus semicontinuous intra-oral administration of Levodopa/Carbidopa in patients with advanced Parkinson's disease

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Background: Continuous administration of standard Levodopa/Carbidopa (LCD) via duodenal infusion dramatically reduces motor fluctuations but requires surgical implantation of a PEG tube. We investigated whether a noninvasive approach using continuous intraoral delivery of LCD would safely reduce variability in plasma Levodopa concentrations.

Methods: This is a proof-of-concept study to assess the safety, tolerability, plasma pharmacokinetics and efficacy of intermittent LCD oral administration vs. semi-continuous intra-oral 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 neurologist-based assessment of motor state and dyskinesia by UPDRS Part III.

Results: Continuous intra-oral 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. Off time was reduced by 43% over the 8-hour observation period, from 2.20 to 1.26 hours ($p < 0.001$) and the UPDRS Part III score improved ($p = 0.010$). Off time was reduced in 15 patients, remained the same in 3 patients, and increased in 0 patients. No treatment-related adverse events were observed. There were no tolerability issues of any severity.

Conclusions: Continuous intra-oral 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 in patients with motor fluctuations.

P41

Mild Parkinson's disease patients: long efficacy of rotigotine. Clinical follow up

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It is already known the transdermal efficacy of rotigotine on reducing the parkinsonian symptoms. In a previous study we evaluated clinically and by gait analysis a cohort of 24 outpatients (mean age 71.3, SD 6.7) suffering from Idiopathic Parkinson's Disease. Clinical scale and gait analysis was performed always in the morning: at the beginning and after at least two weeks of stable administration of 16 mg of rotigotina system. Antiparkinsonian therapy was not changed in the time space between the two gait recordings. The data obtained before and after Rotigotine showed: Mean Velocity reduction ($p=0.005$): Swing R increase ($p=0.05$), Double support, R reduction ($p=0.02$); Stance L reduction ($p=0.02$); Swing L increase ($p=0.04$). Our data indicated the efficacy of rotigotina transdermal system for relieve the extrapyramidal signs; and supported the importance of long lasting action of dopaminergic stimulation. In this retrospective study, clinical follow up of the same cohort of PD patients, was performed after 1 and 2 years. 35% stopped the Rotigotine transdermal system after 1 year. At 2 years, 65% of PD patients were still in treatment with 16 mg Rotigotine and kept taking the same amount of L-Dopa (438 mg vs 445mg). Our data confirm the efficacy of the long lasting effect of continue dopaminergic stimulation.

P42

Non-endoscopic placement of PEG-J for Levodopa-Carbidopa intrajejunal gel therapy (LCIG): a long-term follow-up

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Objective: To compare the long-term clinical outcome after PEGJ for LCIG infusion inserted with interventional radiology techniques (IR group) or “conventional” endoscopic procedure (EN group).

Patients and methods: 42 patients with advanced PD were enrolled from 2 movement disorders clinics in Sardinia: 12 from Nuoro S. Francesco Hospital (IR group) and 30 from Cagliari Brotzu Hospital (EN group). Main outcomes were: procedure success rate, incidence of perioperative adverse events (30-day), long-term adverse events (i.e. dislocation or peristomal complications, malabsorption including evidence of polyneuropathy, severe weight loss), time span for PEG-J replacing and drop out.

Results: The baseline clinical characteristics (PD median duration, UPDRS scores, cognitive status) were comparable between the two groups. PEGJ placement was successful in 30/30 patients in EN group and 12/12 patients in IR group. Perioperative severe adverse events occurred in 1/30 patient in EN group and in 1/12 patient in IR group (in both case peritonitis). Major complications requiring reintervention were: colcutaneo fistula (1 patient, IR group) and peristomal granuloma (1 patient, EN group). Drop-out occurred in 7/30 (6/7 unrelated to device) in EN group, 4/12 (2/4 unrelated to device) in IR group. No evidence of polineuropathy or significant weight loss was reported in IR group while 2/30 patients of EN group showed axonal neuropathy. The mean time span for PEGJ replacement was 18 months in EN group, 12 months in IR group.

Conclusions: We observed a higher frequency of PEGJ drop-out and substitutions in IR group compared to EN group. However, PEGJ placement showed similar perioperative and late outcomes in both groups and was effective in providing an equivalent clinical improvement.

The IR technique might be considered as an acceptable alternative when LCIG is needed and traditional endoscopic procedure is not available or it is not viable for concomitant diseases of the upper digestive tract.

P43

Unilateral deep brain stimulation of subthalamic nuclei does not affect reactive inhibition in Parkinson's patients

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Objectives: The ability to stop a pending action is fundamental for survival because it allows to adapt to unpredictable changes in the external environment. Despite the importance of this executive function the roles of its neural substrates are still debated. It has been suggested that inhibitory control relies upon a right-lateralized network comprising the right subthalamic nucleus (STN) [1]. The aim of the present work was to assess its role.

Methods: We administered a countermanding reaching task to fifteen Parkinson's patients receiving deep-brain stimulation (DBS) of the STN either of the left (n=7) or of the right hemisphere (n=8), and to 20 age-matched subjects. We compared the performance of Parkinson's patients in two experimental conditions: DBS-ON, DBS-OFF.

Results: We found that inhibitory control is not improved when DBS are active, i.e. the reaction time to the stop signal (SSRT) is not significantly different in the DBS-ON versus DBS-OFF condition. Furthermore the SSRT did not differ according to the location of DBS, but, as expected, it was always significantly shorter in age-matched subjects than in patients.

Conclusions: Our results confirm that (i) reactive inhibitory control is affected by Parkinson's disease; (ii) only bilateral stimulation of STN restores the inhibitory control to a near-normal level [2], suggesting that the right STN does not play a key role.

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P44

Theatre is a valid complementary therapeutic interventions for emotional rehabilitation of Parkinson's patients

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Objectives: Whether art therapy can be a useful rehabilitative tool is a long standing and debated question [1]. In a previous study [2], we showed that after three years of theatre therapy Parkinson's patients significantly improved their emotional well-being in comparison to patients undergoing conventional physiotherapy for the same amount of time. The aim of this work was to replicate these findings, improving at the same time the efficacy of the treatment.

Methods: We run a randomized, controlled and single-blinded study lasted 1.5 years, on 24 subjects affected by a moderate form of idiopathic Parkinson's disease. Twelve were assigned to a theatre program in which patients underwent an 'emotional' training. The other 12 underwent group physiotherapy. Patients of both groups were evaluated at the beginning, and at the end of their treatments, using a battery of 9 clinical scales and 5 neuropsychological scales.

Results: We found that the 'emotional' theatre was extremely effective and allowed to improve emotional well-being of patients in only 1.5 years time. Conversely, control patients did not exhibit significant such ameliorations. Interestingly, both groups did not show improvements either in motor symptoms or in the cognitive abilities tested by the neuropsychological battery.

Conclusions: All in all, we fully replicated our previous results. Importantly we also found a form of theatre-therapy which allows to speed up the appearance of benefits.

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P45

Multidisciplinary Intensive rehabilitation treatment improves sensorimotor plasticity in wearing OFF in Parkinson's disease

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Introduction: Multidisciplinary intensive rehabilitation treatment (MIRT) has been proved to be effective to treat motor fluctuations in Parkinson's disease (PD). The neural correlates of effective MIRT in PD are unknown.

Objective: To evaluate the effect of MIRT on sensorimotor plasticity (SMP) during wearing-OFF in PD.

Methods: We included 9 PD patients (disease duration ≥ 3 and ≤ 8 years) with motor fluctuation and without dyskinesias, treated with a combination of levodopa plus dopamine-agonists or IMAO-B. Exclusions criteria were: age < 65 years, Montreal Cognitive assessment (MOCA) > 24 , presence of postural deformities, active psychosis. All patients were evaluated by UPDRS-III and tested by Transcranial Magnetic Stimulation before and after MIRT (>15 and < 30 days) in the wearing-OFF state (before assuming the second daily dose). A group of 10 healthy age-matched subjects also underwent TMS. SMP was induced by means of the rapid paired associative protocol (rPAS) which involves median nerve stimulation and TMS at an interstimulus interval of 25 ms, at 5 Hz for 600 stimuli. Motor evoked potentials were recorded at baseline and for 15 minutes after rPAS (T5,T10,T15).

Results: SMP was deficient in PD in wearing-OFF compared to healthy controls (main effect of group, $p < 0.0001$; time x group interaction, $p < 0.001$). SMP in wearing-OFF after MIRT was significantly improved in PD compared to evaluation before MIRT (main effect of group, $p < 0.0001$; time x group interaction, $p < 0.0001$); this was shown by a significant increase of MEP amplitude after rPAS in the post-MIRT state compared to the pre-MIRT state. Magnitude of increase of MEP after MIRT was correlated to decrease of UPDRS-III in wearing-OFF after MIRT ($p < 0.01$).

Conclusions: Our results demonstrate that MIRT improve motor disability in PD by shaping sensorimotor plasticity.

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Predictors of quality of life and caregiver burden in Parkinson's disease (PREDICT study)

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Introduction: Caring for a person with Parkinson's Disease (PD) is associated with an increased risk of psychiatric morbidity and persistent distress.

Objectives: The primary objective of this study is to evaluate the caregiver burden and its predictors among caregivers of PD subjects using the Zarit Caregiver Burden Interview (ZBI).

Methods: This cross-sectional, epidemiological study conducted in 13 Italian sites enrolled PD patients treated either with continuous dopaminergic delivering system treatments (either infusions with Levodopa/Carbidopa intestinal gel (LCIG) or subcutaneous apomorphine (CSAI) or continuing with the conventional oral therapy (SOC) and had a familiar caregiver. Subjects and caregivers quality of life was assessed through Parkinson's Disease Questionnaire on Quality of Life (PDQ-8) and ZBI.

Descriptive statistics, analysis of variance (ANOVA) and multiple regression linear analysis are presented.

Results. 126 patients (mean age 69.3±8 years) and their caregivers (mean age 57.9±12.9) were enrolled. Caregivers were mainly represented by spouses. Fifty-three patients were treated with LCIG, 19 with CSAI and 54 with SOC. The mean ZBI scores in the caregivers of the 3 groups were respectively 29.6±14.4 for LCIG group, 35.8±20.2 for CSAI, and 31.4±16.0 for SOC group. Caregivers of LCIG/CSAI/SOC patients showed no burden or mild/moderate burden in 74%, 53% and 63% of the cases, respectively. Mean PDQ-8 score were 11.25±5.67, 11.26±5.55, and 14.22±6.51 in LCIG/CSAI/SOC patients.

Clinical Global Impression-Global Improvement Scale (CGI-I) expressed by neurologists on the current therapy was considered "very much or much improved" in 89% of LCIG group, 58% of CSAI and 13% of SOC group.

P46 (segue)

The predictors significantly associated with caregiver burden at multivariate level were patients and caregivers judgment of quality of life and caregivers' need to change work.

Conclusions: Our findings suggest that caregiver burden is lower if the patients are treated with advanced therapies, such as LCIG, influencing quality of life.

P47

Effectiveness of two different intensive rehabilitative approaches (with and without Lokomat[®]) in patients with Progressive Supranuclear Palsy

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Introduction: Progressive Supranuclear Palsy (PSP) is the most common degenerative form of parkinsonism characterized by postural instability with recurrent backward falls, decreased step length and velocity, vertical gaze and pseudobulbar palsy, bradykinesia, axial rigidity and subcortical dementia. There is no pharmacological treatment for this condition and no defined rehabilitative approaches have been defined before. Previous data showed the efficacy of a Multidisciplinary Intensive Rehabilitation Treatment (MIRT) in patients with Parkinson's Disease (PD) but evidences in PSP subjects are lacking. Treadmill training (included in MIRT) has been shown to be useful in improving gait and balance in PD. Instead, few evidences indicate positive effect on the gait parameters with robot-assisted gait in PSP patients. In this scenario, the electromechanical-driven gait Lokomat[®] demonstrated its utility in neurological rehabilitation.

Aims: To evaluate the effectiveness of MIRT and whether the use of Lokomat[®] is helpful in the rehabilitation of PSP patients.

Methods: We recruited 24 PSP patients hospitalized in our ward for a 4-weeks MIRT (described in previous studies). 12 patients underwent MIRT (with treadmill training 5 times/week) and 12 underwent MIRT+Lokomat (Lokomat training 5 times/week). The outcomes measures were: PSP rating scale (PSP-RS), Six Minutes Walking Test (6MWT), Berg Balance Scale (BBS), Timed up and Go test (TUG), gait parameters (right and left stride lengths), stabilometric parameters (length, area and velocity of center of pressure).

Results: Total PSP-RS (including the sub-items for gait), 6MWT, BBS, TUG and right and left stride lengths improved significantly by the end of the training in both groups (MIRT and MIRT+Lokomat[®]). Results of the outcome variables for conventional MIRT vs MIRT+Lokomat[®] patients indicate that the effect of rehabilitation treatments was similar in both groups.

Conclusions: MIRT is effective for gait and balance rehabilitation in patients with PSP. Lokomat[®], compared with treadmill training, does not add benefits within MIRT approach.

Gender and non motor fluctuations in Parkinson's disease: a prospective study

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As Parkinson's disease (PD) progresses, non motor symptoms (NMS) can fluctuate either along or irrespective to motor fluctuations. Predictors of motor fluctuation have been extensively studied. Yet, the predictors of development of non motor fluctuations (NMF) are less clear.

Herein, we show the results of a prospective study on the relationship between NMF and gender along with other potential risk factors.

Early, drug-naïve patients with PD have been enrolled and followed up for 4 years since diagnosis. NMF were assessed with the 19-item Wearing off Questionnaire (WOQ-19). Associations were explored by means of multivariable logistic regression models for binary outcomes (WOQ-19 Total score ≥ 2 and WOQ-19 Non motor score ≥ 1) and multivariable ordered logistic regression models for ordinal variables (WOQ-19 Total score and WOQ-19 Non motor score). Models were adjusted for age of onset, NMS Questionnaire, UPDRS-III and Levodopa intake.

Fully completed WOQ-19 were available for 47 (16 women and 31 men) out of 75 patients enrolled, who, therefore, represented the cohort considered in the present study. At 4-year visit and according to the WOQ-19 Total score cut-off, wearing off symptoms were present more frequently in women [12(75%) versus 14 men(45.2%), $p=0.04$]. Accordingly, there was a trend towards significance for higher WOQ-19 Total scores in women compared to men [4(6) versus 1 (5), $p=0.06$]. NMF were more frequently reported by women compared with men [10(62.5%) versus 8(25.8%), $p=0.01$], with particular regard to anxiety, mood changes and pain ($p=0.05$, 0.03 and 0.01 respectively). Correspondingly, the WOQ-19 Non motor score was higher in women compared with men [1.5(3) versus 0(1), $p=0.01$]. No gender differences were detected in motor fluctuations. According to multivariable logistic regression models, female gender represented a risk factor for a diagnosis of NMF (adjusted odds ratio, AOR=5.33, 95%CI=1.21-23.4, $p<0.05$), but not for diagnosis of generic wearing off at 4 years (OR=3.66, 95%CI=0.8-16.8, $p<0.05$). According to multivariable ordered logistic regression models, at T4 women tended to develop higher WOQ-19 Non motor scores (AOR=4.58, 95%CI=1.23-17.03, $p<0.05$) but not higher WOQ-19 Total scores (AOR=2.88, 95%CI=0.86-9.71, $p<0.05$) compared to men.

We showed that female gender represented the most important risk factor for the development of NMF after 4 years since PD diagnosis, irrespective of levodopa intake, motor disability and NMS burden at diagnosis.

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Introducing “PD-Manager” European Project: a multicentre pilot study on 20 patients

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The EU funded project PD_Manager (Horizon 2020) aims to build and evaluate an innovative, m-health, patient-centric system to monitor Parkinson’s disease (PD). In this pilot study, we present the first data on 20 PD patients, obtained thanks to the collaboration of the involved partners (IRCCS Fondazione Ospedale San Camillo, IRCCS Santa Lucia Foundation and University of Ioannina – UOI, Greece). The purpose of this specific task of the project is to collect clear as well as defined raw motor data together with clinical observations, nevertheless raw data about non-motor aspects have been taken into account, such as cognitive abilities monitoring and speech analysis. Motor data have been collected using innovative pressure insoles, a smartwatch with specifically dedicated PD_manager App that analyzes data from gyroscopes and accelerometers, a smart-wristband and video recordings. A specifically developed Cognitive App, thought to monitor patients’ cognitive status, have also been tested. During the pilot study, we also have gathered data about the usability of technical devices and software and the feasibility of the recordings. To ensure a uniform and reproducible data collection between partners, a specific recording protocol has been drawn up.

The analysis of raw motor and non-motor data collected during this pilot study will be performed on the next steps of the Project. The devices showed a very good wearability and all patients showed interest in the possibility of an home-based monitoring of disease symptoms

P50

Olfactory dysfunction in de novo drug-naïve Parkinson's Disease: a resting state and DTI functional connectivity study

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Introduction: Olfactory dysfunction often manifests years before the development of parkinsonian motor symptoms. Resting-state fMRI and Diffusion Tensor Imaging (DTI) has been used to investigate brain function and connectivity.

Objectives: To assess the pattern of RS functional connectivity and microstructural damage of DTI examination, in de novo drug-naïve PD patients, related to olfactory psychometric test, to further elucidate olfactory-dependent cortical-subcortical functional networks.

Methods: We enrolled 30 de novo drug-naïve PD patients (UPDRS median motor subscores was 25, median disease duration was 1.8±1.1 years) and 30 sex-aged normal controls (NC). All subjects were not cognitively impaired. None of the patients took anti-parkinsonian drugs. Olfactory function was studied with the Sniffin' Sticks Test. The study was performed with a 3T MRI scanner.

Results: PD patients were hyposmic (TDI scores 19.2±1.9), if compared with NC (P<0.05). At MRI examination, all subjects did not present structural abnormalities. The caudate was the ROI defined to study olfactory-dependent RS functional networks in PD patients. The PD patients showed increased positive striato-cortical connectivity in the left frontal areas and decreased connectivity in the right occipital area. The cortical functional connectivity with the caudate was negatively correlated with the TDI scores in the bilateral frontal areas, left occipital area and precuneus. The DTI examination showed a decreased fractional anisotropy (FA) in bilateral orbito-frontal cortex, with close correlation with TDI score.

Conclusions: RS functional connectivity and microstructural damage differ according to olfactory performance in de novo and drug-naïve PD patients. A correlation analysis revealed that olfactory performance was negatively associated with cortical connectivity with the caudate. In addition, FA is decreased in olfactory cortical area. Our findings suggest that RS and DTI functional connectivity should be closely correlated with the level of olfactory performance, which could be used as predictive marker in de novo PD patients.

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Gender differences in autonomic cardiovascular modulation assessed by heart rate variability analysis among patients affected by Parkinson's disease

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Background: Previous studies have reported the presence of gender differences in motor and non-motor symptoms of Parkinson's disease (PD) patients. Among non-motor symptoms, autonomic cardiovascular disturbances represent a frequent cause of disability. To date, specific differences between male and female PD patients in cardiovascular modulation have not been extensively examined.

Objective: To investigate gender differences in cardiovascular dysmodulation in PD patients, we performed a study using heart rate variability (HRV) analysis.

Methods: An HRV study with a 24-hour ambulatory ECG recording was performed in two groups of PD patients subdivided for sex (13 male and 12 female patients) matched for age and duration of disease. A control group of 24 healthy subjects matched for age and gender was also enrolled. Among the HRV spectral parameters in the frequency domain, the values of low frequency (LF) and high frequency (HF), were assessed and expressed in normalised units (nu). The ratio of LF/HF power was also evaluated.

Results: Male PD patients showed a significant reduction of LF values both with respect to the control group (LF nu $46,75 \pm 12,95$ vs $62,22 \pm 14,79$; $p < 0,01$) and to the group of female PD patients (LF nu $46,75 \pm 12,95$ vs $55,28 \pm 9,81$; $p < 0,01$). Furthermore, HRV study showed a significant reduction of LF/HF in male PD patients with respect to female PD patients ($1,64 \pm 0,72$ vs $2,36 \pm 0,85$; $p < 0,01$). No significant differences were detected among male and female patients in HF parameter in the 24 hours.

Conclusions: We have identified the presence of specific gender differences in cardiovascular modulation among PD patients without orthostatic hypotension. These results confirm the importance of the accurate detection of gender differences in PD patients. In this regard, the presence of specific gender differences in cardiovascular dysmodulation might be useful to better predict the onset of possible dysautonomic symptoms and to improve pharmacological treatment, preventing cardiovascular side effects of dopaminergic drugs

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Gender effect on non-motor symptoms in Parkinson's disease: are men more at risk for most of them?

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Introduction: Non-motor symptoms (NMS) are common in Parkinson's Disease (PD) patients. Nonetheless, NMS are prevalent also in the aging population and only few studies compared their occurrence in PD patients and in the general population.

Aims: To evaluate the burden of NMS among PD patients with respect to the general population and possible gender differences in their occurrence.

Methods: The FRAGAMP study is a large multicenter case-control study. Patients affected by PD diagnosed according to the Gelb's diagnostic criteria were consecutively enrolled. Controls were gathered from among healthy people who accompanied non-parkinsonian patients and were matched by age and area of residence.

Sleep, gastrointestinal, urinary and sexual dysfunction were investigated using a standardized questionnaire. Cognitive impairment and depression were assessed using the Mini Mental State Examination and the Hamilton Depression Rating Scale respectively.

Results: The study enrolled a total of 585 cases and 481 controls.

Among PD patients, excepting for sexual dysfunction, almost all NMS investigated were more frequent among women; a close prevalence was recorded only for cognitive impairment and sleep disorders. However, when compared with the control population, logistic regression stratified by sex showed a higher risk of developing almost all NMS among men with ORs ranging from 2.52 (95% CI 1.54 - 4.11) to 37.3 (95% CI 5.12-271.40).

Conclusion: Compared with the normal aging population, our study shows a greater risk of developing NMS among PD men, probably due to a different background risk.

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Key role of gamma band frequency as underlying factor along levodopa-induced involuntary movements; evidence from 6-OHDA-lesioned rats.

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A solid experimental tradition has found, in rodents subjected to standard model of Parkinson's disease (PD), the dopamine (DA) depletion by 6-hydroxydopamine (6-OHDA), some specific electrophysiological alterations, which may underlie the development of dyskinesia, such as the loss of synaptic de-potentialization in striatal medium spiny neurons. However, evidence are accumulating in favor of the contention that also concomitant changes in extra-basal ganglia stations do participate to motor phenotypes and the occurrence of involuntary movements [1].

Here, we have investigated the distribution of beta (11-30 Hz) and gamma (50-60 Hz) bands in frontal cortex (CX) and globus pallidus (GP) of 6-OHDA-lesioned adult rats and studied, week by week, both histology and local field potential (LFP) discharge. To note, experiments were performed in freely-moving animals, hence avoiding artifacts.

Since the very first days following lesion (d4), an increased beta band occurred, synchronously, into GP and bilateral frontal CX, confirming its pathogenetic role underlying akinesia. On the other hand, when LD substitutive therapy (orally administered) took place, only rats exhibiting severe involuntary movements featured also a significant increase of the gamma band in the same macro-areas. A preliminary analysis of these data has been published recently [2].

Conclusions: Gamma-Band, already known as "prokinetic", may represent an electrophysiological counterpart of involuntary movements. Further studies are in progress to clarify the modulation of beta/gamma rebalancing by dopamine.

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Motor fluctuations indices in Parkinson's disease

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Background: Motor fluctuations are routinely identified in Parkinson's disease (PD) by clinical scales and self-reported tools whose short-cut and subjective nature of evaluation affects diagnostic accuracy of motor status. A prolonged observation for 12-hours, Waking-day Motor Assessment (WDMA), could be an appropriate tool for the clinical detection and quantification of motor fluctuations.

Objectives: To develop WDMA-based indices for quantifying motor fluctuations in PD.

Methods: Two independent samples of PD patients (exploratory population N=51 and testing population N=109) were examined. Patients underwent a WDMA and were evaluated for 12 hours by using the Unified Parkinson's disease Rating Scale (UPDRS). Motor conditions were reported as graphs. Six experts in movement disorders evaluated the WDMA-derived graphs and classified the 51 patients of the exploratory population as having or not motor fluctuations. To quantify motor fluctuations the Worsening Index (WI), the Mean Fluctuation Index (MFI) and the Coefficient of Variation (CV) were computed for each patient on WDMA-derived graphs. The optimal cut-off of each index distinguishing patients with or without fluctuations was calculated on the exploratory population. Indices cut-off accuracy was then verified in the testing population.

Results: In the 51-exploratory population optimal cut-off scores for the detection and quantification of motor fluctuations were identified for WI (8.34), CV (5) and MFI (12.9). Accuracy of the cut-offs verified in the 109-testing population showed a sensitivity and a specificity of 91.2% and 87.8% for the WI, 75% and 90.2% for the MFI, 69.1% and 95.1% for the CV .

Conclusions: Our study proved that the WI, the MFI and the CV represent sensitive and reliable indices of motor condition giving a specific and quantitative estimation of motor fluctuations in PD.

P55

A web resource on Levodopa-induced dyskinesia genetics

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Objective: Establish a web resource summarizing literature-based genetic information on levodopa-induced dyskinesia in Parkinson's disease.

Background: Levodopa induced dyskinesia (LID) is a very disabling side effect of therapy in patients with Parkinson's disease (PD). To date, only few publications have investigated the potential genetic predisposition and no central resource is available online to guide the planning of genetic studies.

Methods: An extensive literature search was performed in MEDLINE. Data regarding authors, sample size, age at PD onset, race and type of dyskinesia were extracted from the relevant publications. Genetic variations and the associated genes were annotated with their dbSNP and HGNC identifiers and an online resource was developed to present those curated LID data.

Results: The genetic variation data is presented in a textual and tabular form. A complementary visualization of the LID genes in an integrated dyskinesia network was generated by combining associations from protein-protein interactions, metabolic and signaling pathways, and functional annotations. Furthermore, users can upload their own lists of genetic variants or genes for analysis. In addition to incorporating the user-defined genes into the aforementioned LID network, the genes with the strongest associations to known LID genes can be identified by means of disease gene prioritization. All the results and the curated data are freely available for download.

Conclusions: We present the first online resource summarizing published variants and genes related to LID. The resource allows to easily retrieve information on LID genetics and verify whether certain mutations or genes of interest have been previously identified or linked to LID.

P56

Body distribution of rest tremor in Parkinson's disease

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Background: Rest tremor in Parkinson's disease has been more frequently reported in the upper limb. No study has systematically assessed the distribution of rest tremor in different body sites at disease onset and on follow-up.

Methods: We collected data on rest tremor localization at disease onset and on follow-up in 289 consecutive outpatients with early Parkinson's disease (scoring 1 to 2 on the Hoehn&Yahr stage).

Results: At disease onset, RT was present in 65.4% of patients and upper limb was the most frequent tremor localization. During the follow-up, RT spread to one or more new sites in 29.6% patients who had RT at disease onset. Analysis of patients who did not report RT at disease onset indicated 26% of new cases of RT (affecting more frequently the upper limb) appearing during the course of the disease; in this group rest tremor developed sooner in the upper limb than in lower limb or jaw/lips. During the follow-up, the time elapsing between disease onset and appearance of rest tremor was shorter than disease duration of patients who did not manifest rest tremor.

Conclusions: This study provides new information about body distribution and timing of rest tremor appearance during the early course of Parkinson's disease that may help clinicians to better counsel parkinsonian patients with regard to rest tremor.

P57

Urinary dysfunction in Parkinson's disease patients

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Background: Autonomic nervous system dysfunction that affects 70–80% of Parkinson's disease (PD) patients, causes significant morbidity and it is correlated with poor quality of life.

Objective: We assessed in a consecutive series of PD patients frequency of autonomic symptoms by means of the Scale for Outcomes for Parkinson's disease AUTonomic (SCOPA-AUT) and we correlated it with the results of noninvasive urological studies (nUS).

Methods: PD patients with known conditions that might have influenced urinary function were excluded. Clinical assessment of PD patients included the H&Y staging, UPDRS, BDI, NPI, PDQ-39, PDSS, ESS, and the SCOPA-AUT scale. nUS consisted of uroflowmetry and ultrasound of the urinary tract with measurement of postvoid residual (PVR) urine volume. The quantitative parameters measured during the voiding phase included maximum flow rate (Qmax) and postvoid residual (PVR).

Results: 45 PD patients (26 males and 19 females) were included (mean age at interview 62.1 ± 10.6 ; mean disease duration: 6.5 ± 4.3 years). PD patients had a mean SCOPA-AUT score of 14.1 ± 7.1 . PD patients with urinary dysfunction, had higher SCOPA-AUT scale score, longer disease duration and an higher dosage of levodopa calculated as levodopa equivalent dose (LED). At least one clinical symptom of dysautonomia was found in all of our PD patients and urinary symptoms were the most common complain (92.8%). The mean Qmax was 17.9 ml/s (SD 9.1 ml/s), and the mean PVR was 33.7 ml (SD 68.7 ml), with no patient having a PVR>200 ml. Ultrasound documented possible causes of urinary disorders in 44% of patients (prostate hypertrophy was observed in 11 of 26 males).

Conclusion: Our findings suggest that urinary symptoms and abnormal findings in nUS are common in PD patients. The autonomic dysfunction might be related to nigrostriatal degeneration, though urinary dysfunction in patients PD could be, especially in males, attributed to other conditions.

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Pisa syndrome in a drug-naïve Parkinson's disease patient

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Introduction: The term Pisa Syndrome (PS) is used to indicate a tonic lateral flexion of the trunk often associated with slight spinal rotation along the sagittal plane, described in patients on neuroleptic drugs and in idiopathic Parkinson's disease (PD) patients on dopaminergic drugs, but never been described in drug-naïve PD patients as a presenting symptom. We report on a patient who presented a reversible PS without any dopaminergic treatment at onset and before PD diagnosis.

Objective: Demonstrate that Pisa Syndrome may be present at the onset of Parkinson Disease and not only in the complicated and overtreated disease forms.

Methods: A 81-year-old woman presented with a 1-year clinical history of PD and no history of trunk lateral flexion. At the neurological examination, she presented a moderate lateral flexion to the right side alleviated completely by passive mobilization or on lying supine, compatible with a diagnosis of PS. Brain MRI was normal, while ^[123I]FP-CIT-SPECT showed a marked reduction of tracer uptake of the right side of putamen.

She was then treated with levodopa/benserazide with beneficial effects on motor rigidity and tremor, and satisfactory improvement of trunk flexion.

Results: The diagnosis of PS requires a pronounced (at least 10°) lateral flexion, which can be alleviated by passive mobilization or on lying supine.

The onset of PS in PD patients has been described following a change in dopaminergic treatment, on the contrary, the introduction of central dopamine receptor blockers. In most of these cases, PS often represents a motor complication of advanced forms of disease.

Conclusions: This report shows that PS may be present at the onset of PD and in addition to cardinal motor symptoms. In this case, the response to dopaminergic treatment and the asymmetry showed in the brain ^[123I]FP-CIT-SPECT, omolateral to the direction of truncal deviation, strongly suggests a mechanism of dopaminergic unbalance as a probable key factor in the development of this postural disturbance.

P59

Malignant Syndrome-like heatstroke evoked by exposure to high temperature in a complicated parkinsonian patient

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Introduction: Malignant Syndrome (MS) in Parkinson's disease (PD) and heatstroke share many clinical features and are both characterized by severe hyperthermia [1]. We report the case of a PD patient that during the heat wave "Flegetonte" developed a MS-like heatstroke.

Case report: The patient was a 77-year-old man with a twelve year history of PD complicated with motor fluctuations, consistent peak-of-dose and biphasic dyskinesias. After the exposition for two hours to high temperature the patient developed a progressive and severe alteration of consciousness till the stage of coma associated with hyperthermia (42°C), tachycardia and massive dyskinesias of the limbs and trunk. The patient was under therapy with Levodopa/Carbidopa 100/25 mg twice a day, melevodopa 125/12,5 mg twice a day, rasagilina 1mg/day, pramipexole PR 2,1 mg/day, amantadine 300 mg/day but no variation in therapy in the period before the accident were detected. Laboratory tests showed for several days elevated serum CK levels until 1564 IU/L, piastrinopenia and prolonged PT-INR values. Hemoculture, urinoculture, CSF analysis, chest X-ray and brain CT were all normal. The patient was intubated and hydrated with intravenous fluid and ice pack application.

Dyskinesias decreased with continuous infusion of Midazolam. The therapy for PD was administered trough nasogastric tube. After three weeks the recovery of consciousness was excellent but cognitive impairment and dysarthria worsened from the pre-existing state.

Discussion: We described a MS-like heatstroke in a PD patient in an advanced stage. Besides weather conditions some other factors could be involved in the development of this syndrome, such as thermoregulation disturbances [1], the presence of dyskinesias correlated to long term treatment with levodopa [2] and also the anti-cholinergic effect of a chronic therapy with amantadine [3].

Conclusion: Considering the global warming of the planet and the possible risk of MS-like heatshock in PD patients, it may be useful to adequately inform PD patients about this risk.

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P60

The relationships of pain to motor and non-motor symptoms in Parkinson's Disease

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Background: The pathophysiology of pain in Parkinson's disease is unknown. Previous studies raised the possibility that the dopaminergic system and/or motor manifestations could contribute to pain mechanisms. No study has explored the relationships, if any, between pain and other nonmotor parkinsonian symptoms, an information that may be relevant to better understand the mechanisms of pain in Parkinson's disease.

Methods: Three-hundred and twenty-one consecutive patients affected by Parkinson's disease (190 men/131 women aged 68.3 (SD, 9.2) years) attending four Italian movement disorder clinics were studied. Demographic and clinical data were obtained by means of a standardised interview and non-motor symptoms questionnaires. Logistic regression models with pain as the outcome variable were used to check the association with motor and nonmotor symptoms.

Result: On study time, 180 PD patients (56%) reported chronic pain. In most cases (56%) pain was described as musculoskeletal pain more frequently affecting leg/foot (33%). Pain preceded the onset of motor signs in 36/180 patients. On univariate analysis, pain was associated with female sex and with higher HY staging, UPDRS-III axial symptom score, and frequency of medical conditions associated with or predisposing to pain. Cardiovascular, sleep/fatigue, mood/cognition, attention/memory, and urinary disturbances were significantly more frequent in the pain group. In the main effect model, female sex, medical conditions predisposing to pain, sleep disturbances, and mood disorders were independently associated with pain. Although significantly associated with pain on univariate modelling, measures of motor severity (UPDRS-III scale and HY staging) did not contribute to the main effects model, which probably resulted from confounding by other variables.

Conclusions: Our study confirms that pain in Parkinson's disease is more frequent in women and in subjects with medical conditions predisposing to painful symptoms, and strengthens the association of pain with sleep/mood disturbance rather than with severity of motor signs.

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Usefulness of the frailty concept applied to non-motor symptoms of Parkinson's disease: a preliminary study

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Introduction: Frailty has been recognized as a clinical syndrome resulting from ageing associated with a decrease in the body's physical and psychological reserves. Frailty and Parkinson's disease (PD) are clinically distinct entities with differing underlying pathophysiology. Nonetheless, they share a predilection for the elderly, and the appearance of physical vulnerability. Indeed, frailty can be confused with poor therapeutic control of PD, and, conversely, PD patients can be mistakenly considered frail.

Objective: To consider the appropriateness of the frailty construct applied to non-motor symptoms in PD and provide information about the relationship between frailty and cognitive impairment.

Methods: Eight idiopathic PD patients receiving levodopa treatment and presenting motor fluctuations (M/F= 6/2; age mean±SD= 60.3±5.7 years; MMSE mean ±SD= 27.59±1.80) underwent a preliminary neurological assessment (MDS-UPDRS, NMSS). An extensive neuropsychological battery including screening test (such as MMSE and FAB) was administered. Neuropsychiatric aspects were investigated using questionnaire on behavioral mood changes. Frailty was assessed using a Comprehensive Geriatric Approach involving the Multidimensional Prognostic Index (MPI).

Results: We found a severe level of non-motor symptoms as measured by NMSS scale. While 75% of the sample was classified as pre-frail (MPI mean±SD = 0.18±0.11), 25% were frail (MPI mean±SD = 0.38±0.00). Frail-PD subjects show worst executive functions as measured by the FAB and exhibit selective attention deficit.

Conclusions: Selective attention seems to be a potential marker of cognitive frailty associated with ascertained physical frailty in PD. Our piloting study suggest the need to focus on this syndrome in PD and encourage further investigation into the clinical, neuropsychological and pathophysiologic links between these two disorders. PD does not assure a diagnosis of frailty, however identifying frailty in PD subjects may have prognostic and therapeutic implications.

P62

Genotype-phenotype paradoxes in an Italian family with asymptomatic homozygous and symptomatic heterozygous carriers of a Parkin multiexon duplication

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Biallelic mutations in Parkin gene are the commonest cause of autosomal recessive early-onset Parkinson disease (EOPD), with full penetrance and frequency inversely correlated with onset age. Conversely, single heterozygous Parkin mutations are detected both in PD patients and healthy subjects, and are considered as minor susceptibility factors towards the risk of sporadic late-onset PD.

We report a 41-year-old male patient presenting a rigid-bradykinetic form of EOPD (onset at 36 years), with slow progression and good levodopa response, who was found to carry three copies of Parkin exons 2 and 3. No further mutations emerged from a comprehensive genetic screening of EOPD genes. To define the allelic distribution of the two exon duplications, mutation analysis was proposed to available relatives, all reportedly healthy. The duplications were excluded in the patient’s mother and brother but, surprisingly, four copies of exons 2 and 3 were identified in the paternal aunt (father was unavailable). Familial segregation demonstrated that the patient was heterozygous for exon 2-3 duplication (in cis on the same allele), while the asymptomatic aunt, aged 71 years, was homozygous for the same duplication. A detailed examination of this lady failed to identify parkinsonian signs, and only disclosed a postural-kinetic tremor and dystonic posturing of her right hand during writing. Conversely, the phenotype of the heterozygous nephew resembled a typical form of EOPD as seen in carriers of biallelic Parkin mutations, while the same heterozygous exon 2-3 duplication has been so far detected in occasional patients with sporadic late-onset PD.

This paradox underlines the difficulty in establishing genotype-phenotype correlates, and confirms that monogenic disorders are more complex than previously thought. The identification of genetic, epigenetic or environmental factors able to modify the penetrance and expressivity of single gene mutations represents the great challenge of genetic research.

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Telemedicine and Parkinson's disease: a pilot study

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Travel distance, disability, uneven distribution of neurologists limit access to care for most PD patients worldwide. Telemedicine, i.e. the use of telecommunications technology to deliver care at a distance, can help overcome these barriers. It permits a convenient and reliable communication between patient and medical staff, and the transmission of laboratory and imaging data.

PD appears suitable for telemedicine because patient/doctor interaction is primarily visually-based. An almost complete clinical evaluation (including cardinal features such as hypomimia, tremor, dyskinesias, bradykinesia) can be afforded through videocontact. Moreover it's possible to check some activities (tapping, walking, balance, prono-supination).

Our study will assess feasibility and efficacy of remote clinical evaluations in order to reduce formal outpatient visits in the hospital, together with the degree of satisfaction of both medical staff and patient/family.

5 Movement Disorders specialists will take part in the study. Internet connection and laptop will be available at Parkinson Puglia Association bureau. 20 PD patients already known by one of the 5 specialists and treated on a routine outpatient practice, are expected to be enrolled. Two visits for each patient are planned.

An internet connection with a webcam and a secure web-based videoconferencing software (for example Skype) will be required. The "visit" will essentially be a secure videochat, the neurologist will confirm or modify the drug therapy and eventually discuss new treatment options such as, continuous drug infusion, surgery, rehabilitation.

The duration of the study is nine months (January-September 2016). At the end of this period, patient/caregivers and doctors will complete a questionnaire specifically designed to test the degree of satisfaction of both figures related to their experience with telemedicine.

A final study report will be developed at completion of data analysis. This report will be a clinical statistic integrated report related to time, cost, stresses, and reduction of distance travel through the use of telemedicine.

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Reckless driving as Impulse Control Disorder in Parkinson's Disease: case report

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Introduction and Objectives: Impairment of risk perception in Parkinson's Disease (PD) as a result of dopaminergic denervation of meso-limbic and meso-cortical pathways, often plays a crucial role in generating impulse control disorder, (ICDs) leading the patient to overestimate benefit and rewards towards the risk, even in daily-life activities. Driving is certainly a task in which an accurate risk evaluation is crucial for every single action. Since now, in literature are reported only few case of patient with PD who experienced a pathological change in driving behaviour in the setting of dopamine-disregulation syndrome.

Material and Methods: We present the case of a 69 years old male patient with Parkinson's Disease diagnosed 5 years before and treated with L-Dopa 450 mg/die, L-Dopa modified release 100 mg/die, rasagiline 1 mg/die and ropinirole extended release 4 mg/die (LEDD: 700 mg/die), with good response (UPDRS III: 3/108), complaining only of apathy, anxiety and fatigue.

In April 2015 patient, since then reported as a careful and reflexive driver, begin to show inappropriate and reckless behaviour while driving, especially during yielding and overtaking, and generally travelling at high speed. Caregiver reported also a sort of taste for thrilling situations while driving, conversely patient didn't notice any disturbances, being annoyed of passengers' complaints. In the same period pathological gambling begin to emerge.

Ropinirole was downtitrated and then withdrawn and replaced with L-Dopa , quetiapine was added to therapy, with full resolution of both gambling and driving behaviour.

Conclusions: Reckless driving can be considered as a uncommon but dangerous form of ICD, sharing with pathological gambling an impaired risk evaluation, and the perception of thrilling and risky situation as rewarding. Early identification and recognition of reckless behaviours in patient with PD can help to diagnose and prevent the onset and of ICDs.

P65

Creative thinking and parkinsonism: preliminary clinical data on the role of frontal area.

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Objective: To evaluate divergent thinking (DT) by means of Abbreviated Torrance Test for Adults (ATTA) in parkinsonism (PKS) with different deficit in cognitive functions.

Background: Creativity is a complex phenomenon and generally defined as the ability to generate ideas that are both original and useful in a particular social setting. Poor DT was found in patients with fronto-temporal dementia (FTD). No data have been collected in patients affected by PKS i.e. progressive supranuclear palsy (PSP), multiple system atrophy (MSA).

Methods: Three groups of consecutive out-patients affected by PSP (N=10), MSA (N=10) and PD (N=10) were included. All patient groups were matched for gender and age at assessment. We included a control group (HC, N=10) matched for gender and age. Inclusion criteria were: MMSE >24. All patients and HC were no professional artists. Patients treated with atypical and typical antipsychotics, lithium, deep brain stimulation, duodopa and apomorphine infusions were excluded. Creativity was evaluated by means of the ATTA. Neuropsychological evaluation included MMSE, Frontal Assessment Battery (FAB), Geriatric Depression Scale (GDS).

Results: ATTA total score was significantly lower in PSP group when compared to the other groups (P-value <0,05). ATTA total score in MSA group although lower was not significant different when compared to PD and HC. ATTA sub-score for Fluency, Elaboration and Originality were significantly lower in PSP when compare to MSA e PD. No differences were found between PD and MSA groups. FAB adjusted score was significant lower in PSP when compared to the other study groups. GDS was similar in all study groups.

Conclusion: DT measured by means of ATTA seems compromised in PSP when compared to the other study groups and correlated to frontal functions abilities.

P66

Reliability and validity of Italian version of the Dimensional Apathy Scale in Parkinson's Disease

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Introduction: Apathy is a non-motor symptom of Parkinson's Disease (PD). The prevalence rate of apathy ranges from 13.9% to 70% in PD. Since an association between high level of apathy and more severe motor symptoms was reported in PD patients, the evaluation of apathy in PD could be influenced by motor disability at different stage of diseases. Recently, Dimensional Apathy Scale (DAS) has been developed to evaluate and measure apathy and its aspects in patients with neurological disorders excluding possible confounding effects of motor impairments.

Objectives: The aim of the present study was to explore reliability, factor structure, divergent and convergent validity of the Italian version of the DAS (I-DAS) in non demented PD patients.

Methods: To achieve this aim, we recruited 107 non-demented patients with diagnosis of idiopathic PD who underwent the I-DAS, the self-report version of the Apathy Evaluation Scale (AES), the Beck Depression Inventory-II, Parkinson Anxiety Scale (PAS) and Mini Mental State Examination (MMSE). Internal consistency, convergent and divergent validities were evaluated. Construct validity was examined by Principal Components Analysis (PCA).

Results: In PD sample, the I-DAS showed high internal consistency (Cronbach's alpha=0.871). The main score of I-DAS were 25.25 (standard deviation: 12.7) and median was 23. The correlation between I-DAS and AES were positive and moderate ($r=0.539$, $p<0.001$) indicating a good convergent validity. As for divergent validity, I-DAS scores correlated moderately with BDI-II score and poorly with the PAS and the MMSE scores, indicating good divergent validity. The I-DAS showed three factorial structure similar to the original DAS.

Conclusions. In conclusion, our study showed that the I-DAS had good psychometric properties in PD. Since apathy is a common non-motor symptom in neurodegenerative diseases, the I-DAS can be a valid and reliable tool to assess multidimensional apathy in PD patients.

P67

Cognitive assessment in early Parkinson's disease: role of anxiety and depression

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Introduction: PD patients suffer from a variety of non-motor symptoms, including cognitive and neuropsychiatric disturbances. Also, in the early stages of PD, neuropsychiatric symptoms and cognitive alterations involving functions based on frontostriatal loops linking the caudate and ventral striatum to distinct portions of the prefrontal cortex are frequently observed.

Objective: We assessed whether anxiety and depression affected impulsivity traits and executive functions in PD de novo.

Methods: Thirty PD de novo patients (mean age of 67.9±6.08 years) were consecutively enrolled. The neuropsychological evaluation consisted of Montreal Cognitive Assessment (MOCA) for global assessment and Wisconsin Card Sorting Test (WCST) to evaluate executive functions. Depressive and anxiety symptoms were evaluated using Beck Depression Inventory (BDI-II) and Anxiety (Ham-A) and impulsivity using Barratt Impulsiveness Scale 11 (BIS-11). Correlations between variables were computed by Spearman's coefficient. We performed a multiple regression analysis which revealed the influence of demographic and clinical variables on the patients.

Results: Patients did not show significant cognitive impairment (MOCA 26.07±2.45), however they presented alterations in executive functions (WCST global score 110.1±28.06). The mean BDI-II scores was 16.87±5.47 whereas the mean HRS-A was 17.03±5.42. The mean BIS-11 score was 61.83±8.28. However we obtained a higher correlation between BDI-II and BIS-11 cognitive impulsivity score ($r=0.49$; $p=0.0006$). We also observed a significant correlation between HRS-A and BIS-11 attentional impulsivity score ($r=0.57$; $p=0.001$). No significant correlation between executive functions and neuropsychiatric disorder (impulsivity, anxiety and depression) was found. Multiple regression analysis showed that the clinical condition of the patients has not a significant impact on scores of all BIS-11 subscales. Age, education, BDI-II and HRS-A did not influence performance of any subscale.

Conclusion: Our results showed that depression and anxiety were correlated to cognitive impulsivity but not to executive functions in PD de novo.

P68

The role of Vitamin D levels on neuropsychological profile of patients with Parkinson's Disease

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Introduction: Vitamin D may have effects on symptoms of Parkinson's Disease (PD) and perhaps even on the risk of disease development or disease progression. Only one cross-sectional study in PD patients investigated the role of vitamin D levels on neuropsychiatric functions and found that higher plasma vitamin D is associated with better cognition and better mood in PD patients without dementia.

Objective: This prospective longitudinal study was performed to investigate whether low vitamin D levels at baseline are predictors of poor cognitive performances and more severe apathy and depressive symptomatology in PD patients after two years.

Material and method: A sample of 48 untreated, drug-naïve PD patients was enrolled in the study. At baseline (T0), serum 25-hydroxyvitamin D and severity of motor symptoms were examined. Moreover, neuropsychological profile was assessed by cognitive tests assessing long-term memory, executive functions, visuospatial functions; Hospital Anxiety and Depression Scale (HADS) and Apathy Evaluation Scale (AES) to assess severity of depressive symptomatology and apathy. After two years (T1), 40 PD patients were evaluated and underwent the same neuropsychological battery administered at T0.

Results: At baseline, low vitamin D levels correlated significantly with poor cognitive performance on verbal immediate and delayed recall tasks, phonological fluency task, semantic fluency task, and with high score on HADS and AES. Linear regression analysis showed that low vitamin D levels contribute to poor performance on cognitive tasks assessing long-term memory, semantic fluency and high score on HADS and AES. Moreover, we found that low vitamin D level recorded at T0 correlated significantly with poor performance on immediate verbal recall, semantic fluency task, interference task of Stroop Test, and with high level of cognitive apathy evaluated at follow-up. Linear regression analysis showed that low vitamin D levels were associated significantly with poor scores on cognitive tasks assessing long-term memory, semantic fluency and with high level of cognitive apathy.

Conclusions: Lower level of plasmatic vitamin D at baseline is associated with higher apathy and worse performance on cognitive tests assessing mainly frontal/executive functions at both baseline and follow-up assessment in PD. Therefore, our findings suggested that lower vitamin D levels may be a biomarker of dysexecutive syndrome in early PD patients.

P69

Clinical and neuropsychological characterization of very late stage Parkinson's disease

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Introduction: During the last decades, the advanced therapeutic options for Parkinson's Disease (PD) have led to significant improvement in the treatment of motor symptoms, highlighting issues related to the non-motor features and the multi-systemic nature of the disease

Objectives: To analyze the characteristics of very late stage PD (>35 years of disease) in a selected group of patients treated with subthalamic nucleus-DBS (STN-DBS)

Methods: Five young-onset patients with average disease duration of 36.6 ± 2.2 years were enrolled. Neurological assessment included: Unified PD Rating Scale (UPDRS), Non-Motor Symptoms Scale and Questionnaire, electrophysiological study (including autonomic tests), neuro psychological tests and PD Questionnaire-39. Moreover, patients underwent an otorhinolaryngological evaluation and a comprehensive cardiologic assessment. Brain MRI, [^{123}I]FP-CIT SPECT and cardiac [^{131}I]MIBG scintigraphy were also obtained.

Results: Age and DBS duration were 71.2 ± 5.2 and 14.5 ± 1.7 years. All patients demonstrated a sustained motor response to dopaminergic treatment and STN-DBS, with average UPDRS-III improvement of 56.8%. All patients had constipation and hyposmia. Three patients reported urge-incontinence. RBD was present in 4 subjects, as well as speech impairment; 3 patients had drooling and mild dysphagia. Autonomic tests were altered in 3 subjects, only in one case associated with symptomatic orthostatic hypotension. Cardiovascular examinations were normal in all patients. Two subjects had mild sensory and one sensory-motor axonal polyneuropathies. One patient was demented, one had a single- and one a multiple-domain PD-MCI. All patients presented severe alterations of DaTSCAN and [^{131}I]MIBG scintigraphy. PDQ-39 scores showed that mobility, cognition and communication problems were the main responsible of quality of life impairment.

Conclusion: The sustained control of motor symptoms achieved with the advanced therapies, even after many years of PD, allows a better understanding of the disease evolution in its very advanced phases, demonstrating that the disability is mainly due to the progressive worsening of non-levodopa-responsive symptoms, non-motor symptoms and cognitive decline.

P70

Attention deficit hyperactivity disorder prevalence in Parkinson's disease with impulse control disorders

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Background: Parkinson's disease (PD) and Attention Deficit Hyperactivity Disorder (ADHD) share several genetic, physiopathological and clinical aspects: these common issues concern impulsivity, which can lead to Impulse Control Disorders (Dopamine Dysregulation Syndrome, pathological gambling inappropriate sexual behaviour, compulsive buying) in PD. This study aims to explore the connection between ADHD and PD.

Methods: Fifteen patients affected by PD in several stages of the disease and ICDs were compared to fifteen patients affected by PD without ICD. The two groups were matched for sex and age. Patients were assessed for ADHD with ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist and Diagnostic Interview for ADHD in Adults 2.0. Impulsiveness was assessed using Barratt Scale of Impulsiveness (BIS).

Results: Our preliminary data showed a prevalence of ADHD of 30% in the group of patients affected by PD with ICDs and 0% in the group of patients affected by PD without ICDs. Data also showed a significant difference between the BIS scores in the two groups and the dose of dopaminergic drugs ($P < 0,01$) and a significant correlation ($P < 0,01$) between BIS score and dopaminergic therapy dose (both higher in ICD group).

Discussion: Although in our preliminary data in a small sample of patients the difference in ADHD prevalence between the two groups was not statistically significant ($P > 0,05$), we assume that, extending the study to a wider population, we may demonstrate the presence of a significant correlation between these two clinical conditions.

P71

The affective value of faces in patients with Parkinson's disease

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Background: Although the motor symptoms of Parkinson's Disease are well known, this condition is also associated with a spectrum of non-motor dysfunctions, such as cognitive impairment (memory and executive functions) and neuropsychiatric disturbances (depression, anxiety, apathy, and emotional dysregulation) occurring also in PD patients who do not have overt dementia. In addition, difficulties in affective and emotional processing have also been reported in PD patients. We aimed to study different aspects of facial expression evaluation in a group of not demented PD in treatment with common antiparkinsonian drugs, matched for sex, age, and education served with healthy subjects.

Methods: In the study were enrolled 30 patients (13 male; age mean 63.3 ± 6.7 ; age range 46-73, onset of the disease mean 56.5 ± 7.1 , range 40-70, duration of the disease 6.7 ± 2.6 , range 2-12) with PD under dopaminergic replacement therapy and 30 healthy controls (HC) with negative neurological and psychiatric history. Patients were assessed for neuropsychological and psychological profile in their optimized medication-on condition (MED ON).

Results: The total number of errors in facial emotion recognition task is higher ($p < 0.001$) in patients than controls and it is due to errors in identifying sadness ($p < 0.001$), anger ($p = 0.02$) and fear ($p < 0.001$). There are not significant differences between the two groups in the total amount of activation, valence (pleasantness), and intensity. The total number of errors correlates with the level of depression ($r = 0.37$ $p < 0.01$). This is mainly due to the emotional tones of fear and sadness, respectively $r = 0.41$ and 0.38 ($p < 0.01$).

Conclusion: In the course of PD, non-verbal emotional information processing is disturbed. This suggests that in PD, nigrostriatal dopaminergic depletion leads not only to motor and cognitive disturbances but also to emotional information processing deficits. From a clinical point of view, the consequences of these emotional disturbances in daily living and their relationship to mood and behavioral disorders such as depression, anxiety and apathy, often observed in PD, remain to be clarified.

P72

Cognitive profile of parkinsonisms at onset: description of the first 100 patients of the BoProPark Study

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Background: Parkinsonisms at onset can be associated to non motor symptoms such as cognitive impairment.

Objective: To describe the cognitive characteristics of patients with parkinsonism at onset. We reported the data of the first 100 consecutive patients recruited from September 2007 to July 2015 within the on-going prospective observational study “Bologna motor and non-motor Prospective study on Parkinsonisms at onset” (BoProPark).

Method: We consecutively selected patients with parkinsonism and disease duration up to three years. Each patient underwent history taking and neurological examination; quantification of motor impairment and disease severity, quantification of motor response to levodopa, cardiovascular reflex tests, video-polysomnographic study and a comprehensive neuropsychological assessment evaluating global cognition, verbal and visual memory, attention, executive and visuospatial function, language, depression and anxiety. If at least one test was impaired in two or more cognitive domains according to cut-off score of corrected score according to Italian standardization the patient was defined cognitively impaired.

Results: We recruited 100 patients: 68 affected by Parkinson Disease (PD), 3 by Progressive Supranuclear Palsy (PSP), 3 by Multiple System Atrophy (MSA), 3 by Cortico Basal Degeneration (DCB), 1 by Lewy Body Dementia (LBD) and 22 by unspecified Parkinsonian Syndromes (PS). Cognitive impairment was detected in 5 PD, 1 DLB, 2 PSP and 3 PS. In these patients we observed a similar pattern of cognitive impairment. They showed pathological scores in test assessing global cognition, memory, attention and executive function.

Conclusions: Cognitive impairment at onset in parkinsonian patients may be heterogeneous. Global cognitive deterioration can be present at onset and with similar features independently from diagnosis.

P73

Impulse control disorder in Parkinson's disease: a lateralized monoaminergic frontostriatal disconnection syndrome?

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Background: Impulse Control Disorder (ICD) in Parkinson’s disease (PD) has been recently associated with impaired cortico-striatal connectivity, especially between left putamen and frontal associative areas. Few studies evaluated dopamine transporters binding (DAT) in PD-ICD+ with no conclusive results.

Objective: The present study aimed at evaluating the correlation between striatal and extrastriatal DAT binding and ICD in PD, using dopamine 123I-FP-CIT (DATSCAN) imaging.

Methods: PD patients underwent standardized neurological, neuropsychological and behavioural assessment and DATSCAN imaging. The presence of ICD was assessed by Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS). We used BRASS software (Hermes, Sweden) for the quantification of striatal tracer uptake and Statistical Parametric Mapping (SPM) with a normalized template for whole-brain analysis. Both analyses were adjusted for age, gender, disease duration and clinical phenotype.

Results: 84 patients entered the study (21 PD-ICD+ and 64 PD-ICD-). Adjusted BRASS analysis showed a significant reduction of left putaminal tracer uptake in PD-ICD+ compared to PD-ICD-. Whole-brain SPM analysis confirmed a DAT binding reduction in left putamen, as well as in left inferior frontal gyrus. Functional covariance analysis using left putamen as the seed point showed the impairment of inter- and intra-hemispheric dopamine binding in PD-ICD+, prominent in cingulate cortex and right contralateral basal ganglia.

Discussion: The results support and expand the concept of a functional disconnection syndrome linked to ICD in PD patients through an asymmetric molecular frontostriatal network breakdown with left basal ganglia as central hub.

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Accuracy of clinical diagnosis of dementia with Lewy bodies: a systematic review and meta-analysis

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Introduction: The identification of dementia with Lewy bodies (DLB) as a distinct disease is relatively recent. Its diagnosis is based on diagnostic criteria, which were updated over the years.

Objective: To perform a systematic review of the studies on diagnostic accuracy in DLB and to meta-analyse sensitivity, specificity and accuracy of the used diagnostic criteria, in order to evaluate how they changed over time.

Methods: We performed electronic searches of MEDLINE and SCOPUS databases to identify all relevant studies reporting diagnostic parameters regarding the clinical diagnosis of DLB until December 2015. We performed the meta-analysis on those studies that used pathological examination as gold standard, sub-classified based on the different diagnostic criteria used.

Results: We selected 21 studies on 21 populations and 1520 patients. The pooled sensitivity, specificity and accuracy were respectively 59.9%, 93% and 79.3% for criteria antecedents to those of McKeith 1996, 56.1%, 86.9% and 75.6% for McKeith criteria 1996 and 84.5%, 59.6% and 75.8% for McKeith criteria 2005. Looking at the "possible" or "probable" DLB diagnosis separately, the sensitivity, specificity and accuracy were respectively: i) 65.6%, 80.5% and 77.8% for McKeith 1996-possible in early stages of disease; ii) 66.1%, 71.5% and 68.6% for McKeith 1996-possible in late stages; iii) 19.4%, 95.1% and 77.6% for McKeith 1996-probable in early stages; iv) 46.7%, 93.2% and 83.7% for McKeith 1996-probable in late stages; v) 86%, 36.7% and 69.4% for McKeith 2005-possible in late stages; vi) 83.8%, 66.9% and 77.6% for McKeith 2005-probable in late stages. No studies evaluated McKeith criteria 2005 in early stages.

Conclusions: One out five patients with DLB has a misdiagnosis. DLB diagnostic criteria have become more sensitive and less specific over time. Diagnostic accuracy did not substantially changed in the last years. Further improvement is needed to optimize the clinical diagnosis of DLB, eventually using biomarkers.

P75

Essential tremor and brain metal accumulation disease in a patient with Klinefelter syndrome

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Introduction: Klinefelter syndrome (KS) [karyotype 47,xxy] is the most frequent sex chromosomal disorder in males and characterized by testosterone deficiency and increase of gonadotropins FSH and LH, with a prevalence of about 500-1000 subjects born alive. Patients affected by KS present with infertility and hypergonadotropic hypogonadism. A recent report has described the presence of tremor in patients affected by KS sharing similar features with essential tremor (ET).

Objective: To report on a case of KS associated with tremor and concomitant brain accumulation disease.

Materials and methods: A 35-year-old man affected by hypergonadotropic hypogonadism (Klinefelter syndrome) presented with a history of upper limbs predominant postural tremor, more evident to the right side, with clinical features more evocative of an ET.

Results: Brain MRI showed bilateral pallidal hyperintensity on T1 weighted and gradient echo images, and minor abnormalities on FLAIR and T2- weighted images, according to a brain metal accumulation. DAT-SPECT was normal. Screening for Wilson disease and neuroferritinopathy was negative, as far as PANK 2 gene sequencing did not identify any pathogenetic variant (PANK2 analysis showed in exon 1 two homozygous polymorphisms - rs71647828 CTG>CAG Leu111Gln; rs3737084 GGG>GCG Gly126A- whose clinical significance is reported as benign). Treatment with testosterone administration worsened features of tremor.

Discussions and conclusions: To the best of our knowledge, this is the first case of a KS patient presenting with ET and brain metal accumulation disease. In this patient, the tremor was worsened by testosterone administration. The presence of a brain metal accumulation and the response to testosterone raise several issues about the definite correlation of the tremor with the hormonal disorder, the correct treatment of this condition and a hypothetical role of the PANK 2 polymorphisms as modifiers on KS phenotype.

P76

Functional imaging with FDG PET in atypical parkinsonisms

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Introduction: Atypical parkinsonisms are a heterogeneous spectrum of parkinsonian disorders characterized by poor levodopa response, extrapyramidal signs and early manifestation of additional clinical features, as autonomic failure, supranuclear palsy, dysarthria, and cortical signs. Making a proper diagnosis of a specific form of atypical parkinsonism may be difficult, especially in the early stage of the disease. Positron emission tomography (PET) imaging with F-18 fluorodeoxyglucose (FDG) is emerging as a useful technique that allows to evaluate neuronal and synaptic dysfunction in neurodegenerative parkinsonisms.

Aims of the study: Characterize metabolic pattern of atypical parkinsonisms and correlate glucose metabolism with clinical signs.

Methods: 27 consecutive patients diagnosed with atypical parkinsonism (11 with multiple system atrophy –MSA, 9 with progressive supranuclear palsy –PSP, and 7 with corticobasal syndrome –CBS) underwent FDG PET examinations. PET scans of each group of patients were compared with a group of normal controls and with each other, using Statistical Parametrical Mapping (SPM). In each group of patients, correlations with different clinical signs were analyzed.

Results: SPM analysis showed specific changes in the pattern of glucose metabolism in different atypical parkinsonisms: in MSA in putamen bilaterally, in PSP in medial frontal, anterior cingulate cortices, caudate nuclei and mesencephalon, and in CBS in cortical (frontal and parietal) and sub-cortical (striata and thalami) regions of one hemisphere. In each group of patients, correlations with different clinical phenotypes have been found.

Conclusions: Specific glucose metabolic patterns have been demonstrated in each group of patients clinically diagnosed with atypical parkinsonisms, such as MSA, PSP and CBS. At the same time a correlation between glucose metabolism and clinical signs and symptoms has been shown. FDG PET imaging provides further information in order to characterize the disease and contribute to an early and accurate differential diagnosis between atypical parkinsonian syndromes.

P77

Putaminal bilateral hemorrhage and parkinsonism: description of a clinical case

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Introduction: Multiple, simultaneous ICHs are rare (2-3%). They are associated with hypertension, coagulation defects, amyloid angiopathy, sinus thrombosis.

Objective: To describe the case of a patient who developed bilateral parkinsonism with MRI evidence of bilateral putaminal hemorrhage.

Patient:

- 71-year-old man.
- Arterial hypertension. Carotid endoarterectomy.
- Four years ago onset of “mild action and resting tremor” of the right hand with mild “slowness”.
- Treated by a neurologist with Ropinirole, and then with Rotigotine, Melevodopa, and Levodopa/Carbidopa: all withdrawn because of adverse events (weakness, severe hypotension).
- Our observation, two years after the onset:
- Neurological examination: mild cognitive slowing, mild hypomimia; hypophonia; no evidence of tremor; bilateral slowness of repetitive movements without clear fatigue or decrement; moderate limb rigidity; reduced arm swing; moderate gait impairment
- Brain-MRI: Former, bilateral putaminal hemorrhages.
- Intracranial Angio-CT: Normal
- DaT-SPECT: Decreased right striatal and left putaminal dopamine transporter binding
- APOE polymorphism: Genotype epsilon3/epsilon3
- No anamnestic evidence of stroke
- Follow-up: only slow progression of symptoms. Dopamine drugs not tolerated except Rasagiline (with poor efficacy).

Discussion: This case is interesting because:

- Simultaneous bilateral ICHs are rare. Even more unusual are simultaneous, symmetrical ICHs.
- Literature reports only 14 cases of bilateral, symmetrical putaminal hemorrhages.
- Clinical manifestations are headache, hemiparesis, confusional state, coma; parkinsonism has been never reported.
- However the patient developed an initially unilateral and then bilateral and slowly progressive parkinsonian symptomatology, even if not quite typical, as usual in PD

Questions:

- Is it a case of PD casually associated with further symmetrical, putaminal, hypertensive hemorrhage? Or is “only” a rare case of Parkinsonism due to bilateral, putaminal hemorrhages?
- In the first hypothesis could the pre-existent symptoms of PD have masked the symptoms of the hemorrhagic stroke?
- Which mechanism leads to a simultaneous, symmetrical rupture of the small vessels?

P78

Wilson disease associated with immotile cilia syndrome: a case report

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Introduction: Wilson’s disease (WD) and primary ciliary dyskinesia (PCD) are rare autosomal-recessive disorders with a prevalence of 1:30000 and 1:15000 respectively. We present a unique case of associated with PCD.

Case presentation: A 24 year-old woman was admitted with a history of headache, fatigue, anorexia and weight loss. Liver hardness, diffuse hypotonia, hypoelicitable deep tendon reflexes, slight ataxia and Kayser-Fleischer rings were noted. Lab testing revealed increased liver functioning tests. Patient history highlighted 5 hospital admission for broncopneumonia before age 12. Each time, lab testing demonstrated increased transaminasemia with normal ceruloplasminemia. Ultrasonography and liver biopsy documented moderate steatosis. Phase-contrast and electron microscopy revealed ciliary immobility, with no dynein in axonemes: she was diagnosed with PCD.

At admission to our clinic, Fibroscan demonstrated hepatic fibrosis. Brain MRI unveiled the “panda-sign”. Normal ceruloplasminemia, increased cupruria (2260mg/24h, normal value –nv- :<70), fibrosis with high copper per gram of dry liver tissue (349 mg/g; nv:<9.9) were found. Analysis of the DNAI1, DNAH5, DNAH11 genes was normal, while compound heterozygosity for the mutations 2304-2305insC and R1041W in the ATP7B gene was found, confirming WD. Patient was started on penicillamine, with benefit: 8 year after, she is asymptomatic. No evolution in neurological signs has been noted, and brain MRI only confirmed the “panda-sign”. Recurrences of broncopneumonia and sinusitis, due to PCD, have been treated with antibiotics.

Discussion: WD and PCD coexistence has never been reported. Loci adjacent to ATP7B may contain dynein-codifying sequences, affected by mutations of closest genes. In this case, liver impairment was grossly reverted with de-coppering agents. Moreover, the reduction of ceruloplasmin, being an acute phase reactant, was hindered by recurrent bronchopneumonia due to PCD. Being dogmatic about ceruloplasmin levels can drag away from correct diagnosis and treatment.

P79

Two unusual cases of reversible movement disorders

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Background: Most movement disorders (MDs) reflecting degenerative disorders, develop in a slowly progressive fashion [1]. Some movement disorders, however, manifest with an acute onset. These include drug-induced, lesional (e. g. tumors, stroke), autoimmune and dysmetabolic MDs.

Objective: Acute dysmetabolic MDs are a subgroup of MDs that can be reversible if promptly recognized and treated. The aim of the present case description is to describe two unusual cases of reversible dysmetabolic MDs and to discuss the clinical approach to these conditions.

Methods: Case 1. A 46 year old male was admitted to our institution for acute-onset of generalized dystonia without remarkable personal or familial history of MDs nor taking drugs. He had no history of diabetes but his serum glucose was >400 mg/dl and no ketones were present. Restoration of euglycemia led to resolution of dystonic symptoms. MRI scan showed a central pontine lesion suggestive of myelinolysis. Case 2. A 74 year old female was admitted to our institution for subacute onset of bilateral akinetic-rigid syndrome with ataxia and tremor not responsive to L-Dopa. MRI scan did not show abnormalities. She referred a Proton-pump inhibitors chronic use. Blood exams showed a severe hypomagnesemia (0,3 mg/dl) and its correction led to a progressive improvement of neurological symptoms.

Results: In the first case the proposed diagnosis was acute dystonia due to severe nonketotic hyperglycemia with central pontine myelinolysis. In the second case the proposed diagnosis was encephalopathy mimicking parkinsonism due to severe hypomagnesemia.

Conclusion: The clinical approach to acute MDs should include a careful consideration of all potential secondary causes of extrapyramidal symptoms, because most of them can be treated.

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P80

Cognitive features of essential tremor investigated by a resting-state functional MRI (rs-fMRI) study

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Introduction: Essential Tremor (ET) is a heterogeneous clinical entity, characterized by several motor features, other than tremor, and non-motor features, including cognitive deficits [1]

Objective: We used resting-state fMRI to assess the brain networks associated with ET, focusing mainly on cognitive aspects.

Methods: 23 definite/probable ET patients and 23 healthy controls (HC) underwent a 3T-MRI acquisition of a resting state sequence. Data were analysed using Independent Component Analysis and a dual regression approach that was applied on the 10 Resting State Networks (RSNs) [2] that were identified using FSL software. To detect functional connectivity (FC) differences between groups in the boundaries of group-ICs and within grey matter plus basal ganglia region we performed nonparametric permutation test. Family-wise error correction for multiple comparisons was performed implementing threshold-free cluster enhancement ($p < 0.05$). 13 ET patients and 13 HC also performed a battery of neuropsychological tests exploring executive functions, attention, verbal memory, verbal fluency.

Results: ET patients showed significantly increased FC compared to HC in the frontoparietal networks and in the anterior part of Default Mode Network (aDMN). Both ET patients and HC neuropsychological tests' scores were in the range of normality; however ET performed significantly worse than HC the Rey Auditory-Learning Verbal test, Stroop and Trail-Making Test. By correlation analysis between RSNs and neuropsychological tests' scores, a negative correlation with Stroop (error) was found in frontoparietal network and a positive correlation with Stroop (time) was detected in aDMN.

Conclusions: DMN and frontoparietal networks are the most relevant RSNs for cognition. Increased FC in these RSNs in ET patients could have a compensatory meaning, showing the effort of ET patient to compensate for cognitive deficits with respect to HC. The correlation between FC changes in aDMN and frontoparietal-networks and Stroop test support the role of these RSNs in cognitive deficits in ET.

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P81

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

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Background: 7 Tesla MRI (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 Rapid-eye-movement (REM) sleep behaviour disorder (RBD) can develop synucleinopathies 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.

Aim: We report preliminary data from a study aiming to evaluate 7 Tesla MRI anatomy of the SN in patients with RBD as paradigm of premotor PD.

Methods: We enrolled 5 patients (4 M, 1 F, mean age 72,8 ys) with RBD (disease duration range 1-11 years) and a brain SPECT with FP-CIT-SPECT suggestive for dopaminergic nigrostriatal dysfunction. All patients were clinically evaluated to exclude the presence of parkinsonism. 7T Susceptibility-Weighted-Imaging MR targeted to the midbrain was obtained in all subjects. SN abnormality was judged according to recently published radiological criteria.

Results: Four out of 5 patients exhibited abnormal 7T-MRI SN. Two patients showed asymmetrical SN involvement, two of them showed bilateral symmetrical involvement.

The patient with normal MRI had the shortest disease duration (1 year).

Conclusion: Our data, although on a small sample of patients, support the SN involvement in at least some of the patients with RBD and suggest the use of SWI MRI as possible marker of neurodegenerative background in patients with RBD. Longitudinal evaluation on a larger group of subjects will clarify the impact of 7T SN abnormality in predicting the "motor" conversion of RBD patients and the relationship with SPECT imaging results.

P82

Amyotrophic Lateral Sclerosis as a clinical presentation of LRRK2 mutations?

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Introduction: Leucine-Rich Repeat Kinase 2 (LRRK2) mutations are the most common in Parkinson's disease (PD). They are thought to produce a clinical phenotype almost indistinguishable from idiopathic PD[1].

Objective: To evaluate clinical spectrum of LRRK2 in a family with different clinical phenotypes.

Methods: A 72 year-old man presented at our Clinic with one year history of progressive weakness of the left limbs, walking impairment and lack of accuracy in arm movement. He later developed bradykinesia, muscular cramps, fasciculations, dysphagia and dysarthria. At neurological examination he presented hypomimia and bradykinesia, and increased muscular tone at lower and upper limbs which showed also distal weakness. Tetrahyperreflexia was present. He performed brain MRI (chronic vascular encephalopathy) and FP-CIT SPECT which showed a bilateral nigroputaminal degeneration. Electromyography exhibited denervation and fasciculations in upper and lower limbs (not in cranial district) and Motor Evoked Potentials were consistent with upper motor neuron involvement in all limbs. CSF was normal. Patient's uncle and three cousins (paternal line) had all a diagnosis of PD.

Results: A diagnosis of Motor Neuron Disease and PD was done to our patient. Taking account into his family history for PD, we looked-for LRRK2 mutations. G2019S mutation was found both in our patient and in all his cousins. SOD1 mutations were excluded.

Conclusion: Limb muscle weakness, atrophy and fasciculations were found in two affected members of a large German-Canadian family presenting LRRK2 mutation [2]. Following studies failed to reveal LRRK2 mutations in ALS patients [3] even when they exhibited extrapyramidal signs. However isolated cases of frontotemporal dementia [4], Corticobasal Syndrome, Primary Progressive Aphasia [5] have been reported in LRRK2-mutation carriers and more recently an ALS patient with extrapyramidal signs and positive FP-CIT SPECT showed LRRK2 mutation, but a coincidental association could not be ruled out. LRRK2 phenotypic spectrum is broader than expected, consistent with its pleomorphic histopathology [6].

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P83

BDNF and LTP/LTD-like plasticity of the primary motor cortex in Gilles de la Tourette Syndrome

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Introduction: Gilles de la Tourette Syndrome (GTS) is characterized by motor and vocal tics and often associated with obsessive-compulsive disorder (OCD)[1]. Responses to intermittent/continuous theta-burst stimulation (iTBS/cTBS), which probe long-term potentiation (LTP)/depression (LTD)-like plasticity in the primary motor cortex (M1), are reduced in GTS. iTBS/cTBS-induced M1 plasticity can be affected by brain-derived neurotrophic factor (BDNF) Valine66/Methionine (Val66/Met) polymorphism [2, 3].

Objective: We investigated whether the BDNF polymorphism influences iTBS/cTBS-induced LTP/LTD-like M1 plasticity in 35 GTS patients. Methods: Motor and OCD symptom severity were rated using the Yale Global Tic Severity Scale (YGTSS) and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). We compared M1 iTBS/cTBS-induced plasticity in patients with different BDNF polymorphism (Val/Val versus Met carriers).

Results: iTBS/cTBS-induced M1 LTP/LTD-like plasticity was similar in both Val/Val and Met carriers. YGTSS scores were comparable, whereas Y-BOCS scores were higher in Met carriers than in Val/Val subjects.

Conclusions: We conclude that the BDNF polymorphism in GTS does not affect iTBS/cTBS-induced LTP/LTD-like plasticity in M1.

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P84

Muscle ceroid-lipofuscine like deposits in a patient with FTLD due to a Progranulin mutation

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Objective: We report a case of a Cortical Basal Syndrome (CBS) due to heterozygous Granulin (GRN) mutation who develops a lysosomal storage pathology characterized by autofluorescent ceroid-lipofuscine-like muscle deposits.

Background: Pathogenic mutations in GRN mostly create null alleles resulting in haploinsufficiency of the protein and being a frequent cause of autosomal-dominant forms of frontotemporal degeneration with TDP-43-immunoreactive inclusions (FTLD-TDP43) as well as the most common genetic cause of CBS phenotype. Total deficiency of secreted PRGN induces lysosomal dysfunction leading to the neuronal ceroid lipofuscinoisis (NCL type IV).

Methods: A 48-year-old man with a progressive asymmetrical parkinsonism unresponsive to levodopa, ptosis and hearing loss underwent neuropsychological evaluation, Cerebral magnetic resonance imaging (MRI), Cerebral SPECT with 99m Tc-HMPAO, CSF and genetic analysis and, in the suspicion of a mitochondrial syndrome a muscle biopsy.

Results: Clinical and instrumental data confirmed a FTDL syndrome characterized by atypical Parkinsonism CBD-like due to a heterozygous GRN mutation (GRN met1 - g.2T> C, rs63751006). Cerebrospinal and plasmatic levels of PGRN confirmed halved levels compared to healthy controls. Muscle biopsy disclosed slight myopathic changes with few vacuoles, autofluorescent cytoplasmic granules and increased acid phosphatase activity; electron microscopy showed lipofuscine and ceroid-lipofuscine-like deposits.

Conclusions: PGRN deficiency can uniquely produce, due to the residual protein activity, adult onset NCL and FTDL. Indeed, previous studies on GRN mutations, have suggested a phenotypic overlap between FTD and lysosomal storage disorders. Moreover, pathological marker proteins characteristic for NCL/lysosomal impairment were found in brains of FTLD-TDP-43/GRN patients. We report that, in FTDL due to a heterozygous GRN mutation, a muscle accumulation of abnormal ceroid lipofuscine like deposits, resembling the neuronal inclusions typical of NCL was documented. Thus, our findings support the hypothesis that lysosomal storage disorders and GRN-associated FTLD share common features.

P85

Central pontine myelinolysis-like lesion associated with Wilson disease in a 72-year-old woman: an atypical onset of hepatic or neurological Wilson disease?

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Background: Wilson disease (WD) is an inborn error of copper metabolism caused by a mutation in the copper transporting gene ATP7B on chromosome 13q14.3. This condition leads to copper deposition in liver, brain, kidneys, eyes, bones and blood tissues and may be responsible of hepatic dysfunction (40%) neurological (40%) and psychiatric (16%) disorders, associated with other rare manifestations (3%).

Objective: To report the case of a woman with central pontine myelinolysis (CPM)-like lesion associated with WD.

Case report: A female patient presented with rapid progression to cirrhosis at the age of 67. The ATP7B gene was analyzed and a homozygous state of the -441/-427 mutation was found. Kayser-Fleischer rings were not seen on slit lamp examination. WD diagnosis was made and treatment with penicillamine was initiated. After 4 years, walking difficulties with postural instability and frequent risk of falls were reported and a brain MRI showed only the presence of "a triangular hyperintense signal on T2-weighted images involving the peduncle of the pons similar to pontine myelinolysis". Neurological examination showed the presence of signs of pyramidal tract lesion with increased deep tendon reflexes and pathological reflexes such as Hoffman's sign.

Discussion: Findings of CPM-like at MRI in WD are uncommon and the univocal interpretation of the underlying physiopathological mechanism is difficult. In fact, CPM is usually detected in chronic alcoholism, malnutrition, and rapid correction of sodium in patients with severe hyponatremia. Currently, three patterns of CPM-like changes in WD have been described. Our patient showed the classic pattern; however, she did not exhibit any of the neurological symptoms which are the most frequently reported such as bulbar symptoms and drooling. Our case documents as CPM-like lesion may be present also in WD with hepatic injury as the first manifestation, but it could be also predictive of a neurological involvement.

P86

Acute choreoathetosis as unusual first Multiple Sclerosis presentation: two case reports.

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Introduction: Hyperkinetic movement disorders, in particular chorea and ballism, have been rarely reported in patients with Multiple Sclerosis and almost never represent the first clinical manifestation. We report two patients with acute choreoathetosis as the presenting symptoms of MS.

Case reports: A 18 years old man subacutely developed left arm and leg's involuntary movements, dysarthric speech and mental slowing. Neurologic examination showed intermittent choreoathetoid movements associated with a dystonic posture affecting predominantly the left forearm, hand and fingers. Brain MRI revealed a right subthalamic contrast enhancing demyelinating lesion extending to the homolateral cerebral peduncle associated with multiple infratentorial and periventricular demyelinating lesions. A MS diagnosis was made and the patient was treated with high dose methylprednisolone. The involuntary movements completely resolved in 6 days.

A 39 years old woman subacutely developed right arm and leg involuntary movements. Neurological examination revealed subcontinuous right limbs choreic movements prevailing in the arm, worsened during postural tasks. She occasionally had right limb ballistic movements and abnormal dystonic postures. Brain MRI revealed a tumefactive contrast enhancing demyelinating lesion in the left cerebral peduncle, extending to the substantia nigra and subthalamic nucleus (STN). Multiple demyelinating lesions in subcortical white matter, brainstem and cerebellum were also found. A MS diagnosis was made and the patient was treated with high dose methylprednisolone with symptoms improvement.

Discussion: The acute onset of unilateral dyskinesias with semeiology ranging from choreoathetosis to ballism or dystonia, similar to those induced by levodopa, should suggest a functional inhibition of the STN, with imbalance of motor control operated by the basal ganglia network. Except common cases induced by vascular lesions, in young subjects this clinical picture could suggest an unusual debut of a demyelinating disease.

P87

Clinical effects of different montages of Transcranial Direct Current Stimulation (tDCS) in patients with Parkinson's Disease

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Background: Parkinson's disease (PD) is characterized by motor deficits which may not completely respond to the dopaminergic therapy, thus posing a therapeutic challenge. Non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) have shown promising results as possible alternative of treatment in different neurological disorders including PD. The therapeutic effect of tDCS, which may increase (anodal currents) or decrease (cathodal currents) the cortical excitability level, likely relies on modulation of cortico-subcortical interactions and abnormal patterns of cortical activation.

Objective: To investigate safety and therapeutic potential of different montages of tDCS in PD patients with asymmetric motor symptoms.

Patients and methods: Patients with asymmetric PD were recruited. While on-treatment, participants underwent 7 separate experimental sessions. The tDCS was applied with the following different electrode montages: anodal and cathodal stimulation of the primary motor cortex (M1) contralateral to the more affected body side, anodal and cathodal stimulation of M1 contralateral to the less affected body side, and sham-stimulation. We evaluated the clinical effects on motor function by means of the MDS-UPDRS, by evaluation of bradykinesia of the arms and by the finger tapping test. All experiments were performed according to a double-blinded design. The dopaminergic medication was continued in all subjects throughout the course of the experiment.

Results: 16 patients (8M/8F) were included (aged 58±11.5 years). Compared to baseline and sham stimulation, the motor performances improved in both hands after anodal tDCS of M1 contralateral to the more affected body side. Also the cathodal stimulation of M1 contralateral to the less affected body side was shown to improve the motor performances.

Conclusions: Our results confirm the therapeutic potential of tDCS in PD patients, providing useful information on which is the best tDCS montage to apply as a treatment option.

P88

Choral singing therapy for speech and voice impairment in Parkinson's disease

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Speech and voice impairment have a significant impact on quality of life of patients with Parkinson's disease. Many studies indicate the efficacy of LSVT LOUD[®] voice and speech therapy (Lee Silverman Voice Therapy), but a growing number of works suggest that musically based voice and speech therapy can be a potentially useful method of rehabilitation.

The aim of this study was to investigate the effects of a choral singing treatment protocol on the speech of individual with Parkinson's disease. Seven patients (5 males and 2 females, from Bari Parkinson's Association), who voluntarily took part to the study, were selected.

Recordings of voice patients during spontaneous speech, readings, diadochokinesis (DDK) and vowels production were collected. The sample evaluation included a questionnaire for self assessment (ROMP-speech, Kalf, 2011) to quantify the impact of speech and voice impairments on patients's quality of life.

Patients underwent two months sessions of choral singing therapy; one hour and half weekly session. Sessions were directed by speech language pathologists. Rehabilitation material for everyday home training was delivered.

Pre and post-treatment recordings were analysed and compared to quantify the efficacy of the therapy. Voice intensity, duration of vowel production, DDK rate, voice frequency and speaking rate were adopted as parameters.

After a two months training it was observed a modification in intensity, articulation and speech intelligibility. This suggests the possibility of utilizing the choral singing protocol to maximize immediate treatment effects in a motivating and social setting.

P89

Interaction between adaptive deep brain stimulation and Levodopa in patients with Parkinson's disease

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Introduction: New adaptive deep brain stimulation (aDBS) systems imply that DBS is adjusted on-line, according to the actual state of patients with Parkinson disease (PD), thus delivering an optimized stimulation. Reducing stimulation in relation to the effects of levodopa treatment would avoid the transient summation of DBS and pharmacological therapy. Local field potential (LFP) beta oscillations (11-35 Hz), directly recorded from electrodes implanted for DBS, reduced after levodopa administration correlating to the patient's clinical state and therefore was used to control aDBS.

Objectives: We designed a randomized, double-blind, cross-over trial to study the aDBS functioning and the efficacy both before (med OFF) and after levodopa administration (med ON). Conventional DBS (cDBS) was the control treatment.

Methods: The 5th and 6th day after the DBS electrodes implant, 10 patients with PD underwent 2 hours of stimulation using an external dual mode (aDBS or cDBS) wearable device controlled by beta LFPs (one treatment per day). To study the aDBS functioning we compared the mean voltage delivered by the device during med OFF and med ON conditions. The clinical effects were evaluated through the UPDRS III (motor part) and the Unified Dyskinesia Rating Scale III-IV (UDysRS).

Results: During aDBS the voltage changed according to the beta modulations: the beta band dropped when patients achieved the transition from med OFF to med ON and accordingly, the mean voltage significantly reduced (med OFF vs med ON: 2.1 ± 0.4 V vs 0.8 ± 0.3 V; $p < 0.05$). aDBS improved the UPDRS III and the UDysRS scores both in med OFF and med ON. Compare to cDBS, aDBS significantly reduced UDysRS score (med OFF: $1.5 \pm 1.6\%$ vs $10.8 \pm 6.5\%$; med ON: $22.9 \pm 2.8\%$ vs $34.0 \pm 5.6\%$; $p < 0.05$).

Conclusions: LFP beta-based aDBS approach was able to "follow" the patient's beta changes. The beta reduction, induced by levodopa, decreased the voltage stimulation. This leads to a significant reduction of patients' dyskinesias compared to those obtained during cDBS.

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Complex therapies for advanced Parkinson's disease: what's the role of doctor-patient communication?

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Introduction: Communication is a central process within patient-doctor relationship. Few studies have considered the communicative processes in Parkinson's disease (PD). The influence of doctors' communication regarding advanced treatment on compliance and satisfaction about therapy was underlined [1]. An adequate communication is needed, especially during the advanced phases of PD, characterized by demanding therapeutic adjustments and the possible introduction of advanced therapy.

Objective: To investigate the role of communication and patient-doctor relationship in the transition to complex therapies for advanced PD.

Methods: Twenty-two idiopathic PD patients (M/F = 14/8; mean age: 61.9±8.8 years; disease duration: 12±5 years) eligible for advanced therapy (DBS, continuous infusion of levodopa-carbidopa intestinal gel or Apomorphine) were submitted to an audiotaped semi-structured interview aimed to investigate communication-related cognitions, feelings and behaviours concerning PD and the eventual introduction of a complex therapy. Moreover, the Patient-Doctor Relationship Questionnaire (PDRQ-9) was administered.

Results: Patients' satisfaction about relationship with physicians (PDRQ-9: 37±7.6) was highlighted. All patients had a personal session about the eventual transition to advanced therapies. This communication aroused feelings of fear (10/22 patients) and concern (15/22 patients), but also fostered the hope for a motor improvement (13/22 patients). Almost half of patients (45%) desired to receive information about the therapeutic options even after the conversation.

Conclusion: Further study and a larger sample are needed, however our pilot study underlines the importance of doctor-patient communication even in the possible transition to advanced therapies. Three guide principles arise: give realistic but supportive information; recognize negative thoughts and replace them with less-exaggerated beliefs as an alternative; elicit collaboration in developing a strategy or treatment plan for the future.

References:

[1] Lökk J. Lack of information and access to advanced treatment for Parkinson's disease patients. *Journal of Multidisciplinary Healthcare* 2011;4, 433-439.

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Pisa Syndrome successfully treated with subthalamic deep brain stimulation: a case report

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Introduction: Pisa syndrome (PS) is a complication of Parkinson's disease (PD), clinically defined as the sustained lateral bending of the trunk. No specific therapeutic options are available and different approaches demonstrated limited efficacy.

Objective: To report the case of a 67-year-old parkinsonian patient with disabling PS successfully treated with subthalamic deep brain stimulation (STN-DBS).

Methods: A case of PS with sensible amelioration after STN-DBS is described.

Results: A 67-year-old patient developed sub-acute right bending of the trunk (angle=35°) 5-years after PD diagnosis, a few weeks after the administration of rasagiline. No beneficial effects were observed after withdrawal of rasagiline and pramipexole. During the following 3 years, he developed severe motor fluctuations and bilateral STN-DBS surgery was proposed. Preoperative MDS-UPDRS part-III score was 55 in OFF-medications and 38 in ON-medications; therapy was carbidopa/levodopa 900 mg daily and clonazepam. After surgery the levodopa daily dose was lowered to 575 mg and the stimulation switched-on with the following parameter settings: 1.8 V, 60 mcs, 130 Hz, contact 1- (monopolar stimulation), for the left STN; 2.0 V, 60 mcs, 130 Hz, contact 9- (monopolar stimulation), for the right STN. An improvement of the PS was achieved early after stimulation activation, contributing to a relevant amelioration of quality of life. The 1-year follow-up assessment showed a sensible amelioration of the MDS-UPDRS-III score (47 ON stimulation/OFF medication; 22 ON stimulation/ON medication) and of the right bending of the trunk (angle= 10°).

Conclusions PS is a rare and disabling complication of PD, with a limited response to dopaminergic or other oral therapies. Few cases of DBS in PD patients with PS were reported in the literature, with conflicting results. We report a new case of remarkable PS successfully relieved by STN-DBS, confirming that the surgical option should be considered in selected PD patients with disabling postural abnormalities.

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Efficacy of a computer-assisted cognitive rehabilitation protocol on walking in Parkinson's disease patients with freezing of gait: a pilot study

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Background: The interplay between cognitive functions and gait is usually investigated by evaluating a secondary task while walking. Despite the growing interest on gait and cognition, to date there are no studies demonstrating the effect of a cognitive rehabilitation protocol on gait disorders in Parkinson's Disease (PD).

Objectives: To evaluate if a computer-assisted cognitive rehabilitation protocol may improve walking as single task and during double task performance in people with PD and freezing of gait (FOG).

Methods: Patients affected by PD with FOG participated to the study. Patients were treated twice a week for 1-h sessions for six consecutive weeks by a computer-assisted training of attention ability and information processing tasks. Gait parameters in single and dual-task were recorded at baseline, after six weeks and three months.

Results: Seven patients completed the evaluations at six weeks, six at three months. In single-task, we observed at six weeks a significant reduction in the cycle length in both legs with an increment in mean velocity and cadence. In dual task, we found a positive trend for all gait parameters, with slight decrement in dual-task cost. Most of gait parameters returned to baseline values after three months.

Discussion: A computer-assisted rehabilitation protocol based on executive functions training may improve walking in PD with FOG. This approach should be part of a multidisciplinary rehabilitation program to obtain prolonged results.

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Freezing of gait improves with intestinal Levodopa infusion in advanced Parkinson disease patients

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Objective: To determine whether levodopa-carbidopa intestinal gel (LCIG) infusion is able to improve freezing of gait (FOG) in advanced Parkinson disease (PD).

Background: FOG is a common and disabling problem in advanced PD. The constant dopaminergic drug delivery obtained by LCIG infusion allows a significant reduction of motor fluctuations and dyskinesia in patients with advanced PD. There is preliminary evidence that in selected patients, LCIG treatment may improve FOG refractory to oral dopaminergic therapy.

Methods: We retrospectively evaluated the effects of LCIG in 32 consecutive PD patients treated at our centre between 2010 and 2015. Clinical assessments were performed before starting LCIG (both in “OFF” and “ON” condition) and during “daily ON” condition with LCIG infusion. The main outcome measures were changes in FOG related UPDRS subscore, UPDRS motor and axial score, motor complications, Hoehn & Yahr (HY) stage and levodopa equivalent daily dose (LEDD). Preoperative characteristics of patients with and without FOG improvement were compared.

Results: Patients were followed for a mean of 2.59 ± 1.12 years during which a progression of disease was evident (H&Y ON-medication score deteriorated ($p=0.015$)). LEDD was unchanged ($p=0.383$). There was a 61% reduction of daily OFF periods ($p=0.001$) and a 25% reduction in daily dyskinesia duration ($p=0.021$).

FOG related UPDRS-subscore improved 34.5% in ON condition ($p=0.027$). FOG improved in 12 (37%) patients, it was unchanged in 17 (53%) and it worsened in 3 (9%). Patients with FOG improvement had worse FOG and gait score ON medication, worse UPDRS motor and axial score ON medication, and a shorter duration of motor complication at LCIG initiation compared to patients with no change or worsening of FOG during LCIG.

Conclusion: Our data support the notion that in selected patients, LCIG treatment may improve FOG unresponsive to oral dopaminergic therapy.

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State of the art on Levodopa/Carbidopa duodenal gel infusion in advanced Parkinson disease: 10 years of the Italian experience

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P94 (segue)

Introduction: Since 2004 continuous infusion of Levodopa Carbidopa Intestinal Gel (LCIG) treatment has been approved in Europe for its beneficial treatment for advanced and/or complicated PD. Nevertheless, in Italy patient selection criteria and clinical practice guidelines are still lacking.

Objectives: To map the diffusion of LCIG treatment in Italy and to assess the therapy management in movement disorders centers.

Methods: A questionnaire with clinical, practical and reimbursements aspects was distributed via mail and included both fixed answer categories and free text boxes for responses.

Results: 653 patients data of 32 respondent centers were collected. The majority of movement disorders centers are involved in other device-aided therapies and reported uniform criteria about practical management: involvement of multidisciplinary group, biochemical, neurophysiological and neuropsychological test evaluation. Selection criteria, drug dispensing mode and reimbursement are heterogeneous. Tube occlusion, weight loss, chronic polyneuropathy and stoma infection were the most frequent adverse events. The mean tube replacement frequency is every 12 months (± 3.9), in most of cases because of deterioration. Discontinuation of therapy is not rare and primarily caused by device or drug-related adverse events. The partnership with primary care faculties is considered unsuitable in 53% of cases.

Discussion and conclusions: In our country, clinical, practical and management aspects of this treatment are well organized, even if they are not homogenous along national territory. These findings may improve LCIG Italian expertise and put the basis on shared national guidelines about selection criteria and clinical practice.

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Factors affecting battery duration in neurostimulators for deep brain stimulation

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Background: Deep Brain Stimulation (DBS) is an effective treatment for Parkinson Disease (PD) and other movement disorders. In latest years, new implantable pulse generators (IPG) have been developed, allowing advanced programming paradigms such as selection of either constant voltage (CV) or constant current (CC) stimulation and activation of different stimulation fields (e.g.: interleaving mode). Moreover, several programming data can be stored in the devices and are easily retrievable. Aim of this study is to compare the performances of new IPGs with older devices, in order to identify any difference in battery duration.

Methods: The study was conducted at 3 italian DBS centers (Torino, Arcugnano (VI) and Udine). Data of all PD patients who underwent at least one IPG replacement in the last 5 years were retrospectively collected from clinical charts.

Results: These preliminary results are referred to 50 patients from the three centers. At first DBS surgery, 32 patients were implanted with Kinetra IPG (Medtronic©, Minnesota, US) and 18 patients were implanted with Activa-PC IPG (Medtronic©, Minnesota, US). The mean duration of Activa-PC IPGs was $3,86 \pm 0,63$ years and was significantly lower than Kinetra IPGs duration ($5,86 \pm 0,98$) ($P < 0.01$). Stimulation amplitude, frequency and pulse width were similar for Activa-PC and Kinetra IPGs. In the Activa-PC group, 10 patients were programmed in CV and 8 patients in CC. Battery duration of the CC programmed Activa-PC was similar ($3,6 \pm 0,5$ years) to CV programmed Activa-PC ($4,2 \pm 0,7$ years).

Conclusions: Activa PC IPGs have shorter battery life compared to Kinetra IPGs, independently from programmed parameters and stimulation modality. Further data collection, from a multicentric italian study, is in progress to confirm our data.

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