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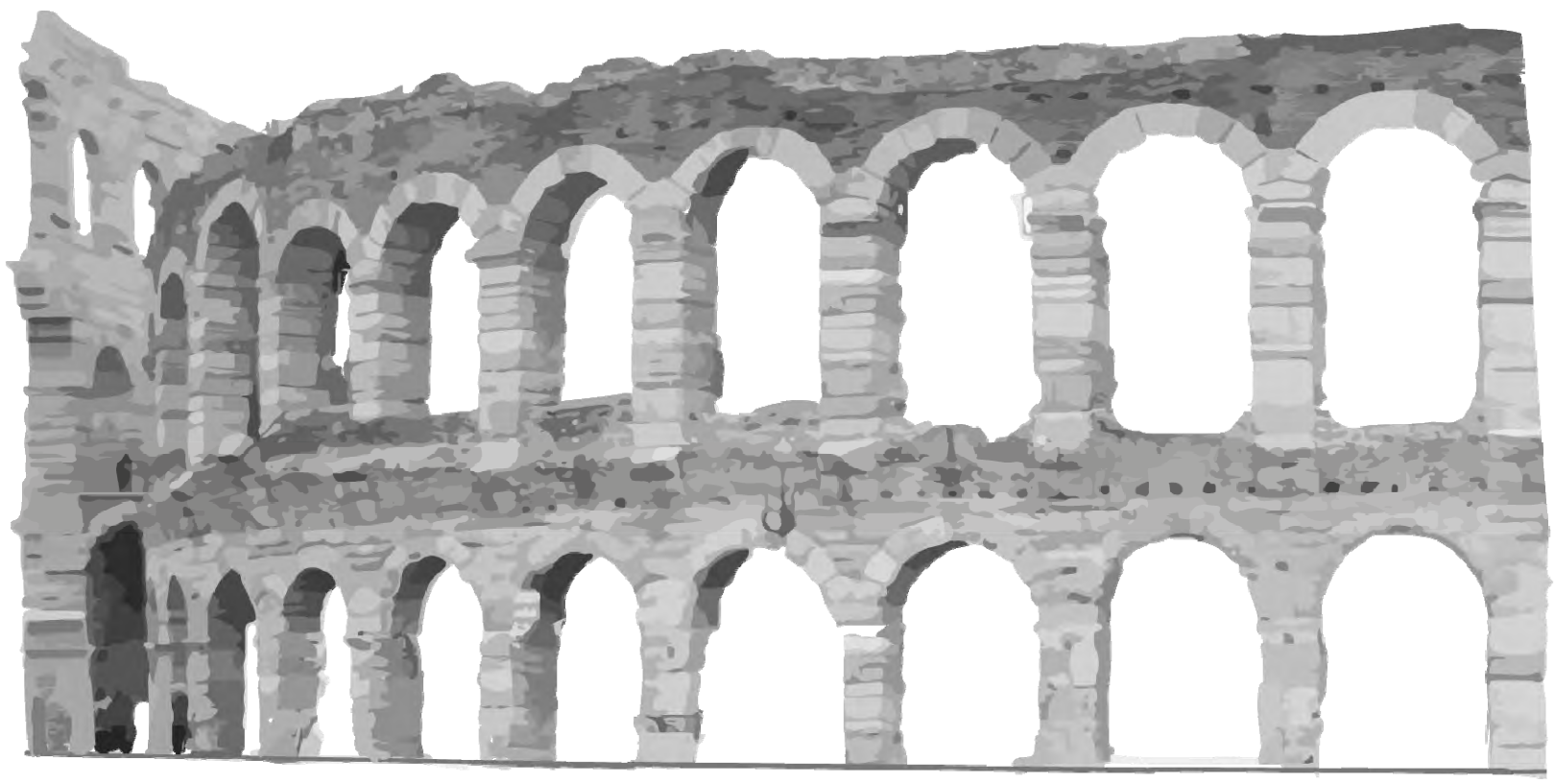

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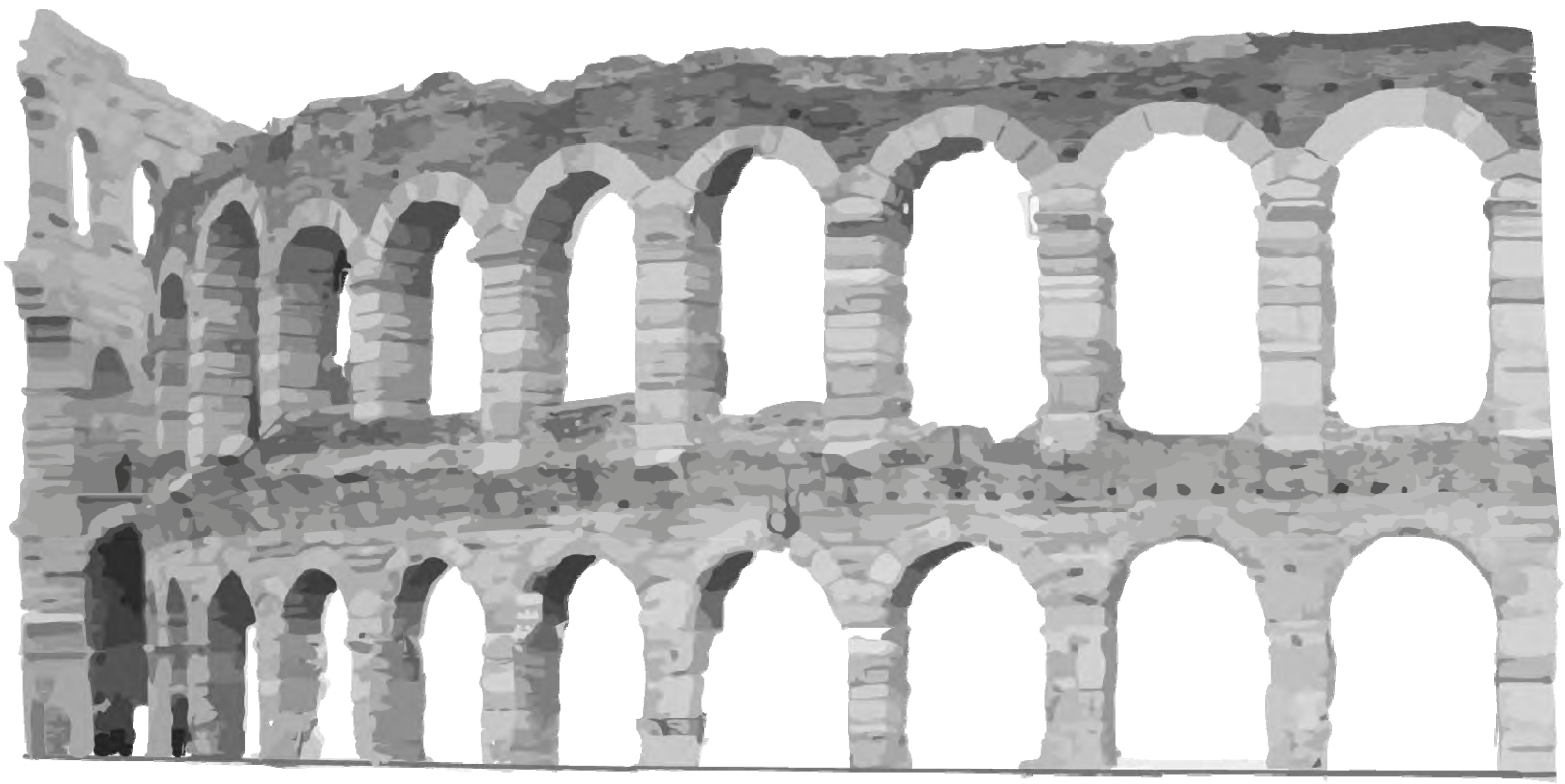

C1

Skin nerve phosphorylated alpha-synuclein deposits in idiopathic REM sleep behavior disorder

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Objective: We tested if p-alpha-syn deposits can be detected by means of skin biopsy in patients with idiopathic RBD (iRBD), as a potential early histopathological marker of impending synucleinopathy.

Methods: Proximal (cervical) and distal (legs) samples of skin biopsy have been obtained from 12 patients with polysomnographically-confirmed iRBD and 55 sex and age-matched healthy controls (HC). P-alpha-syn deposits were assessed by a monoclonal antibody against phosphorylated alpha-synuclein at Serine 129, disclosed by an immunofluorescence method. Additionally, patients underwent an extensive work-up in order to search for non-motor symptoms and neuroimaging findings usually associated with impending neurodegeneration and to exclude subtle motor or cognitive signs.

Results: P-alpha-syn deposits were detected in nine (75%) out of 12 patients with iRBD and none of the HC. In iRBD, the sensitivity of the test was higher at the cervical site (67%), when compared to the leg site (58%).

Conclusions: Our preliminary findings suggest that skin biopsy in patients with iRBD might be a safe and sensitive procedure to be further tested in order to detect p-alpha-syn deposits in the pre-motor stage of synucleinopathies.

C2

Loss of dorsolateral nigral hyperintensity on 3.0 tesla susceptibility-weighted imaging in dementia with Lewy bodies

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Introduction: The diagnosis of dementia with Lewy Bodies (DLB) may be challenging. Alzheimer's Dementia (AD) is the most frequent misdiagnosis. Susceptibility-weighted imaging (SWI) using 3T MRI can detect a dorsolateral hyperintense signal area ("swallow tail" sign) in the Substantia Nigra (SN) of healthy controls. It corresponds to the nigrosome-1 and lacks in Parkinson's disease. We evaluated its diagnostic utility in DLB patients.

Methods: We recruited 15 DLB patients (8 men, mean age 76.2 ± 7.1), 11 AD patients (4 men, 73.7 ± 7.8) and 10 subjects with subjective memory complaint (SMC) (5 men, 67.2 ± 9.4). All subjects performed MRI study including axial SWI sequences, visually assessed by two blinded neuroradiologists independently. A third rater resolved disagreements. DLB diagnosis required unilateral or bilateral loss of nigral hyperintensity.

Results: Age ($p = 0.09$, Kruskal Wallis Test) and sex ($p = 0.68$, chi2 test) among the groups did not differ. Raters agreed 89% (kappa = 0.77, $p < 0.001$). Twelve out of 15 DLB patients lacked nigral hyperintesity unilaterally or bilaterally, unlike the other groups (AD: 4/11; SMC: 1/10; $p = 0.002$, chi2 test). Sensitivity, specificity, PPV, NPV and accuracy of DLB diagnosis by SWI were respectively 80%, 64%, 75%, 70% and 73% vs AD, 80%, and 90%, 92%, 75% and 84% vs SMC.

Conclusions: The assessment of dorsolateral nigral hyperintensity using 3T SWI was able to differentiate DLB from AD and SMC with good diagnostic accuracy. It can be a reliable and noninvasive method to help clinical diagnosis of DLB.

C3

Impaired temporal coupling of motor action and tactile perception in Parkinson's disease

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Introduction: Previous studies showed that Somatosensory Temporal Discrimination Threshold (STDT) is abnormally enhanced in patients with Parkinson's Disease (PD). The role of the increased STDT in the pathophysiology of motor symptoms in PD is unclear. In healthy subjects, STDT processing is modulated by movement execution, through mechanisms of sensory gating.

Objective: To investigate whether and how voluntary movement modulates STDT in PD.

Methods: We enrolled 19 PD patients and 20 sex- and age-matched healthy subjects. STDT was measured at baseline and during index-finger abduction (at movement onset "0 ms", 100 ms and 200 ms thereafter). The kinematic features of index finger abductions were also measured. Patients were tested off and on treatment and on the right and the left hand.

Results: In healthy subjects and in PD patients on treatment movement execution significantly increased STDT values at 0 ms, 100 ms and 200 ms after movement onset. In PD patients off treatment, STDT increased significantly at 0 ms and 100 ms but returned to baseline values at 200 ms. Differently from healthy subjects, in PD the mean velocity of the finger abductions decreased according to the interval between movement onset and the delivery of the paired electrical stimuli for STDT.

Conclusions: PD patients have an abnormal temporal coupling between tactile information and motor output. Our findings suggest that the abnormal temporal processing of sensory information might play a role in the pathophysiology of motor symptoms in PD.

C4

Effects of voluntary movement execution on somatosensory temporal discrimination threshold in patients with cervical dystonia and blepharospasm

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Introduction: Evidence showed altered Somatosensory Temporal Discrimination Threshold (STDT) in Dystonia in comparison to healthy subjects. In healthy subjects movement execution modulates STDT through mechanisms of sensory gating mediated by basal ganglia-thalamus interplay.

Objective: In this study in patients with dystonia we investigated whether STDT modulation during movement execution differs from healthy subjects and sought possible differences between patients with Blepharospasm (BPS) and Cervical Dystonia (CD).

Materials and methods: 39 patients (22 CD and 17 BPS) and 35 healthy subjects underwent STDT tested (on the right index finger) at baseline and during index finger abductions at movement onset, 100 ms and 200 ms thereafter. STDT was defined as the first of three intervals at which participants recognize two stimuli as separate. We also recorded kinematic features of index finger abduction.

Results: Between-group ANOVA for STDT values at baseline showed that patients with BPS and patients with CD had higher STDT values in comparison to healthy subjects. In patients with BPS, in patients with CD as well as in healthy subjects index finger abductions significantly modulated STDT values. In healthy subjects the increase in STDT values was significant at 0 ms, 100 ms and 200 ms. In patients with BPS the STDT values showed a pattern of STDT modulation similar to healthy subjects although set to higher STDT values. In CD patients during index finger abductions STDT increased to a higher extent and lasted longer than in healthy subjects.

Conclusions: Our findings showed that although BPS and CD share increased STDT values at baseline, the two types of focal dystonia differ in the mechanisms of temporal coupling between tactile information temporal processing and motor output during movement execution. CD and BPS differ in the extent of disruption of basal ganglia-thalamus interplay involved in sensory gating.

C5

Tremor and other movement disorders in patients affected by Klinefelter Syndrome

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Background: Klinefelter Syndrome (KS) represents the most common sex chromosomal disorder in males with key finding of hypergonadotropic hypogonadism. Previous research suggests that psychiatric and neurologic disorders might be overrepresented in KS patients, although the specific evaluation of movement disorders appears largely unexplored.

Objective: To evaluate the presence and categorization of tremor and other movement disorders in KS patients.

Material and Methods: Consecutive male patients with genetically confirmed KS were enrolled. Each patient underwent a clinical evaluation including: demographic data, age at KS first signs onset and diagnosis, type of presenting symptoms, current medications and dosage, presence of comorbidity. The correct identification by standard karyotype (chromosome analysis) was registered for each patient. Each patient underwent a complete neurological evaluation, with special focus on presence of tremor and other movement disorders such as: bradykinesia, rigidity, dystonia, ataxia and myoclonus.
Tremor and other parkinsonian symptoms were also evaluated with the UPDRS-III (items 20-26), the Essential Tremor Rating Assessment Scale (TETRAS) ADL subscale and an assessment tool specifically designed for this study. In KS patients with evidence of movement disorders a brain MRI was performed, while those with lateralized resting tremor undergo a brain [(123)I]FP-CIT SPECT. A control group of matched healthy subjects was also enrolled.

Results: Sixteen male KS patients with a mean age 40.1±15.4 years were included. At chromosome analysis, 13 presented with 47, XXY, two with 48, XXYY, and one mosaicism 47 XXY/46XY. Nine patients presented tremor, statistically increased compared to control group ($p<0.001$). Tremor was of mixed type in six patients. More specifically, postural tremor was detected in 8 patients, intentional tremor in 6 patients (always concomitant with the postural component), while resting tremor was present in 4 patients. One patient presented with dystonic tremor.
Mean score of UPDRS-III (only items 20-26) was 5.1 ± 6.6, while TETRAS-ADL score was 8.0 ± 7.8. In patients with lateralized tremor, [(123)I]FP-CIT SPECT was positive in one of them with evidence of a dopamine nigrostriatal terminal defect. Bradykinesia and rigidity were detected in three patients. Finally, two patients presented with myoclonic movements.

Conclusions: Movement disorders are common in patients affected by KS and often underevaluated. Among them, tremor represents the most frequent and the role of testosterone administration, often worsening these symptoms, should be adequately investigated.

C6

Prevalence and clinical correlates of mild cognitive impairment subtypes in Parkinson's disease: cross-sectional data from the PACOS study

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Introduction: About 30% of Parkinson's Disease (PD) subjects have cognitive performance suggestive of Mild Cognitive Impairment (MCI). However, several definitions were used for PD-MCI, leading to large variations in reported frequencies.

Objectives: To evaluate the prevalence and clinical correlates of PD-MCI in a large, hospital-based, cohort of PD patients from Southern Italy.

Methods: We collected cross-sectional data from the Parkinson's disease COgnitive impairment Study (PACOS), a multicenter study involving two Movement Disorder Centers located in Southern Italy. Patients affected by PD were diagnosed according to the Gelb's diagnostic criteria [1]. PD-MCI was classified with modified level-II Litvan's criteria [2] . PD severity was evaluated with the UPDRS–Motor Evaluation (UPDRS-ME) and the Hoehn-Yahr (HY) scale. Activities of daily living and depressive symptoms were also measured.

Results: The study included 659 PD patients (57.5% men; mean age 67.0±9.7years), with a mean age at onset of 63.2±10.5 years, and a mean disease duration of 3.8±4.6 years. The mean UPRDS-ME score was 25.8±12.30 with a mean HY stage of 2.0±0.6. PD-MCI was diagnosed in 261 (39.6%) subjects, and was more common among men than women (58.2% versus 41.8%, respectively). 259 subjects out of 659 had early PD (disease duration ≤1 year), and in those subjects MCI was diagnosed in 30.1% of individuals. An amnestic MCI multidomain phenotype was the most frequent MCI subtype in PD (39.1% of the overall sample and 43.9% in early PD).

Conclusions: About 40% of patients with PD in the PACOS showed a MCI phenotype, thus confirming previous data collected by hospital-based samples with the latter condition. PD-MCI was significantly more frequent in old subjects with severe motor impairment. Prospective data on our cohort will further detailed the prognostic role of PD-MCI in predicting dementia in PD.

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C7

A new neurophysiological tool for differential diagnosis in tremor syndromes: The Tremor Stability Index

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Objective: We present a robust new neurophysiological measure, the Tremor Stability Index (TSI), which can discriminate Parkinson's disease tremor (PD) and Essential Tremor (ET) with high diagnostic accuracy.

Background: Misdiagnosis among tremor syndromes is common, and can impact on both clinical care and research. To date no validated neurophysiological technique is available that has proven to have good classification performance, and the diagnostic gold standard is the clinical evaluation made by a movement disorders expert.

Methods: The TSI is derived from kinematic measurements of tremulous activity. It was assessed in a test cohort comprising 16 rest tremor recordings in tremor-dominant PD and 20 postural tremor recordings in ET, and validated on a second, independent cohort comprising a further 50 tremulous PD and ET recordings. Clinical diagnosis was used as gold standard. 100 seconds of tremor recording were selected for analysis in each patient. The classification accuracy of the new index was assessed by binary logistic regression, and by receiver operating characteristic (ROC) analysis. The diagnostic performance was examined by calculating the sensitivity, specificity, accuracy, likelihood ratio positive, likelihood ratio negative, area under the ROC curve, and by cross-validation.

Results: TSI with a cutoff of 1·05 gave good classification performance for PD tremor and ET, in both test and validation datasets. TSI sensitivity, specificity and accuracy ranged between 88-95%, 88-95% and 90-92%, respectively. ROC analysis showed an AUC of 0·916 (95% C.I. 0·797 – 1·000) for the *Test* dataset and a value of 0·905 (95% C.I. 0·812 – 0·998) for the *Validation* dataset. Classification accuracy proved independent of recording device and posture.

Conclusion: In conclusion, the TSI can aid in the differential diagnosis of the two most common tremor types, presents a high diagnostic accuracy, can be derived from short, cheap, widely available and non-invasive tremor recordings, and is independent of operator or postural context in its interpretation.

C8

Activation of peripheral immunity in Parkinson's disease favors a pro inflammatory phenotype

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Introduction: Parkinson's disease (PD) is a frequent neurodegenerative disease characterized by both motor and non-motor features. Accordingly, neuronal loss strikes not only the midbrain substantia nigra but also other widespread neuronal populations, from the bowel to the cerebral cortex. Surviving neurons show intraneuronal inclusions, the Lewy bodies, whose main component is α-synuclein (α-syn). α-syn exerts several functions, among which the cross-talk with the immune system might be of particular relevance for therapeutic purposes.

Objective: To characterize the role of peripheral adaptive immunity in an Italian cohort of PD patients.

Methods: We enrolled 82 PD patients (49 men; mean age at onset 69.2±8.7) and 47 healthy controls (HC, 25 men, mean age 66.9±10). After informed consent, we obtained complete clinical-demographic data and samples of peripheral blood. All subjects were tested for complete blood count with WBC subtypes. We then analysed T cell surface antigens with flow cytometric analysis (particularly Treg and Teff) and their cytokines production with ELISA. Moreover dopamine receptor (DR) expression was assessed with real-time PCR.

Results: PD patients showed a higher proportion of pro-inflammatory and lower proportion of anti-inflammatory lymphocyte subpopulations compared to HC (Th1: 100x106 in patients vs 80x106 in HC; Th2: 80x106 in patients vs 40x106 in HC p=0,007). Pro-inflammatory cytokines production was higher in PD patients than in HC (IFNγ: 230 vs 50 pg/mL; TNFα 230 vs 100 pg/mL; p<0,05). DR expression on Treg was lower in PD patients than in HC (especially for D2 like receptors).

Discussion: Our study showed that PD patients have a peripheral pro-inflammatory phenotype compared to HC. Activation of adaptive immune response in periphery may prime the central effect of microglia, contributing to neurodegeneration in PD. The possibility that such cascade is triggered by α-syn acting as a peripheral antigen, is worth further investigation.

C9

Gender-specific pattern of sensori-motor network connectivity in *de novo* Parkinson's disease patients

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Background: Epidemiological studies have revealed that male sex is a prominent risk factor for developing Parkinson's disease (PD). Contrariwise, as the disease progresses, female PD patients seem to be at higher risk to develop motor complications. Compelling evidence suggest that a gender-specific pattern within the nigro-striatal dopaminergic pathway may underlie these differences. Previous imaging studies have suggested the presence of a gender effect on brain morphology and functional connectivity.

Objectives: To investigate the gender-difference effect on the spontaneous neuronal activity within the Sensori-Motor Network (SMN) in early untreated PD patients, using the Amplitude of Low-Frequency Fluctuation (ALFF).

Methods: Fifty-six de novo PD patients (30/26 males/female) and 23 (13/10 males/females) matched healthy controls (HCs) were enrolled in the study. Whole brain structural and functional imaging was performed on a 3T GE MR scanner. Statistical analysis of functional data was completed using BrainVoyager QX software. Voxel-Based Morphometry (VBM) was used to test whether between-group differences in connectivity were related to structural abnormalities.

Results: Compared with female PD patients, male PD patients showed an increased ALFF connectivity within the SMN ($p<0.05$ corrected) in the 5-slow band. No ALFF differences were detected between male and female HCs. VBM analysis did not reveal any statistically significant differences in local grey matter between female and male PD patients and between all patients and HCs ($p<0.05$. FWE).

Conclusions: Our findings revealed that the organization of the intrinsic functional connectivity within the SMN in PD differs between genders, even in the early stage of the disease. The abnormal ALFF resulting from the gender-difference effect might help our understanding of epidemiological and clinical PD features. We hypothesize that this specific pattern may be related to the presence of a gender-specific nigro-striatal dopaminergic pathway and may also rely on the development of divergent clinical features between males and females throughout the disease course.

C10

Impaired pain processing in functional dystonia

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Introduction: Pain is often experienced by patients with functional dystonia and might occur also in body segments not affected by involuntary movements.

Objective: In this study, we evaluated the sensory-discriminative and cognitive-emotional aspects of pain in patients with functional and idiopathic dystonia. To this aim, we assessed pain threshold and pain tolerance in both the affected and unaffected limbs.

Methods: We enrolled 10 patients with idiopathic Cervical Dystonia (CD), 10 patients with functional dystonia (F-dys) and 15 age- and gender matched Healthy Controls (HC). All F-dys patients had symptoms restricted to the left hemibody, except for 2 with right side involvement. Clinical evaluation included Burke-Fahn-Marsden Rating Scale (BFMRS), the pain score of the TWTRS, Hamilton's Depression and Anxiety Rating Scales (HDRS, HARS). We assessed tactile threshold, Pain Threshold (P-Th) (intensity at which sensation changed from unpainful to faintly painful) and Pain Tolerance (P-Tol) (intensity at which painful sensation was intolerable) by delivering electrical pulses of increasing intensity to the index finger of each hand.

Results: Compare to CD patients, those affected by F-Dys showed a significant increase of P-Th only in the affected hand ($p=0.04$) and a significant increase of P-Tol in both the affected ($p = 0.03$) and unaffected ($p=0.04$) hands. No difference was found between idiopathic CD and HC in pain thresholds, regardless of the presence of pain in CD. No correlations were show between P-Th or P-Tol with pain score, HDRS, HARS, BFMRS, disease duration, age at onset.

Conclusion: Patients with functional dystonia have an impairment of the sensory-discriminative component of pain in the affected hand and of the cognitive-emotional component of pain in both hands, regardless of the presence of abnormal movements.

C11

Assessment of CSF biomarkers for Progressive Supranuclear Palsy

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Background: Progressive Supranuclear Palsy (PSP) is a severe condition whose phenotypic spectrum underlies either different topographical distribution or occurrence of neurodegenerative events [1]. Measurement of cerebrospinal fluid (CSF) proteins allows to measure the brain pathological changes and follow diseases' progression [2]. Despite the neuropathological hallmarks of PSP are well-established, possible CSF biomarkers are yet unavailable.

Objective: To assess the value of CSF amyloid-beta-42 (Aß42), total and phosphorylated-181 tau proteins (t-tau and p-tau) as biomarkers of PSP.

Methods: Differences in CSF concentration of Aß42, t-tau and p-tau of 40 PSP patients and 60 controls (CTL) with non-neurodegenerative diseases, matched for age and gender distribution, were measured by means of one-way-ANOVA. Cut-off points were then calculated with the ROC-analysis. Correlations of markers with clinical features of PSP patients (age, disease duration, PSP-Rating-Scale score, MMSE score) and CSF parameters (lactate, albumin, total proteins content) were investigated with the Spearman's test.

Results: PSP patients, with respect to CTL, exhibited significantly lower concentrations (pg/ml) of Aß42 (550.94±201.9 vs 737.8±192.8 mean±st.dev., $p<0.0001$), t-tau (202.0±99.7 vs 243.1±77.5, $p<0.05$) and p-tau (35.1±16.8 vs 41.3±12.6, $p<0.05$). Cut-off points were: Aß42=578.5 (80% sensitivity (Se), 60% specificity (Sp); AUC=0.75,$p<0.0001$); t-tau=206.5 (70%Se, 60%Sp; AUC= 0.67, $p<0.01$); p-tau=34.5 (70%Se,62%Sp, AUC=0.69, $p<0.01$). Correlation analysis showed a significant inverse relationship between Aß42 and PSP-Rating-Scale score ($R=-0.474$, $p<0.01$).

Conclusions: In PSP, CSF levels of Aß42, t-tau and p-tau are reduced. Of interest, unlike t-tau and p-tau, Aß42 decreases in parallel with the clinical worsening, as measured with PSP-Rating-Scale. CSF reduction of Aß42 may account for amyloid mismetabolism and extensive synaptic dysfunction [3], pathological events occurring in the neurodegenerative process of PSP [4]. In this light, Aß42 might represent a potential biomarker to monitor disease progression in PSP.

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C12

Neurological side effect of immunosuppressants: tremor after kidney transplantation

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Introduction: Neurologic complications are a significant cause of morbidity due to immunosuppression after transplantation. Although tremor is one of the commonest symptoms in transplanted patients, there are no studies systematically assessing its phenomenology and etiology in this population.

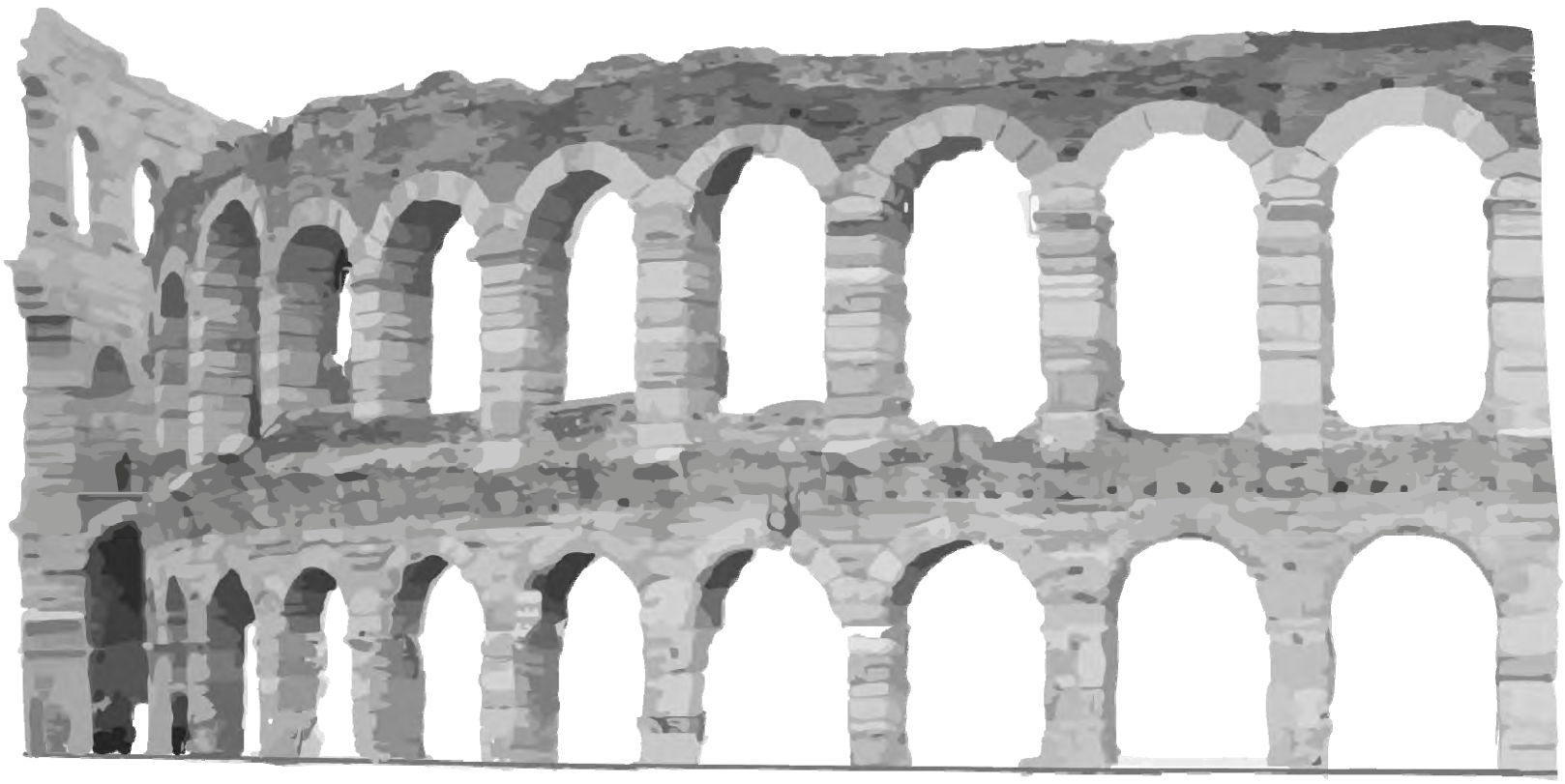
Objective: To assess the prevalence, phenomenology, and putative pathophysiology of tremor in transplanted patients under treatment with different immunosuppressive drugs.

Materials and Methods: One-hundred-twenty consecutive patients (46 women/74 men; mean age: 57.1±12.8 years) kidney transplanted were enrolled. Sixty-six were treated with tacrolimus (Ta) (34 with the prolonged-release formulation and 32 with the immediate-release formulation), 32 with Cyclosporin A (CsA) and the remaining 23 with other non-Calcineurin Inhibitors drugs (n-CnI). All subjects were assessed using the Fahn-Tolosa-Marin (FTM) Tremor Rating Scale and the Scale for the Assessment and Rating of Ataxia (SARA) by evaluators blinded to treatment allocation.

Results: Fifty-one patients (77.3 %) in the Ta group reported to be affected by tremor, 17 (53.2 %) in the CsA group, and 5 (9.1%) in the n-CnI group ($p<0.01$). FTM rating score was higher in the Ta than in the n-CnI ($p<0.01$) and CsA group ($p<0.05$). Postural and action tremor were the commonest components and tremor more frequently affected the arms. ADL were significantly impaired in Ta group compared to both other groups ($p=0.002$). There was a significant correlation between FTM and SARA scores ($rho=0.526$, $p<0.0001$). No difference between drug formulation were disclosed.

Conclusion: n-CnI (mostly Ta, regardless of the formulation) are a common cause of tremor in transplanted patients. More frequently tremor features both a postural and kinetic component and affects the arms. The correlation between the FTM and SARA scores suggests a centrally-acting mechanism underpinning the development of tremor in this population of patients.

Poster



P1

The natural history of a cohort of isolated autonomic failure patients

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Introduction: Synucleinopathies are a group of neurodegenerative diseases that can begin with isolated autonomic failure (AF) as the sole clinical feature. Usually within 5 years most patients develop cognitive/motor involvement converting from AF to other synucleinopathies.

Objective: To evaluate the natural history of a cohort of patients with isolated AF referred to a tertiary centre.

Methods: We retrospectively identified patients with a 5-year history of isolated AF referred to our Department between 1981 and 2010 and evaluated at least once a year during the disease course. Clinical data were collected from medical records and updated at every follow-up visit. Neurogenic orthostatic hypotension was confirmed by Tilt-test. T-test, Wilcoxon rank-sum test and x2 test were performed as appropriate.

Results: A total of 47 patients with AF were included (36 males, mean age at disease onset: 54.4±9.5 years), 19 were deceased at the time of the study (mean disease duration: 13.6±7.1 years). At last follow-up visit 31 patients showed isolated AF (AF group) while 16 of them developed motor/cognitive impairment (converters groups) after a 5-year latency from the dysautonomic onset (10 met the consensus criteria for Multiple System Atrophy, 2 for Dementia with Lewy Bodies, 1 for Parkinson Disease while 3 remained undefined parkinsonism). Converter patients showed a higher percentage of deaths (68.8% vs. 25.8%,p=0.004) and lower disease duration (9.8±3.3 vs. 15.6±7.7 years,p=0.0058) than AF group. The first group showed an earlier urinary dysfunction onset (1.6 vs. 5.0 years,p=0.0237) and more frequently required intermittent catheterization (28.6% vs. 6.5%,p=0.043) than the second one.

Conclusions: This is one of the largest follow-up studies reported to date on the natural history of AF patients. About 34% of patients with at least 5-year history of AF develop motor/cognitive impairment. The converters group had a shorter median disease duration than those with isolated autonomic failure and showed more frequently urinary involvement.

P2

Addition of non-immersive virtual reality to treadmill training drives changes in cholinergic activity and obstacle negotiation in patients with Parkinson's disease and older adults

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Background: Deficits in the cholinergic system may contribute to a change in gait characteristics under multitasking situations and heightened risk of falls in older adults and people with Parkinson disease (PD). The link between cholinergic system, cognition and mobility may be bidirectional. Based on the assumptions that brain plasticity requires interventions tailored to reorganize specific brain circuits, exercise in a virtual reality environment could enhance neuroplasticity targeting both motor and cognitive circuitry.

Objective: The aim of the present study was to test whether an intervention combining treadmill training (TT) with non-immersive virtual reality (VR), targeting both motor and cognitive aspects of safe ambulation, would impact cholinergic functions and multitasking mobility more than treadmill training would alone.

Methods: We recruited 39 participants with a history of two or more falls (24 patients with PD and 15 age and gender matched older adults). Cholinergic activity was estimated by means of short latency afferent inhibition, a transcranial magnetic stimulation (TMS) technique. Gait speed was measured both during usual walking and while negotiating physical obstacles (multitasking situation). Participants were randomly assigned to TT (22 participants) or TT plus VR (17 participants) trainings arms. Participants were trained for 6 weeks, 3 times a week. TMS and mobility evaluations were performed at baseline, immediately after the training, and 6 months after the end of the treatment.

*Results***:** Immediately after training, gait speed under usual walking condition improved in both training groups. Gait speed under obstacle negotiation improved after training only in the TT plus VR group. Furthermore, only the TT plus VR rehabilitation induced measurable changes of short latency afferent inhibition, thus suggesting plastic modifications of cholinergic transmission.

*Conclusions***:** Addition of non-immersive virtual reality to treadmill training drives changes in cholinergic activity and obstacle negotiation in patients with Parkinson's disease and older adults.

P3

Functional connectivity of the supplementary motor area in *de novo* PD patients with fatigue

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Background: Fatigue is a common non-motor symptom in Parkinson's disease (PD), arising either in early or later stage of the disease. Previous neurophysiological and imaging studies have consistently demonstrated that fatigue is associated with a dysfunction within brain areas involved in the motor planning, suggesting a pivotal role played by the supplementary motor area (SMA).

Aim: To investigate the functional connectivity of the SMA in *de novo* PD patients with and without fatigue, by using a seed-based resting-state functional MRI.

Methods: Twenty PD patients with fatigue (f-PD) and 20 PD patients without fatigue (nf-PD), and 20 age and sex-matched healthy controls (HCs) were enrolled in the study. 16-items Parkinson fatigue scale (PFS) was used to assess presence and severity of fatigue. Whole brain structural and functional imaging was performed on a 3T GE MR scanner. Statistical analysis of functional data was completed using BrainVoyager QX software. A seed-based approach was used to compare f-PD and nf-PD patients, selecting the SMA and the pre-SMA as regions of interest. Voxel-based morphometry (VBM) was used to test whether between-group functional changes were related to structural differences.

Results: Compared with nf-PD patients, f-PD patients showed a decreased connectivity within the left SMA and the left middle frontal gyrus as well as an increased connectivity within the left pre-SMA and the left post-central gyrus ($p<0.05$ corrected). VBM analysis did not reveal any significant volume difference between f-PD and nf-PD patients and between all patients and HCs ($P < 0.05$; family-wise error).

Conclusions: In the present study f-PD patients showed the presence of a disrupted connectivity between the SMA and several cortical areas involved in motor planning and executive attention. This aberrant functional connectivity may rely on an impairment during both programming and controlling the motor execution, likely leading to the difficulty in performing self-initiated movements which characterized f-PD patients.

P4

Extrapyramidal involvement in Amyotrophic Lateral Sclerosis (ALS): results of a prospective population-based study

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Objective: To assess frequency, clinical characteristics and functional neuroimaging correlates of parkinsonian signs in new-diagnosed ALS patients.

Background: Parkinsonian signs in ALS patients have been reported in few papers, and their pathophysiological correlates are largely unknown.

Methods: We recruited ALS patients resident in Piemonte, Italy, diagnosed during 2013. All patients were evaluated by two neurologists expert in movement disorders to detect the presence of parkinsonian signs (ALS-P) at diagnosis, 1 and 2 years. Patients underwent genetic tests and neuropsychological examination, and severity of parkinsonian symptoms was rated by MDS-UPDRS. SPECT with [123]FP-CIT was analysed visually and semiquantitatively; FDG-PET was compared between patients with or without parkinsonian signs by means of SPM8.

Results: Out of a total of 114 eligible ALS patients, 101 (64 men and 37 women; mean age at onset of 65.1 ± 11.7 years) were recruited. 28 patients (27.7%) were classified as ALS-P at the first visit. MDS-UPDRS scores were higher in ALS-P than ALS patients, in particular ALS-P patients showed more serious bradykinesia, rigidity and tremor ($p<0,05$). ALS-P patients were more frequently male (relative risk 1.36, c.i. 1.04-1.80; $p=0.05$). Age and site of onset, cognitive impairment, ALSFRS-R and MRC scores, genetics and survival were similar in ALS and ALS-P patients. Both visual and semi-quantitative analysis of SPECT with [123]FP-CIT revealed a normal scan in all but two ALS-P patients. On FDG-PET, ALS-P patients showed lower FDG uptake in left cerebellum and a relatively more preserved metabolism in right insula and in some right frontal regions compared to ALS patients.

Conclusions: In this population-based study, more than one fourth of ALS patients showed parkinsonian signs. In ALS-P patients no significant nigrostriatal involvement could be demonstrated. Instead, relative hypometabolism in the left cerebellar hemisphere together with more preserved right prefrontal metabolism were found. These data suggest the involvement of brain circuitries other than classical nigrostriatal ones in ALS patients with parkinsonian signs.

P5

Sensorimotor modulation during motor imagery

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Introduction: Sensorimotor integration can be studied with a Transcranial Magnetic Stimulation (TMS) paradigm, known as Short latency afferent inhibition (SAI). When TMS stimulus over the Motor cortex (M1) is preceded by peripheral nerve stimulation, M1 excitability is reduced. SAI could be involved in "surround inhibition", a neural mechanism to facilitate selective motor execution. It has been shown that SAI reduced exclusively in movement-related muscles, and this reduction begins as the preparation to movement initiates. Reduced SAI may be due to somatosensory input providing less inhibition on M1 corticospinal output (sensorimotor modulation). Even if actual and imagined movements share overlapping circuits, sensorimotor modulation during imagined movements has not been studied so far.

Objective: The aim of the present study was to investigate whether SAI modulation in movement-related muscles occurs during a motor imagery task.

Methods: Participants had to perform and to imagine (Kinesthetic Motor Imagery) an abduction of their index or little finger, in response to an acoustic cue. SAI was evaluated in two preparation phases between a 'warning' and a 'go' signal and in the reaction time after the 'go' signal, before any EMG activity.

Results: During the reaction time phase there was a reduction of SAI in movement-related muscle. We found similar results for the motor imagery task, where a decrease of SAI was also observed, even if with a smaller extent compared to motor execution. Further, we found a correlation between SAI values and fifth KVIQ-10 kinesthetic item: the higher was the score (i.e., greater the ability to imagine finger movements), the stronger was the modulation of SAI.

Conclusion: Changes in SAI observed during a motor imagery task suggest that sensorimotor modulation occur already at a cognitive level during motor preparation. This paradigm could be applied for assessing sensorimotor integration and motor planning in patients with movement disorders.

P6

Oxytocin blood levels as predictor of social cognition in Huntington's disease

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Introduction: The role of Oxytocin (OT) as social hormone is supported by the improvement of recognition of the faces' expression after intranasal OT. Impaired social behaviour, partly related to altered perception of emotions, is commonly reported in Huntington's Disease (HD).

Objectives: To evaluate OT plasma level as possible predictor of social cognition performances in a population of symptomatic HD patients.

Methods: 12 patients with symptomatic HD (stage II S&F) without cognitive impairment were evaluated at the baseline and after 2-years follow-up (8 pts) for social cognition through an extensive battery of neuropsychological tests (Faux Pas test, Bush vignettes test, emotion recognition from both faces expression and verbal stimuli, Strange stories test). Plasma OT levels at the baseline were sampled in the whole cohort of subjects and the relationship between the levels of OT and social cognition at the baseline and at follow-up was analysed. OT plasma levels were also compared to that of a population of healthy age-matched controls.

Results: OT levels did not differ in the two populations, however with a trend for lower values in HD group (average 9.9 ± 7.2 controls, 6.5 ± 2.4 HD). At the baseline OT blood levels did show any significative correlation with social cognition and cognitive tests. After 2 years follow-up, higher OT levels correlated with better performances at the Neutral\Faux Pas score ($p<0.05$) and with higher ability to recognize happiness from verbal stimuli ($p<0.05$).

Conclusions: In HD patients compared to controls we found with a significant trend lower OT circulating levels; moreover, the follow-up analysis pointed out a possible role of OT in predicting the progression of social cognition in HD. The present data, limited by the sample size and by the biological tissue studied, need to be confirmed in a larger population analysis even by correlating with cerebrospinal fluid measurement.

P7

Substantia nigra neuromelanin assessment as an imaging biomarker of disease progression in Parkinson's disease

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*Introduction***:** A specific T1-weighted Magnetic Resonance Imaging (MRI) sequence has been shown to detect Substantia Nigra (SN) neuromelanin (NM) signal changes that accurately discriminate Parkinson's disease (PD) patients from controls, even in early disease stages. However, it is unclear what happens to these SN changes in later disease stages.

*Objective***:** To investigate the pattern of SN-NM area loss and Contrast Ratio (CR) intensity changes in Late-Stage Parkinson's disease (LSPD) patients, compared to *de novo* PD patients and PD patients with a 2-5 year disease duration in order to evaluate NM changes throughout disease progression.

Methods: A comparative cross-sectional study was performed, analyzing SN-NM MRI signals in late stage PD patients (LSPD) (Schwab and England Activities of Daily Living Scale score 3), comparing them with other disease stages, i.e. *de novo*, 2-5 year PD and controls. For all groups SN-NM signal area and contrast ratio (CR) values for the internal and lateral SN regions were obtained with semi-automated methods.

Results: 13 LSPD, 12 *de novo* patients with PD, 10 PD patients with a 2-5 year disease duration, and 10 controls were included. NM signal area was significantly decreased in *de novo* PD compared to LSPD (*P-value* = 0.005; sensitivity: 75%; specificity 92% and AUC: 0.86). In the lateral SN region, a decrease in the CR was detected in all PD groups compared to controls; despite not reaching statistical significance, a slight increment was observed comparing LSPD to 2-5 year PD. NM signal area significantly correlated with HY (R=-0.37; *P<0.05*) and MDS-UPDR part II (R=-0.4; *P <0.05*) while a weak correlation was found with MDS-UPDRS part III (R=-0.26; *P*: 0.1).

*Conclusion***:** SN area evaluated by NM-sensitive MRI may be a promising biomarker of nigral degeneration and disease progression in PD patients.

P8

GPi deep brain stimulation for re-emergent dyskinesia and axial symptoms after long-standing, well-targeted subthalamic stimulation in Parkinson's Disease: a case series

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Introduction: Deep Brain Stimulation (DBS) of either Subthalamic Nucleus (STN) or Globus Pallidus interna (GPi) is currently the gold standard therapy for Parkinson's Disease (PD) with motor fluctuations. Choice between the two targets is based on each patient's prominent clinical features. Axial impairment and dyskinesia, which cannot be controlled by management of stimulation and drugs, may arise during disease progression in STN-implanted patients, requiring new therapeutic strategies.

Objective: To describe the outcome of GPi-DBS on dyskinesia and axial symptoms (mainly freezing of gait and postural instability) after chronic subthalamic stimulation in patients with advanced PD.

Methods: Ten out of 220 STN-implanted patients with insufficient clinical control due to disease progression despite well-targeted stimulation (7F, 3M, mean age 61.7±8.1y, mean disease duration 22.2±6.2y, mean time between implants 7.6±2.5y, follow-up range from 1 to 7y from second surgery) were selected for a second GPi-DBS surgery. A thorough evaluation of disease severity (UPDRS parts III and IV), grade of dyskinesia and axial symptoms over time was carried out at follow-up visits.

Results: No permanent adverse effects were observed. GPi stimulation was effective in reducing axial symptoms, dyskinesia (UPDRSIV) and Levodopa Equivalent Daily Dose (LEDD) in many cases, with continuous efficacy being detectable up to 7 years after surgery. In one case, GPi-DBS allowed an increase in LEDD thanks to improved control of dyskinesia. In five cases STN-DBS stimulation has been progressively tuned down and eventually turned off, while the other patients required maintenance of low intensity STN stimulation to effectively control tremor and/or bradykinesia.

Conclusion: Re-emergent dyskinesia and new axial symptoms in STN-DBS patients can be lastingly controlled by GPi chronic stimulation. In our experience, selected patients with early-onset PD who underwent STN surgery before their sixties can benefit from a second GPi-DBS implant to manage disease progression.

P9

Transcranial direct current stimulation and Spinal Direct current stimulation for treatment of gait disorders in Parkinson Disease: a pilot triple cross-over study

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Introduction: Progression of Parkinson's disease (PD) is characterised by motor deficits which respond less to dopaminergic therapy. Interest in neuromodulation technique is increasingly emerging in the rehabilitation treatment of PD. Direct Current Stimulation (DCS), is a non-invasive brain stimulation technique able to modulate the activity of brain areas through the application of small electrodes on the scalp or at spinal level. Previous studies suggested that transcranial DCS (t-DCS) is effective in improving motor symptoms in patients with neurological diseases. On the contrary, literature on the effect of spinal DCS (s-DCS) is scant.

Objective: The aim of this study is to evaluate the efficacy of t-DCS and s-DCS in the treatment of gait disorders in PD.

Methods: This study was performed on 14 subjects with PD, according to a randomized, double-blind, cross-over design. All participants underwent to anodal t-DCS over primary motor cortex, anodal and cathodal s-DCS applied to the 10th dorsal segment. Each treatment foresees 5 daily sessions lasting 20 minutes each. Each stimulation cycle was followed by a 30-day observation period. Assessment included: Timed Up and Go (TUG), Tinetti Assessment Scale, Freezing of Gait Questionnaire (FOG) and Unified Parkinson's Disease Rating Scale (UPDRS-III).

Results: An improvement in all outcome measures was observed in t-DCS group after the end of treatment with a stable effect at 1-month follow-up. At the end of treatment, an improvement in UPDRS-III and FOG scores were observed in cathodal s-DCS group while anodal s-DCS group showed a significant improvement in Tinetti and FOG scores. Both spinal groups demonstrated no effect at follow-up.

Conclusion: The application of anodal t-DCS may be a relevant tool to improve motor abilities in PD and might be a useful therapeutic strategy in addition to traditional treatments.

P10

Parkinson Disease: what relationship is there between neuropsychological functioning and subjective measures of sleep quality?

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Introduction: PD is increasingly recognized as a multidimensional disorder, characterized by several non-motor symptoms, including cognitive and sleep disturbances. Cognitive alterations encompass mainly executive dysfunction, though visuospatial functions and memory may also be compromised. Sleep disturbances are extremely frequent in PD affecting up to 90% of patients. There are some preliminary evidences of a relationship between neuropsychological functions and self-reported nocturnal sleep disturbances. Excessive daytime sleepiness was found to be a significant predictor of slowed processing speed whereas RBD predicted working memory and verbal fluency performances.

Objective: To analyze the relationship between subjectively reported sleep alterations and cognitive functions in a large series of advanced Parkinson Disease (PD) patients evaluated with an extensive neuropsychological test battery.

Methods: We enrolled 122 PD patients who completed two self-administered sleep measures: the modified version of Parkinson's Disease Sleep Scale (PDSS-2) and the Epworth Sleepiness Scale (ESS). Neuropsychological assessment encompassed five cognitive domains: reasoning [Raven Coloured Matrices Test (CPM47)]; memory [Corsi's Block Tapping Test (CBT), Paired Associate Learning (PAL)]; attention [Digit Cancellation Test (DCT), Trail Making Test A (TMTA)]; frontal executive functions [Trail Making Test B (TMTB), Frontal Assessment Battery (FAB)] and phonemic and category verbal fluency to evaluate language skills (PVF, CVF).

Results: Mean neuropsychological scores were within normal ranges (CPM47 28.2±6.1; DCT 46.5±9.9; TMTA 58.3±48.9; TMTB 174.4±148.9; FAB 15.4±2.7). Patients showed only low levels of sleep disturbances (PDSS-2 23.3±11.3) and daytime sleepiness (ESS 8.8±5.1). A significant correlation was found between PDSS-2 scores and non-verbal reasoning (CPM47 p=-0.0297), as well as attentive skills (DCT p=-0.295; TMTA p=-0.111), executive functions (TMTB p=0.285; FAB p=-0.330) and language abilities (PVF p=-0.201; CVF p=-0.255).

Conclusion: This study show that in advanced PD patients sleep disturbances are selectively related to sub-cortical neuropsychological functions and not to short term memory and consolidation.

P11

Relationship between neuropsychological and motor profile in early and late Parkinson's disease

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Introduction: Approximately 25% of the patients with Parkinson's disease have cognitive deficits since the beginning of their illness, mainly regarding executive functions and working memory, however correlation between cognitive and motor profile is not clear.

Material and methods: 119 patients diagnosed with idiopathic Parkinson's disease were included in this study and divided into two groups: PD early (60 pts), newly diagnosed and naive to dopaminergic medication, and PD late, with longer history of disease (mean 12ys) and treated with dopamine replacement therapy according to clinical practice. This latter group was highly selected, being composed by patients eligible to DBS procedure. The two groups were matched according to age at the time of the evaluation. Neurological (UPDRS and L-dopa response) and complete neuropsychological battery investigating cognitive domains of language, attention, memory, executive and visuo-spatial functions (trail making test, attentional matrices, token test, verbal fluency tests, short story, raven progressive matrices, clock test) were carried on. We investigated the correlation between cognitive and motor performances, at first in the whole sample and then into the two groups.

Results: In our cohort of patients lower motor impairment and higher response to levodopa are related to better cognitive performances in the executive and language domains, while poorer motor functions are related to a more deteriorated cognitive setting. This correlation is found both for PD early and PD late patients; however the number of significant correlations and their strength appears to be higher in PD late group.

Conclusion: Our results show that in advanced PD patients with no overt signs of cognitive impairment levodopa reponse is highly correlated with cognitive integrity. On the other hand in PD early population the correlation is weaker probably due to higher heterogeneity of the population and unknown evolution of the disease in these patients. Follow-up studies are needed to clarify this aspect.

P12

Dietary habits , motor and cognitive impairment in Parkinson's Disease

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Background: Diet and nutrition play an important role in brain aging and might influence disease progression in neurodegenerative diseases.

Aim: To evaluate the relationship between diet habits and motor or cognitive function in Parkinson's disease (PD) patients.

Methods: Consecutive PD patients underwent a cross-sectional standardized motor, cognitive and functional assessment and fulfilled a food frequency questionnaire. The relationship between dietary habits and the following variables were evaluated by using non parametric testing after multiple comparison correction ($p<0.005$): age, gender, disease duration, motor impairment (UPDRS-III), global cognition (MMSE), levodopa daily equivalent dose (LEDD), presence of behavioural disturbances. The results were confirmed in multivariate analyses adjusted for age, gender and disease duration.

Results: Two-hundred eighty-three patients entered the study; the mean age was 72.6 + 9 years with a mean disease duration of 7 + 5 years. The mean UPDRS-III and MMSE scores were 21 + 13 and 25 + 4 points, respectively. Red meat and total fish consumption significantly correlates with clinical features in PD, while vegetables, fruits, vitamins, coffee, thee, wine or alcohol intake did not. Higher red meat consumption was associated with worse UPDRS-III motor scores ($p=0.003$) and slightly higher LEDD ($p=0.02$). Fish intake was significantly associated with better MMSE scores ($p=0.005$) and did not correlate with motor scores or levo-dopa intake.

Conclusion: Red meat consumption might worse motor progression PD. However, higher proteins intake might be a compensatory response of energy need in complicated patients. Higher fish consumption might specifically protect against cognitive dysfunction in PD patients. The interaction between dietary habits, social status and general activity probably explain these interesting results. Longitudinal studies are need to explore the potential role of diet intervention on disease progression in PD patients.

P13

The role of cognitive rehabilitation on cognitive and motor performance in patients with Parkinson's disease

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Objective: To investigate the effect of a combined cognitive and physical rehabilitation program on the cognitive and motor outcomes in patients with Parkinson's disease (PD) without dementia.

Methods: Twenty non-demented PD outpatients (H&Y stage <2.5) were randomized to a group receiving a combined cognitive and motor rehabilitation program (Experimental group, n= 10) or a Motor Rehabilitation program (Control group; n=10). A battery of neurological scales and neuropsychological tests were administered at baseline and after two months of rehabilitation.

Results: At baseline, the two groups did not differ in age, education, age at disease onset and in cognitive screening tests. After rehabilitation training, the experimental group showed an improvement of cognitive performance on rule shift cards tests ($p<0.05$), included in the Behavioural Assessment of the Dysexecutive Syndrome (*BADS)*. Moreover, the experimental group showed an improvement of mobility and psychological well-being domains of the Parkinson's Disease–Questionnaire 39. With regard to motor outcome, the experimental group showed an improvement on *Timed Up and Go test* (TUG) and on Leg Agility task of the Unified Parkinson's Disease Rating Scale–part III. Control group showed an improvement on psychological well–being domain of the PDQ–39 and TUG. Experimental group significantly improved on prose memory test as compared to Control group.

Conclusions: The results of the present study suggest that a combined cognitive and motor rehabilitation program can improve some cognitive functions and aspects of quality of life. Moreover, it seemed to show beneficial effect on mobility, balance and walking ability in PD.

P14

Descending pain modulation in cervical dystonia and blepharospasm

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Introduction: Pain affects up to 70% of patients with Cervical Dystonia (CD), but its underlying mechanisms are largely unknown; although less frequently, also patient with blepharospasm (BS) are affected by pain (up to 30% of cases) probably with different pathophysiology. Previous reports showed that nociceptive pathway assessed by laser-evoked potentials (LEP), is normal in CD. No LEP data exists regarding BS; moreover, the role of the 'diffuse noxious inhibitory control' (DNIC) in focal dystonia has not yet been explored.

Objective: To explore DNIC system in CD and BS.

Methods: We recruited 13 CD patients (6M/7F; mean age: 56.4±11,2), 12 BS patients (1M/11F, mean age: 62,1±15,5) and 12 healthy controls (HC). Patients rated their maximum pain on an NRS scale ranging from 0 to 10; HC were pain-free. Latency and amplitude of N2/P2 component of LEP for the dominant hand were measured at baseline (T0); during the application of a heterotopic noxious stimulation (T1); 10 minutes after removal of noxious stimulation (T2).

Results: We didn't observe significant difference in N2/P2 amplitude at T0 between CD, BS and HC. We registered a significant N2/P2 amplitude reduction during T1 in HC and BS (p0.05). N2/P2 reduction during T1 was similar in BS and HC. N2/P2 amplitude returned to baseline in the three group during T2.

Conclusions: Our results suggest that the DNIC system is altered in CD and is normal in BP, regardless the clinical presence of pain. This abnormality might explain why CD patients are prone to develop pain more frequently than BP patients. Our findings would also imply that additional factors are required for pain to develop clinically.

P15

The PRIAMO study: urinary dysfunction as marker of disease progression in early Parkinson's disease

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*Background***:** New venues are currently being explored to predict disease progression in Parkinson's disease (PD), as non motor subtypes and models merging motor and non motor symptoms (NMS).

*Objectives***:** By involving a subgroup of 585 patients from the PRIAMO (PaRkinson dIseAse non MOtor symptoms) study, the present 24-month longitudinal prospective analysis aims to demonstrate that urinary dysfunction is an early marker of higher motor and non motor burden as well as lower health-related quality of life.

Methods and results: Multivariable mixed-effect logistic regression models controlling for demographic and clinical variables showed that the following NMS domains were associated with urinary dysfunction: gastrointestinal (OR:2.57,95%CI:1.67-3.97, p<0.001), cardiovascular (OR:2.22,95%CI:1.18-4.17, p=0.013), skin (OR:1.81,95%CI:1.06-3.08, p=0.029), sleep (OR:2.06,95%CI:1.34-3.16,p=0.001), pain (OR:1.85, 95%CI:1.21-2.83,p=0.004), fatigue (OR:2.40, 95%CI:1.56-3.68, p<0.001), apathy (OR:2.79,95%CI:1.72-4.52, p<0.001) and respiratory (OR:1.82,95%CI:1.02-3.23,p=0.039). Analysis also demonstrated that urinary dysfunction was associated with higher motor disability (coeff.:1.73, 95%CI:0.68–2.78, p=0.001) and lower health-related quality of life (coeff.:-0.05, 95%CI:-0.08 - -0.02, p<0.001 and coeff.:-3.49, 95%CI:-5.21 - -1.77, p<0.001), but not with more severe cognitive disability (coeff:-0.34, 95%CI:-0.92–0.24, p=0.251).

*Conclusion***:** This is the first prospective longitudinal study involving a large cohort of PD patients demonstrating the relevance of urinary dysfunction as an early marker of higher motor and non motor disability as well as lower health-related quality of life. These findings support a role for urinary dysfunction as an early marker of more severe disease progression.

P16

Pulmonary function in Parkinson's disease

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Introduction: Several lines of evidence have suggested that patients with Parkinson's Disease (PD) may have an array of respiratory abnormalities and it is well recognized that aspiration pneumonia and pulmonary embolism are the main causes of death in PD.

Objective: The aim of this manuscript is to improve knowledge about the performance of respiratory muscle function in PD, assessing ON versus OFF state pulmonary function. We also report the longitudinal spirometric findings in a subgroup of PD patients.

Methods: All patients were tested both in the OFF and in the ON state (T0). UPDRS-III scores and modified Borg scale were administered in both conditions. Pulmonary function tests included spirometry with flow-volume loops, lung volumes and airway resistance. Moreover pulmonary function tests were repeated for 14 PD patients, in ON state, between 3 and 4 years after first evaluation (T1).

Results: *Clinical Characteristics*: 34 patients with PD (26 males, 8 females), H&Y stages 1-3, mean age 63.29±11.26 years and mean duration of disease 5.74±3.41 years, were recruited. *Pulmonary Function:* At T0 patients had no pathological percentages of normal values (VC%OFF, FVC%OFF, FEV1%OFF, RV%OFF, TLC%OFF); significant differences in measurement of FEV1, FEV1%, VC% and FVC% OFF state and ON state values were highlighted. At T1, there were no significant changes from baseline in all percentages of normal values (corrected for height, sex and age).

Conclusion: Pulmonary function patterns, reported in literature for PD patients, include upper airway obstructive patterns and restrictive disorders. Our patients had no pathological percentages of normal values at T0 and no significant changes at longitudinal spirometry evaluation. However, in our study significant differences in measurement of FEV1, FEV1%, VC% and FVC% OFF state and ON state values were observed.

P17

Speech response to levodopa in late-stage Parkinson's Disease patients

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*Introduction***:** Parkinson's disease (PD) patients are affected by hypophonia, dysprosody and dysarthria that worsens with disease progression. The influence of levodopa intake on the quality of speech is inconclusive, and no data are available for late-stage PD (LSPD) patients.

*Objective***:** To assess the change of speech and voice after an acute L-dopa challenge in LSPD.

*Method***:** LSPD patients (Schwab and England ADL Scale (SE) >50 or Hoehn Yahr (HY) Stage >3 (MED ON)), underwent a levodopa challenge with a supra-maximal dose (150%). Before and after levodopa intake, each participant performed several vocal tasks selected from the European Portuguese version of the Frenchay Dysarthria Assessment version 2 in order to assess the following parameters: respiratory support for speech, voice quality, voice stability, voice variability and speech rate. Motor performance was evaluated by the MDS-UPDRS part III. All voice samples were recorded using a tabletop unidirectional microphone and subsequently analyzed by a speech and language therapist blinded to patients' therapeutic condition using the *Praat* 5.1 software.

Results: Twenty-four (14 men) of the twenty-seven LSPD patients included in the study succeeded in performing the voice tasks. Patients had a median age of 79 [IQR: 71.5-81.7] years and median disease duration of 14.5 [IQR: 11-15.7] years. A positive correlation was found between disease duration and voice quality ($R=0.8$; $p<0.05$) and variability ($R=0.793$; $p<0.05$). Levodopa significantly improved the MDS-UPDRS-III score (20%), with a beneficial effect on axial signs with the exception of speech (MDS-UPDRS item 3.1). Levodopa had no significant improvement in any speech or voice features by means of automated analysis.

Conclusion: Speech is severely affected among LSPD patients. Although levodopa still had some effect on motor performance including some axial signs, no improvement was found on speech neither by means of a clinician rating scale nor by automated analysis.

P18

Dysphagia and nutritional risk in Parkinson's disease

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Introduction: Dysphagia (feeding and swallowing difficulties) affects 80% of Parkinson's disease (PD) patients in early stages and 95% in advanced stages[1]. Dysphagia and PD are the main factors contributing to malnutrition [2]. PD patients may be at higher risk of malnutrition because of the symptoms associated with the disease and the side effects of drug therapy. The true prevalence of malnutrition in PD has yet to be accurately quantified. A systematic review found the prevalence of malnutrition can vary from 0% to 24% in PD, while 3-60% of patients were reported to be at risk of malnutrition [1].

Objective: The purpose of our study was to identify the correlation between dysphagia and nutritional risk in PD patients.

Methods: In this study 28 patients (23 ♂ and 5 ♀, mean age = 71, age range 53-87) suffering from Idiopathic Parkinson's disease and rated with the Hoehn and Yahr Scale (mean stage= 3), were included. Patients underwent the Bedside Swallowing Assessment Scale (BSAS), in combination with the oxygen saturation monitoring, and a nutritional screening using the Mini Nutritional Assessment-Short Form (MNA-SF). The Dysphagia Outcome and Severity Scale (DOSS) was used to establish the severity of dysphagia.

Results: 68 % of assessed patients showed a mild to moderate swallowing impairment (DOSS: level 5,4,3). Using the questionnaire MNA-SF, 42% of patients were at risk of malnutrition and 14% were malnourished.

Conclusion: The severity of dysphagia resulted to be statistically correlate with the nutritional risk. Hence, they should be early identified in PD for a better management of the disease.

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P19

Cerebrovascular CO_2 reactivity in symptomatic and asymptomatic orthostatic hypotension in Parkinson's disease

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Introduction: Orthostatic Hypotension (OH), one of the most debilitating feature of autonomic dysfunction, has an estimated prevalence of 30-50% in Parkinson's disease (PD); however, only 40% of patients with OH report the classic orthostatic symptoms whereas most cases remain asymptomatic [5]. Among the various mechanisms hypothesized to be involved in the occurrence of symptoms, impaired cerebral autoregulation (CA) and cerebrovascular CO_2 reactivity are considered especially relevant [2]. In particular, as already hypothesized for the cerebral autoregulatory range [4], also CO_2 reactivity may exhibit some adaptation to recurrent OH, a phenomenon that could be interpreted as a compensatory mechanism to chronic OH.

Aims: Aim of the present study is to evaluate cerebrovascular CO_2 reactivity in PD patients with OH either with or without symptoms.

Methods: Cerebrovascular CO_2 reactivity was evaluated in 30 patients with PD and OH, 15 asymptomatic and 15 symptomatic, and 15 PD-without-OH patients and compared between groups. In addition, continuous recordings of end-tidal CO_2, and cerebral tissue oxygenation and blood volume using near infrared spectroscopy were monitored during CO_2 reactivity test (inspired CO_2, 5%) [3]. CO_2 reactivity was calculated as the relative change from baseline in the values of cerebral tissue oxygenation index and tissue hemoglobin index per Torr increase in end-tidal CO_2 [1].

Results: In PD-OH patients cerebral CO_2 vascular reactivity differed significantly from PD-without-OH patients. In asymptomatic patients CO_2 reactivity was preserved, whereas in symptomatic patients it was slightly impaired and unable to fully supply metabolic demands of cerebral tissue.

Conclusions: Cerebrovascular CO_2 reactivity may increase in response to chronic OH thus substantially contributing to the overall adaptation of cerebral autoregulation and to the absence or delay of symptoms.

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P20

Urinary symptoms and associated clinical features in Parkinson's disease

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Lower Urinary Tract Symptoms (LUTS) are highly prevalent in patients with idiopathic Parkinson's disease (IPD) thus leading to a decrease in quality of life (QoL). Aims of the study were to analyze the prevalence of LUTS in different subgroups of IPD patients, the relationships between LUTS and patients' clinical features, psychological and cognitive involvement and QoL. Thirty IPD consecutive patients underwent the Unified Parkinson's Disease Rating Scale (UPDRS) motor section part III, and the Hoehn-Yahr (H&Y) scale to assess motor symptoms and severity of disease.
According to UPDRS, patients were divided into tremor-dominant type, akinetic-rigid type and mixed type PD subgroups. Cognitive status was assessed with the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MOCA). Urinary symptoms were investigated with the 3-day voiding diary, uroflowmetry and a standardized questionnaire on incontinence (Incontinence-QoL).
The Hamilton Anxiety Scale (HAM-A) and the Hamilton Depression Scale (HAM-D) were used to investigate patients' psychological status. 21 men and 9 women (mean age: 66.6 ± 10 yrs) were enrolled. Mean ± SD values of UPDRS and H&Y stage were 23.5 ± 4.6, and 2.4 ± 0.7, respectively. All patients complained of overactive bladder symptoms. Urinary incontinence (16 patients) was significantly associated with higher H&Y stages ($p<0.005$), and frequency of nocturia with higher UPDRS scores ($p<0.003$).
Old age, longer disease duration and higher H&Y stages were significantly associated with low HAM-A scores ($p<0.002$). UPDRS scores related inversely with MOCA scores ($p<0.01$) and H&Y scores related with MMSE ($p<0.01$), and I-QOL scores related with the MMSE scores ($p<0.01$). We did not observe any significantly difference between the three clinical subtypes of PD. To our knowledge, there are few studies correlating PD clinical aspects with this autonomic feature. LUTS are strictly related to age, disease duration and the severity of motor impairment.

P21

Objective and subjective data to pain evaluation in Parkinson's disease

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Introduction: Pain is a common symptom in patients whit Parkinson's disease (PD). Recent studies showed altered latencies and amplitudes of N2-P2 complex and the N1, P1 waves, considered as objective markers of impaired pain perception in PD.

Objective: To assess nociceptive pathways by using laser evoked potentials (LEPs) and to correlate electrophysiological findings with clinical scale of pain, to exploit whether the subjective perception of pain can be compared with objective electrophysiological data.

Materials and Methods: We enrolled 10 PD patients (mean age 68± years, Hoehn and Yahr stage 1,5±1), with a diagnosis of less than five years and 10 healthy subjects, without nerve and neurological diseases, matched for age and sex. Patients underwent to neuropsychological tests to exclude cognitive impairment and sensory conduction velocity (SCV) to exclude of sensory nerve pathologies. Subjective pain was evaluated with the Visual Analogue Scale (VAS), Visual Rating Scale (VRS) and Nociceptive Rating Scale (NRS). Objective pain was recorded with LEPs of upper limb by using Nd:YAG stimulator.

Results: From the inter-groups analysis results we observed significant differences between PD patients and healthy controls for N2-P2 latencies ($p=0.05$) and for N2-P2 amplitudes ($p=0.02$) in right upper limb. No significant correlations were found between LEPs parameters and clinical scales.

Discussion: These results demonstrated that the nociception system is impaired in PD, even in a not advanced stage. In particular, the impairments involved the right side, probably because the patients were right-handed and several patients showed tremor mainly on the right side. Our findings suggest that the subjective and objective perceptions of pain are not related each other, given the different individual pain feeling. Thus the neurophysiological potentials may be more reliable than the subjective individual responses to investigate the nociception system in PD, to monitor disease progression and to adjuste pharmacological treatment.

P22

Dream content in Parkinson's disease

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Introduction: In the prodromal and early stage of the disease, Parkinson's disease (PD) is frequently associated with sleep disorders (vivid dreams, nightmares and REM sleep behavior disorder -RBD). Several factors can influence dream experience, such as RBD, depressive symptoms and dosage and quality of dopaminergic drugs and other psychotropic medications.

Objective: To perform an analysis of dream characteristics in a large sample of PD patient and their relation with clinical and demographic variables.

Methods: A consecutive series of idiopathic PD Italian mother-tongue patients who attended the Parkinson's Disease Center at the Humanitas San Pio X Clinic of Milan were prospectively observed from May 2016 until October 2016. Patients with a Mini-Mental State Examination score of 24 or below and younger than 50 years old were excluded from the study. Patients were assessed with the Unified Parkinson's Disease Rating Scale part III (in ON), type and daily dosage of medications, and demographic informations. Dream content was assessed with the 'Typical Dreams Questionnaire' (55-TDQ) and an interview about the presence/absence of RBD, dreamlike narrative and the most recent drem recalled.

Results: 85 PD patients fulfilled inclusion criteria (33 women, mean age 70 ± 10.5, mean duration disease 8.5 ± 5.5 years) and recalled, on average, 6 dreams and 2,53 nightmares per month. Most common dream contents, as resulted by the 55-TDQ, consisted in: "a person now alive as dead", "falling" and "being on the verge of falling". Patients with RBD episodes with violent arm and leg movements referred a higher prevalence of dreaming of "being smothered, unable to "breathe"(χ2,$p<0.01$), "lunatics or insane people" (χ2, $p<0.05$) and "being chased or pursued"(χ2, $p<0.001$). Thepresence or absence of specific items of the 55-TDQ were significantly correlated with different dosages of levodopa and dopamine-agonists.

Conclusions: RBD patients had a higher percentage of violent dreams compared to non-RBD patients. Dopaminergic and non-dopaminergic drugs play a role in PD dream content.

P23

Severe depression after rasagiline withdrawal in patient with Parkinson's disease

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Objectives: MAO-B inhibitors has demonstrated as well-tolerated and effective in the treatment of early Parkinson's disease (PD) and added to dopaminergic treatment in motor fluctuations. Long-term efficacy of rasagiline on motor symptoms in early PD has been previously well-documented. However, regarding non motor symptoms, rasagiline did not show significant effects versus placebo on depressive symptoms in PD patients with moderate depression[2].

Methods: Here we report a patient who developed a severe depressive syndrome after rasagiline withdrawal. A 68-year-old woman, with a 1-year history of tremor and a positive familiar anamnesis for PD (mother), went to our centre. She was put on treatment with rasagiline 1 mg/daily with mild improvement of tremor after two months, suspended to a supposed allergic reaction.

Results: At follow-up visit, although PD symptomatology was clearly improved by levodopa introduction instead of rasagiline, depressive symptoms were unchanged.

Conclusions: Despite the knowledge of antidepressant efficacy of MAO inhibitors, their clinical has been limited by their side effects. While the action of selegiline and rasagiline on PD motor symptoms is clear, their efficacy on depressive symptoms has been scarsely explored. A previous study [1] did not demonstrated clear effect of rasagiline against depressive symptoms, while other observations documented a significant impairment. However, the effect of the withdrawing of these drugs has not been clearly investigated. This case provided an alternative side of view about mechanisms of action of MAO inhibitors and may open a speculation on the multitrasmettitorial effects of these drugs, which probably is not simply dopaminergic.

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P24

Impact of anxiety, apathy and reduced functional autonomy on perceived quality of life in Parkinson's disease

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Introduction: Parkinson's disease (PD) is characterized by a wide spectrum of non-motor symptoms that may impact negatively on the activities of the patient's daily life and reduce quality of life (QoL).

Objectives: To explore the impact of specific non-motor symptoms on the QoL in PD.

Methods: A sample of 84 PD outpatients were enrolled and underwent the Montreal Cognitive Assessment (MoCA) assessing global functioning and several questionnaires to assess depression (by the Beck Depression Inventory-II, BDI-II), apathy (by self-rated version of the Apathy Evaluation Scale, AES-S and the Dimensional Apathy Scale, DAS), impulse control disorders (by the Minnesota Impulsive Disorders Interview), anxiety (by the Parkinson Anxiety Scale, PAS), and anhedonia (by the Temporal Experience of Pleasure Scale). The functional impact of cognitive impairment was assessed by the Parkinson's Disease-Cognitive Functional Rating Scale (PD-CFRS) and the perceived QoL was assessed by Parkinson's Disease Questionnaire (PDQ-8). The PD sample was divided into two subgroups: patients with high QoL and patients with low QoL. The t-test for independent samples was used to compare the two subgroups. A linear regression analysis in which the global functioning, apathy, depression, anxiety, anhedonia, impulse control disorders and the functional autonomy scores were entered as independent variables and the score on PDQ-8 as dependent variable, was performed.

Results: Patients with lower QoL were more depressed (BDI-II; $p<0.001$), more apathetic (DAS and AES-S; $p<0.001$), more anxious (PAS; $p<0.001$), and showed more severe reduction of functional autonomy (PD-CFRS; $p<0.001$) and global functioning (MoCA; $p=0.006$). Regression analysis revealed that higher anxiety (Beta: 0.430, $t=2.814$, $p=0.007$), and reduced functional autonomy (Beta: 0.324, $t=2.544$, $p=0.014$) were significantly associated with reduced QoL.

Conclusions: The finding indicates that higher anxiety and reduced functional autonomy contribute significantly to reduction of QoL in PD, suggesting that improving anxiety and functional autonomy should be viewed as an important part in the management of PD.

P25

Susceptibility weighted MRI correlates with motor and cognitive dysfunction in Parkinson's disease

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Introduction: In Parkinson's disease, brain iron accumulation represents one of the main hallmarks of neurodegeneration.

Objective: Our aims were to evaluate 1) the differences on brain iron load between PD patients and controls and 2) the correlation of brain iron deposition with both motor and cognitive dysfunctions in Parkinson's disease.

Methods: A total number of 32 patients with Parkinson's disease and 10 healthy subjects were included. PD patients were evaluated both for motor (referring to UPDRS-III and H&Y stage) and cognitive aspects (referring to MoCA and to other specific tests for different cognitive domains, according to Movement Disorder Society Task Force). Patients were also tested for medication-related complications, neuropsychiatric symptoms and daily functional abilities (ADL-IADL). Data from 3.0 T MRI obtaining SWI images were analyzed. Seven ROIs were considered for each emisphere: putamen, globus pallidus, caudate nucleus, red nucleus, substantia nigra (SN), dentate nucleus and frontal white matter. For each of them we evaluated mean intensity value and intensity standard deviation: lower values correspond to high iron content.

Results: Compared to controls, PD patients showed higher iron content in all the ROIs. SWI values of the SN have a significant negative correlation with disease duration, UPDRS-III *off* and MoCA score. Moreover SWI values show a positive correlation with *WAIS-R Similarities* scores and with *Grading Named Test* and *Spatial Span*.

Conclusion: In Parkinson's disease iron load of deep gray matter structures, and particularly of substantia nigra, showed a significative correlation with both motor dysfunctions and cognitive impairment.

P26

Quantitative assessment of levodopa motor response in the differential diagnosis between Parkinson's disease and atypical Parkinsonism

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Introduction: A standardized subacute challenge test with levodopa/benserazide (LD/BZ) or carbidopa (CD), based on objective assessment of motor effect through alternate finger tapping test has become part of the diagnostic work up for patients referred to our clinic for a parkinsonian syndrome.

Objective: We aimed to examine the extent of LD responsiveness in patients with a progressive neurodegenerative disease starting with parkinsonian features, recruited for the "'Bologna Motor and Nonmotor Prospective Study on Parkinsonism at Onset" and to disclose potential differences in the response pattern among subgroups eventually diagnosed as Parkinson's Disease (PD) or atypical Parkinsonism (AP).

Methods: The patients received an oral morning fasting dose of LD/BZ or CD (100/25 mg) after a 12-h washout of LD and any concomitant antiparkinsonian drugs. Motor response to the LD dose was assessed by the alternate finger tapping test (number of times the patient can alternately tap two buttons 20 cm apart in 60 s with the most affected hand), using a computerized touch screen. Overall extent of the motor response was estimated by the area under the 3-h tapping effect–time curve (AUCTap), corrected for baseline measures.

Results: Seventy-four patients underwent the LD test. Median values of AUCTap were similar [(5190 vs 5925 taps/min) x min] in subgroups classified as possible (n=37) or probable (n=23) PD, while were more than halved in AP [(2190 taps/min) x min, n=7]. Sparse patients with possible Multiple System Atrophy (n=3), Progressive Supranuclear Palsy (n=2) and Corticobasal degeneration (n=2) showed AUCTap ≤ 2100 [(taps/min) x min].

Conclusions: Estimation of the extent of the tapping motor response after a subacute low LD dose may help to differentiate PD and AP patients early in the disease course. This pharmacodynamic parameter is objective, useful for a more standardized comparison of clinical and therapeutic assessments from different medical centres.

P27

Retrospective assessment of falls in Parkinson's disease

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Falls are a common problem in Parkinson's disease (PD), can impact a person's mobility and quality of life and often result in injures. It is also common for a patient to develop constant fear of falling, which may become overwhelming. We retrospectively rewiewed 47 pts (28 males and 19 females with an age between 63 to 87 yrs) affected by Parkinson's disease with a history of falls, to assess risk factors and co-morbidities frequently associated with falls. Thirty-eight falls caused in the pts soft tissue injuries, seven bone fractures and two head trauma. All pts had an impaired function of the presynaptic reuptake with cerebral Spect study. Thirty-two pts had a longer disease 8 yrs old and the other 15 between 3 and 6 yrs; 26 pts were taking benzodiazepines several times a day and 11 with once-evening. Among the comorbidities, 17 pts also had a diagnosis of dementia, 21 of diabetes and hypertension. Thirteen pts were not adhering to therapy with L-dopa and dopamine agonists. Falls are an important problem in PD and some of the major risk factors are potentially modifiable. There is a need for future studies to look at interventions to prevent falls in PD.

P28

Are static and dynamic balance correlated in Parkinson's disease? A quantitative study based on force plate and inertial sensors

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Background: Balance disorders are common in Parkinson's disease (PD) and represent a key factor in increasing falls risks. Usually, balance abilities assessment is performed either in static or dynamic conditions using clinical tools (i.e. Tinetti, Timed-Up-and-Go [TUG]). However, a more detailed and accurate evaluation of the postural control system performance during quiet stance can be performed by analyzing postural sway measured with a force platform. As regards dynamic balance, in recent times, an instrumented version of the TUG which makes use of wearable inertial sensors test has been proposed. Such approach, allows obtaining not only the overall time necessary to perform it, but also kinematic data about all TUG sub-phases (sit-to-stand, intermediate and final turning, stand-to-sit).

Objective: To investigate possible relationship between static and dynamic balance in individuals with PD, quantitatively assessed by postural sway analysis and instrumented TUG test.

Methods: Sixteen individuals with PD (age 71.7±5.3, H&Y 2.0±0.5) performed static posturography (bipedal standing, open eyes) and instrumented TUG. Sway parameters were estimated from the center of pressure (COP) time-series acquired using a force platform. The participants also performed instrumented TUG, using an inertial sensor, attached at the lower lumbar level. Accelerometric data were processed to calculate TUG sub-phases time. Correlations between TUG and sway parameters were analyzed using Spearman correlation coefficient.

Results: No statistically significant correlations between any of sway and TUG parameters were found (i.e. TUG duration: $r=0.28$ $p=0.27$ for ML displacement, $r=0.05$ $p=0.83$ for AP displacement, $r=0.24$ $p=0.36$ for sway area, $r=0.13$ $p=0.63$ for path length).

Conclusions: The absence of correlation between static and dynamic balance objectively assessed indicates that such tests provide information about different aspects of balance control. Thus, stabilometry and TUG tests cannot be used interchangeably, but are rather complementary. A complete assessment of balance disorders in PD should be performed using both types of tests.

P29

The role of Olfactory Event-Related Potentials in diagnosis and prognosis of Parkinson's disease

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Introduction: Parkinson's disease is a multisystemic neurodegenerative disorder characterized by a triad of motor cardinal symptoms (tremor, bradykinesia, rigidity, and gait difficulty) and by several non motor symptoms such as olfactory dysfunction that can precede the onset of the disease of about seven years [1].

Objective: The aim of this study was to assess olfactory system in PD patients with alterations of the sense of smell of various degrees through the innovative electrophysiological technique of Olfactory Event Related Potentials (OERPs) [2].

Methods: Thirty-five, no smoker patients, in early stages of Parkinson's disease and 30 healthy subjects underwent to an OERP examination and PD patients were evaluated by the Hoehn & Yahr scale and UPDRS. PD patients were divided in relation to the OERPs presence of into two groups : a) 16 OERPs absent (OERPs-); b) 19 OERPs present but altered (OERPs+).

Results: The data analysis showed highly significant differences between OERPs+ and control groups relatively to the latencies ($p < 0.001$) while no significant differences for the OERPs+ amplitudes. Pearson's correlation highlighted a positive relation between UPDRS and OERPs latency and a negative correlation with amplitude. In the same way is emerged a positive correlation between the duration of disease and latency and negative correlation with amplitude.

Conclusion: Olfactory event-related potentials allow an objective value of olfactory system. The finding of absence or specific alteration in latency, amplitude and morphology of olfactory event-related responses represent useful pre- clinical marker of PD [3]. The importance of recognizing as soon as possible the disease is directly related to the ability to exploit the so-called "window of opportunity", expression used to indicate the interval of time in which appropriate therapeutic strategies can interfere with the pathogenic mechanisms underlying the disease and delay its evolution.

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P30

Structural changes in Parkinson's disease manifesting Freezing of Gait

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Introduction: Freezing of Gait (FOG) is characterized by inability to start locomotion and to move forward, mostly occurring during turning or step initiations in many Parkinson's Disease (PD) patients. Recent Magnetic Resonance Imaging (MRI) studies already underlined the involvement of certain brain areas in FOG patients.

Objective: To study structural Gray Matter (GM) and White Matter (WM) changes in PD patients with FOG.

Methods: We recruited 21 PD patients with FOG, 16 PD patients without FOG (nFOG) and 19 healthy subjects (HS). Motor symptoms were evaluated by Hoen & Yahr (H&Y) and Unified Parkinson's Disease Rating Scale part III (UPDRS III). Cognitive impairment was excluded by using Mini Mental State Examination (MMSE) (> 26). Depression was evaluated by means of the Hamilton Depression Scale (HAM-D). FOG was assessed using FOG Questionnaire (FOG-Q). Participants underwent a standardized 3T MRI protocol. We analysed *GM measures* Cortical thickness (CTh) and Surface Area (SA) using FreeSurfer and *WM measures* calculated by Tracts Constrained by Underlying Anatomy (TRACULA).

Results: Compared to HS, whole PD group showed significant reduction in CTh in the left superior frontal area and in the right caudal middle frontal area. When we divided PD in subgroups, FOG patients showed significantly smaller SA in the right supramarginal and superior parietal areas compared to nFOG patients. Moreover, significant WM changes were observed in FOG patients in the temporal bundle of the superior longitudinal fasciculus, uncinate fasciculus and cingulum cingulate gyrus (mostly in the right hemisphere) and in the frontal radiation of the corpus callosum.

Conclusions: Structural abnormalities observed in the right frontal and posterior parietal areas in FOG than in nFOG and HS possibly reflect the relationship between FOG severity and executive dysfunction. This suggest that FOG could results from neuronal circuitry dysfunction of the parietal areas in the right hemisphere.

P31

Trait impulsivity and response-inhibition in Parkinson disease. An fMRI study

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Introduction: Dopamine agonists have been implicated in Impulse-Control Disorder (ICD) development since they can induce alterations in the fronto-striatal network that manage reward and mediate impulse monitoring and control [1]. The neuropsychological approach considers two measurable functions from which ICD can be detected: 1) integration of reward/punishment contingencies in individual choices; and 2) response-inhibition.

Objective: To consider trait impulsivity and response-inhibition in PD and provide information about behavioral and neural basis of response-control.

Methods: Ten cognitively non-impaired PD were recruited. They underwent a neurological evaluation, a neuropsychological assessment and questionnaires on behavioral mood changes. The Barratt Impulsiveness Scale (BIS-11:[2]) provided an integrated measure of trait impulsivity. During an fMRI acquisition, the subject was asked to perform a go/nogo task [3] in which the subject had to inhibit the response to infrequent nogo stimuli. Associations between blood oxygen level dependent response of the whole brain during the response-inhibition task and trait impulsivity were investigated.

Results: Subject with greater scores on BIS-11 and who made more errors had greater activation of the bilateral supplementary motor area, bilateral anterior Insula, bilateral anterior cingulate cortex, and right temporal parietal junction during response-inhibition. A significant association between higher impulsivity scores and worse performance for the nogo condition exists (rho = -0.69; p= 0.038).

Conclusions: Our results suggest that a deficit in inhibitory processes may affect everyday life, causing impulsive conduct which is generally detrimental for PD patients. Response-inhibition tasks may be useful in PD for better characterizing the clinical profile and evaluating treatment options. Since impulsivity is a detrimental and underreported side effect of dopaminergic medication, such an assessment is supposed to be particularly useful in the post-diagnostic phase, to better identify individuals at risk of developing ICD with dopaminergic medication.

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P32

Assessment of tremor in subjects with idiopathic Parkinson disease by using a wearable measuring systems

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Introduction: Tremors are commonly encountered in clinical practice and are one the most common movement disorders. It is defined as a rhythmic, involuntary oscillatory movement of a body part around one or more joints. Parkinsonian tremor is the most common cause of rest tremor. The typical tremor of Parkinson's disease is a 4-6 Hz rest tremor. By using wearable measuring systems it is possible to evaluate tremor, movement quality and posture for PD subjects.

Objective: To assess the level of tremor in patients with idiopathic PD using a wearable measurement system with accelerometers to measure the frequency and the amplitude by analyzing the movements of the fingers in the three axes (x, y, z), to objectify the clinical practice and evaluate the disease progression.

Methods: We recruited 12 patients (5 females and 6 males, mean age 68; Hoehn and Yahr stage 1.5±1) with idiopathic PD with a diagnosis confirmed by at least one year. All patients take levodopa treatment. A recording was made through a card Linkit ONE and an array of four 3-axis accelerometers ADXL345 (Analog Devices). It provided the placement of accelerometers in the fingers of the hand (from the thumb to the index).

Results: The record data of the hands showed a tremor frequency value compatible with Parkinson subjects (at around 5 Hz and always below to 10 Hz), with a close correlation with clinical scores ($p < 0.1$).

Conclusion: In this study we reported the development of a low cost, high configurable measurement system for movement quality. The system was employed in the evaluation of tremors in patients with PD. The results show how the system can be employed in real clinical setting for monitoring the disease progression and treatment strategy.

P33

Handwriting in Parkinson's disease: bradygraphia beyond the micrographia

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Introduction: Micrographia, classically defined as a consistent and/or progressive reduction in the size of handwriting, represents a clinical feature commonly associated with Parkinson's disease (PD). Neurophysiological mechanisms underlying micrographia in PD are unknown but different studies suggest that micrographia is an expression of bradykinesia. Although micrographia has been found to have a high positive likelihood ratio of being associated with an accurate diagnosis of PD, there are no easy-to-use tools to assess it in PD at this time.

Materials and methods: We propose a standardized method to assess handwriting features in patients with PD, the Pangram Repetition Test (PRT). To perform the test, the patient has to write the same pangram nine times. Writing lengths, times, and speeds are measured at the first, fifth, and ninth repetition. We used PRT in 28 patients with PD and in 28 sex and age-matched healthy controls. In the PD group, writing features were correlated with cognitive (MMSE score, MoCA score) and motor (UPDRS part III total score, bradykinesia and rigidity items scores) parameters.

Results: We found a statistically significant difference between PD patients and the control group in the length, time, and speed at the first repetition of PRT; not statistically significant differences have been identified at the fifth and ninth repetition in writing features. In PD patients there was a significant correlation between writing time and speed at the first repetition of PRT and MoCA scores. Lower MoCA scores are related with longer times and lower speeds of writing.

Conclusions: Through PRT, we confirm the presence of micrographia and we report bradygraphia in PD patients. Correlation studies show as writing alterations can be related to cognitive problems in addition to motor symptoms. Because MoCA is sensitive to executive dysfunctions, these cognitive abnormalities could contribute to handwriting impairment in PD.

P34

Neuropsychological assessment in initial clinical stages of Parkinson disease

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Background and aims: To compare cognitive performances in newly diagnosed patients with Parkinson's disease (PD) at Hoehn and Yahr (HY) stage I or stage II at their first medical evaluation.

Materials and method: Forty-four drug-naïve patients with newly diagnosed PD at HY Stage I and 40 patients at HY Stage II, matched for all variables but UPDRS total score and its sub-scores, completed a standardized neuropsychological battery. A one-way multivariate analysis of variance (MANOVA) was used to compare cognitive scores of the groups, complemented by Bonferroni corrected univariate analysis of variances (ANOVA). Finally, the prevalence of mild cognitive impairment (MCI) was estimated for patients classified in HY stage I or II.

Results: A general significant difference was found between patients at HY stage I or stage II on neuropsychological performances (Wilks' lambda = .645, $F(16, 67) = 2.31$, $p = .009$), with patients at HY stage I showing higher scores than patients at stage II. Moreover, univariate ANOVAs revealed significant differences between HY stages on Rey's Auditory Verbal Learning Test - immediate recall ($p < .0001$), prose recall test ($p < .002$), 10 points Clock Drawing Test ($p < .002$), and Rey-Osterrieth Complex Figure Test-copy ($p < .002$). PD-MCI occurred in 5 of 44 (11.36%) patients in the HY stage I, and in 15 of 39 (38.46%) patients in the HY stage II.

Conclusion: In drug-naïve, newly diagnosed PD patients, motor disability is associated with cognitive deterioration and higher rate of prevalence of mild cognitive impairment at the first medical evaluation (HY stage).

P35

Diagnosing and subtyping mild cognitive impairment in Parkinson's disease: which tests perform best in the Italian population?

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Mild cognitive impairment (MCI) is common in patients with Parkinson's disease (PD) and should be early recognized because it represents a predictor of PD-related dementia and worse disease course. Diagnostic criteria for PD-related MCI (PD-MCI) have recently been defined by a Movement Disorders Society (MDS) task force. The present study explored which neuropsychological tests perform best for level II (i.e., comprehensive neuropsychological assessment) diagnosis of PD-MCI according to the MDS task force criteria in Italian-speaking PD patients. To this aim, we assessed a comprehensive 23-item neuropsychological battery, derived the best-performing 10-test battery (i.e., two tests per each of the five cognitive domain), and explored its accuracy for diagnosing and subtyping PD-MCI according to single-domain vs. multiple-domain involvement in comparison to the full battery in a group of PD patients. The 10-test battery showed 73% sensitivity and 100% specificity for diagnosing PD-MCI, and 69% sensitivity and 100% specificity for PD-MCI subtyping. In patients older than 70 years, we derived a slightly different 10-test battery with 84% sensitivity and 100% specificity for PD-MCI diagnosis, and 86% sensitivity and 100% specificity for PD-MCI subtyping. These 10-item neuropsychological batteries might represent a good trade-off between diagnostic accuracy and time of application, and their role in PD-MCI diagnosis and subtyping should be further explored in future prospective studies.

P36

Screening for mild cognitive impairment in Parkinson's disease. Comparison of the Italian versions of three neuropsychological batteries

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Mild cognitive impairment (MCI) is frequent in Parkinson's disease (PD). Recently proposed criteria for MCI in PD (PD-MCI) indicate level I diagnosis based on abbreviated assessment, and level II based on comprehensive neuropsychological evaluation. The study explored the sensitivity and specificity of the Italian versions of three neuropsychological batteries for level I diagnosis of PD-MCI. We recruited 100 consecutive PD patients. After screening for inclusion criteria, 43 patients were included. The sensitivity and specificity of the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA) and the Addenbrooke's Cognitive Examination Revised (ACE-R) in comparison to level II diagnosis of PD-MCI was examined. PD-MCI was diagnosed (level II) in 51% patients. Disease duration was significantly longer and PD motor scales were more severely impaired in MCI group. The receiver-operator characteristics curve documented non-significant difference in the performance of the three batteries, with slight advantage of MMSE (corrected data). The time of administration favored MMSE. In Italian-speaking PD patients, MMSE might represent a good screening tool for PD-MCI, because of the shorter time of administration and the performance comparable to those of MoCA and ACE-R. Further studies are needed to validate new PD-MCI criteria across different languages and cultures.

P37

Locomotion on four limbs: a systematic review of Nordic Walking in Parkinson disease

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Introduction: Nordic Walking is a relatively high intensity activity that is becoming increasingly popular. It involves marching using poles adapted from cross-country skiing poles in order to activate upper body muscles that would not be used during normal walking. Several studies have been performed using this technique in Parkinson disease patients with contradictory results.

Objective: Thus, we reviewed here all studies using this technique in Parkinson disease patients and further performed a meta-analysis of RCTs where Nordic Walking was evaluated against standard medical care or other types of physical exercise.

Methods: Nine studies including four RCTs were reviewed for a total of 127 patients who were assigned to the Nordic Walking program. Descriptive analyses were performed on all studies, whereas data from randomized controlled trials (RCT) were pooled into a random-effects model with regards of the Unified Parkinson's Disease Rating Scale (UPDRS), motor subscale (UPDRS-3), e.g., a specific disability score for PD, in agreement with the Cochrane Handbook for Systematic Reviews of Intervention.

Results: The majority of studies reported beneficial effects of Nordic Walking on either motor or non-motor variables, but many limitations were observed that hamper drawing definitive conclusions and it is largely unclear whether the benefits persist over time. It would appear that little baseline disability is the strongest predictor of response. The meta-analysis of the 4 RCTs yielded a statistically significant reduction of the UPDRS-3 score, but its value of less than 1 point does not appear to be clinically meaningful.

Conclusion: Well-designed, large RCTs should be performed both against standard medical care and other types of physical exercise to definitively address whether Nordic Walking can be beneficial in PD. It will be also important to see whether Nordic Walking is beneficial throughout the disease progression or not.

P38

Efficacy and tolerability of Botulinum Toxin type A in Corticobasal Syndrome.

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Introduction: A common feature of Cortico-Basal-Syndrome (CBS) is upper limb dystonia, whereas the neck is less frequently affected. Poor response to levodopa is typical and dose increase often unsuccessful. Benefit from non-dopaminergic treatments such as benzodiazepines is rare and transient, often burdened by side effects. Although Level B recommendations for Ona/Abobotulinumtoxin A (BoTNA) for isolated limb dystonia, no controlled data are available for dystonia in atypical parkinsonisms, with few clinical reports mainly in the treatment of clenched fist.

Objectives: To improve our understanding of the role of BoTNA in the treatment of dystonia in CBS patients, also taking into account caregiver impression.

Methods: 7 patients (females, age 73,7 years +/- 5,5) referring to the Movement Disorders Center of Pisa with a diagnosis of CBS (disease duration 49,7 months+/-25,4) were injected with BoTNA. Dystonia affected left/right arm (6 patients, Ashworth score 2.9+/-0.9), one had cervical dystonia. Injected muscles depended on clinical phenotype and neurophysiological recordings. Caregiver impression was measured with a visual scale and severity of associated pain with Visual Analogic Scale (VAS).

Results: Patients were followed up every 3 months up to 21 months, LED remained unchanged in most cases ($p>0.01$). No side effects were reported. Six patients underwent at least 3 treatments, three discontinued due to poor efficacy, four are ongoing with benefit. Mean efficacy after each treatment was 47,8 days +/- 11.1, with Ashworth score significantly improved (2.0+/-0.6; $p<0.005$,mean reduction 29%); caregiver impression ranged between “good” and “very good”. Pain was present only in 3 subjects with a reduction of VAS of 56%.

Conclusion: This study confirms the long-term efficacy and tolerability of BoTNA in dystonia associated to CBS, underlining the importance to consider local treatment as a valid alternative to drug increase. Caregiver impression should be considered as an endpoint for the effectiveness of the treatment in such patients.

P39

Safinamide in advanced Parkinson's disease

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Introduction: Safinamide (Xadago®, Zambon S.p.A.) is a new drug with a multi-modal mechanism of action (dopaminergic and non-dopaminergic) reversible inhibition of the MAO-B enzyme and the modulation of the glutamate release available in Italy since 2016 for Parkinson's Disease motor fluctuations treatment.

Objective: To prospectively evaluate the clinical effect of safinamide as adjunct therapy in a cohort of patients with idiopathic PD and motor fluctuations.

Methods: 55 patients with PD and motor fluctuations were evaluated with clinical scales: Unified Parkinson's Disease part III (UPDRS III), Hoehn & Yahr, Time spent in OFF, Unified Dyskinesia Rating Scale (UDysRS) and mean daily drug dosages prior and after the addition of safinamide 50 or 100 mg.

Results: 50 patients (23 women, 68,3 ± 13,5 years old, 11,7 ± 6,28 disease duration, 26 with advanced treatment) completed the observational period. After 5,1 ± 1,85 months with safinamide (40 patients with 50 mg) time spent in OFF (79,61 ± 39,60 vs 32,76 ± 37,75 minutes) and Total Hours of on-Dyskinesia (53,4 ± 83,4 vs 34,8 ± 60 minutes) decreased significantly ($p<.05$) such as levodopa equivalent total daily dose of dopaminergic drugs (1026,78 ± 396,34 vs 653,66 ± 423,98). Five patient withdrawn safinamide because of uneasiness.

Conclusions: Safinamide can be considered a safe and effective ad-on treatment in PD patients with motor fluctuations. PD patients with deep brain stimulation showed a meaningful improvement over patients with only medical treatment.

P40

Adapted motor activity with pleasant music in Parkinson's disease: a 18 months follow-up study

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Introduction: Previous studies suggest the relevance of the Adapted Motor Activity with Pleasant Music (AMAPM) in improving motor activities, in triggering positive emotions and in enhancing quality of life of patients suffering from Parkinson's disease (PD) [1,2,3,4].

Objectives: In this study the evolution of cognitive functioning, functional integrity, psychological condition and quality of life were evaluated in patients with idiopathic PD who followed a program of AMAPM for 18 months. The follow-up included also the evaluation of caregiver burden.

Methods: Sixteen patients (M/F:10/6) with Idiopathic PD (mean duration: 7,12yrs; range: 2-18; s.d. 3,93), with mild to moderate motor impairment, without significant cognitive impairment (MMSE ≥ 21/30), not very dependent (Schwab & England > 50%), in "ON" condition and not treated with Apomorphine or PEG, were assessed in a first session (January 2015) and in a follow-up session at 18 months (June 2016). Patients were tested with MMSE, UPDRS, GHQ-28, GDS, PDSS-2, PDQ-39 and CBI.

Results: At the follow-up assessment no significant differences were observed in psychometric rating scales, with the exception of a significant improvement in the Communication Subscale of PDQ-39 (p=0,027). There was also a significant reduction in UPDRS part I (p=0,25), part II (p=0,001), part III (p=0,000), in UPDRS total score (0,001) and in Schwab and England ADL scores (p=0,007).

Conclusions: After 18 months of AMAPM patients showed a significant improvement in motor symptoms and in functional domain, with substantial stability in cognitive functions, mental conditions and quality of life. Also caregiver burden didn't change. This study suggests the possibility that AMAPM might help to slow down the progression of PD, contributing to preserve both psychological and physical well-being and to maintain an acceptable quality of life. These results, however, should be confirmed with a larger sample and with a control group.

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P41

Effects of integrated speech and physical therapy on voice in PD patients

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Introduction: In PD population communicative, vocal and respiratory symptoms are well-known. We propose an integrated approach of speech and physical therapy, dedicated to increase and normalize breathing and vocal parametes.

Objective: Describe changes induced by therapy, mainly on voice, secondary on associated breathing capability. Evaluate possible relations among vocal and respiratory parameters.

Methods: T0, T1, T2 measurements of vocal and respiratory capabilities. T0-T1 week, 5 sessions of physical-therapy concerned with respiratory and postural patterns, in order to better activate abdominal and paravertebral muscles. T1-T2 week, 6 sessions of speech-therapy regarding: better abductorial tone of vocal cords, increase of breath-voice coordination, improve maximum phonation time and archive better levels of intensity and suprasegmental feature.

Results: 20 PD patients (3DBS). Age: 60.7±9.7; disease duration: 6.5±3.9; UPDRSIII: 21 (16-29.5). Breathing (median at T0, T1, T2 and p-value at T2, T0 as a reference): CVF% 96.0, 100.5, 104.0, 0.0302. VEMS% 98.0, 100.5, 101.5, 0.0957. MIP%: 54.0, 61.0, 79.5, 0.0007. MEP%: 61.0, 61.1, 70.5, 0.1505. Voice: VHI 5.5, 5.0, 4.0, 00068. PRAAT: mF0 143.2, 156.7, 159.4, 0.0111. varF0 3.0, 2.8, 2.3 0.5257. Jitter% 0.6, 0.4, 0.3, 0.0002. Shimmer% 6.1, 3.8, 3.5, 0.0005. Nhr 14.8, 16.4, 19.0, 0.0001. MPT: no significant change. GIRBAS: significant improvement after T2. Relations: CVF-MPT (cross-functional) ρ=0.31 p=0.1799; GIRBAS-PRAAT none.

Conclusion: Clinical evaluation doesn't seem completely capable to point-out those patients whom, on the contrary, show pathological levels at PRAAT. Effectiveness of speech-therapy and physical-therapy seems to be present, even if the restricted number of patients suggests analyzing the issues observed with further studies. Anyway, protocols with early evaluation, both clinical and instrumental, should be encouraged. Better analysis should also be promoted in order to evaluate the relationship between the different kinds of rehabilitation and their mutual interactions.

P42

Clinical management of swalllowing and nutrition in primary parkinsonisms: a proposal

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Introduction: In Parkinsonian Syndromes swallowing and nutrition are common issues. Possible malfunctions cause several complications in the whole healing process. Often the consequences are faced when already unavoidable, with delay and higher costs. We propose an approach, based on the precautionary evaluation of possible deficiencies related to dysphagia and modified nutritional status.

Objective: Evaluate all the patients, irrispective of the stage of illness and the overt presence of signs attributable to dysphagia or malnutrition. Classify them for future follow-up. Promote therapeutic actions, comply with the guidelines, calling for a qualitative increase in care. Collect data as base for researches and experimental protocols, if possible.

Methods: Illness stage: H&Y. Swallowing evaluation: Swallowing Disturbance Questionnaire, Volume-Viscosity Swallow Test, Northwestern Dysphagia Check-Sheet, Dysphagia Outcome Severity Scale. Nutritional evaluation: MNA-SF, AMA, BMI, blood analysis, BioImpedentiometry.

Results: 26 patients (20 PD, 6 Parkinsonisms). Overall: age: 64±11; disease duration: 7±4; H&Y: 2.5±0.4. SDQ failed 34.6%; V-VST failed: 26.9%; NDCS: 3.1±3.6; DOSS <5=dysphagic: 34.6%. MNA-SF: patient at risk 15.4%; BMI: 24.7±2.7; 11.5% 85 percentile; none shows blood anomalies, BioImpedentiometry: pathological phase angle and bivector 19.2%, abnormal biagram 23.1%. Possible relations, overall: SDQ-MNA (screening; cross-functional) ρ=-0.28 p=0.17, none; BMI-DOSS (cross-functional): none; BMI-MNA (nutrition): ρ=-0.42 p=0.03; DOSS-SDQ (swallowing): ρ=-0.85 p<0.0001 possible inversely.

Conclusion: Precautionary approach, especially screening tests, seems to be effective in order to point-out subjects with possible risks of dysphagia and malnutrition. Among PD and parkinsonisms there is no particular difference. Among the functions doesn't seem to be any relation; there's no evidence that a dysphagic patient, at these stages, has to be malnourished. The limited number of evaluated patients makes the conclusions partial: long-term monitoring with further studies should be provided in order to examine in depth the issues.

P43

Rasagiline for dysexecutive symptoms of wearing-off in Parkinson's disease

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Wearing-off (WO) refers to the predictable worsening of motor and/or non-motor (NMS) symptoms of parkinsonism occurring at the end of levodopa (LD) dose in Parkinson's disease (PD) patients that improves with the next dose. Rasagiline is an irreversible MAO-B-inhibitor with therapeutic efficacy in PD. Here we investigated the effects of rasagiline on executive functions during WO in non-demented PD patients. Fourteen PD patients experiencing WO were enrolled. They were all treated with LD, either as monotherapy (n=8) or in combination with dopamine agonists (n=6). At baseline visit (V1) WO was verified as the difference of 25% or more of the UPDRS-III score between a first (30 min before the second daily dose of LD) and a second assessment (45 min after the second daily dose of LD). Exclusion criteria were: cognitive impairment as measured by a MMSE<26; comorbidity with depression and/or treatment with antidepressant; disabling dyskinesia; therapy with other MAO-B-i. At V1 subjects were submitted to the Frontal Assessment Battery (FAB) 20 min before the second scheduled daily dose of LD. Rasagiline (1 mg/day) was initiated the day next to V1 and maintained for 16 weeks. The remaining pharmacological therapy was unmodified. At the end of observation period patients underwent the final visit (V2), including the FAB and the UPDRS-III scale with the same daily time schedule as V1. Paired t-test was used to analyze differences at the FAB and the UPDRS-III scores between V1 and V2. There were 2/14 (14%) withdrawals due to hallucinations (n=1) and worsening of pre-existing dyskinesia (n=1). In the remaining patients (n=12), a significant improvement of the FAB score was measured at V2 as compared to V1 (12.70±2.22 vs. 11.10±3.07, $p<0.05$). We show the beneficial effect of rasagiline on dysexecutive symptoms during WO, as measured by improvement at the FAB.

P44

Use of ground reaction forces to assess the effectiveness of a rehabilitation treatment in people with Parkinson's disease

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Introduction: Quantitative techniques for human movement analysis can effectively integrate clinical tools and scales to describe the effectiveness of a rehabilitative treatment. However, the complexity of a 3D gait analysis often represents a barrier to its use.

Objective: To assess the effectiveness of a 17-weeks rehabilitative treatment carried out in hospital (5 weeks) and at home (12 weeks) in a cohort of individuals with Parkinson's disease (PD)

Methods: Fifteen individuals with PD (11 male, 4 female, mean age 67.1±8.4 years) were enrolled in the study. Participants performed 5 weeks of supervised rehabilitative treatment (which included gait training with rhythmic auditory stimuli), and 12 weeks of unsupervised physical activity at home according to a program defined by physical therapists. Using a force-plate platform and an optoeletronic-system, ground reaction forces (GRF) and mean gait velocity (MV) were assessed at T0 (before treatment), T5 and T12 (after supervised, and unsupervised rehabilitative treatment respectively). Starting from GRF curves, we calculated: the ratio between the fore-aft propulsive area (PA) and the sum of the breaking and propulsive area (PB_index), mean amplitude of GRF vertical component (MA_GRFv), mean amplitude of the GRF propulsive part of the propulsive part of the fore-aft component. Statistical analysis was performed using one-way analysis of variance for repeated measure (ANOVA RM).

Results: MANOVA RM revealed significant effects of rehabilitative treatment only for PB index and MV. In particular, PB index significantly increased for T0 vs. T12 and T5 vs. T12 ($p=0.034$, $p=0.036$ respectively), but not T0 vs. T5 ($p=0.844$). Significant increases of MV were found only for T0 vs. T12 comparison ($p=0.024$).

Conclusion: Synthetic indexes based on GRF can reveal subtle yet clinically relevant variations in gait kinetics in people with PD who underwent a rehabilitative treatment. This procedure is easy to apply and can be repeated often to verify when further improvements are no longer achievable.

P45

A combined effect of anodal tDCS and music to trait gait disorder in Parkinson's disease: a preliminary study

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Introduction: Motor impairment are among the most disabling symptoms in Parkinson's disease (PD). Non-pharmachological treatments, such as anodal transcranial direct current stimulation (AtDCS), shows to be effective on gait disorders improving motor functions. Furthermore, music seems to support memorization and execution of a motor sequence, due to the automatic engagement of motor areas. Since specific beneficial effects are known about AtDCS and music in motor rehabilitation, no research has investigated a combined approach with them.

Aims: To evaluate the effect of combined approach (AtDCS and music) on gait size in PD.

Method: 8 subjects with PD [(mean±SD) age=68.5±6.27; female=3; Hoen & Yahr stage (≤3) were included. We delivered anodal (2 mA, 15 minutes, five consecutive days) and sham tDCS over the motor cortex bilaterally, in two experimental groups (AtDCS/music, n=4; Sham-tDCS/music, n=4). During anodal and sham stimulation, all patients observed a video showing movement sequences to learn, accompanied by music, and at the end, they had to repeat it. We recorded patients' performance with Microsoft's Kinect, to get detailed kinematic values concerning gait size. To evaluate the effect of tDCS on gait size each patient had to perform the observed movement, at the baseline (T0), after 5 days (T1) and after one month (T2).

Results: AtDCS/music enhanced gate size at T2 (Anodal T0 vs T2: .29±.09 vs .38±.06, $p=0.023$) whereas had no significant effect at T1 (Anodal T0 vs T1: .29±.09 vs .36±.07, $p>0.5$). Sham tDCS/music failed to significantly influence all the variables studied ($p>0.05$).

Conclusion: Preliminary data suggest that tDCS in combination with music and motor training could be a new rehabilitation approach to improve the gait ability/size in PD.

P46

Italian Survey on Parkinson's Disease patients: results of SYNAPSES (StudY to observe SafiNAmide in clinical Practice during the firSt post-commErcialization phaSe) study feasibility evaluation

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Introduction: Safinamide is an α-aminoamide derivative, orally administered, with dopaminergic and non-dopaminergic actions. It is indicated for treatment of patients with idiopathic PD as add-on therapy to a stable dose of levodopa alone or in combination with other PD medications in mid-tolate-stage fluctuating patients.

Objective: Here we describe the design of a Drug Utilization Study of safinamide conducted during the first post-commercialization phase, and the results of the study feasibility conducted in Italy.

Methods: SYNAPSES study is an ongoing, observational, European, multicentre, retrospective-prospective cohort study. Primary objective is to describe the occurrence of adverse events in patients treated with safinamide in real-life conditions, overall and stratified by age (>75) and relevant concomitant conditions. Secondary objectives include the description of patients characteristics treated with safinamide according to clinical practice and safinamide treatment patterns in real-life setting. The study will observe 1600 patients in 140 centres across 7 European countries during 1 year after safinamide treatment initiation. To evaluate the feasibility of conducting SYNAPSES study, Italian neurologists underwent a phone structured interviews from December 2015 to May 2016. Statistics are provided as overall proportion or as a median calculated across sites.

Results: Among 42 Italian sites participating in the survey, 18525 PD patients, in fluctuating mid-tolate- stage, received a stable dose of levodopa in 2015, and 7770 (42%) also received MAOB-inhibitors. The median (25-75th percentiles) number of patients/site was 300 (200-500). Concomitant hepatic impairment and ophthalmological history were reported for 538 (3%) and 302 (2%) patients, respectively. The median (25-75th percentile) portion of patients aged >75 years was 31% (20%-47%; N=5665). Patients suffering from psychiatric conditions were 660 (3.6% of overall sample).

Conclusion: The structured survey confirmed the feasibility of the study in Italy. The SYNAPSES study will improve the knowledge about safinamide safety profile and treatment patterns.

P47

Blink reflex recovery cycle to differentiate Progressive Supranuclear Palsy from Corticobasal Degeneration: a pilot study

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Introduction: Progressive Supranuclear Palsy (PSP) and CorticoBasal Degeneration (CBD) are rapidly progressive neurodegenerative disorders, clinically featured by parkinsonism and additional debilitating symptoms. Phenotypic spectrum of these disorders, which belong to the group of tauopathies, is wide. The differential diagnosis between PSP and CBD is extremely difficult because of the overlap of common clinical features. R2 Blink Reflex Recovery Cycle (BRRC) is a neurophysiological tool used to evaluate brainstem excitability. R2 BRRC is abnormal in several movement disorders as Parkinson's disease [1] and dystonia [2].

Aims: We evaluated R2 BRRC in differential diagnosis of PSP and CBD determining sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV).

Methods: Patients affected by PSP and CBD were prospectively enrolled, according to currently accepted diagnostic criteria. Patients underwent clinical (Hoehn&Yahr stage, UPDRS-ME) and neurophysiological (R2 BRRC) assessments. R2 BRRC was performed at interstimulus intervals (ISIs) of 100-150-200-300-400-500-750 ms.

Results: Thirty subjects were enrolled: 12 PSP and 8 CBD patients and 10 healthy controls. A significantly different amplitude of R2 was observed at ISIs of 100-150-200-300 ms between PSP and CBD patients ($p=0.006$, $p<0.00001$, $p<0.00001$ and $p=0.02$ respectively) and also between PSP and healthy controls ($p<0.00001$, $p<0.00001$, $p<0.00001$ and $p=0.0004$ respectively); no significant differences were found between CBD and controls. An early R2 BRRC differentiated PSP from CBD with a sensitivity and a specificity of 87.5% and 91.7% respectively; PPV and NPV were 91.7% and 87.5% respectively.

Conclusions: R2 BRRC is a useful tool in differentiating PSP from CBD patients. The predominant brainstem 4-repeat-tau aggregates distribution in PSP, in contrast with the involvement of neocortex in CBD, could explain the brainstem disinhibition observed in PSP patients.

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P48

Neuropsychiatric and cognitive predictors of early diagnosis of Progressive Supranuclear Palsy

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

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

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

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

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

P49

Towards understanding supraspinal control failure of human locomotion: electrophysiological alteration during freezing of gait episodes in one subject with Parkinson's disease

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Background: Freezing of gait (FOG) is a disabling symptom of advanced Parkinson's disease (PD) described as sudden and unpredictable failure of gait1. The pathophysiology of FOG is unclear1 and treatments are limited, although deep brain stimulation of the Subthalamic nucleus (STN-DBS) can be beneficial in some cases [2].

Aims: To assess the supraspinal control failure of human locomotion during *freezing* episodes in PD.

Methods: We recorded cortical (64-channels EEG, MOVE, BrainAmp) and subcortical activity (Activa PC+S®, Medtronic PLC) during *freezing* episodes in one subject with PD and STN-DBS. Of note, recordings were performed 24 months after surgery with the chronically-implanted device. FOG occurred during steady state unperturbed walking and was monitored with wearable sensors (Opal, APDM).

Results: Cortical-subcortical interaction, expressed as cross-spectrum, was characterised during normal walking by low-frequency coupling (i.e. theta frequency). A selective suppression of this activity, with a shift towards beta-coupling (the fingerprint of PD-related motor impairment[3]), anticipated *freezing* episodes. The restoring of low-frequency coupling between cortical and subcortical structures preceded the recovery of an effective walking pattern.

Conclusion: These preliminary results show for the first time the dynamic interaction of cortical and subcortical structures during *freezing* episodes. In subjects with PD and FOG, a sudden lack of cortical compensatory activity might unmask basal ganglia's deficiency thus determining locomotion failure [4,5]. These results are still presumptive, but they foster our understanding of FOG pathophysiology as complex alteration of locomotor control across multiple neural networks.

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P50

Reversal of long term potentiation plasticity in primary motor cortex in patients with progressive supranuclear palsy

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Objective: To investigate the reversal (depotentiation) of long term potentiation-like plasticity in primary motor cortex in patients with progressive supranuclear palsy using transcranial magnetic stimulation techniques.

Background: Experimental evidence suggest that abnormal synaptic plasticity of primary motor cortex might be involved in the pathophysiology of progressive supranuclear palsy. However no study has yet investigated possible abnormalities of depotentiation of long-term potentiation-like synaptic facilitation in patients with progressive supranuclear palsy, a putative mechanism involved in the regulation of primary motor cortex plasticity.

Methods: Motor cortex excitability, tested by single and paired pulse transcranial magnetic stimulation, as well as long-term potentiation-like plasticity and its reversibility, where studied using theta burst stimulation in 13 patients with progressive supranuclear palsy and 10 healthy controls. Participants underwent two sessions using (1) the intermittent theta-burst stimulation (potentiation protocol) and (2) intermittent theta-burst stimulation combined with a short continuous theta-burst stimulation (depotentiation protocol). The effects of the two protocols on motor cortex excitability and plasticity were assessed before and after the experimental interventions.

Results: Patients with PSP had higher corticospinal excitability, as indexed by the slope of the input-output curve of motor evoked potentials, and lower intracortical inhibition, assessed by short-interval intracortical inhibition, then healthy controls. Intermittent theta-burst stimulation elicited an abnormally increased long term potentiation-like effect in patients in comparison to healthy subjects. However, the depotentiation protocol was able to reverse the iTBS-related effects on motor cortex excitability either in patients or in healthy controls.

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Polyneuropathy in Parkinson's disease: a biomarker of disease severity?

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*Background***:** Peripheral Neuropathy **(**PNP) is a frequent and probably underestimated feature of Parkinson's disease (PD), with a prevalence of 19-55%, as compared to 8-9% of controls. Although the iatrogenic effects of levodopa may play a role in the development of PD-associated PNP (PD-PNP), there may also be a direct role for neurodegenerative mechanisms in the peripheral nervous system.

Objective: To analyze the association between PD-PNP, motor and non-motor PD features, age and levodopa dose, in a cross-sectional multi-center pilot study.

Methods: Two hundred consecutive PD patients were screened from three specialized Movement Disorder Centers; patients with alternative causes of peripheral neuropathy or taking medications affecting the autonomic nervous system were excluded. Patients enrolled (n=161) underwent the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), four-limb nerve conduction studies, supine and orthostatic blood pressure measurements, laboratory tests (Vitamin B12, Homocysteine, and Folate), and a battery of cognitive (Montreal Cognitive Assessment), non-motor (Non-Motor Symptoms Scale), and autonomic (Scale for Outcomes in Parkinson's Disease-Autonomic) assessments.

Results: PD-PNP was identified in 29.2% of patients. Unadjusted data showed that patients with PNP were older (70.45 vs. 64.81 years; p:0.001), had a later PD onset (63.28 vs. 56.83 years; p:0.004), and higher levodopa dose and total LEDD (1140.62 and 1205.90 vs. 627.73 and 822.96 mg; p:0.001) compared to patients without PNP. After adjusting for levodopa equivalent daily dose, age, and disease duration, PD-PNP was independently associated with cognitive impairment (p=0.008), autonomic dysfunction (p=0.035), non-motor symptoms (p=0.042), and axial motor features (p=0.045) compared with patients without PD-PNP.

Conclusions: Despite some limitations, our study suggests the possible existence of a link between PD-PNP and a more aggressive disease phenotype. PD-PNP may represent a peripheral marker of severe PD, characterized by worse axial symptoms, autonomic dysfunction, and cognitive impairment.

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Transcranial magnetic stimulation for the differential diagnosis of atypical parkinsonisms

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Introduction: Early differential diagnosis of atypical parkinsonisms, i.e. Dementia with Lewy bodies (DLB), Progressive Supranuclear Palsy (PSP) or Corticobasal Syndrome (CBS) still remains problematic. Furthermore, DLB and Alzheimer's disease (AD) may overlap in the early disease stage, and currently the presynaptic dopaminergic imaging is the main diagnostic tool in the differential diagnosis[1,2]. In this view, transcranial magnetic stimulation (TMS) allows the assessment, non-invasively and *in vivo*, of specific neurotransmitter circuits, whose deficit reflects the underlying neuropathological process.

Objective: Assess the diagnostic accuracy of specific neurophysiological parameters, aiding the differential diagnosis of AD, DLB, PSP-CBS and Healthy Controls (HC).

Methods: Paired pulse TMS was used to investigate short-interval intracortical inhibition (SICI) and facilitation (ICF), and short-afferent latency inhibition (SAI), in patients and HC, in order to measure the activity of GABAergic, glutamatergic and cholinergic circuits, respectively. A decision tree was developed to characterise patients in each group according to neurophysiological parameters and report diagnostic accuracies.

Results: A total of 89 subjects met inclusion criteria (47 AD, 20 DLB, 12 CBS, 10 PSP, 42 HC). We observed that AD patients are characterized by a specific impairment of SAI, PSP-CBS of SICI-ICF, while DLB patients are characterized by an impairment of both SICI-ICF and SAI intracortical circuits. Based on SICI-ICF and SAI values, decision tree analysis showed a diagnostic accuracy of 89.5% for HC, 92.3% for AD patients, 87.5% for DLB patients and 76.5% for PSP-CBS patients.

Conclusions: TMS is a non-invasive procedure which can distinguish DLB from PSP-CBS and from AD, representing a useful supportive diagnostic tool in clinical practice.

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Complexity of fronto-temporal electrocortical activity in untreated Parkinson's disease. Evidences of a topographical neuronal organization

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Introduction: Complexity is a characteristic of fractals, which are self-similar structures. Self-similarity of biological signals can be evaluated by analyzing the presence of a power law relationship between frequency and size of process variation. When detected in electrocortical activity of specific sites, this could indicate an increased level of local neuronal organization.

Objectives: To evaluate self-similarity of electrocortical activity as expression of brain signal complexity in L-dopa untreated Parkinson's disease (PD) subjects.

Methods: We analyzed data of N = 34 L-dopa naïve PD subjects who underwent standardized electroencephalography. We also selected N = 18 subjects group-matched by age, sex and hand dominance (right handed) with normal electroencephalography and no parkinsonism and/or cognitive decline as controls. A Welch's periodogram was applied to electroencephalographic signal epochs recorded from specific homologous pairs of electrodes over each hemisphere (F3/4, F7/8, T3/4, P3/4, O1/2) to compute the power spectral density. The power law exponent β was then obtained for each coordinate as minus the slope of the power spectrum versus frequency in a Log-Log scale to evaluate the relationship between frequency and size of process variation.

Results: In both PD subjects and controls, β values detected at each electrode coordinate increases with an antero-posterior gradient, changing from values around one in the fronto-temporal sites to values around two among parieto-occipital sites due to posterior predominance of low frequency components. PD subjects present overall lower β values among different sites compared to control, with significant differences for the left fronto-temporal sites (F7: 1.31 ± 0.47 *vs* 1.6 ± 0.36, p = 0.025; T3: 1.3 ± 0.51 *vs* 1.63 ± 0.54, p = 0.038).

Conclusions: Our findings suggest that in untreated PD, the presence of a power law functional relationship of electrocortical activity in unilateral fronto-temporal sites could underlay an increased level of local neuronal organization, probably due to cortico-subcortical networks.

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Early synaptic dysfunction in Parkinson's disease: a "double hit" model.

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Background: Compelling evidence supports a combined involvement of genetic susceptibility and environmental modifiers, a condition named "double hit theory", the pathogenesis of Parkinson's disease (PD). Heterozygous mutations in the PINK1 gene are considered a susceptibility factor to develop early-onset PD, as supported by dopamine hypometabolism in asymptomatic mutation carriers. Thus, combining this genetic model with exposure to environmental stressors offers the opportunity to reproduce such a multifactorial condition.

Objective: To investigate the effects of the exposure to low-dose pesticides (both rotenone both paraquat) of heterozygous PINK1 knockout (PINK1+/-) mice, compared to their wild-type littermates (PINK1+/+), on dopamine-dependent striatal synaptic plasticity, in the absence of apparent structural alterations.

Methods: Mice were chronically treated with low-doses of rotenone and paraquat. Immunofluorescence experiments on striatal slices of rotenone-treated mice were performed to assess the localization of two mitochondrial proteins, Tom20 and Cytochrome C. Moreover, we measured ATP content in mesencephalic and striatal slices by ATP bioluminescence assay. Electrophysiological recordings of striatal Medium Spiny Neurons (MSNs) were performed through conventional sharp and patchclamp techniques.

Results: Both chronic rotenone (up to 0.8mg/Kg) and paraquat (up to 0.6mg/Kg) treatment did not alter mitochondrial integrity and ATP production, neither caused alterations of basic electrophysiological properties of nigral dopaminergic and MSNs neurons. Conversely, a complete loss of both Long-Term Depression (LTD) and Long- Term Potentiation (LTP) was recorded in MSNs from PINK1+/- mice.

Conclusions: Chronic exposure to low-dose pesticides is not sufficient to induce structural alterations nor nigral neurodegeneration, but profoundly impairs the expression of long-term plasticity at corticostriatal synapses in PINK1+/- mice, suggesting that disruption of synaptic plasticity represents an early event in the course of PD and a potential tool to test novel neuroprotective agents.

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Persistence of limb dystonia and myoclonus during sleep in a patient with Corticobasal Syndrome

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Background: Corticobasal Syndrome (CBS) is an unusual clinical manifestation of different neurodegenerative pathologies, mainly tauopathies, characterized by a combination of basal ganglia and cortical dysfunction, with a typical asymmetric symptoms presentation. Thus far, literature about sleep disorders in CBS is limited to reports of infrequent REM sleep behaviour disorders and periodic limb movements during sleep.

Methods: A 62-year-old woman, affected with head tremor from the age of 55, developed a left-side akinetic-rigid syndrome, unresponsive to L-Dopa treatment. The patient described her left arm as feeling foreign, with cramps, tingling and increasing tendency to adopt abnormal postures. Her personal medical history was unremarkable. Neurological examination revealed dystonic tremor of head and left arm. Rigidity, bradykinesia, ideomotor apraxia and sensory dysfunction were more prominent in the left side. The left arm and hand were held abducted in a pronated position with ulnar deviation; spontaneous and action-induced myoclonus were present. FP-CIT SPECT showed reduced uptake in the right putamen, MRI asymmetric cortical atrophy and FDG-PET right parietal lobe metabolic reduction. MMSE and cerebrospinal fluid biomarkers of neurodegeneration were normal. Because of complaints of poor sleep quality, a nocturnal polysomnografy (PSG), including an extensive EMG montage, was performed.

Results: Based on clinical features, diagnosis of probable CBS was made. PSG revealed severely reduced sleep efficiency. Myoclonus and spasms were recorded on the left biceps brachii and the extensor carpi ulnaris muscle, sometimes recurring in a periodic fashion (every 20 seconds), persisting even during slow wave sleep. On the top of that, prolonged painful contractions of left arm, both during wakefulness and sleep (all stages), were observed.

Conclusions: This is the first report documenting the persistence of abnormal limb movements during sleep in a patient with CBS.

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Freezing Of Gait in parkinsonism: is an early predictor of cortical dementia?

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Introduction: Freezing of gait (FoG) is a severe gait disorder commonly attribuited to Parkinson's disease (PD); however, an early occurrence of FOG is more likely attributable to atypical parkinsonisms. There are few published data on the frequency of FoG in Dementia with Lewy bodies (DLB).

Objective: To examine whether FoG is an early feature of DLB.

Methods: We performed a case–control study with retrospective analysis of 20 DLB patients, matched with 20 PD (de novo pts) for gender, disease duration, age and motor phenotype at onset, UPDRSIII at first visit (T0, within two years after clinical onset). FoG presence and severity were assessed at T0 and follow-up yearly visits (T≠0) from the clinical charts of patients with a minimum follow-up of 3 years, based on history and clinical examination through the 14 item of UPDRSII and rated as FoG ≥ 1 and FoG ≥ 2. Groups were compared by using contingency tests (Fisher exact test) to analyze differences in the proportions FoG.

Results: At T0, 14 DLB patients (70%) and 2 PD patients (10%) had FoG ≥ 1 (*p=0.001*); FoG ≥ 2 was present in 5 DLB patients (25%) but in any of the PD patients (*p=0.001*). FoG showed a greater frequency and severity in DLB than PD also at the follow-up: at T5, 19 DLB patients (95%) and 9 PD patients (45%) had FoG ≥ 1 (*p=0.05*), while 12 DLB patients(60%) and 2 PD patients (10%) had FoG ≥ 2 (*p=0.05*). Patients differed significantly in MMSE (p=0.000).

Conclusions: This study confirms our preliminary data that an early appearance of FoG might be associated with DLB. Moreover, the greater and earlier prevalence of FoG in DLB with respect to PD sustain the interplay between FoG and cognitive impairment and strengthen the role of cortical regions in FoG pathogenesis.

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Acoustical analysis of a peculiar motor speech disorder in a case of probable progressive supranuclear palsy

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Introduction: Dysarthria is an early clinical manifestation of Atypical Parkinsonian Syndromes (APS) such as Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA). In APS, the predominant dysarthric pattern is the hypokinetic type, followed by the ataxic and spastic patterns. The majority of patients show variable combinations of these components, outlining a condition of "mixed dysarthria".

Case report: A 81 year-old man presented with a 4 years history of progressive speech slowing; during the last year he developed pseudobulbar palsy with clear dysarthria and dysphagia, pathological laughter and crying, and postural instability with frequent falls. Neurological examination showed vertical supranuclear gaze palsy, frontal release signs, a positive applause sign, retrocollis, symmetrical hypokinetic-rigid parkinsonism, diffuse hyperreflexia and bilateral Hoffmann's sign. Perceptual analysis of spontaneous speech and reading revealed severe intelligibility impairment, with inability to produce complete sentences, short rushes of speech, strained-strangled voice and imprecise articulation. Acoustical analysis of sustained vocal phonation and spontaneous speech was performed using PRAAT software showing high fundamental frequency and uncontrolled alterations in voice pitch with excessive pitch fluctuations. Phoniatric evaluation with videoendoscopy showed a central air leak during phonation with preserved vocal cords mobility. Brain MRI revealed mesencephalic atrophy. Neuropsychological evaluation revealed bilateral ideomotor apraxia, selective attention and spatial memory deficits. Genetic testing for C9orf72 and TDP43 was negative. According to current diagnostic criteria, a diagnosis of probable PSP was made and a levodopa therapy was started, without significant improvement.

Conclusion: Speech disorders in PSP could vary from "mixed dysarthria" to pure apraxia of speech or progressive non-fluent aphasia. Literature data consider excess pitch fluctuations as a distinctive feature of ataxic dysarthria, more common in MSA. In our case, speech disorders precede the parkinsonian symptoms suggestive of probable PSP. Moreover, the perceptual and acoustic speech alterations move towards a spastic-ataxic dysarthria rarely seen in PSP.

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Movement disorders as serotonin syndrome induced by unusual drug interaction : a case report

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Serotonin syndrome is a potentially fatal iatrogenic syndrome that can occur as a result of the terapeutic use of some drugs as antidepressant, opioids, CNS stimulants, triptans. Data in the literature have shown that a serotonin syndrome can be due to overstimulation of the 5-HT2A; the 5HT1A receptors contributes to the syndrome when an increased concentration at the synaptic level of an agonist of the serotonin determines a saturation of all subtypes of receptors; even the agonists of the NMDA and the GABA receptors may play a role in the development of the syndrome. We describe the case of a 65 yrs old woman suffering from depressive syndrome and in chronic treatment with escitalopram 10 mg/die that was hospitalized for the appearence of right femoral osteomyelitis. In the second treatment day with linezolid 600 mgx2, she developed involuntary movements of the four limbs, tachycardia and intermittent tremors. Neuroradiological and biochemical investigations were negative. She was then suspended therapy with escitalopram without result on the symptoms that completely regressed after discontinuation of linezolid. Linezolid is a protein synthesis inhibitor that stops at the level of the ribosomal mRNA translation process; the maximum plasma concentrations is reached in two hours and the steady state is achieved within 48 hours. The serotonin syndrome with the associations of these two molecules is not descibed and the pharmacological mechanism is unclear.

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Patients affected by functional motor symptoms are not liars: an experimental deception study with the Guilty Knowledge Task

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Introduction: The relationship between functional neurological symptoms (FNS) and feigning is not an easy one for many clinicians. Most neurologists do not see the two as entirely distinct and would rather not get involved in the uncomfortable business of distinguishing them. Research conducted in the past decades has tried to challenge a common clinicians' view according to which patients affected by FNS are liars. Nevertheless, no study has systematically investigated deception in these patients.

Materials and methods: Thirteen patients affected by functional motor symptoms and 14 healthy controls, matched for age and gender, underwent a modified version of the Guilty Knowledge Task (GKT), a computer-controlled procedure used to detect truthful and deceptive responses. All participants were also screened for depression (HAM-D), anxiety (HAM-A) and alexithymia (TAS-20).

Results: No significant difference was found between the two groups either in terms of reaction time (for true responses p=0.865, for false responses p=0.765), or in terms of accuracy (for true responses p=0.654, for false responses p=0.643). No significant correlation was found between responses at the GKT and HAM-D, HAM-A and TAS-20 score.

Discussion: Our data showed that patients affected by functional motor symptoms have the same capacity to lie than healthy controls. These results are reinforced by the fact that depression, anxiety and alexithymia did not correlate with the GKT responses, excluding they might represent confounding factors.

Conclusion: Patients affected by functional motor symptoms are not liars. Clinicians should start considering these patients as genuine as patients with multiple sclerosis or Parkinson's disease.

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Theory of Mind is impaired in mild to moderate Huntington's disease independently from global cognitive functioning

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Objective: To assess whether the affective ToM ability was impaired in the mild to moderate stages of Huntington's disease, and whether there was an association between compromised ToM ability and the presence of cognitive impairment.

Background: Affective "Theory of Mind" (ToM) is the specific ability to represent own and others' emotional states and feelings. Previous studies examined affective ToM ability in patients with Huntington's disease (HD), using the "Reading the Mind in the Eyes test" (RMET). Results were consistent in showing difficulties in inferring complex mental states from photographs of people even in the early stage of HD. However, there has been no agreement as to whether or not cognitive impairments in HD population might have contributed to poor performance on the RMET test.

Methods: We evaluated ToM by means of RMET and global cognitive functioning by means of the MoCA questionnaire in 15 patients with mild to moderate HD and 15 healthy subjects (HS). Both groups were matched for age and level of education.

Results: Results showed that the ability to judge a person's mental states from a picture of their eyes was impaired in HD patients compared to controls. Indeed, HD subjects gave the 34% of correct responses on RMET, whereas healthy control subjects' percentage of correct responses was 71%. Furthermore, this impairment was not correlated with global cognitive functioning except for the visuospatial task.

Conclusions: Our study showed that using RMET to assess affective ToM ability could be a useful tool to evaluate HD patients who are in different stages of the disease, independently from their cognitive status. On this basis, affective ToM in HD might be instrumental for explaining why patients with HD can experience social difficulties and interpersonal problems, and, as a result, in developing psycho-educational interventions.

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A case report of acute dystonia of the trunk: arising doubts on the role of SSRIs and dopamine antagonists

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Dystonia is a rare disorder with abnormal motion and posture. It may be often acquired. Beside LDopa treatment in Parkinson Disease, drug-induced dystonia is described with the use of neuroleptic and also rarely associated with the use of SSRIs. We report the case of a woman 73 y, on dialysis, taking Risperidone 0,5 mg daily for the recent onset of BPSD (delusion of jealousy), who presented after the addition of Sertraline 50 mg daily with dystonia of the trunk. She had a diagnosis of MCI on the cognitive assessment and a normal neurological status except for mild resting tremor. Treatment with Risperidone had been beneficial on the BPSD and acute dystonia was reversible after Sertraline withdrawal. The pathophysiology of dystonia is unknown but abnormalities of brain dopamine are supposed to be a common mechanism of the different forms of the disorders. Despite the known extrapyramidal side-effects of dopamine antagonists, there are several reports which show an ameliorating effect of Risperidone due to its high affinity to the D2 DA Receptor. SSRIs are also a rare but under recognised cause of dystonia, as reported in several case series. Their EP Symptoms may be secondary to a relative imbalance between decreased dopamine and increased acetylcholine activity in basal ganglia. In conclusion, despite the well established potential of EP side effects of neuroleptics there is an increasing evidence of the role of SSRI in acute dystonia. This idea, also supported by our anecdotal report should be proved with larger clinical trials.

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The motor aspects of paraneoplastic encephalitis

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Introduction: Immune-mediated movement disorders may result from paraneoplastic or autoimmune mechanisms. Symptoms usually develop before an underlying tumor is recognized, and abnormal movements may represent an early feature in the course of disease. Here we consider the motor aspects in two patients with paraneoplastic encephalitis.

Case 1: A 76-year old man presented with subacute onset uncertain gait and behavioral changes since one month. A few days after admission some hyperkinetic movements developed. Postural and kinetic tremor involved arms and chin, while gait instability worsened. Nocturnal sleep confusion developed as well. Ascertainments disclosed serum anti-Ma2 antibodies, and a subsequent diagnosis of Hodgkin's lymphoma was made. Early IVIg administration led to a prompt improvement of movement disorders as well as cognition lasting some weeks.

Case 2: A 69-year old woman came to our attention for subacute onset difficulty of gait and mental slowness since five months. She developed progressive gait ataxia and involuntary movements. They consisted in mixed stimulus-sensitive myoclonus and tremor involving both arms, and spreading to chin and legs within few days. Nocturnal confusional episodes presented as well. Serum anti-Yo antibodies were detected, and a following ovarian cancer was disclosed. IVIg administration led to a fast but short-lasting improvement of motor symptoms.

*Discussion***:** Both our patients developed a paraneoplastic encephalitis related to onconeural antibodies. They presented with rapidly progressive involuntary movements such as tremor and myoclonus, combined with gait instability. Cognitive and sleep features followed in the disease. In both cases the involuntary movements subsequently spread to face. In conclusion, complex and rapidly progressive movement disorders may represent an early diagnostic clue for immune-mediated disease. Since paraneoplastic syndrome is a treatable condition, these motor aspects should alert clinicians to deeply investigate patients for tumors.

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The closing-in phenomenon in patients with Huntington's disease

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Introduction: In visuo-constructional tasks, patients may reproduce drawings near-to or superimposed on a model, showing the so-called Closing-in (CI). This phenomenon has often been ascribed to frontal/executive dysfunctions related to a defective inhibition monitoring of attention-action circuits. Several studies investigated CI in patients with different kinds of dementia, and others studies also reported CI in individuals with neurodegenerative disorders without clinically relevant associated dementia. However, no studies explored this phenomenon in patients with Huntington's disease (HD), a neurodegenerative disease often involving the frontal cortical-subcortical circuits.

Objective: In the present study, we searched for the occurrence of CI in a large sample of HD patients, and systematically investigated the mechanisms underlying this phenomenon in our patients' sample.

Methods: We retrospectively analysed the graphic reproductions in a coping task of 130 HD patients, who had also completed neuropsychological, psychiatric, motor, and functional screening assessment.

Results: CI phenomenon occurred in 52/130 (40%) HD patients; most of them reproduced the copy directly on the model. MANOVA showed that HD patients with CI had poorer score on Symbol digit modality test, Stroop-color word- reading task, Stroop-color- interference task, Phonological verbal fluency test, and Trail making test - part B. However, a logistic regression analysis revealed that the only significant predictor of the occurrence of CI was the score on Stroop-color word - interference test.

Conclusions: HD patients may show CI in graphic copying tasks, especially when the frontal monitoring defects that could hamper inhibition of action and attention toward a model.

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[123I]Ioflupane SPECT and clinical features in idiopathic normal pressure hydrocephalus: comparison with newly diagnosed Parkinson's disease

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Background: Idiopathic normal pressure hydrocephalus (iNPH) is a chronic neurological disorder typically affecting the elderly population and usually presenting with dementia, urinary incontinence, and gait/balance disturbances. The phenotypic spectrum of iNPH may also be wider, including extrapyramidal parkinsonian-like features. Furthermore, a nigrostriatal dopaminergic impairment evaluated by [123I]Ioflupane ([123I]FP-CIT) SPECT can be present.

Objective: We compared semiquantitative [123I]FP-CIT SPECT and clinical findings in iNPH versus newly diagnosed Parkinson's disease (PD) to detect possible differences.

Methods: We examined thirty iNPH patients with positive [123I]FP-CIT SPECT and thirty patients with newly diagnosed PD. We then evaluated [123I]FP-CIT SPECT tracer uptake values, MDS-UPDRS part 3 total and single items scores, and levodopa response between the two patients groups.

Results: Compared to newly diagnosed PD, iNPH patients with positive [123I]FP-CIT SPECT have: not significant asymmetric and generally lower nigrostriatal dopaminergic impairment; lower difference in [123I]FP-CIT SPECT tracer uptake values between putamen and caudate nucleus (more affected putamen 1.96±0.48, contralateral putamen 2.09±0.40, more affected caudate 2.59±0.39, contralateral caudate 2.69±0.37, putamen/caudate ratio 0.79±0.12 in iNPH; more affected putamen 1.51±0.17, contralateral putamen 1.81±0.19, more affected caudate 2.27±0.38, contralateral caudate 2.51±0.41, putamen/caudate ratio 0.68±0.09 in newly diagnosed PD); a prevalent bradykinetic-rigid phenotype (93%), with tremor-dominant subtype in the remaining patients; more symmetric extrapyramidal motor signs; no correlation between MDS-UPDRS part 3 total score (17.17±8.34 in iNPH, 7.21±3.19 in newly diagnosed PD) and nigrostriatal dopaminergic impairment; no significant levodopa response (under 30% improvement). We underlined a predominant PD-like gait phenotype only in 57% of iNPH patients with positive [123I]FP-CIT SPECT, whereas a typical gait apraxia is more relevant in the remaining iNPH cases.

Conclusions: Our findings of a distinct pattern of nigrostriatal impairment in iNPH, compared to PD, might suggest a pathogenesis other than truly degenerative one. Clinical phenotype is an important variable to evaluate and predict the effects deriving from shunt surgery, then correct diagnosis and treatment can become more challenging in iNPH patients with positive [123I]FP-CIT SPECT.

P65

Construction and validation of the Hemifacial Spasm Grading Scale

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Introduction: Hemifacial spasm (HFS), is characterized by unilateral, intermittent contractions of the muscles of facial expression. Periorbital muscles are commonly involved [1], even leading to involuntary eyelid closure. Frequently its evolution causes the involvement of an increasing number of muscles and patients at a first assessment can present a wide range of clinical features. Botulinum toxin (BoNT) is the therapy of choice, but evidence from controlled clinical trials are few. There is a broad variety of rating scales used in clinical studies and no consensus has been reached on how to assess the disorder and its treatment outcome. [2]

Objective: To create and validate an objective assessing tool to diagnose and monitor HFS and the efficacy of its treatments.

Methods: Prospective observational cohort study protocol approved by the local ethics advisory committee (CEAS Umbria). A group of Neurologists with experience on HFS tratment, outpointed from a list of phenomenological aspects potentially related to HFS, three main features (localisation, intensity and frequency of involuntary muscolar contractions). Four indipendent drafts of the scale were created and then merged to obtain the final version of HFS Grading Scale (HFSGS).

Results: Intra-rater reproducibility ranged between ICC 0.73 (95% CI=0.54-0.86) and 0.83 (0.68-0.92), inter-rater reproducibility between 0.62 (95% CI=0.44-0.77) and 0.82 (0.69-0.90). A significative correlation (Spearman) was also observed with another rating scale previously tested on a BoNT efficacy study [3].

Conclusion: An objective tool for the assessment of HFS was created and validated. HFSGS also showed to be reliable in monitoring BoNT treatment efficacy in time.

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P66

cVEMPS analysis differentiates PD from SWEDD patients: pathophysiological implications

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Introduction: The pathophysiology of rest tremor in patients without evidence of dopaminergic denervation at I123beta-CIT cerebral SPECT (SWEDD) is still largely unknown. Recently, *cervical Vestibular Evoked Myogenic Potentials (cVEMPs*) have been used to evaluate brainstem function in PD patients. cVEMPs are an expression of an ipsilateral pathway linking the VIII and XI cranial nuclei and correspond to the vestibulo-collic reflex; they are hence a simple tool to evaluate brainstem functioning.

Objective: To study brainstem functioning by cVEMPs recording in SWEDD patients, compared to PD patients and healthy controls.

Methods: We enrolled 23 patients diagnosed with PD, 9 SWEDD patients and 19 healthy controls. They all underwent neurological and otoneurological examination; then cVEMPS were recorded. Differences in categorical and continuous variables were respectively calculated with the chi-square test and the one-way ANOVA test with Bonferroni correction.

Results: No gender and age distribution differences were found among groups. cVEMPs were bilaterally recorded in 18/19 healthy controls, in 15/23 PD patients and in 9/9 SWEDD patients: absence of potentials was higher in PD patients than in controls or SWEDD group (respectively p=0,02, p=0,04), while no difference was found between the latter two groups (p=0,49). No differences in cVEMPs latencies and amplitudes among groups were observed.

Conclusion: Rest tremor in absence of dopaminergic denervation is a poorly understood clinical condition, alternatively assimilated to early stages of PD or to dystonic tremor. In addition, some studies showed a cerebellar involvement, similar to that seen in essential tremor. In our study, SWEDD patients didn’t show any difference in cVEMPs compared to healthy controls, while PD patients exhibited a greater incidence of cVEMPs alterations (mostly absence of potentials), in line with previous evidences. Our results didn’t show brainstem involvement in SWEDD patients, supporting the hypothesis of a different pathophysiology underlying this condition as compared to PD.

P67

Sense of agency and sense of body ownership in functional movement disorders: new evidences from the moving rubber hand illusion paradigm.

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Introduction: Functional Movement Disorders (FMD) manifest with motor symptoms that are similar to voluntary movements but are experienced as involuntary by patients [1]. This gap might be related to abnormal self-recognition of bodily action, which involves two main components: sense of agency and sense of body ownership.

Objective: Here, we applied the moving Rubber Hand Illusion (mRHI) [2] to investigate whether sense of agency, sense of body ownership, and their interaction are altered in FMD during voluntary movements.

Methods: In the mRHI, participants look at a rubber hand while moving their hidden hand. Passive and active movements can differentially elicit sense of agency, sense of body ownership or both, depending on the posture of the rubber hand (plausible or implausible) with respect to the participants' body. Explicit measures of agency and ownership are obtained via a questionnaire.

Results: When the rubber hand is in a plausible posture, active movements elicit strong agency and ownership; rotating the rubber hand by 180 degrees abolishes ownership but not agency; conversely, passive movements suppresses agency but not ownership. Similar results were observed between patients with FMD (n=21) and healthy controls (n=21), indicating that explicit sense of agency and body ownership are preserved in FMD.

Conclusion: The latter finding is shared by a previous study in FMD [3], whereas the former appears to contrast with studies that used implicit measures of agency (e.g., sensory attenuation) and demonstrated altered sense of agency [4]. These contrasting findings suggest a dissociation between the explicit (being preserved) and the implicit (being impaired) components of sense of agency in FMD.

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P68

When appearances are deceptive: idiopathic brain calcification in a patient with hereditary haemochromatosis

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Introduction: Detection of MRI-brain T2-hypointensity compatible with iron accumulation could lead to a differential diagnosis work-up which includes conditions like neurodegeneration with brain iron accumulation (NBIA). [1] Besides NBIA, hereditary haemocromatosis, characterized by systemic iron deposition, can be rarely associated with neurological symptoms and MRI-brain T2-hypointensity.[2] However, idiopathic (Fahr disease) or secondary brain calcium deposition can be also associated with neurological involvement and brain T2-hypointensity.[3,4]

Case report: A 59 year-old man came to our observation for hyperferritinemia without any neurological symptoms. Brain-MRI, performed as hypeferritinemia work-up, detected bilateral T2 hypointensity within globus pallidus, substantia nigra, dentate nucleus and pulvinar. Laboratory examination revealed high ferritin (4728 ng/ml), serum iron (282 μg/dl) and transferrin levels, with high transferrin saturation. No alterations of ceruloplasmin, plasmatic and urinary copper or vitamin D–PTH axis were seen. Neurological examination revealed only mild right-sided akineto-rigid syndrome. A genetic study for HFE-hemocromatosis was performed resulting in a homozygous C282Y mutation compatible with the classic form of hereditary hemochromatosis of the adult. Liver MRI showed a moderate hepatic siderosis and therapeutic phlebotomies were started every 7-10 days. After the diagnosis, a brain computed tomography (CT) was performed in order to better characterize the suspected and unexplained brain iron accumulation. CT showed symmetrical hyperdensity compatible with bilateral calcifications in the same area that had been seen hypointense on brain MRI. Genetic analysis of the genes whose mutations have been associated with primary familial brain calcification are ongoing.

Discussion: Brain calcifications appear with various signal intensities by MRI, including T2 hypointensity that is also a typical feature of brain iron accumulation.[4] For this reason CT scan is considered the gold standard in detecting calcification.[3] In our case the misleading diagnosis of cerebral siderosis was avoided through the use of CT scan which could represents an important tool in ambiguous cases of suspected cerebral siderosis.

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P69

SNCA duplication and heterozygous STUB1 mutation in a patient whit spastic ataxia

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Introduction: A 59 years old man came to neurological attention because of a ten-year history of progressive gait impairment and dysarthria. The patient presented a positive family history for Parkinson's disease (PD) associated with dementia.

Objectives: To define clinically and genetically the disease affecting this patient.

Methods: Patient's familial and clinical history was collected and neurological examination was performed. Brain MRI, SPECT con [123]FP-CIT and [18F]FDG-PET were performed. Whole-Exome Sequencing (WES), Real Time-PCR of SNCA gene and array-CGH of SNCA locus were performed. Genetic screening of spinocerebellar ataxia types 1, 2, 4, and 6, Friedreich ataxia were done. Identified *STUB1* mutation was validated with Sanger sequencing.

Results: Gait disturbance and deterioration of balance insidiously developed when the patient was 47, dysarthria started 5 years later. His neurological examination was consistent with cerebellar and pyramidal dysfunction. No parkinsonian signs were present. Neuropsychological assessment did not show any cognitive deficit. MRI brain scans revealed cerebellar atrophy and hypointensity of basal ganglia in T2 sequences. SPECT con [123]FP-CIT was normal. [18F]FDG-PET showed cerebellar hypofunctioning. Real Time PCR revealed *SNCA* duplication. Array-CGH confirmed the duplication and defined the duplication boundaries. WES revealed a missense heterozygous mutation (c.124T>A; p.Tyr42Asn) in the *STUB1* gene. No other *STUB1* variants were found with WES and Sanger sequencing. The p.Tyr42Asn is predicted to be deleterious by all in silico pathogenicity prediction tools.

Conclusion: Inherited spastic ataxias are a diverse group of clinically and genetically heterogeneous neurodegenerative disorders. *STUB1* missense mutations cause autosomal recessive spinocerebellar ataxia-16 (SCAR16), which is characterized by truncal and limb ataxia resulting in gait instability. Further neurological features are dysarthria, nystagmus, spasticity of the lower limb and mild peripheral sensory neuropathy. The identification of a non-penetrant *SNCA* duplication associated with a heterozygous *STUB1* mutation arouses questions about the genetic contribution of the identified mutations in this patient's disease.

P70

A novel RAB39B gene mutation in an Italian family

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Introduction: Mutations in *RAB39B* gene localized on Xq28 cause early onset parkinsonism associated with intellectual disability. As few *RAB39B* mutations have been so far identified, the genotype-phenotype correlation is still to be clarified. We described a novel *RAB39B* mutation in two Italian brothers with early onset parkinsonism, macrocephaly and mild intellectual disability.

Methods and Results: The younger brother was a 67-year-old man who had experienced learning disabilities at primary school and, at the age of 11 years, had developed a postural tremor at both hands. At the age of 62 years he had developed rest tremor at right hand, bradykinesia and gait difficulty with good response to L-Dopa. Neurological examination revealed right hand rest tremor and a bilateral postural tremor. The gait was moderately slow and arm swing was decreased. Brain MRI showed globus pallidi, pulvinar, red nucleus and substantia nigra hypointensities at T2-weighted and GRE sequences and brain CT scan displayed globus pallidi moderate calcification. [123I]-FP-CIT SPECT imaging showed a severe reduction of the radioligand uptake at the level of left putaminal nucleus. His older brother had developed tremor, bradykinesia, rigidity and bucco-lingual dyskinesias. Sequencing of *RAB39B* identified a novel frameshift mutation (c.137dupT, pSer47Leufs*44) in the two brothers. Karyotype, array CGH, fragile X syndrome molecular test, mutational screening of *SNCA/PARK1, PARK2, PARK8* genes were wild type in both sibs.

Conclusion: We describe the first Italian family carrying a *RAB39B* mutation. The mutation is associated with cognitive impairment and early onset extrapyramidal symptoms covering postural or rest tremor, bradykinesia and dyskinesias. It is still unclear if calcification is part of the wide spectrum of features related to *RAB39B* mutations. L-dopa responsiveness and [123I]-FP-CIT SPECT suggest that this *RAB39B* mutation causes SNc degeneration.

P71

Levodopa responsive Parkinsonism with abnormal brain [123I]-FP-CIT SPECT in a patient affected by Down's syndrome

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Introduction: Adult patients affected by Down's syndrome (DS) are at higher risk of developing Alzheimer-type dementia and epilepsy, while parkinsonian symptoms are not common, although occasionally basal ganglia calcification are sometimes observed.

Objective: To report on a case of DS associated with parkinsonian symptoms responsive to levodopa.

Materials and methods: A 52 year-old man affected by DS presented with a history of one year of significant resting tremor, more evident to the right arm, associated with hypomimia, bilateral bradykinesia, bradyphrenia. Mild postural tremor was also associated, together with a dysmorphism of the hands with the distal phalanges in flexion.

Results: Brain MRI showed only a bilateral pallidal hypointensity on FLAIR weighted images, while brain SPECT with [123I]-FP-CIT SPECT showed a marked bilateral reduction of dopamine transporter (DAT) at striatal level, more prominent in the putamina. Treatment with levodopa/benserazide was started (400/100 mg daily) with good response and significant motor improvement.

Discussion and conclusions: To the best of our knowledge, this is the first case of a DS patient presenting with levodopa responsive parkinsonism and a marked bilateral reduction of DAT at striatal level on a brain SPECT. Previous neurochemical investigations have showed as the dopamine concentration in the striatum is decreased in some of the older and demented patients affected by DS. We retain that parkinsonism might be relatively present in DS patients, although probably overshadowed by clinical signs of Alzheimer- type dementia.

P72

The hexanucleotide repeat expansion GGGGCC in the C9ORF72 gene in Sardinian patients with atypical parkinsonism, frontotemporal dementia and motor neuron disease: a retrospective cohort study on the full spectrum of psychiatric disorders

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Background: Large expansions of the non-coding GGGGCC-repeat (more than 30) in the first intron of the C9orf72 gene have been demonstrated to cause amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Mutations in the *C9ORF72* gene may be a major cause not only of frontotemporal dementia with motor neuron disease but also of late onset psychosis. Several clinical studies highlight a high prevalence of psychotic features associated with this mutation. Early isolated psychiatric presentations such as mood deflection, apathy and social withdraw, have been described in patients with *C9ORF72* mutations. However, the anatomical underpinnings of psychotic symptoms in *C9ORF72* carriers remain unclear. Recent papers have investigated the possible pathogenic role of intermediate *C9ORF72* repeat expansions ranging between 20 and 29 repeats in typical Parkinson's disease with psychosis and atypical parkinsonisms.

Objective: To screen for the presence of psychiatric disorders in Sardinian patients with atypical parkinsonism syndromes, frontotemporal dementia and motor neuron disease carrying the hexanucleotide repeat expansion GGGGCC in the C9ORF72 gene larger than 20 repeats.

Methods: We conducted a retrospective chart review of 68 patients who had C9ORF72 mutations with 20 or more repetitions on genetic testing. A wide range of different types of psychiatric disorders were investigated according to DSM-5 criteria. The missing retrospective data were obtained through phone call to the caregiver's patient and administration of clinician- and patient-rated neuropsychiatric scales.

Results: Sixty eight patients (40 men, 28 women) were studied. Fifty nine patients was found to be carriers of C9ORF72 repeat expansions with more than 30 repeats. Intermediate 20–29 repeat expansions were detected in nine (6 females and 3 males) patients. Among the fifty nine patients with more than 29 repeats, 44, 14 and 1 presented respectively clinical features of motor neuron disease, FTD and PD. Among the nine patients with intermediate repeat expansions (20-29 repeats), 4,1,3 and 1 patient presented respectively clinical features of motor neuron disease, FTD, atypical parkinsonian syndromes and PD. A wide range of psychiatric disorders have been detected such as anxious syndromes (n=50; 73.5%), panic disorders (n=8; 11.7%), mixed anxiety-depressive disorder (n=29; 42.6%) major depression (n=7;10.2%) bipolar affective disorders (n=6; 8.8%), cyclotimia (n=2; 2.9%), schizophrenia spectrum disorders (n=31; 45.5%), episodic delirium (n=7; 10.2%), ICD (n=20; 29.4%). No suicide attempt have been documented.

Conclusion: The psychiatric disorders have a high frequency in subjects with intermediate (75%) and larger than 30 repeats expansion (85%) of the esanucleotide of C9ORF72. Frequently, the psychiatric disorders may precedes the onset of the neurodegenerative disorder. The most frequent psychiatric disorders were anxiety and depression disorders, followed by schizophrenia spectrum disorders. Major affective disorders were rarely detected and ICDs were diagnosed mainly in FTD. Episodic delirium is most frequent in PD.

P73

Primary Familial Brain calcifications: results from a monocentric study and a novel XPR1 mutation

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Background: Primary familial brain calcifications (PFBC), previously known as Fahr disease, is characterized by calcium deposition in basal ganglia, dentate nuclei and subcortical white matter. Clinical presentation includes parkinsonism, dementia or psychiatric disturbances. Four causative genes (*SLC20A2, PDGFB, PDGFRB, XPR1)* have been discovered so far.

Aim: To analyze the clinical, radiological and genetic spectrum of a group of patients with PFBC and report on a novel XPR1 mutation.

Methods: All brain CT scans of in- and outpatients referred to the Neurology Department of Maggiore Hospital, Novara between 2008 and 2016 and consistent with PFBC, according to Nicolas et al [1] were reviewed. Clinical data of patients were collected. Secondary causes of PFBC were ruled out and subsequent genetic analyses performed.

Results: About 13000 cerebral CT were reviewed. 28 (0,2%) were consistent with PFBC, of which 8 were due to secondary causes (especially hypoparathyroidism). 20 patients underwent genetic analyses with NGS revealing in 7 of them (35%) mutations in *PDGFRB* (5%) (c.676C>T), *SLC20A2* (25%) (c.1765G>A; c.1463A>G; IVS-8 A>G; c.338C>G) and *XPR1* (10%) (c.697A>T in two unrelated patients).

Discussion: PFBC represents a rare genetic condition. Aside from movement disorders, cognitive impairment and psychiatric symptoms, nonspecific symptoms can be present. We identified a novel mutation in *XPR1* (c.697A>T) in two unrelated patients with different clinical presentation (mild cognitive impairment and vertigo). The negative results in about 70% of our cases indicates that other genes may be involved in PFBC pathogenesis.

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Neuropsychological and 18F-fluorodeoxyglucose PET study in *LRRK2* patients

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Objective. LRRK2 gene mutations underlie one of the most common mendelian forms of Parkinson's Disease (PD), designed PARK8. PARK8 clinical features are similar to those observed in idiopathic PD (IPD), and functional imaging studies with 18F-6-fluoro-L-dopa PET showed findings indistinguishable from that of IPD. The aim of this study was to assess the cognitive functions and the pattern of cerebral metabolism measured with 18F-fluorodeoxyglucose (FDG-PET) in PARK8 patients compared with IPD subjects.

Material and Methods: We enrolled 8 patients (2 F and 6 M) carrying *LRRK2* gene mutations and 8 patients (3 F and 5 M) with idiopathic PD (IPD), comparable for onset age, severity and disease duration. All subjects underwent a full neuropsychological battery and a 18F-fluorodeoxyglucose PET study (FDG-PET). Cerebral regional relative metabolic maps were compared in PARK8 and IPD patients using voxel-based analysis with statistical parametric mapping.

*Results***:** PARK8 patients and IPD cases were comparable for the asymmetry of motor signs, the response to l-dopa, the presence of fluctuations and dyskinesias, and non motor features. Furthermore, there were no significant differences in neuropsychological test results, since the two groups were comparable for all cognitive functions assessed. Compared to controls, FDG-PET revealed relative cerebral hypometabolism involving mainly the parieto-occipital cortex in the IPD and to a lesser extent in *LRRK2* carriers. No significant difference could be revealed between IPD and *LRRK2* carriers.

*Conclusions***:** Preliminary results suggest that the cortical and subcortical patterns of relative cerebral metabolism in PD associated to *LRRK2* gene mutations were similar although appeared less severe compared with those in IPD. These findings are in agreement with the overall similar neuropsychological profile, apart one patient with IPD and clinical dementia. Whether the overall milder involvement of cortical hypometabolism in *LRRK2* might be related to a different and/or less marked pathology in specific areas than in IPD should be further explored in a larger series of patients

P75

TMEM230 mutations are not frequent in Italian patients with autosomal dominant Parkinson's disease

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Introduction: A recent linkage analysis in a large autosomal dominant Parkinson's disease (ADPD) kindred identified a new locus for ADPD on chr.20p13. A missense Arg141Leu mutation within the TMEM230 gene has been suggested as causative of the disease [1]. Additional variants in the same gene have been found in two young onset US PD cases and seven Chinese PD patients, of which five were homozygous for the new identified mutation.

Objectives: To determine the frequency of TMEM230 mutations in Italian patients with ADPD.

Methods: We performed a sequencing analysis of the TMEM230 gene in 86 Italian familial PD patients compatible with an autosomal dominant inheritance (two or more PD cases in at least two consecutive generations) collected between 2012 and 2016. The clinical diagnosis of PD was based on the presence of at least two of the following signs: bradykinesia, resting tremor and rigidity, along with a positive response to Levodopa treatment and absence of other causes of parkinsonism. All subjects were screened for SNCA, GBA and common LRRK2 mutations and those carrying pathogenic variants were not removed from the analysis. To detect mutations, we performed a polymerase chain reaction of all exons and intron-exon boundaries of the TMEM230 gene. Sanger sequencing of all exons was performed.

Results: No pathogenic variants were identified. Two intronic (c.174+5G>C, c.412-44G>A) and four exonic known polymorphisms were detected (p.Met64Thr, p.Pro102Pro, p.Lys103Lys, p.Ala110Ala).

Conclusion: These results suggest that TMEM230 mutations are not a frequent cause of PD with autosomal dominant inheritance in the Italian population. Additional screening in familial cases would be important in order to assess the co-segregation of TMEM230 variants with Parkinson's disease.

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P76

Identification of a *de novo C19orf12* frameshift mutation in a patient with dystonia-spasticity syndrome and Neurodegeneration with Brain Iron Accumulation (NBIA)

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Introduction: An Italian young woman, aged 16, presenting gait disturbances, lower limbs spasticity, feet dystonia and cognitive impairment, with a negative family history for neurological disorders, has come to the attention of the outpatient clinic of Policlinico Hospital of Milan, looking for a possible genetic diagnosis.

Objectives: To characterize clinically and genetically the disease affecting this patient.

Methods: A neurologist with expertise in movement disorders collected familial and clinical history and performed neurological examination of the patient. Brain MRI with T2* and SWI sequences and CT of the young woman were performed. Sanger sequencing of all exons and intron-exons boundaries of *PANK2*, *PLA2G6*, *FTL1*, *C19orf12, WDR45, FA2H* and *COASY* was done.

Results: At the age of six the proband developed a progressive alteration of gait with imbalance and a learning disability (QI 70). The most recent neurological examination showed moderate dysarthria, lower limbs spastic hypertonia with hyperreflexia, bilateral fixed foot dystonia, Babinski's sign on the left and a prominent gait disturbance caused by spasticity and dystonic feet posture. Family history was negative for neurological disorders. Brain MRI displayed marked bilateral pallidal, subtalamic and nigral hypointensity in T2 sequences. Brain CT showed a mild bilateral pallidal hyperdensity, compatible with microcalcifications. Sanger sequencing of *C19orf12* gene unraveled a *de novo* heterozygous frameshift mutation in the proband (c.265_266delAT; p.Met89GlyFs*12). The mother and the father did not harbour the mutation.

Conclusion: MPAN is characterized by iron accumulation in basal ganglia, and is associated with a hypokinetic movement disorder, spasticity, optic atrophy and cognitive decline. In this case the neuroradiological features suggested the MPAN. The absence of any other mutations in other NBIA genes may indicate a dominant negative effect of the heterozygous de novo p.Met89GlyFs*12 mutation.

P77

Phosphorylated α-synuclein in the skin of idiopatic and parkin-related Parkinson's disease

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Introduction: Deposition of phosphorylated α-synuclein (P-α-syn) in cutaneous nerve fibers has been shown in patients with Lewy body (LB) pathology such as Parkinson disease (PD). Homozygous Parkin mutations are a common cause of early-onset PD without LB brain pathology, while the role of heterozygous mutations in the pathogenesis of the disease is still not clear. There are only two reports of the neuropathology of heterozygous early-onset Parkin-mutation PD patients that show a LB disease similar to that of idiopathic PD (iPD). [1,2]

Objective: To determine if there is a difference in the deposition of P-α-syn in cutaneous nerve fibers comparing patients with PD associated with homozygous and heterozygous parkin-mutations and with iPD.

Materials and methods: We used double immunofluorescence for PGP 9.5 and P-α-syn in 3-mm punch biopsy performed at cervical and arm sites in three PD patients (homozygous and heterozygous parkin-related disease and iPD). All of the patients had an early onset PD (range from 17 to 45 years old) and were on Levodopa therapy.

Results: We found aggregates of P-α-syn on cutaneous nerve fibers in the heterozygous parkin PD at arm site and in the iPD at both sites, while no P-α-syn immunoreactivity was found in the homozygous parkin PD in either sites. The finding that deposition of P-α-syn is present in cutaneous nerve fibers of iPD and heterozygous parkin- PD patients, but not in the homozygous parkin-PD patient is in line with the neuropathological profile that is commonly observed in the brain of these types of PD.

Conclusion: Our results suggest that heterozygous parkin PD patients share the same pathological profile of iPD in peripheral tissues, even if they present as early onset PD.

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P78

Success and pitfalls of subthalamic nucleus Deep Brain Stimulation in Parkinson's disease: focus on neurochemistry

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Introduction: Deep Brain Stimulation (DBS) has become a standard therapy for Parkinson's disease (PD) and dystonia. Although many scientific, clinical and ethical issues are still open, DBS delivered into the subthalamic nucleus (STN) has improved the quality of life of severalthousands of people around the world and was recently proposed to PD patients as soon as motor fluctuations occur [1].

Objective: To clarify which biochemical cascade may explain efficacy or pitfalls of STN-DBS.

Methods: This paper will review the more appropriate literature dealing with biochemical changes as detectable during effective surgical procedures. Hence, we are examining the main results achieved, in the past, by collecting micro-dialysis samples or, more recently, the preliminary findings of voltammetry.

Results: Crucial and only partially understood are the interplays occurring between STN-DBS and levodopa (LD)-centred therapy [2]; we are evaluating whether specific motor items specifically respond to each therapeutic approach. In addition, our goal, here, is to investigate to what extent the improvedmotor control, based on STN-DBS therapy, is reached not merely by optimizing the LD-DBS synergy but also by the additional modulation of other neurotransmitters, such as noradrenaline (NA), serotonin (5-HT) and acetylcholine (ACh). Further, it is worth identifying acute and chronic changes involving cyclic nucleotides, capable of modulating circuit plasticity [3].

Conclusions: Our excursus highlights the need to seek new investigational routes, which take into account the possibility that novel players such as Glia, or revisited old ones such as acetylcholine, contribute to rebalancing cortical and sub-cortical oscillatory properties. Moreover, our on-going understanding of specific changes in brain chemistry promoted by STN-DBS may propel its utilization, albeit costly, in any disease phases, instead of irreversible lesioning approach.

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[3] Stefani et al., Progr Neurobiol. in press

P79

Isolated dystonia caused by ATP1A3 mutation unresponsive to deep brain stimulation

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Introduction: Mutations in the ATP1A3 gene are associated with a wide spectrum of neurologic disorders encompassing rapid-onset dystonia-parkinsonism (RDP) and alternating hemiplegia of childhood (AHC). Isolated dystonia has been occasionally reported. The efficacy of deep brain stimulation (DBS) in cases of isolated dystonia with ATP1A3 gene mutations has not been established.

Methods: We reported the outcome, after ten years of stimulation adjustments, in a patient with ATP1A3 isolated dystonia who received a GPi DBS implant and then compared the results to all published cases of ATP1A3.

Results: Our patient bore a heterozygous *de novo* missense mutation (c.1250T>C, p.L417P) in the ATP1A3 gene, had isolated dystonia and did not respond to GPi DBS. Seven cases with isolated dystonia were reported. Four ATP1A3 patients have received stereotactic surgery in the GPi; no patient has received surgery in other targets. The mutation found in this case of isolated dystonia has been previously observed in one patient with RDP.

Conclusion: We report failure of GPi stereotactic surgery overall in five patients with ATP1A3, including this observation with isolated dystonia and one case of pallidotomy without mention of parkinsonism. We also confirm clinical and genetic heterogeneity of this condition. ATP1A3 dystonia may possibly represent a case of “surgicogenomics”, meaning that such genetic diagnosis may be a negative indication for stereotactic surgery in the GPi. It remains unknown whether DBS in other targets may be efficacious.

P80

San Pellegrino Terme Ecological test in Parkinson's disease treated with DBS

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Introduction: Ecological rehabilitation is based on the natural evidence patients need to interact with the environment surrounding them in order to get best performances in daily life activities and to be ready to go back home when they will be discharged.

Objective: Aim of our study is both evaluating and improving motor, heart and breathing activities in patients with Parkinson's disease treated with DBS admitted in our Neurorehabilitation Ward of Istituto Clinico Quarenghi.

Methods: Ecological walking test of San Pellegrino Terme is organized in ten different tasks: walking on the gravel, walking on the meadow, walking along a street, getting up and down from the sidewalk, overcoming an obstacle, walking on the cobblestones, walking on the path, going upstairs, going downstairs, walking among people. We evaluate each task with a specific score: 0 points activity not executed, 1 point executed with help, 2 points executed with difficulties, 3 points executed with confidence. There are four ways with different length: 400m, 765m, 1345m, 1950m. A physiotherapist always checks each task evaluating heart rate and oxygen blood saturation. At the end of the test all collected data are evaluated by physician. All the patients are evaluated both with FIM scale and with Ecological Walking Test Scale.

Results: From 2007 we evaluated 35 patients affected by Parkinson's disease treated with DBS, 23 males and 12 females, average age 59.5 years old. We recorded an improvement about FIM Scale score of 10.9% and about Ecological Walking Test Scale of 20%.

Conclusion: Despite the little sample of patients this study demonstrates San Pellegrino Terme Ecological Test is useful to achieve improvements in daily life activities among patients affected by Parkinson’s disease with DBS. This is a low cost test, appreciated both by patients and by physiotherapists; is also safe and once discharged patients may carry the test on also at home.

P81

Impedance variation of directional DBS lead in chronic follow-up of parkinsonian patients

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Introduction: Deep Brain Stimulation of STN is an effective treatment for Parkinson Disease . In order to provide a proper therapeutic current one crucial aspect is the control of the impedances fluctuations of the lead contacts. This topic is interesting in consideration of the recent availability of directional DBS systems, in which the directional contacts have a 1,5mm^2 surface, respect to the 6mm^2 standard cylindrical ring contacts. The lower surface area physiologically implicates an increment of the impedances values and potential higher fluctuations.

Objective: The aim of this study is to evaluate the impedances variation overtime in Parkinsonian subjects who underwent to DBS surgery with a directional system capable of directional current steering.

Methods: 10 consecutive Parkinsonian patients went to surgery in bilateral STN using a Directional DBS system (DB-2202 Cartesia LEADS and Vercise PC IPG, Boston Scientific-Valencia, California). During the activation visit and the follow up visits the impedances values have been measured and collected. All the patients have been programmed with the best configuration and stimulation settings in terms of clinical outcomes.

Results: We report values of the impedance from baseline to up to 11 months follow-up, measured in 160 contacts in total (120 directional, 40 cylindrical). At baseline is 1976 Ohm for the directional contacts and 931 Ohm for the cylindrical ring contacts. Considering only the therapeutic contacts among the 7 patients who have reached the 6 month follow up, across a total of 40 contacts activated, 39 are directional.

Discussion: The fluctuations of the impedances in the active directional contacts appear to be greater than in the standard cylindrical contacts. Moreover, high changes has been recorded also between adjacent active directional contacts. The use of a Directional DBS system with independent power sources seems to be a proper tool to use constant-current stimulation to maintain the therapeutic stability when more than two contacts are activated in the same lead.

P82

Acute reversible depression state provoked by subthalamic Deep Brain Stimulation

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Introduction: Subthalamic nucleus deep brain stimulation (STN-DBS) is a surgical therapeutic option for Parkinson's disease (PD) patients. Not only motor but also psychic functions are modulated by STN-DBS.

Objective: To describe a PD patient treated with STN-DBS developing a reproducible and reversible acute depressive state when stimulated within the left STN.

Case report: A 47-year-old woman underwent STN-DBS surgery after 16-years of PD. In spite of PD and a single episode of hallucinations, recovered after dopamine-agonist withdrawal, the past medical history was unremarkable. The pre-surgical Unified-Parkinson's-Disease-Rating-Scale (UPDRS) part-III score was 57 in OFF-condition and 7 in ON-condition and the neuropsychological and psychiatric assessments were normal. A bilateral STN electrode implantation was performed and, during the intra-operatory assessment, acute sadness appeared with the activation of the electrode 1-C+ in the left STN at 2V, 130Hz and 60μs. Post-surgery MRI scan showed correct anatomical placement of the electrodes within the STN regions. The onset of acute depression with cry occurred again in the post-operative parameter setting few seconds after the activation of contact 1-C+. The voltage threshold for the onset of cry was 2mA at 130Hz, 4.5mA at 80Hz and 5mA at 60Hz. Chronic therapy with levodopa/carbidopa 600 mg/day and stimulation setting at 2.8mA, 180Hz and 60μs (right-STN, contact 10-C+) and 3.5mA, 180Hz and 60μs (left-STN, contact 3-2+) were administered, with optimal control of motor symptoms and no psychiatric disturbances. The phenomenon was reproducible at the 1-year follow-up examination while the psychometric assessment excluded current depression, anxiety and apathy.

Conclusions: Acute and usually transient changes of behavior or mood after STN-DBS activation are commonly reported as stimulation of unintended targets. We report a new case of reproducible acute and severe depression in a patient with optimally-placed electrodes; moreover, we observed a different modulation of the psychiatric side-effect by changes of stimulation frequencies.

P83

Directional leads for subthalamic deep brain stimulation in chronic follow-up of parkinsonian patients: experience in two Italian centers

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Objective: We report the clinical evaluation in chronic follow-up and the stimulation settings used in nine patients with Parkinson’s disease implanted with a DBS Directional system in bilateral STN.

Background: Deep Brain Stimulation of Subthalamic Nucleus (STN) is an effective treatment for Parkinson disease (PD) .The most common side effects are due to sprouting of stimulation to area outside the target (i.e. hypertonia for stimulation of internal capsula, ocular shrew deviation for stimulation of oculomotor fibers, paresthesias, etc). Recently developed directional leads (D-LEADS) allow either conventional programming, with homogenous radial distribution of stimulation among 3 segmented contacts (RING MODE), or directional setting (D-MODE), focusing electric field in a preferential direction.

Methods: Nine consecutive patients, with diagnosis of PD, have been implanted since December 2015 inbilateral STN using a Directional DBS system (DB-2202 Cartesia leads connected to Vercise PC IPG, Boston Scientific-Valencia, California), with no specific selection criteria. At the stimulation activation visit, all the contacts have been tested, starting from ring mode and then moving to directional mode, according to the clinical effects. During the follow up visits the stimulation settings have been adjusted according to clinical needs, in order to avoid adverse events and maximizing the therapeutic effect.

Results: We collect a report of the stimulation settings and the configurations now activated in 9 patients. The mean amplitude used is 2,44mA and 78% patients use a directional configuration. Clinical improvements in terms of UPDRS scales and LEDD are collected and reported for the patients who already reached the six month follow up: in terms of UPDRS III is 64%.

Discussion: In our experience, directional current steering has been an advantageous tool which has allowed meaningful clinical improvements maintained for up to 12 months, preventing adverse events, by focusing stimulation on target and limiting diffusion to adjacent areas.

P84

Efficacy and tolerability of low-frequency Deep Brain Stimulation (LFS) during daytime only in Parkinson's disease: a pilot study

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Objective: To compare the efficacy and tolerability of LFS during daytime only to LFS applied 24 hours a day, in PD patients bilaterally implanted for STN-DBS who develop drug- and stimulation resistant Freezing of Gait (FOG)**.**

Background: High-frequency electrical stimulation (HFS) of the STN, typically in the range of 130 – 185 Hz, is effective to treat parkinsonian symptoms such as tremor, bradykinesia and rigidity. Nevertheless, in the long term a number of patients develop gait disturbances, especially FOG, that is poorly responsive to HFS and/or dopaminergic treatment. Several studies reported that LFS (typically 60 – 80 Hz) could be useful to improve gait disturbances and FOG. However, not all patients tolerate LFS well due to worsening of motor symptoms, and need to return to conventional HFS.

Methods: Prospective, randomized, cross-over, double-blind study of PD patients treated with STN-DBS at conventional HFS for at least 12 months, who developed disabling FOG (FOG-questionnaire item 3≥3). Patients will be randomized in two groups: one group will receive continuous LFS (60 Hz) 24 hours a day, while the second will receive LFS only during daytime, and switched back to 130 Hz during the night. After one month, the two groups will be crossed over. Neurological evaluations will be performed at the time of study entry, after one and two months. Patients and neurologists involved in the clinical evaluation will be unaware of the stimulation settings.

Results: The study will evaluate the efficacy of LFS on disabling FOG and establish whether LFS applied only during the daytime reduces the number of patients who need to return to HFS due to worsening of motor symptoms.

Conclusions: This study explores the possible role of neuroplasticity mechanisms in conditioning changes in clinical response to continuous DBS. Furthermore, it could help to better understand the relation between variations of stimulation frequency and improvement of freezing of gait during STN-DBS.

P85

Can technologically-assisted programming optimise deep brain stimulation efficacy? Preliminary results of a double-blind, randomised, cross-over study in subjects with Parkinson's disease and deep brain stimulation

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Introduction: Subthalamic deep brain stimulation (STN-DBS) is a mainstay treatment for advanced Parkinson's disease (PD). DBS efficacy depends on leads location and on stimulation parameters. Neurosurgical advancements improved the precise location of the leads, whereas stimulation parameters remain based on clinical observation. Of relevance, this process is the most complex and time-demanding step of the DBS-procedure. The development of volume tissue activation (VTA) might now improve it by directly visualising the stimulation related effect.

Aim: We aim to evaluate the impact of technologically-assisted programming on PD care as measured by the clinical improvement obtained by means of the technologically-assisted programming vs. the clinically-based one.

Methods: We evaluated the motor improvement in four subjects with PD and STN-DBS in meds-OFF/Stim-ON (i.e. after 12h withdrawal of all dopaminergic treatments) and meds-ON/Stim-ON. Stimulation parameters were selected according to: i) clinical-observed benefit and ii) with a dedicated software (SureTune®, Medtronic, PLC).

Results: In our preliminary data technologically-assisted programming was superior to clinically-based on in two out of four patients, reducing the motor symptoms with lower energy delivered. The remaining two patients were clinically-reprogrammed because of suboptimal control of freezing of gait and dyskinesia.

Conclusion: The technically-assisted programming may support stimulation setting but complex symptoms care requires clinically-based refinement of the stimulation.

P86

Lethargic state as a result of abrupt apomorphine withdrawal in Parkinson's disease patients.

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Introduction: Continuous apomorphine subcutaneous infusion represents an established treatment for motor complications in Parkinson's disease (PD), allowing to reduce pulsatile dopaminergic stimulation [1]. Abrupt interruption of apomorphine infusion in PD patients can be observed in relation to technical issues preventing apomorphine delivery, or to dopaminergic medication withdrawal during deep brain stimulation (DBS) surgery and programming. In these conditions leading to abrupt apomorphine withdrawal, we repeatedly observed an acute lethargic state.

Objective: To describe an unreported side effect of apomorphine treatment.

Methods: The behavior of a PD patient was assessed during acute apomorphine withdrawal in different occasions (DBS surgery and programming).

Results: After apomorphine withdrawal a lethargic state consistently occurred in our patient. Only resuming apomorphine allowed recovering of arousal.

Conclusions: This is the first description of a lethargic state after abrupt apomorphine withdrawal. In our patient, lethargia was consistently reproduced each time apomorphine was abruptly interrupted, confirming our previous unreported observations. Since its first applications, dopaminergic medication has been described to increase arousal in never treated PD patients, as nicely reported by O. Sacks in Awakenings [2]. One of the first sign of apomorphine kick-in is yawning, representing an increased arousal. Moreover, apomorphine is used as treatment for severe disorders of consciousness [3]. As such, the abrupt interruption of chronic 24-hour continuous apomorphine infusion induces a withdrawal state, resulting in a lethargic state in severe cases. Similarly, addicts to amphetamine, a strong and rapid inhibitor of dopamine re-uptake, might fall into a profound lethargic state after amphetamine withdrawal [4]. The occurrence of a lethargic state as a result from abrupt apomorphine withdrawal should be taken into account in the management of PD patients.

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P87

Impact of autonomic neuropathy in Parkinson's disease patients treated with advanced therapies

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*Background***:** The proven efficacy of subthalamic deep brain stimulation (STN-DBS) and levodopa-carbidopa intestinal gel infusion (LCIG) on advanced Parkinson's disease (PD) may be limited by associated autonomic dysfunction, resulting in reduced activities of daily living (ADL) and quality of life (QoL) performances [1,2].

Objective: To analyze the prevalence and the functional burden of autonomic neuropathy (AN) in advanced PD patients who underwent STN-DBS or LCIG.

Methods: 60 advanced PD patients treated with STN-DBS (n= 30) or LCIG (n= 30) underwent a complete autonomic assessment; AN was defined by at least two abnormal parasympathetic tests and at least one abnormal sympathetic test. ADL impairment, autonomic symptoms, cognitive status, motor performances and QoL were evaluated by means of ADL/iADL scales, SCOPA-AUT, MoCA, MDS-UPDRS-III, and PDQ-8.

Results: The prevalence of AN was 48.3% (50% DBS vs 46.7% LCIG; p:0.796); 55.2% patients reported thermoregulatory, 44.8% urinary/sexual, 27.6% gastrointestinal, 17.2% cardiovascular, and 17.2% pupillomotor dysfunctions. AN+ patients, adjusting for cognitive impairment and motor disability, showed a three-fold increased prevalence of ADL/iADL impairment compared with AN- (OR=3.042; p:0.046). Orthostatic hypotension prevalence was 26.6% (23% DBS vs 30% LCIG; p:0.559) and was indipendently associated to higher ADL/iADL impairment ($p \leq 0.047$). SCOPA-AUT score correlated with QoL impairment, in particular for gastrointestinal ($p<0.001$), urinary/sexual ($p=0.01$) and cardiovascolar ($p=0.017$) regions. No differences were observed between DBS and LCIG patients, apart for worse cardiovascular impairment in LCIG ($p = 0.039$) and worse pupillomotor impairment in STN-DBS ($p = 0.026$), as measured by the SCOPA-AUT.

*Conclusions***:** AN is an independent risk factor for functional disability and QoL impairment in advanced PD patients treated with STN-DBS and LCIG. Thus, in addition to addressing motor disability, identifying and managing autonomic targets may be required to optimize the full potential of these advanced therapies [2].

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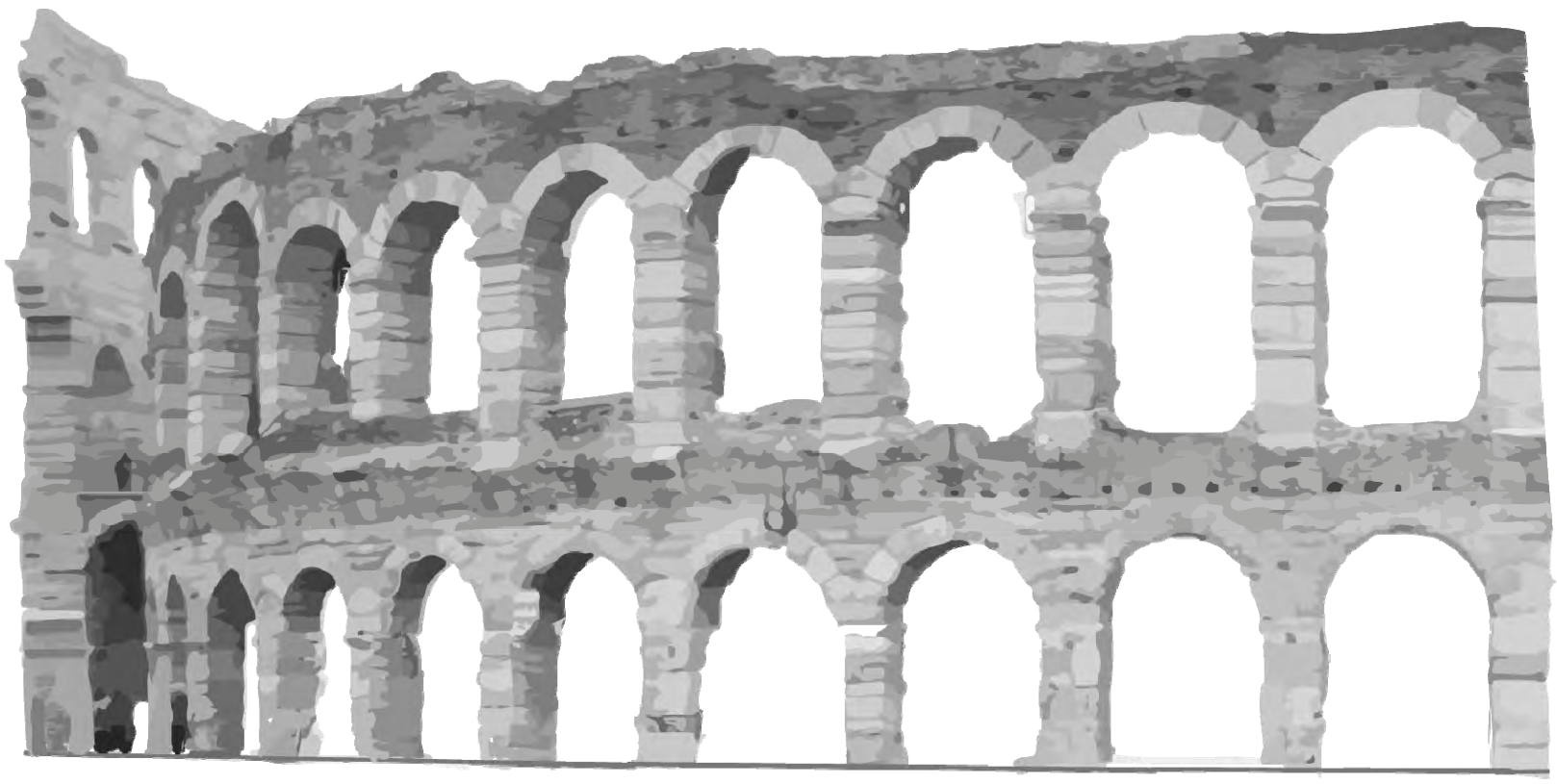
Indice Autori



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