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ACCADEMIA LIMPE-DISMOV
ACCADEMIA ITALIANA
MALATTIA DI PARKINSON
E DISORDINI DEL MOVIMENTO

C1

Anosognosia of motor deficit in Huntington's disease

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Introduction and objectives: Anasognosia (or unawareness) of choreic movements has often been reported in Huntington's disease (HD) although its origin is not entirely clear. We wanted to study anosognosia of motor deficits in HD.
Methods: Seventy-one patients with stage I or II HD, recruited from outpatient clinics at the Besta Institute and Parkinson-CTO Center, participated in the study. The motor section of the UHDRS, the total functional capacity, a short battery of cognitive tests, the SANS and SAPS scales for negative and positive psychiatric symptoms and the Hamilton scales for depression and anxiety were performed. A semi-structured four-point questionnaire was also administered to assess the degree of awareness of motor problems in daily life.

Results: Twenty-seven patients (38%) (group 1) were aware of their motor symptoms while 44 (62%) (group 2), to various degree, were not. Twenty-nine patients in the group 2 (66%), scored 1 on the anosognosia scale while 11 (25%) scored 2 and 4 (9%) scored 3. The two patient groups (1 and 2) were compared for demographic, motor, cognitive and psychiatric variables. Patients with anosognosia (group 2) performed worse on the visual search test ($p = 0.04$) and on the SANS scale ($p = 0.02$). Anosognosia correlated directly with UHDRS ($r=0.32$; $p=0.04$) and indirectly with anxiety ($r=-0.33$; $p=0.03$). Note that all patients who scored 3 on the anosognosia test maintained a delusional belief that there was no motor impairment.

Conclusions: Most of our patients were anosognosic for motor symptoms. They had higher SANS score, indicating more severe apathetic syndrome, and were worse on the visual search test, indicating slower cognitive processing, than non-anosognosic patients. The finding of delusional beliefs in patients with severe anosognosia shows that psychiatric changes may play a role in generating anosognosia in some HD patients. HD anosognosia appears to have a varied origin.

C2

Description of data on oromandibular dystonia from the Italian Dystonia Registry

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Introduction: Oromandibular dystonia (OMD) can be isolated when there is no other body part affected by dystonia or combined with other types of dystonia [1]. Combined forms can origin from a isolated OMD with later spreading or can affect oromandibular site only after the occurrence of dystonia in other muscles [2,3]

Aim: to identify main clinical and demographic features of OMD in the Italian population.

Methods: Data were obtained from the Italian Dystonia Registry (IDR). The following clinical data were considered: isolated OMD, combined OMD, and etiology. In combined forms we also distinguished cases with OM origin, cases with OM spreading and cases with combined onset.

Results: 312 patients with OMD were found. Age at the onset was 50 +- 20,5 (Mean +- SD). The most common etiology was idiopathic (86,5%). 272 of 312 patients presented combined phenotype. 16 of those patients (6% of combined forms) had a OM focal onset, remaining cases had a combined onset (125 patients) or in other body regions (131 patients). The two groups did not show significant differences (chi square and linear regression) neither of demographic features nor for etiologies (parkinsonism, drug induced dystonia).

Discussion: data from IDR show that OM dystonia is prevalently idiopathic and combined. Moreover, most of combined forms affect OM site only after the occurrence of dystonia in other body regions therefore isolated OMD may have a very low risk of spread. Further analysis on the relative risk of spreading are ongoing.

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C3

Progression over 4 years of patients with late or common onset Huntington's disease from the Enroll-HD PDS5 dataset

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Introduction: Recent literature showed that late onset Huntington's disease (LoHD) is characterized by a more severe motor and cognitive impairment than the common adult onset phenotype (CoHD), probably for additional ageing effect. Scarce evidence is avalaible regarding LoHD progression.

Objective: To investigate changes over time on clinical, cognitive and psychobehavioral features in CoHD and LoHD patients.

Methods: This is a retrospective observational study on 854 European CoHD and 99 LoHD subjects from the Enroll-HD PDS5, followed-up up to 4 years.
Linear mixed models were performed to evaluate differences between the two groups and 'time' effect at 3 different timepoints: t0 (baseline), t1 and t2 (respectively, 2 and 4 years). Body Mass index (BMI), Total Functional Capacity (TFC), Total Motor Score (TMS), Problem Behaviors Assessment (PBAs), Mini-Mental State Examination (MMSE) and a short cognitive battery were reported at each timepoint.

Results: CoHD patients were males in 50.4%, mean age at baseline was 52.57±8.96 years, mean higher allele CAGn was 43.50±2.47. LoHD patients were males in 41.4%, t0 mean age was 70.88±4.74 years, mean CAGn was 40.83±1.31.

In both groups, BMI remained stable at t1, but significantly reduced at t2; TMS significantly worsened at t1 and t2 and TFC was reduced at t1 and t2 .

Significant differences between groups emerged on many cognitive tasks, with LoHD showing less preserved cognitive functioning. Time effect emerged in most tests, with significant worsening at both timepoints. At PBA-s, depression significantly reduced at t2 while apathy increased. No significant changes were detected in irritability and psychosis along time.

Conclusions: Clinical progression of both HD groups is characterized by worsening in motor and cognitive performance and reduction in daily functionality over 2 and 4 years. Over 4 years, depression significantly reduced whereas apathy worsened, suggesting that these neuropsychiatric features follow different trajectories along HD course.

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C4

A bayesian approach to Essential Tremor Plus: a preliminary analysis of the TITAN cohort

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Introduction: The entity of ET-plus was introduced for those patients with ET and additional rest tremor or other neurological signs of uncertain significance. Whether these patients belong to the ET spectrum or not is unknown.

Objective: In this work we applied a Bayesian approach to patients with ET-plus recruited in The ITAlian Tremor Network (TITAN), to estimate their probability of not having ET.

Methods: The sensitivity/specificity of each soft sign, and consequently their positive and negative likelihood ratios, were calculated based on published literature or from unpublished data of one of the authors (RE). Given that these values have been calculated in the literature either against a particular syndrome (dystonia, parkinsonism, etc) or against elderly healthy subjects, the cumulative effects of the soft signs here reported indicate the estimated probability of not having ET.

Results: We extracted from the TITAN database data of 274 patients with ET-plus (117 female, 157 male; mean age 69.8 ± 11). Age at onset was 54.5 ± 18.1 years. The majority of patients (240/274; 87.5%) had a single soft sign. The post-test probability of not having ET for these patients was as follows: 0.64 (rest tremor), 0.46 (questionable dystonia), 0.85 (questionable bradykinesia), 0.19 (soft gait impairment), and 0.09 (questionable cognitive issues). The remaining 34 patients (12.5%) had multiple soft signs: post-test probabilities of not having ET were lower than 0.5 in 55.8% of cases, especially for patients with soft gait impairment and/or questionable cognitive issues.

Conclusion: The effects of multiple soft signs are not addictive. Therefore, the post-test probability of not having ET for a patient with ET-plus depends on each soft sign and their combination. Future studies should calculate sensitivity/specificity values of each soft sign against a particular syndrome: by applying a Bayesian approach this would enhance the interpretation ET-plus.

C5

Neurodegeneration and inflammation in Huntington's disease: an insight from blood biomarkers

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Background: Huntington's disease (HD) is a hereditary neurodegenerative disorder due to a CAG expansion in the HTT gene. Besides pathological deposition of mutant HTT, other mechanisms, including inflammation, seem to underlie HD pathogenesis and progression. Recently, great attention has been put on biomarkers which could follow disease initiation and progression to both monitor disease progression and understand underlying pathophysiological mechanisms.

Aim of the study: To measure blood levels of neurodegeneration and inflammation biomarkers and correlate them with clinical and demographic data.

Materials and Methods: We consecutively enrolled HD patients and evaluated them by means of validated clinical scales (UHDRS, TFC, MMSE, PBA). Then, serum levels of selected biomarkers (Neurofilament light chain, BDNF, IL-1β, IL5,IL-6, IFN, TNF-a, IL4 and IL10) were essayed using commercially available kits on an ELLA™ automated immunoassay system (Bio-Techne, San Jose, CA, USA).

Results: 39 patients were enrolled. IL-1b and IL 17 serum levels negatively correlated with TFC (respectively rho=-0.423, p=0,022 and rho=- 0,548, p=0.002) while IL-4 (rho=0.381, p=0.05), IL-17 (rho=0.419, p=0.001), TNF-a (rho=0.427, p=0.019), IL-6 (rho=0.495, p= 0.01) correlated with higher UHDRS scores. Disease duration positively correlated with serum levels of IL-17 (rho =0.460, p=0.008), TNF-α (rho=0.367, p=0.042), IL-6 (rho=0.417, p=0.021). NFL level positively correlated with disease burden (p=0.04, rho 0.43). Interestingly, we also found a positive correlation of BDNF and UHDRS (p=0.023, rho=0.407), possibly a manifestation of a compensatory mechanism.
A linear regression model with UHDRS score as dependent variable and TNF-a, NfL, BDNF and IL6 as independent variables was able to explain the 49,9% of the variance, with a p value of 0.004.

Conclusion: This study confirms the association between serum NfL and disease burden. Moreover, it shows a tendency to manifest a pro-inflammatory status in patients with a more severe disease or with longer disease duration.

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C6

Spread to an additional body site in patients with functional motor disorders

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Introduction: FMD pattern may change over time in terms of body distribution and semiology of core functional motor symptoms. These changes may contribute to an apparently unpredictable clinical heterogeneity that may render it difficult to track disease pathways.

Objective: The aim of this study is to assess changes in the body distribution of functional motor disorder (FMD). We focused on FMD patients with only one affected body part at onset included in the Italian Registry of Functional Motor Disorders (IRFMD) [1].

Methods: Data were obtained from the IRFMD. Patients with a diagnosis of clinically definite FMDs based on Gupta and Lang's diagnostic criteria were included if their FMD started in a single body site. The relationship between FMD features and spread to other body sites was estimated by Kaplan-Meier survival curves and Cox regression analysis.

Results: Among the 410 patients included in IRFMD, we identified 201 patients (49%) who reported only one affected body part at disease onset. Over the disease course, the phenomenon of spread from the initial site to an additional body site was observed in 43/201 patients (21.4%). Spread occurred during the first year in about half of patients. On univariable Cox analysis and multivariable Cox analysis, the presence of other functional neurological disorders and psychiatric comorbidities were significantly associated to spread.

Conclusion: Our study provides novel information about the natural history of FMD. In patient who presented with FMD starting at one body site, spread to additional body sites occurred in about 20% of cases. Spread was significantly more frequent in patients who also manifested other functional neurological disorders and psychiatric comorbidities.

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C7

Impaired emotion processing and its eye tracking correlates in cervical dystonia

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Introduction: Focal dystonia can have a wide range of non-motor symptoms such as pain, anxiety, depression, and sleep impairment [1]. Less is known about the involvement of cognition, with recent studies showing impairment in executive function and social cognition in patients with cervical dystonia (CD) [2,3]. Social cognition is the ability to attribute mental states to others, and one of its most important components is facial emotion recognition [4].

Objective: To assess emotion processing in CD patients compared to healthy controls (HC) using an eye-tracking paradigm.

Methods: We recruited 35 CD patients and 17 age-, sex- and education-matched HC. An emotion recognition task for eye tracking employing a validated dataset of facial expressions was used [5]. Alexithymia was assessed using the Toronto Alexithymia Scale (TAS-20). Cognition, depression, anxiety, impulsivity, and disease severity were assessed using validated scales. Participants with untreated or major depression were not included in this study.

Results: CD patients had an impaired performance in recognizing emotions compared to HC (correct answer percentage: 77.0% vs. 84.5%; p=0.001). Fear and surprise were the emotions harder to recognize (p=0.005 and p=0.037 respectively). CD patients needed more time to make the first fixation on the left eye region (p=0.030) and made longer fixation on the mouth region (p=0.023) than HC.
Additionally, patients had significantly higher scores on the TAS-20 compared to HC (p=0.003); five patients (14.2%) reached the threshold for alexithymia and six (17.1%) for possible alexithymia. No HC scored positive for alexithymia and only two (11.7%) did for possible alexithymia. TAS-20 score correlated inversely with emotion recognition task performance (r=-0.411; p=0.014).

Conclusion: Our study shows poorer performance in emotion recognition in CD patients compared to HC. The significant higher scores for alexithymia and altered face exploration strategies highlight deficits in emotion processing, further confirming impairment in social cognition in CD.

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C8

Longitudinal evaluation of patients with dystonic and essential tremor treated with MRgFUS thalamotomy: one year outcome and adverse events profile

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Introduction: MRgFUS thalamotomy is increasingly recognized as a safe and effective procedure for drug-resistant tremor in Parkinson's Disease and Essential Tremor (ET). On the contrary, data on its effectiveness and tolerability on patients with Dystonic Tremor (DT) are still scarce.

Aims: To report our preliminary clinical findings on patients with DT treated with MRgFUS thalamotomy and to compare the effectiveness, radiological features and adverse events profile with patients with ET.

Methods: Between January 2019 and November 2021, 51 patients with ET and 9 with DT underwent MRgFUS thalamotomy in our Institute. Patients were evaluated before surgery and 1, 6 and 12-months after unilateral thalamotomy with The Essential Tremor Rating Assessment Scale (TETRAS). The position of the lesion was calculated on T1-weighted MRI one day and one month after thalamotomy.

Results: 9 patients with DT and 42 with ET reached the 6-months follow-up and were included in the analysis. In both groups we found a similar and significant improvement in Activities of Daily Living (ADL) and in the clinical severity of tremor. At 12 months ADL improved by a median of 51.5% in DT and 47.0% in ET patients (p=0.268 between groups). At the same timepoint, tremor score for the treated side significantly dropped by a median of 64.1% in DT and 50.1% in ET (p=0.247 between groups). The analysis of the position of the final lesion revealed that in DT it was positioned a median of 1.5 mm anterior to the initial target, probably in the VoA/VoP complex. No adverse effects were reported in the DT group during the follow-up. Conversely, in the ET group we observed persistent, albeit mild and uncommon, adverse effects.

Conclusions: MRgFUS Thalamotomy may be an effective and particularly safe treatment for dystonic tremor. Studies with larger sample sizes are needed to confirm our preliminary results.

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C9

Efficacy of tele-rehabilitation treatments in patients with Parkinson's disease or post-stroke

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Introduction and Objectives: Tele-rehabilitation (TR) treatments, based on cognitive stimulation (CS), have been recently proposed as useful approaches to improve or stabilize cognitive functions in patients with mild or moderate cognitive impairment [1,2]. The aim of the present study was to investigate whether CS delivered from a distance by a TR system in patients with Parkinson's disease (PD) or post-stroke, with mild to moderate cognitive impairment, may improve cognitive performances and/or stress of caregivers. The present study was founded by a national grant titled MULTIPLAT_Age (cod. NET-2016-02361805).

Methods: Consecutive patients were enrolled in the present study (8 with PD and 10 post-stroke, 12 males / 6 females; mean age: 65.1). PD patients were recruited at the Movement Disorders Center of the University "Magna Graecia" of Catanzaro. Patients post-stroke were recruited at the rehabilitation unit of the S. Anna Institute in Crotone.
Experimental setting and activity:
The CS was delivered for 1 hour / day, 5 times / week, for 4 consecutive weeks.
The system consisted of two PC-based workstations, using the Virtual Reality Rehabilitation System (VRRS, Khymeia, Italy), one installed in the patient's home and the other in the rehabilitation center. All exercises were clinically validated and organized by cognitive domain: memory, attention, praxia, mathematics, logic. At baseline and after the treatment, a complete cognitive, mood and quality of life assessment was performed in all patients. For the family member, Caregiver Burden Inventory (CBI) was performed.

Results: The preliminary results showed a significant improvement in cognitive abilities and mood disorders, after the SC performed by the TR protocol, in comparison to baseline performances. Specifically, there was a significant improvement in the constructive praxis task ($p=0.021$), in learning and short- and long-term memory of verbal information ($p=0.039$) and in visual attention ($p=0.017$). A significant decrease in severity of depression and caregivers stress was observed (BDI: $p=0.038$; CBI: $p=0.002$). The study is still ongoing and data collection is in progress.

Conclusions: The preliminary results of this study suggested that CS performed by a well-defined virtual reality TR tool for cognitive rehabilitation may be efficacious in improving the cognitive functioning of patients with PD or post-stroke with mild/moderate cognitive impairment. This treatment may also reduce depression levels of patients and stress levels of the caregivers. If confirmed in the larger cohort of patients, these data are going to be of particular value for patients living in all geographical areas, such as Calabria, characterized by a scarcity of specialized rehabilitation services.

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C10

Sensitivity and specificity of clinical and kinematic measures of bradykinesia in patients with Parkinson's disease and essential tremor and in elderly healthy subjects

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Introduction: Bradykinesia is the cardinal symptom of Parkinson's disease (PD) [1], and it can be also observed in essential tremor (ET), where it configures the diagnosis of ET-plus, and to some extent in elderly healthy people [2-4]. In some cases, bradykinesia detection by clinical examination can be challenging, and the use of objective techniques for movement analysis may be necessary.

Aims: To assess the sensitivity and specificity of clinical and kinematic measures of bradykinesia in patients and healthy subjects.

*Methods***:** Simultaneous video and kinematic recordings of finger tapping were performed in 44 PD, 69 ET, and 77 healthy controls (HCs). Videos were blindly evaluated by 7 neurologists using standardized clinical scales. Kinematic recordings were blindly analyzed. We calculated the inter-raters' agreement by the Fleiss' K. Clinical and kinematic data were compared in the three groups. Clinical evaluation scores-stratified density plots served to evaluate the overlapping in the distribution of kinematic data. Receiver operating characteristic (ROC) curves were used to identify kinematic cut-offs to distinguish subjects with and without bradykinesia.

*Results***:** We found a fair agreement among raters (Fleiss K=0.32). As expected, we found the highest clinical bradykinesia scores in PD, and higher scores in ET than in HCs (all ps<0.001). At the kinematic analysis, the groups differed in terms of movement velocity, with the lowest values being detected in PD (all ps<0.001). Density plots demonstrated an overlapping between kinematic data curves. ROC curves showed that kinematic distinguished subjects with and without bradykinesia (AUC = 0.845, CI 95%: 0.727 - 0.963). The cut-off of 729.864 degrees/sec had a sensitivity of 0.842 (95%CI 0.604, 0.966) and specificity of 0.865 (95%CI 0.805, 0.913).

Conclusions: We demonstrated a gap between the clinical and kinematic assessment of bradykinesia and proposed objective cut-offs distinguishing subjects with and without bradykinesia. Our results are relevant for a better patients' classification.

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C11

Different patterns of acute saccadic responses to levodopa challenge test in *de novo* Parkinson's disease: possibile prognostic implications

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Introduction: Saccadic eye movements abnormalities were described in Parkinson's disease (PD). To date, few studies with conflicting results assessed Levodopa (LD) effects on a drug-naïve population through a standardized Levodopa Challenge Test (LCT). We hypothesized that these inconsistent findings were related at least in part to an intrinsically heterogeneous saccadic LD response in PD.

Objective: To explore possible different patterns of acute saccadic responses to LCT in a *de novo* drug-naïve PD population and potentially related differences in clinical progression.

Methods: Patients fulfilling MDS criteria for PD were enrolled. Eye movements were recorded by Eyelink 1000 Plus. Visually-guided saccades were assessed at baseline and after 2 hours from the administration of levodopa/carbidopa 250/25 mg. Saccadic velocities, latencies and accuracy were assessed. Nonhierarchical cluster analysis using k-means method was performed based on peak-of-dose parameters. Main sequence and saccadic latencies distribution analysis were performed. Patients were clinically followed-up at 2 years.

Results: Thirty-two *de novo* PD patients were enrolled. Two clusters were identified among PD patients: Cluster A (21 patients) and B (11 patients). No significant differences in demographical characteristics and clinical assessment both at baseline and peak-of-dose were found between clusters. Improved saccadic velocities and accuracy as well as increased latencies were found at peak-of-dose in cluster A. An opposite trend was demonstrated in cluster B. Different main sequence patterns were found between clusters. An increased cumulative frequency of short-latency saccades was found at peak-of-dose in Cluster B. After a 2 years' follow-up, Cluster B patients referred more autonomic symptoms and LD side effects compared to Cluster A patients.

Conclusion: Different patterns of saccadic LD responses were demonstrated among *de novo* PD patients. We identified a cluster of patients with worse oculomotor response to LD who prospectively developed more autonomic symptoms and intolerance to dopaminergic treatment, as expression of poorer outcome.

C12

Efficacy of Sail4Parkinson, a 5-day intensive multidisciplinary program for Parkinson's disease

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Background: Physical exercise programs have been used to boost the effect of pharmacological treatment in Parkinson's disease (PD). Yet, it is unclear the effect on clinical and kinematic parameters of intensive short–lasting exercise programs.

Objective: In this pilot prospective study, we aim to evaluate the effect on motor symptoms, quality of life (QoL) and kinematic parameters of gait of a 5–day intensive physical exercise program (Sail for Parkinson, S4P) in PD.

Methods: We enrolled consecutive PD patients who participated to S4P in May and June 2022. Each S4P consisted of 6 h⁄d of multidisciplinary activities during 5–days at home (meditation and warming up), by the sea, in the water (sailing and paddling), on the beach in the sand (coordination, balance, aerobic and resistance exercises) and open air in the nature (psychological rounds with the support of a photography training program).
Each subject underwent clinical evaluation on the day before (T0) and after S4P (T1), including UPDRS–III, PDQ8, Hamilton depression rating scale (HDRS). Instrumented Timed Up and Go (TUG) and gait tests were carried out using wearable inertial sensors. We also collected measures of postural control and maximum isometric handgrip strength force.

Results: 20 patients were enrolled (13 males, 60.3±7.08 years, disease duration 9.95±3.59 years). All subjects successfully completed the training program and had an improvement of patient's global impression scale. Severity of motor symptoms by UPDRS–III, QoL by PDQ8 and depression by HDRS significantly improved at T1 compared to T0 ($p<0.05$). In most subjects, we observed a reduction of the postural sway under eyes closed condition, and a general improvement in coordination during the TUG turns.

Conclusions: These preliminary data show that the short–lasting intensive multidisciplinary exercise and psychological program provided by S4P is effective in improving motor symptoms, depressive symptoms and QoL of people with PD.

C13

Motion sensor-based kinematic features are associated with different patterns of cognitive impairment in Parkinson's disease

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Introduction: Cognitive decline is one of the most disabling features of Parkinson's disease (PD), involving dopaminergic circuits between the basal ganglia and the cerebral cortex but also non-dopaminergic (i.e., noradrenergic and cholinergic) networks [1]. Preliminary evidence indicates an overlap between the presence and extent of cognitive decline and gait parameters; however, a comprehensive analysis of the association between many kinematic parameters of gait and balance in Off and On therapeutic conditions and tests exploring the functioning of different cognitive domains has never been performed [2].

Objective: To analyze the correlation between gait and balance kinematic features in Off and On therapeutic conditions by means of wearable motion sensors and cognitive performances in different domains.

Methods: Forty PD candidates for device-aided therapies due to the suboptimal control of motor fluctuations underwent an extensive neuropsychological assessment investigating reasoning, memory, language, frontal executive functions, and visual-spatial abilities, reported as the mean of the equivalent scores obtained by each pertinent test raw score according to normative data weighted for age and education in the Italian population [3]. Gait and balance parameters were derived in both Off (a night after withdrawal of dopaminergic therapy) and On (about 45 minutes after levodopa intake) therapeutic condition by means of the Opal (APDM)™ motion sensors. A battery of standardized tests was performed: Two-minute walk test (2MWT); Timed-up and go test (TUG test); Sway test; 360 degrees Turn Test. Spearman correlation analyses were performed to explore correlations between kinematic and cognitive features. Given the multiple analysis, we considered only strong correlations (i.e., $p<0.01$).

Results: Strong correlations were found between stride length in Off and memory (0.334; p:0.006), TUG turn velocity in Off and memory (0.405; $p<0.001$), TUG duration in Off and language (-0.425; p:0.001), double support in On and frontal executive functions (-0.209; p:0.009), Off vs. On difference in TUG duration with memory (-0.348; p: 0.003) and language (-0.527; $p<0.001$), and Off vs. On difference in step duration with reasoning (0.366; p:0.006).

Conclusion: Specific patterns of gait impairment and their response to levodopa are correlated with distinct patterns of cognitive impairment in parkinsonian patients. The importance of kinematic features, specially assessed in both the Off and On therapeutic conditions, emerged from our explorative study. Measures of brain connectivity based on functional MRI data from these patients might contribute to clarifying specific patterns of abnormal neurotransmission.

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C14

Gait under unsupervised, but not supervised conditions, differentiates between Parkinson disease with and without fatigue

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Objective: To Assess the impact of fatigue on gait in Parkinson Disease patients in different evaluation conditions.

Introduction: Fatigue is a common and disabling symptom in Parkinson's disease (PD). How fatigue is associated with gait is not well understood, especially in the home environment under unsupervised conditions(UC) [1].

Methods: The prospective study included cognitively unimpaired PD patients under dopaminergic treatment without motor and non-motor fluctuations and age-matched controls. Each participant underwent an extensive motor and cognitive assessment and a gait analysis using inertial measurement units (IMUs) in supervised conditions (SC), namely 20-meter straight walking under normal, fast and dual-task conditions. Moreover, participants wore a similar IMUs for 4 consecutive days in the home environment (UC). Fatigue was assessed using the PD Fatigue Scale [2]. Differences in gait parameters under SC and UC between patients with (F-PD) and without (NF-PD) fatigue were calculated with ANCOVA adjusting for age, sex and motor severity.

Results: Forty-four controls (65+7 ys) and 37 PD patients (68±8 ys, disease duration 5±3 years) entered the study. Compared to controls, PD patients showed longer step time, higher asymmetry and higher step time variability in both SC and US. F (n=18) and NF (n=19) PD patients were comparable concerning motor, cognitive and demographic variables. Under SC conditions, no relevant gait differences could be observed. Under UC, however, F-PD patients showed significantly longer step time, higher step time variability and higher asymmetry, compared to NF-PD patients, particularly during walking bouts >20 steps.

Conclusion: Fatigue has an impact on gait parameters under UC, but not SC, in PD patients. Our findings support the importance of remote assessment to evaluate fatigue in PD. The findings need to be verified in larger ongoing multicentre studies (e.g., IDEA-FAST, https://idea-fast.eu) focusing on MHT assessment under UC.

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C15

Micrographia in Parkinson's disease: The Contribution of Artificial Intelligence

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Background: Patients with Parkinson's disease (PD) may manifest handwriting abnormalities (i.e., micrographia) since the early stages of the disease [1-3]. Also, in PD, handwriting abilities progressively decline over the course of the disease. Despite qualitative examination for detecting micrographia, an objective handwriting analysis would improve the clinical ability to recognize PD, track the disease progression and evaluate the symptomatic response to dopaminergic replacement treatment [4-5]. We have recently demonstrated in healthy subjects that machine learning captures handwriting changes due to physiological aging [6]. Hence, machine learning would be an ideal tool for the objective analysis of parkinsonian micrographia, thus promoting relevant advances in the field.

Material and Methods: seventy-three patients with PD (45 males; 71±11 years) and 63 healthy subjects (21 males; 71±7 years) were enrolled to participate in this study. Depending on the scores at the Hoehn and Yahr scale (H&Y), PD patients were divided into 51 early-stage (H&Y<2.5; 31 males; 69.2±12.3 years) and 22 advanced stage patients (H&Y>=2.5; 14 males; 71.9±13.7 years). Participants performed an ecological handwriting task that was digitalized through specific electronic devices, including commonly available smartphones. Patients with PD were studied both in OFF (i.e., at least 12 hours after the last L-Dopa intake) (36 males; 70.1 ±11.6 years) and ON therapy (i.e., 30-60 minutes after L-Dopa administration) (31 males; 72.0±11.0 years). Digitalized handwriting samples underwent the DBNet algorithm which allowed the measurement and comparison of the average stroke sizes. Then, a convolutional neural network (CNN) based on machine learning algorithms, was used to automatically classify handwriting samples recorded in controls and PD patients, OFF and ON therapy. Finally, receiver operating characteristic (ROC) curves were calculated to report the diagnostic performance of the algorithm.

Results: Stroke sizes were significantly smaller in PD patients than in controls. Also, handwriting strokes were smaller in patients in advanced-stage of the disease than in those in early-stage. Finally, handwriting was comparable in patients OFF and ON therapy. The CNN classifier objectively discriminated between controls and PD (accuracy=87%). Also, handwriting analysis distinguished early-stage and advanced-stage patients (accuracy=89%). Lastly, machine learning was not able to discriminate between OFF and ON therapy patients (accuracy=50%).

Discussion: Handwriting is abnormal in PD and mainly characterized by micrographia. Handwriting changes manifest since the early stages of PD and progressively degrade in more advanced stages of the disease. Dopaminergic replacement therapy does not improve significantly handwriting abilities in PD patients.) after doubling the levodopa dose.

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C16

Transcutaneous auricular vagus stimulation improves gait and reaction time in Parkinson's disease

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Content: Preclinical vagus nerve stimulation (VNS) and clinical non-invasive neck VNS studies showed promising data on structural and functional aspects of Parkinson's Disease (PD) [1, 2]. Non-invasive VNS can also be obtained through the ascending branch of the vagus nerve at the ear, with remarkable opportunities in terms of feasibility and costs for chronic stimulation - but data are missing. Hence, we aimed at investigating the effect of taVNS on the PD gait in a pilot-controlled study with a double-blind randomized cross-over design. The taVNS was delivered either at the left internal tragus (real) or at the earlobe (control) as 30 second trains lasting and composed of 600 pulses (frequency 20Hz; duration 0.3ms) repeated every 4.5 minutes for 30 minutes (6 cycles). One week following the first experiment, all subjects crossed over to the other condition. Patients were evaluated before and after the stimulation with a Visual Analogue Scale (VAS 0-10, "how do you perceive your walking performance?"), with the UPDRS-III, with a flanker test (reaction time) and with a digital 10 meter timed-up-and-go (10mTUG total time, stride length, number of steps, mediolateral sway, and swing amplitude). All subjects were on chronic levodopa therapy; the experiment took place during a definite ON-DOPA condition. Twelve subjects completed the experiment (25% females, with an age of 75.5±7.1 years). The disease duration since diagnosis was 5.9±3.4 years, all had a Hoehn and Yahr $\leq$ 2.5, a disease duration since diagnosis of 5.9±3.4 years, 3 (25%) had a history of freezing but none reported freezing during the experiment. The UPDRS III and the VAS improved with both conditions, but a better trend after taVNS. Stride length, swing amplitude, total time and reaction time showed significant changes only after taVNS. Despite a possible placebo effect influencing UPDRS-III and VAS, we observed that taVNS in add-on to levodopa improved several objective gait parameters. The significant change that taVNS induced on the flanker test (i.e., an acknowledged VNS-responsive parameter) reinforced our findings. Indeed, invasive and non-invasive VNS could entrain the ascending cholinergic and noradrenergic pathways, which are involved in cognitive processing and in locomotor abilities. Our results are in line with those obtained through the acute and chronic non-invasive neck VNS experiments. Given the easy handling of portable commercialized devices, further experiments are warranted to confirm our observations and evaluate the cumulative taVNS effect in a chronic stimulation setting.

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C17

Locus coeruleus degeneration is associated with cortical glucose metabolism and cognitive impairment in multiple system atrophy

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Introduction: Locus coeruleus (LC) is the main cerebral source of noradrenaline and its integrity is known to be associated with preservation of cognitive functions both in healthy elderly adults and in Parkinson's disease [1,2,3]. Cognitive impairment is increasingly recognized in Multiple System Atrophy (MSA), with executive functions most commonly affected, together with attention, memory and visuospatial abilities [4,5].

Objective: To investigate LC integrity in MSA and its association with cerebral glucose metabolism and cognitive impairment scores.

Methods: 11 MSA patients (within three years of diagnosis), 19 Parkinson's Disease (PD) and 18 healthy controls (HC) participated in the study. Neuromelanin-sensitive MRI was used to investigate LC integrity, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET, performed in MSA patients only) was used to investigate glucose metabolism, and the Montreal Cognitive Assessment (MoCA) was used as cognitive screening score.

Results: LC neuromelanin content in PD and MSA were significantly yet similarly reduced in the rostral, intermediate and caudal subsections compared to HC. In MSA (but not in PD), rostral LC neuromelanin loss was associated with Montreal Cognitive Assessment (rho=0.770, p=0.006). Right frontal FDG-PET uptake was associated with MoCA scores (rho=0.641, p=0.034). Voxel-wise correlation between FDG-PET and rostral LC neuromelanin content showed association between LC neuromelanin loss and reduced FDG-PET metabolism in several frontal and temporal clusters; an association with reduced cerebellar uptake was also shown.

Conclusion: LC neuromelanin loss is associated with both impaired cognitive function and reduced fronto-temporal metabolism in MSA. Similarly to aging and PD, impaired noradrenergic function may be a shared driver of cognitive dysfunction in MSA.

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C18

Relationship between cardiovascular autonomic failure and cognitive performance in the α-synucleinopathies: preliminary cross-sectional analysis of the NHSS registry

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Introduction: Cardiovascular dysautonomia is a disabling non-motor feature of the α-synucleinopathies and may foster end-organ damage. The interplay between cognitive impairment and dysautonomia is however not clear yet.

Objective: To compare cognitive performances of patients with α-synucleinopathies with and without cardiovascular dysautonomia.

Methods: We analyzed data from the Natural History Study of Synucleinopathies. Cognition was tested with the Montreal Cognitive Assessment (MoCA). Orthostatic hypotension (OH) [1], neurogenic OH (nOH) [2] and supine hypertension (SH) [3] were diagnosed with supine-to-standing heart rate and blood pressure (BP) measurements contemporary to cognitive testing.

Results: We included 76 Parkinson's disease (PD), 133 stable pure autonomic failure (PAF) and 282 multiple system atrophy (MSA) patients. In PD, 36% of patients (n=26) had no OH, 15% (n=11) non-neurogenic OH, 11% (n=8) nOH, 38% (n=28) both nOH and SH. In PAF, 8% of patients (n=9) had no OH, 21% (n=24) non-neurogenic OH, 12% (n=14) nOH, 58% (n=66) both nOH and SH. In PD and PAF MoCA scores did not differ across these groups (p=0.108 and 0.453, respectively). In MSA, 25% of patients (n=65) had no OH, 17% (n=45) non-neurogenic OH, 43% (n=16) nOH, 42% (n=114) both nOH and SH. In MSA MoCA scores were higher in nOH patients (p=0.036) and in those with autonomic [28 (25; 30)] versus motor onset [26 (23; 29), p=0.015].

Conclusions: In PD and PAF median MoCA scores did not differ across patients with or without any form of BP dysregulation, suggesting that the neuropathological substrate of dysautonomia and cognitive impairment may differ in neuronal α-synucleinopathies. In MSA, nOH patients showed higher MoCA scores. Different clinical-demographic features across orthostatic BP patterns, e.g. autonomic vs. motor onset, might explain this result. Analysis of longitudinal MoCA score changes according to baseline BP phenotypes will clarify the impact of cardiovascular dysautonomia on the progression of cognitive impairment in α-synucleinopathies.

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C19

Risk of SARS-CoV-2 infection, hospitalization and death for COVID-19 in people with Parkinson's disease or parkinsonism over a 15-month period: a cohort study

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Background: The long term risk of SARS-CoV-2 infection, hospitalization for COVID-19 and related death is uncertain in people with Parkinson's disease (PD) or parkinsonism (Pks).

Objectives: To estimate the risk of SARS-CoV-2 infection, hospitalization for COVID-19 and related death in people with PD or Pks compared to a control population cohort, during the first 15-month period of epidemic, in the city of Bologna, northern Italy.

Methods: The ParkLink Bologna cohort (759 PD; 192 Pks) and 9,226 controls, anonymously matched (ratio 1:10) for age, sex, district of residence and comorbidity were included. SARS-CoV-2 infection rate and hospital admission rate for COVID-19 were estimated using March 1st, 2020 as entry date, and the date of positive swab/hospital admission or May 31st, 2021, as time to endpoint. Data were analysed in the whole period and in the two epidemic peaks (March-May 2020 and October 2020-May 2021).

Results: Adjusted hazard ratio of SARS-CoV-2 infection was 1.3 (95% CI 1.04-1.7) in PD and 1.9 (1.3-2.8) in Pks compared to the controls. The trend was detected in both epidemic peaks, with an increase of infection rate in the second compared to the first. Adjusted hazard ratio of hospitalization for COVID-19 was 1.1 (95% CI 0.8–1.7) in PD and 1.8 (95% CI 0.97-3.1) in Pks. A higher risk of hospital admission was detected in Pks only in the first epidemic peak. The 30-day mortality risk after hospitalization was higher (p=0.048) in Pks (58%) than in PD (19%) and controls (26%).

Conclusions: People with PD and Pks had an independent risk for SARS-CoV-2 infection throughout the first 15-month period of epidemic. COVID-19 hospitalization risk was increased only in people with Pks and only during the first peak. This group of patients was also burdened by a very high risk of death after infection and hospitalization.

C20

Young-onset Parkinson's disease: insights from a longitudinal cohort

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Introduction: Parkinson disease (PD) is a neurodegenerative disorder characterized by the loss of nigral dopaminergic neurons and the widespread accumulation of alpha synuclein. Young-onset Parkinson's disease (YOPD) is defined by an age of onset before 50 years. Evidences suggest that both pathology and phenotype of YOPD differ from those of typical, Late-onset PD [1]. However, because of the relative rarity of this condition, available data are scarce and almost anecdotal. Accordingly, an in-depth analysis is necessary.

Objective: To retrospectively analyse and model the course of a YOPD single-centre cohort.

Methods: A longitudinal cohort of 193 YOPD patients was extracted from a population of 2000 PD patients followed up from 2000 to 2021 at Tor Vergata University Hospital (Rome, Italy). For each patient main demographic and clinical features were collected at onset and at follow up time. Descriptive statistics was run on qualitative and quantitative variables. The course of disease from diagnosis to ten years later in terms of both Hoehn and Yahr (H&Y) stage and levodopa equivalent daily dose (LEDD) was then estimated.

Results: YOPD had a prevalence of 9.7%, with an ascertained genetic origin in 9.3% of cases. It mostly presented as a predominantly motor, rigid-akinetic syndrome, with asymmetric onset. Motor progression in terms of H&Y presented a linear increase of 0.92 points/10 years, whereas the flow of LEDD presented a non-linear trend, with an increase of 526.90 mg/day in 0-5 years, and of 166.83 mg/day in 5-10 years. Motor fluctuations started after 6.5±3.2 years from disease onset, affecting up to 80% of the cohort. Neuropsychiatric troubles affected the 50% whereas sexual complaints the 12%. Gender-specific motor disturbances emerged.

Conclusions: The analysis of YOPD showed a "brain-first" PD subtype [2], characterized by slow, linear motor progression, with non-linear dopaminergic requirements. Major burden resulted from motor fluctuations and dyskinesias, neuropsychiatric complications and marital complaints.

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C21

Salivary biomarkers of pathological molecular pathways in *de novo* Parkinson's disease

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Introduction: In Parkinson's disease (PD), an increasing effort is directed at designing molecular biomarkers in order to support early-stage diagnosis and evaluate disease severity and progression at the molecular level. Alpha-synuclein is the main pathological hallmark of PD [1]. However, additional cellular and molecular pathways may also contribute to neurodegeneration.

Objective: To investigate molecular biomarkers of alpha-synuclein, tau aggregation, autophagy (MAP-LC3beta), and neuroinflammation (TNFalpha) in the saliva of *de novo* PD patients in comparison to healthy subjects (HS), and to correlate molecular data with clinical features of PD patients, in order to establish whether abnormalities of these parameters are associated with specific clusters of *de novo* PD patients, and their potential diagnostic power in differentiating PD patients from HS.

Methods: We measured total and oligomeric alpha-synuclein, total-tau and phosphorylated-tau, MAP-LC3beta, and TNFalpha in the saliva of 80 *de novo* PD patients and 62 HS, using quantitative Enzyme-Linked Immunosorbent Assay analysis.

Results: Oligomeric alpha-synuclein, total-tau, MAP-LC3beta, and TNFalpha levels resulted significantly higher in patients with respect to HS, while no significant differences were detected for total alpha-synuclein or phosphorylated-tau. Phosphorylated-tau directly correlated with MAP-LC3beta, whereas it inversely correlated with TNFalpha in PD patients. An inverse correlation was detected between MAP-LC3beta and non-motor symptoms severity. Principal component analysis showed that molecular and clinical parameters were independent of each other in PD patients. Receiver operating characteristic curve analysis reported an accurate diagnostic performance of oligomeric alpha-synuclein and MAP-LC3beta. The diagnostic accuracy of total alpha-synuclein increased when it was combined with other salivary biomarkers targeting different molecular pathways.

Conclusion: Our study proposes a novel biomarker panel using saliva, a non-invasive biofluid, in *de novo* PD patients, with implications in understanding the molecular pathways involved in PD pathogenesis and the relevance of different molecular pathways in determining clinical PD subtypes.

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C22

Impact of individual autonomic domains on clinical outcomes in Parkinson's disease: a 5-year prospective study

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Introduction: Autonomic failure is a well-known prognostic factor for more aggressive progression of Parkinson's disease (PD), with a 3-to-7-fold higher risk of dementia and death within 10 years after the diagnosis. However, the individual impact of cardiovascular, gastrointestinal, urogenital, thermoregulatory, and pupillomotor autonomic domains on PD clinical outcomes remains unclear.

Objectives: To determine the five-year risk of developing dementia, falls, postural instability, dysarthria, and dysphagia in PD patients with and without autonomic impairment at baseline, and to assess the association of each autonomic domain on these clinical outcomes. Moreover, we determined the impact of each autonomic domain on activities of daily living (ADLs) and quality of life (QoL).

Methods: 65 consecutive PD patients were enrolled in a five-year cohort study involving standardized evaluations of autonomic domains (Scale for Outcomes in PD-Autonomic; SCOPA-AUT), orthostatic hypotension (OH), supine hypertension (SH), and motor and non-motor features. Associations were estimated by means of both univariate and multivariate analyses. Results were adjusted for PD duration, age, and baseline motor impairment.

Results: Cardiovascular dysautonomia was associated with a seven-fold higher risk of developing dementia ($p=0.035$) and a five-fold higher risk of falls ($p=0.039$), as well as significantly higher impairment in ADLs ($p=0.042$) and QoL ($p=0.031$). Neurogenic OH was associated with a five-fold higher risk of dementia ($p=0.029$) and a seven-fold higher risk of falls ($p=0.030$); similar, and even stronger, results were observed when considering hemodynamically relevant OH (i.e., orthostatic mean arterial pressure $\leq$75 mmHg). Only for dementia risk, the concomitant presence of SH determined stronger association (OR:8.265; $p=0.012$). No relevant associations were found between the other autonomic domains and these outcomes.

Conclusions: Cardiovascular dysautonomia, but not other autonomic domains, showed an association with worse five-year clinical outcomes in PD. Our data suggest a specific role for cardiovascular autonomic dysregulation in the pathogenic mechanisms of PD progression.

C23

Intestinal histomorphological and molecular alterations in patients with Parkinson's disease

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Background: Changes in gut microbiota composition, enteric inflammation, impairments of the intestinal epithelial barrier (IEB) and enteric neuro-immune system have been reported in Parkinson's disease (PD) patients and could contribute to the onset of both neurological and gastrointestinal symptoms. However, most of this evidence has been reported in the form of distinct and separate determinants, but their mutual interplay has rarely been investigated [1]. This study evaluated, in an integrated manner, changes in faecal microbiota composition, morpho-functional alterations of the colonic mucosal barrier and changes of inflammatory markers in blood and stools of PD patients.

Methods: 19 PD patients and 19 asymptomatic subjects were enrolled. Blood lipopolysaccharide binding protein (LBP, marker of altered intestinal permeability) and Interleukin-1β (IL-1β), as well as stool IL-1β and tumour necrosis factor (TNF) levels, were evaluated. Gut microbiota analysis was performed. Epithelial mucins, collagen fibres, Claudin-1 and S-100 positive glial cells as markers of an impairment of the intestinal barrier and mucosal remodelling were evaluated on colonic mucosal specimens collected during colonoscopy.

Results: Faecal microbiota analysis revealed a significant difference in the α-diversity in PD patients compared to controls, while no differences were found in the beta diversity. Compared to controls, PD patients showed a significant increase in plasma LBP, as well as faecal TNF and IL-1β levels. The histological analysis showed a decrease in epithelial neutral mucins and claudin-1 expression, and an increased expression of acidic mucins, collagen fibres and S-100 positive glial cells.

Conclusions: PD patients are characterized by intestinal inflammation and increased IEB permeability, as well as colonic mucosal barrier remodeling, associated with changes in gut microbiota composition.

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C24

Prokineticin-2 expression is increased in olfactory neurons of patients with Parkinson's disease and directly correlates with α-synuclein oligomers accumulation

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*Background***:** In Parkinson's disease (PD) field, there is urgent need for novel neuroprotection targets. Prokineticin-2 (PK2) is a chemokine-like peptide, which showed, in experimental PD models, promising neuroprotective effects at early stages of neurodegeneration. However, dynamics of PK2 pathway in PD patients remain unknown. PK2 has preferential expression into the olfactory system, which, in turn, is one of the earliest sites of neuropathology in PD. Olfactory neurons (ONs) can be easy withdrawn, being suitable for molecular analysis.

Objectives: To shape PK2 pathway activity and establish the correlations with synucleinopathy in ONs of PD patients at various disease stages.

Methods: ONs were collected by non-invasive mucosa brushing from n=38 PD patients (n=26 *de novo*, newly-diagnosed and untreated) and n=21 sex/age matched healthy controls. Patients were assessed by H&Y scale, MDS-UPDRS pars III, non-motor symptoms and cognition scores, LEDD calculation. ONs were examined by Real Time-PCR to measure expression levels of PK2 and other PK2 pathway-related factors (PK2 receptors type 1 and 2, PK2-long peptide); immunofluorescence was also performed to quantify PK2 and α-synuclein species (total and oligomeric).

Results: ONs PK2 expression was significantly increased in PD compared to controls; levels were higher in *de novo* patients than those more advanced. In *de novo* group, PK2 expression was directly correlated with MDS-UPDRS pars III. The oligomeric α-synuclein specie, but not the total one, was higher in PD patients than controls. Oligomeric α-synuclein and PK2 directly correlated in PD group.

Conclusions: PK2 pathway was activated in ONs of PD patients, mostly at early disease stages and proportionally to motor impairment. PK2 expression followed oligomeric α-synuclein accumulation, probably as a defensive reaction, which confirms the value of PK2 as a neuroprotection target for PD. ONs resulted a reliable tissue to examine molecular events underlying PD and a valuable source for biomarkers.

C25

Morphometric MRI cortico-subcortical features in Parkinson's disease with mild cognitive impairment

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Introduction: Parkinson's Disease (PD) patients with cognitive impairment undergo progressive atrophy of several cortical and subcortical areas.

Objective: We aimed to study the Magnetic Resonance Imaging (MRI) morphometric features of PD patients with Mild Cognitive Impairment (MCI).

Methods: Patients from the Parkinson's Disease Cognitive Impairment Study (PACOS) cohort with an available structural volumetric brain MRI and morphometric measurements of midbrain and pons areas, Middle Cerebellar Peduncle (MCP), Superior Cerebellar Peduncle (SCP) width and midbrain anteroposterior diameter (A-Pdiam) were included. MCI was diagnosed according to the MDS level II criteria. Additionally, cortical thickness analysis was performed and correlated with morphometric brainstem measurements.

Results: Morphometric measurements were available for 168 subjects, of which 67 (39.9%) were diagnosed with PD-MCI. The mean age (± Standard Deviation, SD) of the sample was 64.2±9.8. Among patients, 84 (50%) were men with a disease duration of 5.2±5.4 years and a Unified Parkinson's Disease Rating Scale-Motor Examination (UPDRS-ME) score of 32.1±12.9. At the univariate and multivariate analysis, after adjusting for age, sex, years of schooling and disease duration, MCI was associated with midbrain area (OR 0.98; 95%CI 0.96-0.99; p=0.048) and A-Pdiam (OR 0.63; 95%CI 0.46-0.86; p=0.005). Furthermore, 121 PD patients underwent cortical thickness analysis, which showed the presence of cortical thinning in lateral orbitofrontal regions of patients with PD-MCI. No correlation was found between cortical thickness and brainstem morphometric measurements.

Conclusions: A mild midbrain atrophy and the presence of frontal cortical thickness reduction might be considered a structural MRI feature of PD patients with MCI.

C26

Axial features in bilateral STN-DBS-treated PD patients: a long-term clinical-instrumental assessment.

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Introduction: Subthalamic nucleus deep brain stimulation (STN-DBS) represents an effective long-term treatment in Parkinson's disease (PD), improving a broad spectrum of symptoms (i.e. tremor, rigidity, and bradykinesia). Axial symptoms are very common in PD, including gait and speech disorders, which are less responsive to stimulation.

Objective: To evaluate the long-term effects of bilateral STN-DBS and levodopa on axial symptoms in PD patients and to find the presence of possible correlations between speech and gait parameters.

Methods: This observational study included consecutive PD patients treated with bilateral STN-DBS. Axial symptoms have been assessed in the long-term using a standardized clinical-instrumental approach. Speech was assessed by perceptual and acoustic analysis while gait by means of the instrumented timed up and go test (iTUG). Disease motor severity was evaluated applying the UPDRS part III total score and subscores. Different stimulation and drug conditions were assessed: on-stimulation/off-medication, off-stimulation/off-medication, on-stimulation/on-medication conditions (single and dual task).

Results: 25 PD patients treated with bilateral STN-DBS with a mean five-year postoperative follow-up were included. Comparing the three postoperative conditions, both stimulation alone and the combination of stimulation and levodopa improved motor scores and most of gait parameters with heterogenous effects on speech variables. In the on-stimulation/on-medication condition patients with a poorer voice quality performed worse the sit to stand and gait phases of the iTUG. On the contrary, patients with a higher speech rate performed well the turning and walking phases of the iTUG, assuming that these specific speech and gait parameters may be influenced in the same way by levodopa and stimulation.

Conclusions: Our results suggest that STN-DBS and levodopa could improve gait parameters in the long-term after surgery, while they had heterogenous effect on speech variables. Moreover, several correlations between speech and gait parameters were identified, allowing to deepen the common pathophysiological basis of these alterations.

C27

Functional MRI and gait analysis characteristics in patients with idiopathic REM sleep behavior disorder

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*Introduction:*Clinical, gait analysis, and MRI features might predict the conversion from idiopathic REM sleep behavioral disorder (iRBD) to clinically manifested alpha-synucleinopathies.

*Objective:*The aims of this study were to assess gait analysis, neurological, neuropsychological and resting-state functional MRI (RS-fMRI) functional connectivity (FC) characteristics in iRBD patients and to study the correlations between clinical features and RS-fMRI alterations.

*Methods:*Ten patients with a polysomnography-confirmed iRBD underwent clinical, cognitive, and RS-fMRI evaluations. Gait analysis was performed using a stereophotogrammetric system to assess asymmetry of spatio-temporal gait parameters during a four-meter walking test with and without a cognitive dual-task. Ten age/sex-matched healthy controls underwent neuropsychological evaluation and RS-fMRI.

*Results:*IRBD patients showed mild asymmetry of spatio-temporal gait parameters, particularly during dual-task gait. IRBD patients showed an increased FC in the right executive control, sensorimotor and dorsal default mode networks compared to healthy controls. Basal ganglia and cerebellar networks showed reduced FC. Correlation analyses showed that an increased asymmetry in the lower limb swing time during gait correlated with an increased FC in the right executive control network, whereas an increased asymmetry of lower limb stride length during dual-task gait correlated with an increased FC in the sensorimotor network.

Conclusions: This study suggested that RS-fMRI and gait analysis characteristics could be promising biomarkers for early alpha-synucleinopathy detection and prediction. The collection of longitudinal data in a larger sample will allow the assessment of conversion from iRBD to parkinsonian syndromes and to test a multifactorial prediction model combining fMRI, gait analysis, clinical and neuropsychological data.

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C28

Divergent sex-specific functional striatal connectivity in drug-naïve patients with Parkinson's disease

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Introduction. Compelling evidence suggests that a sex-specific pattern within the nigrostriatal and striatocortical pathway may underlie the clinical divergence observed in male and female patients with Parkinson's disease (PD) over the disease course.

Objective. We aim to investigate the potential effect of sex on the regional striatal functional connectivity (FC) in a cohort of drug-naïve PD patients applying a seed-based approach to resting-state functional MRI data.

Methods. 147 drug-naïve PD patients (82 male and 65 female) and 38 healthy controls were consecutively enrolled. Motor, non-motor and neuropsychological assessments as well as rs-fMRI were performed at baseline. Using connectivity-based parcellation, we subdivided the striatum into three functional subregions: sensorimotor, limbic and executive. Seed-based resting-state functional MRI was used to compare the FC from each striatal subregions to the whole brain between male and female patients as well as between patients and controls.

Results: Both male and female PD patients showed decreased FC between the sensorimotor striatal subregion and the substantia nigra compared to controls. However, the sensorimotor striatal subregion showed decreased FC with the superior frontal gyrus in female PD patients compared to male PD and controls and decreased FC with the cingulate gyrus in male PD patients compared to female PD and controls. The limbic striatal subregion showed increased FC with the insula in male PD patients compared to controls and increased FC with the hippocampus in female PD patients compared to controls. The executive striatal subregion showed increased connectivity with the insula and decreased connectivity with the superior frontal gyrus in female PD patients compared to controls.

Conclusions. Our findings revealed the presence of a disease-related, sex-specific divergent functional striatal connectivity in PD patients even in the early stages. This pattern may potentially lead to the characteristic vulnerability upon the development of different clinical milestones between genders over time.

C29

Development and validation of automated MR Parkinsonism Index 2.0 to distinguish PSP-P from PD

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Background: The clinical differential diagnosis between PSP-P and PD may be challenging. Several MR imaging biomarkers have proven to be useful in differentiating PSP-Richardson's syndrome (PSP-RS) from PD but failed to accurately distinguish PSP-P from PD patients, probably due to the lower degree of brain atrophy in this milder PSP subtype.

Objective: The current study aimed to develop an automated MR Parkinsonism Index 2.0 (MRPI 2.0) algorithm to distinguish progressive supranuclear palsy-parkinsonism (PSP-P) from Parkinson's disease (PD), and to validate its diagnostic performance in two large independent cohorts.

Methods: We enrolled 676 participants: a training cohort (n=346; 43 PSP-P, 194 PD, 109 controls) from our center, and an independent testing cohort (n=330; 62 PSP-P, 171 PD, 97 controls) from an international research group. We developed a new in-house algorithm for MRPI 2.0 calculation and assessed its performance in distinguishing PSP-P from PD and controls in both cohorts using receiver operating characteristic curves.

Results: The automated MRPI 2.0 showed excellent performance in differentiating PSP-P from PD patients and controls both in the training cohort (AUC=0.93, 95% confidence intervals [0.89-0.98]; AUC=0.97 [0.93-1.00], respectively) and in the international testing cohort (PSP-P vs PD, AUC=0.92 [0.87-0.97]; PSP-P vs controls, AUC=0.94 [0.90-0.98]), suggesting the generalizability of the results. The automated MRPI 2.0 also accurately distinguished between PSP-P and PD in the early stage of the diseases (AUC=0.91 [0.84-0.97]). A strong correlation (r=0.91, $p<0.001$) was found between automated and manual MRPI 2.0 values.

Discussion: Our study provides an automated, validated and generalizable MR biomarker to distinguish PSP-P from PD. The use of the automated MRPI 2.0 algorithm rather than manual measurements could be important to standardize measures in PSP-P patients across centers, with a positive impact on multicenter studies and clinical trials involving patients from different geographic regions.

C30

Diffusion tensor imaging of the olfactory tract in early hyposmic patients with Parkinson's disease

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Introduction: Hyposmia is a key clinical feature of the prodromal phase of Parkinson's disease (PD). Alpha-synuclein pathology occurs in the central olfactory areas and in the olfactory bulb early in the course of the disease. Diffusion-tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique which is suitable for detecting neurodegenerative changes in brain structures. DTI fiber tracking (DTI-ft) allows to detect white matter (WM) alterations in the olfactory tract in hyposmic PD patients [1]. Specifically, DTI analysis of the olfactory tract showed significant fractional anisotropy (FA) and tract volume (TV) decreases in PD patients compared to healthy controls (HC). *Objective:* We performed a subgroup analysis of the published work focused on DTI-ft changes in the olfactory tract in PD patients, in order to investigate whether the statistically significant changes of DTI parameters of the olfactory tract were detectable also in the early stages of the disease.

Methods: Among the overall study population, referring to 23 hyposmic PD patients, we considered the subgroup including early stage patients (early-PD), defined as patients with modified Hoen&Yahr (mH&Y) score ≤2 and disease duration ≤2 years.

Results: The early-PD group included 13 subjects (mean age 63.75±2.91; males/females ratio 5/8; mean mH&Y score 1.73 ± 0.12; mean disease duration 1.54 ± 0.14 years). The HC group encompassed 18 sex and age-matched subjects. In the early-PD group, DTI analysis of the olfactory tract showed statistically significant TV decrease compared to HC (P=0.027). No significant changes of FA values were found.

Conclusion: DTI-ft analysis is able to identify some microstructural changes in the olfactory tract also in the early phase of PD. This technique could provide a potential biomarker for early PD.

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C31

Neuroimaging as a potential tool for driving deep brain stimulation in Parkinson's disease

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Background: Subthalamic nucleus deep brain stimulation (STN-DBS) is an effective treatment for motor symptoms in advanced Parkinson's Disease (PD). Nevertheless, the exact area and paradigms of DBS stimulation to achieve the best control of motor and non-motor symptoms still needs to be defined.

Objectives: To identify the best site of DBS stimulation within or nearby the subthalamic nucleus of patients with advanced PD, to maximize the clinical motor outcome.

Methods: Twenty-five patients treated with bilateral STN-DBS were enrolled in the study. They all received a comprehensive clinical evaluation by means of the MDS Unified Parkinson Disease Rating Scale (MDS-UPDRS) before (baseline) and 1 year after (follow-up) DBS surgery. Presurgical MRI scan including conventional images (i.e., T1-weighted volumes, fluid-attenuated inversion recovery and T2-weighted scans) and post-surgical CT scan images were combined for the identification of the volume of tissue activated (VTA), using Lead-dbs software [1]. Using Voxel-based Lesion-Symptom mapping [2], individual VTAs were modelled to identify possible associations between follow-up subsets at the MDS-UPDRS and voxels belonging to VTAs. Age, disease duration and VTA volumes were entered as covariates of no interest.

Results: A significant sweetspot (p=0.043) accounting for patient improvement in bradykinesia was found covering the left dorso-lateral border of STN and extending to the surrounding white matter within the zona incerta and the most anterior portion of ansa lenticularis (peak coordinates: x=16; y=-13; z=-8). No associations were identified with rigidity and tremor UPDRS subscores.

Conclusions: This study points out the usefulness of neuroimaging for predicting DBS positive and negative outcomes, and its possible translation to clinical settings. From a speculative perspective our finding suggests the importance of zona incerta and fibers surrounding the lateral-posteror part of STN as a potential key target for patients with remarkable bradykinesia. Future studies based on brain connectivity might clarify the underlying mechanisms.

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C32

Axial impairment and falls in Parkinson's disease: 15 years of subthalamic deep brain stimulation

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Introduction: A definite consensus on the short- and long-term effects of subthalamic deep brain stimulation (STN-DBS) on axial impairment and falls in Parkinson's disease (PD) is still absent. Moreover, risk factors predicting the occurrence of these disorders after STN-DBS surgery are largely unknown.

Objective: This study aims to examine the short- and long-term evolution of axial impairment and falls and investigate risk factors for their occurrence in patients with PD and STN-DBS.

Methods: We retrospectively analysed PD patients with STN-DBS operated between 1993 and 2010 and followed longitudinally. Axial scores and falling frequency were collected and compared at baseline, 1, 10 and 15 years after surgery. Several preoperative demographic and clinical data were examined as possible risk factors through Kaplan-Meier and Cox regression analyses.

Results: Of 417 screened individuals, 302 people were included at baseline and 1-year evaluation, whereas 102 and 57 were available at 10- and 15-year follow-ups, respectively. Axial scores were similar at baseline and 1 year, but higher at 10 and 15 years. The prevalence rate of frequent fallers progressively increased from baseline to 15 years. Preoperative axial scores, frontal dysfunction and age at disease onset were risk factors for axial impairment progression after surgery. Similarly, axial scores, akinetic/rigid phenotype, age at disease onset and disease duration at surgery predicted frequent falls.

Discussion/Conclusion: Axial function in PD is unchanged in the short-term after STN-DBS but progressively worsens in the long-term period, especially in those with specific motor, cognitive and demographic features. This likely reflects the natural history of the disease as previously observed in non-operated patients, possibly due to neurodegenerative processes in non-dopaminergic pathways which are unaffected by L-Dopa and STN-DBS. Specific disease-related variables, as well as their relationship with ageing, would contribute to the pathophysiology of axial impairment and falls in PD patients with STN-DBS.

Poster

ACCADEMIA LIMPE-DISMOV
ACCADEMIA ITALIANA
MALATTIA DI PARKINSON
E DISORDINI DEL MOVIMENTO

P1

Is fatigue a disorder of movement preparation? A neurophysiological study

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Background: Fatigue is a common symptom of Parkinson's disease (PD), poorly recognized and not adequately treated [1]. In MRI studies, it has been linked to motor planning impairment [2] and in other diseases like Multiple Sclerosis, it has been linked to reduced pre-movement facilitation (PMF) [4]. Our aim was to understand whether PMF is abnormal in PD and it is related to fatigue.

Methods: Presence and the severity of fatigue were defined based on the 9-item Fatigue Severity Scale (FSS). We enrolled 15 patients with fatigue (PD-F), 16 without (PD-NF) and 16 Healthy Controls (HC). We assessed PMF with transcranial magnetic stimulation (TMS) during a simple reaction time (RT) motor task and TMS was delivered at 50 ms, 100ms and 150ms before movement onset.

Results: The rmANOVA corrected for age did not show significant interactions group x side x time ($F= 0.26$, $p= 0.9$) of amplitude of MEP and at three different intervals during PMF (MEP_{PMF}) compared to MEP_{REST}. However, when computing the rate of MEP increase during PMF (MEP_{PMF}/MEP_{REST}), all groups had a significantly higher rate of PMF at 50 ms ($F =4.3$, $p = 0.014$*), but HC significantly differ from patients ($F =4.6$, $p = 0.01$*) and PD-F and PD-NF did not differ from each other ($p> 0.05$).

Discussion: These results provide preliminary evidence PMF is abnormally reduced in PD patients compared to HC and independent from fatigue.

Conclusions: Abnormally reduced pre-movement facilitation could represents a neurophysiological hallmark of PD patients but it is not linked to fatigue in PD. Future works are necessary to disentangle the mechanisms of fatigue and to verify the meaning of reduced PMF in PD patients, its meaning in clinical and research context.

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P2

Functional Camptocormia and the role of psychotherapy: a case report

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Introduction: Functional Camptocormia (fC) is a rare functional motor disorder (FMD) characterized by a disabling pathological, forward bending of the trunk, not compatible with recognized neurological or medical conditions [1]. The literature suggests an interdisciplinary approach for FMD treatment [2,3], but, more recently, emphasizes the role of physiotherapy over psychotherapy.
Here, we report a case of fC whose symptoms completely remitted after cognitive-behavioral therapy (CBT).

Case presentation: A 59-year-old woman came to attention for a severe fC which developed about 6 years earlier following a psychological trauma. Her fC was severe enough to impair her gait and balance. Several pharmacological and physiotherapy approaches were attempted in the past with no benefit. Although she had received several different diagnosis including that of depression with conversion symptoms, we communicated the diagnosis of functional motor disorders according to recent suggestions and referred her to CBT.

Results: The CBT was focused on emotional literacy, the identification of both the antecedent (situational context) and thought/belief that activates behavior/symptom (functional analysis), disputing of irrational beliefs, and the emphasis on adult leadership with the integration of all parts of the personality. The whole treatment aimed to increase safety sense and meta-cognitive processes. After about 2 years of CBT, the patient learned to recognize and register the presence of physical sensations, emotions, thoughts and behaviors related to the emotional state and to physiologically react to any antecedents and any thoughts/beliefs and she does not have anymore any motor symptoms.

Discussion: In our case, fC completely remitted with CBT. Therefore, although the current suggestions emphasize the role of physiotherapy, we believe that psychotherapy is fundamental for positively treat patients with functional neurological disorders, even in the presence of motor symptoms.

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P3

Retinal thinning in progressive supranuclear palsy: differences with healthy controls and correlation with clinical variables

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Background: Available evidence reports conflicting data on retinal thickness in progressive supranuclear palsy (PSP). In studies including healthy controls [1], PSP showed either the thinning of the retinal nerve fiber layer, macular ganglion cell, inner nuclear, or outer retina layer [2].

Objectives: The goals of the present study were to describe retinal layer thickness in a large cohort of PSP compared to healthy controls and in PSP phenotypes using spectral-domain optical coherence tomography (SD-OCT). The additional objective was to verify the relationship between retinal layers thickness and clinical variables in PSP.

Methods: Using a cross-sectional design, we examined retinal structure in 27 PSP patients and 27 controls using standard SD-OCT. Motor and cognitive impairment in PSP was rated with the PSP rating scale and the Montreal Cognitive Assessment battery (MoCA), respectively. Eyes with poor image quality or confounding diseases were excluded. SD-OCT measures of PSP and controls were compared with parametric testing, and correlations between retinal layer thicknesses and disease severity were evaluated.

Results: PSP showed significant thinning of the inner retinal layer (IRL), ganglion cell layer (GCL), inner plexiform layer (IPL), and the outer plexiform layer (OPL) compared to healthy controls. PSP phenotypes showed similar retinal layer thicknesses. Retinal layer thickness correlated with MoCA visuospatial subscore ($p < 0.001$).

Conclusions: We demonstrated PSP patients disclosed thinner IRL, GCL, IPL, and OPL compared to healthy controls. Furthermore, we found a significant correlation between visuospatial abilities and retinal layers suggesting the existence of a mutual relationship between posterior cognitive function and retinal structure [3].

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P4

Magnetic resonance T1w/T2w ratio in the putamen and cerebellum as a marker of cognitive impairment in MSA: a longitudinal study

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Introduction: The exact pathophysiology of cognitive impairment in multiple system atrophy (MSA) is unclear [1, 2]. In our longitudinal study we aimed to analyze: (I) the relationships between cognitive functions and some subcortical structures, such as putamen and cerebellum assessed by voxel-based morphometry (VBM) and T1-weighted/T2-weighted (T1w/T2w) ratio, and (II) the neuroimaging predictors of the progression of cognitive deficits.

Methods: Twenty-six patients with MSA underwent a comprehensive neuropsychological battery, motor examination and brain MRI at baseline (T_0) and 1-year follow-up (T_1). Patients were then divided according to cognitive status into MSA with normal cognition (MSA-NC) and MSA with mild cognitive impairment (MCI). At T_1 we divided the sample according to worsening/non worsening of cognitive status compared to baseline evaluation.

Results: Logistic regression analysis showed that age (β=-9.45, p=.02) and T1w/T2w value in the left putamen (β=230.64, p=.01) were significant predictors of global cognitive status at T_0, explaining 65% of the variance. Logistic regression analysis showed that Δ-values of WM density in the cerebellum/brainstem (β= 2188.70, p=.02) significantly predicted cognitive worsening at T_1, explaining 64% of the variance.

Discussion: Our results suggest a role for the putamen and cerebellum in the cognitive changes of MSA, probably due to their connections with the cortex. The putaminal T1w/T2w ratio may deserve further studies as a marker of cognitive impairment in MSA [3].

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P5

PSP and FTD: comparison of motor, cognitive and behavioural features

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Introduction: Frontotemporal degeneration (FTD) and Progressive Supranuclear Palsy (PSP) are both tauopathies which can sometimes present overlapping clinical features.

Objective: The aim of this study is to compare motor and cognitive performances between FTD and PSP patients.

Methods: We collected motor assessments (including MDS-UPDRS part III, evaluation of eye movements, dystonia and myoclonus) in 15 consecutive patients within the FTD spectrum (9 with behavioural variant, 5 with PPA, 2 with logopenic and semantic variants, 1 patient with FTD-MND) and 15 patients with PSP (14 with Richardson's syndrome and 1 with PSP with predominant parkinsonism). All patients performed an extensive cognitive/behavioural battery of tests.

Results: FTD and PSP did not differ in terms of demographic features, As expected, PSP showed a greater impairment in saccadic eye movements ($p<0.05$). As for the movement disorders evaluation, PSP showed more frequently face dystonia, while FTD presented more frequently rest and stimulus-sensitive myoclonus ($p<0.05$). MDS-UPDRS part III was greater in PSP ($p<0.05$). As for the cognitive evaluation, FTD presented greater impairment in global cognitive status (assessed with MMSE and MOCA), memory and language (evaluated with deferred recall of Ray's 15 words and repetition of words and auditory understanding of words, respectively). As for the behavioural evaluation (performed with the Neuropsychiatric Inventory), FTD and PSP failed to disclose major differences except for apathy which was more frequent in FTD ($p<0.05$).

Conclusions: Despite being two different diseases, FTD and PSP share similar cognitive/behavioural impairment. PSP present a greater impairment in ocular movements and more frequent face dystonia, while myoclonus is more common in FTD.

P6

Application of the MDS diagnostic criteria to the large cohort of Italian PSP patients: results from the PSP-NET

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Introduction: Supranuclear Progressive Palsy (PSP) is a rare, rapidly progressive, neurodegenerative disease characterized by dysfunction in four core domains including ocular motor function, postural instability, akinesia, and cognition. PSP-NET is the Italian registry of PSP patients promoted by the LIMPE Foundation.

Objectives: The aim of the present study is to describe the preliminary motor data collected until early March 2022.

Methods: We analyzed the demographic and clinical features of the PSP patients enrolled. Difference between PSP subtypes were computed with ANOVA test and post hoc analysis.

Results: A total of 261 PSP patients were evaluated (75 from the North; 47 from the Center and 139 from the South of Italy). One-hundred and thirty-two (50.6%) were women, mean age was 59.67 (13.09) and mean disease duration was 2.89 years (2.05).

Applying previous National Institute of Neurodegenerative Disorders and Stroke-PSP criteria (NINDS-PSP), that recognize PSP-RS as the only form of disease, 229/261 (87,7%) fulfilled PSP diagnosis of whom 104 (39.84%) reached a probability and 125 (47.89%) a possibility level of diagnostic certainty.
According to the Movement Disorder Society-PSP (MDS-PSP) criteria, 236 subjects qualified for probable PSP (90.4%), 6 for possible PSP (2.29%) e and 7 for suggestive of PSP (2.68%). Two-hundred and twelve (81.2%) were PSP-Richardson Syndrome (PSP-RS), 19 (7.27%) were PSP with predominant parkinsonism (PSP-P) and 19 (7.27%) were among the other variants of the disease (vPSP). Mean total PSP-rating scale (PSP-rs) was 39.38 (18.53). PSP-rs was higher in PSP-RS compared with vPSP ($p<0.01$) but not with PSP-P ($p=0.65$).

Conclusions: The MDS-PSP criteria enlarge the number of patients fulfilling PSP diagnosis compared to previous criteria. As expected, the most prevalent phenotype was PSP-RS [1] followed by PSP-P with the remaining phenotypes accounting for only 7%. Finally, PSP-RS showed a greater disease severity compared to all other phenotypes but not to PSP-P.

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P8

Worsening of essential tremor after Sars-CoV-2 infection: 1 year follow up

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Introduction: We recently reported the case of a 60-year-old man diagnosed with essential tremor who complained of significant tremor worsening after asymptomatic SARS-CoV-2 infection. A pre-infection assessment allowed us to demonstrate a temporal relationship between infection and tremor worsening, which probably reflects a causal link. We concluded that tremor worsening was likely due to virus-induced immune-mediated functional alterations in cerebellar networks.

Aim: To follow up on clinical and kinematic tremor features as well as non-motor symptoms, neuroimaging, and laboratory changes in our case one-year after SARS-CoV2 infection.

Methods: Clinical and kinematic assessment of tremor features, postural, kinetic and rest tremor, as well as cognitive and psychiatric evaluation by means of clinical scales were performed one year after SARS-CoV2 infection (1-year follow up). The data were compared with those collected 4 years and 4 months before the infection and 1 month after the infection. Brain magnetic resonance imaging (MRI) and blood laboratory exams were also obtained before and after infection.

Results: At 1-year follow up we observed a reduction in postural tremor amplitude (GRMS^2) as compared to 1 month after infection (average percentage variation -14%). The value, however, was still significantly higher than before SARS-CoV2 infection (average percentage variation +54%). We found no significant variation in tremor frequency (Hz). Measures of kinetic tremor and rest tremor did not change at 1-year follow up. Finally, psychiatric, and cognitive assessment, brain MRI and blood laboratory exams did not significantly differ from previous evaluations.

Conclusions: After the initial worsening due to SARS-CoV2 infection, we observed only a partial recovery one-year after infection. Our observation suggests permanent virus-induced brain damage in key structures responsible for tremor generation, especially the cerebellum and its connections. However, longer follow up may be necessary to better define the effects of Sars-CoV-2 infection in patients with essential tremor.

P9

The alien limb

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Background: Among the neurodegenerative diseases, the Sporadic Creutzfeldt-Jakob disease is one of the most complex to detect. It can start with no-specific symptoms, undergoing a daily rapid change, until death in few months.

Case presentation: We describe a case of Sporadic Creutzfeldt-Jakob disease presenting with a lateralized cortico-basal syndrome as first symptom. In particular, the patient came to our attention for an alien limb syndrome with apraxia/ataxia involving the right hand and a scanned speech. No lack of strength was noticed. At the beginning only some epileptic anomalies in the left parietal lobe were noticed, in absence of important alteration in neuroradiological studies. We saw a daily variation of the clinical picture, until a constellation of symptoms appeared, including bilateral apraxia-ataxia, myoclonus, axial rigidity, with difficulties in postural changes, and palilalia, with repetition of syllables and meaningless words. After three weeks we had an EEG revealing bilateral periodic triphasic waves and an MRI showing FLAIR hyperintensity in different cortical and subcortical regions. Moreover, the CFS analysis revealed a positive RT-QuIC test. According to the diagnostic criteria we were in front of a probable Creutzfeldt-Jakob disease [1]. After two months since the beginning of first clinical manifestations, our patient died.

Conclusions: First symptoms in Creutzfeldt-Jakob disease are variable, making the diagnosis insidious. Furthermore, neuroradiological and neurophysiological examens are not always suggestive of the disease at the beginning. Our case shows a particular start of the disease with a cortico-basal syndrome, and more specific an alien limb phenomenon as first symptom. Not so many cases have been described in literature. Indeed, around 23 cases of cortico-basal syndrome as initial Creutzfeldt-Jakob disease have been reported and only 6 of them with an alien limb syndrome [2]. A rapid clinical picture changing could help to direct the clinician focus towards such a disease.

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P10

Performance Validity Tests in patients with functional motor disorders

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Background: Performance Validity Test (PVTs) are commonly used in the attempt to detect poor effort or symptoms exaggeration in neuropsychological testing [1,2]. Normative data in non in seeking-compensations clinical populations are essential to validate these measures in standard evaluations [1]. PVTs could be of value in Functional motor disorders (FMDs) patients who are, by nature exposed to prejudice of symptoms fabrication and exaggeration [2].

Objectives: The aim of this study was to examine performance of FMD patients at PVTs, compared to healthy controls asked to simulate malingering (healthy simulators, HS) and healthy controls (HC) who did not receive specific instructions. We also assessed diagnostic accuracy to detect deliberate simulation.

Methods: We enrolled 29 patients with a clinical diagnosis of FMDs, 29 HS and 29 HC. Three PVTs, the Coin in the Hand Test (CIH) [3], the Ret 15-item Test (FIT) [4] and the Finger Tapping Test (FTT) were employed [5].

Results: FMD performance resulted statistically different from that of HS and but not from HC ($p < 0.001$). Diagnostic accuracy to detect deliberate simulation were high in each test alone (sensitivity in all >90% and specificity was 100%, 75.9%, 69% for CIH, FIT and FTT, respectively) and excellent in all tests combined (specificity 100% and sensitivity 89.7%).

*Conclusions***:** Patients with FMDs did not show abnormal performance at PVTs. The ability of these tests to detect deliberate simulation is high and greater when tests are used in combination representing a reliable bedside algorithm that should be employed routinely in FMD patients' evaluations.

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P11

Screening of SNCA p.A53T mutation in the Sele river Valley: the Contursi Kindred 2.0

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Introduction: Parkinson disease (PD) is a common progressive neurodegenerative condition with unknow etiology. The majority of cases of PD are sporadic, however, also rare familial forms exist. The first identified mutation was a missense mutation resulting in an alanine to threonine substitution at position 53 (A53T) in the alpha-synuclein gene (SNCA) in the Contursi Kindred.

Objectives: The aim of the study is to describe the prevalence of p.A53T mutation in individuals with Parkinson and/or Dementia in the Sele River Valley and the clinical differences between patients with and without this mutation.

Methods: We tracked the prevalence of individuals with parkinsonism and dementia in the Sele river Valley through the National Health System Electronic Database (NHSED). Neurological examination and blood sampling were proposed to all the individuals in such lists and their relatives as well as to affected and unaffected subjects belonging to families known to harbor the p.A53T mutation. Genetic testing was performed using real-time polymerase chain reaction.

Results: The Sele Valley includes 13 villages for a total of 34.114 inhabitants (16.944 ≤44 years; 9.391 45-64 years; 7.626≥65 years). Exploration of the NHSDED disclosed 185 cases affected by Parkinsonism (0,54% total prevalence; 0,01% ≤44 years; 0,12% 45-64 years; 2,09% ≥65 years) and 124 cases affected by Dementia (0,36% prevalence, all ≥65 years). A total of 179 subjects were visited, 150 subjects performed genetic analysis. The 89% of subjects were p.A53T^{-}, 16 were p.A53T^{+} of which 11 affected and 5 unaffected. Subjects with p.A53T^{+} showed autosomal dominant inheritance pattern and presented heterogeneous manifestations with bradykinesia and rigidity (100%), tremor (62%), pyramidal signs (12.5%), dystonia (25%) and RBD (37%). Conversely, p.A53T^{-} have more frequent myoclonus (3.1%) and apraxia (5.2%).

Conclusions: All subjects with parkinsonism and positive family history from the Sele river Valley should be investigated for SNCA p.A53T.

P12

Differences in kinematic and spatio-temporal parameters assessed by instrumented "timed up and go" test between idiopathic normal pressure hydrocephalus associated with parkinsonism and Parkinson's disease

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Introduction: Idiopathic normal pressure hydrocephalus can be associated with parkinsonism. Both iNPH-P and PD are characterized by hypokinetic gait disorders, with decreased walking speed and short stride length.

Objectives: To assess differences in quantitative gait parameters and motility during standardized tasks between idiopathic Normal Pressure Hydrocephalus (iNPH-P) and Parkinson disease (PD).

Methods: We selected one group of 21 patients with clinical diagnosis of "possible iNPH" by adapted Relkin criteria and the simultaneous presence of parkinsonism in accordance with the MDS diagnostic definition, and a second group of 21 patients of newly diagnosed "clinically probable" PD based on current MDS diagnostic criteria, who were untreated with dopaminergic medication. Both groups of patients performed the instrumented Timed Up-and-Go test (iTUG).

Results: The mean age was higher for iNPH-P as compared to PD (71.4±10.7 vs 60.6±10; p=0.007). MMSE score was significantly lower in iNPH-P (23.9±4.3 vs 27.9±1.3; p=0.003). We found no significant differences in disease duration (2.7±2.3 vs 2.9±2.1; p=0.788) and UPDRS-ME score (23.8±8.6 vs 28.5±10.3; p=0.154). Both turning tasks of the iTUG showed significantly longer duration in iNPH-P, while peak and average angular speeds were lower. Vertical variation in acceleration during the sit-to-stand phase was lower in iNPH-P patients while duration of the stand-to-sit phase was significantly longer. iNPH-P showed smaller stride length and a longer gait cycle duration with a more represented swing and single support phase. At multivariate analysis adjusting the analysis for age and MMSE as potential confounders, average angular speed on turning-before-sitting was the discriminating parameter between groups. Appling ROC curve analysis, an average angular speed cut-off of 49°/s on turning-before-sitting discriminated iNPH-P from PD with a sensitivity of 67% and a specificity of 91%.

Conclusion: Patients with iNPH-P showed abnormal balance performances with respect to untreated PD, specifically during adaptation manoeuvres and postural changes.

P13

Functional foreign accent syndrome and the role of auditory exclusion

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Introduction: Functional Foreign Accent Syndrome (fFAS) represents a rare functional speech disorder, not compatible with recognized neurological or medical conditions, in which listeners perceive the affected individual as speaking with a foreign accent.
We here report on a patient with fFAS to: 1) increase awareness on this entity; and 2) discuss the effect of auditory exclusion, as we believe it provides a better insight on the pathomechanisms underlying functional motor disorder (FMD) more in general.

Case description: A 44-year-old woman had severe FAS that we diagnosed functional in line with clinical criteria [1]. In fact, her clinical symptoms started one year before with acute mutism but her phenotype changed over time. She subsequently developed weakness of one limb and dysarthria, both symptoms resolving spontaneously in few weeks. She then developed fFAS, which is currently her only complaint. The entire neurological examination and brain MRI were negative.
To explore if fFAS was modulated by different activities, we had the patient sing with the exclusion of auditory feedback.
Contrary to our expectations, fFAS worsened with auditory exclusion.

Discussion: Contemporary motor theory proposes that motor control follows a feed-forward model in which self-generated movements are accompanied by a sensory prediction of the motor outcome. In FMD, sensory feedback appears to be intact and the mismatch between prediction and outcome could be due to an abnormality in the internal prediction. The sensory feedback helps the motor program and output and, in our case, the abolition of the auditory feedback might have left the aberrant internal prediction "prior" totally unconstrained, leading to a worsening of the motor output [2]. This would suggest that an increase of sensory feedback awareness could modulate the motor output in FMD in general.

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P14

Screening of cognitive domains with MOCA in PSP: results from the PSP NET

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Introduction: Cognitive impairment is among cardinal features of Progressive Supranuclear Palsy (PSP). The Montreal Cognitive Assessment (MOCA) is the standard test for identifying cognitive disorders in atypical parkinsonism. Attention, executive and visuospatial functions are the most affected domains in such patients. PSP-NET is the Italian registry of PSP patients promoted by the LIMPE Foundation.

Objective: The aim of the present study is to describe the preliminary cognitive data collected until early March 2022.

Methods: Patients were divided in two groups according to the PSP phenotype: PSP with Richardson's syndrome (RS-PSP) and the other variants of PSP (vPSP). Disease severity was rated with the PSP rating scale. We used the t-test and $\chi 2$ to calculate differences between phenotypes, and the Pearson correlation to identify other clinical parameters correlating with the cognitive profile.

Results: One-hundred and thirthy-three patients were included. Worse MOCA performances correlated with higher PSP rating scale ($p<0.05$). Such correlation was greater for PSP-RS. Disease onset with freezing of gait correlated with lower MOCA scores ($p<0.05$). As for cognitive subdomains, attention was the most compromised domain in patients who started with freezing of

gait or cognitive symptoms ($p<0.05$). On the other hand, tremor at onset was associated with worse performance in the memory subscore ($p<0.05$). More than half of PSP-RS (55.5%) had a score below the median value of the MOCA, compared to 35.7% of vPSPs. No other significant differences were detected between PSP phenotypes.

Conclusion: Worse cognitive performances are associated with greater disease severity in PSP, especially in PSP-RS. Freezing of gait, cognitive symptoms, and tremor at onset may be linked to impairment of specific cognitive functions.

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Effect of education on cognitive decline in Parkinson's disease

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Introduction: Education is used as proxy measure of cognitive reserve. Recent evidence would suggest that higher levels of education would not slow cognitive decline in Alzheimer's disease (AD) and healthy elderly subjects [1, 2]. It is unknown whether this is true in Parkinson's disease (PD). Therefore, in this longitudinal study, we sought to analyze the effect of education on cognitive changes of patients with PD.

Methods: A sample of PD patients having at least two evaluations performed one year apart, was stratified in three groups according to their education levels (i.e., junior high school; senior high school, university degree/higher). We calculated z-scores of three main cognitive domains (i.e., memory, visuo-spatial and attentional/executive domain). A composite score, used for measuring global cognition, was obtained by averaging the z-scores of cognitive domains and MOCA and MMSE scores.
The paired-sample T-test and the analysis of variance with repeated measures correcting for disease duration, motor disability at baseline and follow-up duration, were employed to analyze the cognitive changes over time in the entire sample and in the subgroups.

Results: We recruited 133 PD patients with a mean disease duration of 3.39±3.94 years. At T_0 the groups did not differ for clinical and demographic variables. After a mean follow-up period of 2.11±1.33 years, the whole sample significantly worsened in terms of global cognition and memory and visuospatial domain ($p<0.05$). No significant differences were found between the subgroups stratified according to their education ($p>0.05$).

Conclusion: Our results would suggest that education does not influence the degree of cognitive decline in PD patients, mirroring results in AD and in healthy elderly. However, since there has been suggestion that the protective effects of education is evident only in the earliest stage of AD to disappear in later stages [3], this must be investigated in patients with very early PD.

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P16

The psychological correlates of fatigue in Parkinson's disease: contribution of maladaptive metacognitive beliefs

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Introduction: Psychological factors can underlie fatigue in neurological disorders, but its relationship to fatigue in Parkinson's disease (PD) has not been explored [1,2,3].

Objective: To assessed the association between maladaptive metacognitive beliefs and presence of fatigue in PD.

Methods: Ninety-eight consecutive outpatients with PD (61% male; median age: 66.50 years) were assessed in terms of demographic, clinical, medication treatment, cognitive, or behavioural characteristics including metacognitive beliefs (Metacognitions Questionnaire-30 or MCQ). Fatigue was ascertained by PD-related diagnostic criteria. Univariate statistical approach (Mann-Whitney and Pearson chi-square tests) was used to compare PD patients with (*f*-PD) or without (*nf*-PD) fatigue in terms of demographic, clinical, medication treatment, cognitive, behavioural, and metacognitive measures.

Results: Twenty-one PD patients (21%) displayed fatigue. The *f*-PD group scored higher on the MCQ-total score, MCQ-Cognitive Confidence subscale, and all behavioral measures (p_s<0.01) relative to *nf*-PD. They also had a more advanced Hoehn and Yahr stage and Unified Parkinson's Disease Rating Scale-III score.

Conclusion: Maladaptive metacognitive beliefs such as the lack of cognitive confidence may play a key role to trigger and maintain fatigue in PD. Future studies, using a multivariate statistical approach, are needed to confirm these preliminary findings in a larger sample of patients with fatigue and to assess if modification of such metacognitive beliefs has the potential to ameliorate fatigue in PD.

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P17

Longitudinal progression of cognitive impairment in PSP

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Introduction: Progressive supranuclear palsy (PSP) is a rare, rapidly progressive, neurodegenerative disease characterized by cognitive and behavioral [1]. The aim of the present study is to analyze longitudinal changes in cognition in PSP patients using a comprehensive cognitive battery.

Methods: Twenty-nine PSP patients diagnosed according to the Movement Disorder Society criteria, underwent a motor and cognitive assessment at the base-line (T_0) and after 14.73±9.18 months of follow up (T_1).
Based on z-scores, compound scores for five cognitive domains were computed: memory, visuo-spatial, attentional, apraxial and executive functioning. The global cognition was obtained by the mean of five domains with z-scores of Montreal Cognitive Assessment (MOCA). Motor impairment was assessed with the PSP rating scale (PSP-rs).
The Wilcoxon's test, corrected for multiple comparisons, was used to investigate the progression of cognitive symptoms in the all domains.

Results: The global cognition and the visuo- spatial domain presented a significant decline at T_1 ($p<0.05$). The visuo- spatial function tests presented the greatest sensitivity to clinical progression ($p=0.007$).
The PSP Rating Scale (PSP-rs) also revealed a significant motor progression at follow up ($p<0.001$).

Conclusions: Our preliminary data show that the cognitive decline in PSP could be detected by the evolution of visuo- spatial functions over time. Moreover these results also underline that the evaluation of cognitive domains may better detect disease progression in PSP [2, 3].

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P18

PD-MCI in newly diagnosed patients: preliminary data

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Introduction: Cognitive impairment represents one of the most disabling non-motor symptoms of Parkinson's disease (PD). Although it is common to think that it affects the advanced stages of the disease, cognitive impairment can already concern the early stages [1]. However, the prevalence and subtypes of MCI vary depending on the cognitive tests administered and the criteria used.

Objective: This preliminary study aims to evaluate the prevalence and clinical characteristics of MCI in patients with newly diagnosed Parkinson's disease by applying the level II criteria proposed by the task force of the Movement Disorder Society (MDS) [2].

Methods: A level II neuropsychological assessment was performed on 36 newly diagnosed Parkinson's disease patients belonging to the Movement Disorders Clinic of Trento. They do not have other neurological or psychiatric pathologies.

Results: Using 2 sd criteria, 11% of patients show PD-MCI (all multidomain type) from the II-level neuropsychological assessment, while the prevalence increased to 30% using the 1.5 sd criteria. Only two patients (5% of the sample) show PD-MCI from the I level assessment (MoCA). Using 2 sd criteria, the PD-MCI group is comparable to the PD cognitive unimpaired (CU) group for age ($t(34)=-0.43$, $p>0.05$), education ($t(34)=0.66$, $p>0.05$), sex ($\chi^2(1)=1.39$, $p>0.05$), motor phenotype ($\chi^2(1)=0.51$, $p>0.05$) and motor lateralization at onset ($\chi^2(1)=0.01$, $p>0.05$). However, patients with PD-MCI compared to PD-CU have a heterogeneous disease severity with H&Y ranging from 1 to 3 (vs. 75% of PD-CU with H&Y=1; $\chi^2(3)=12.36$, $p=0.006$) and a higher LEDD ($t(34)=-3.29$, $p=0.02$).

Discussion and Conclusion: Preliminary data support the evidence that MCI may already characterize the early stages of Parkinson's disease and that the prevalence varies depending on level assessment (I or II) and criteria used (2 or 1.5 sd). Finally, our results suggest the need to increasingly introduce, from a multidisciplinary perspective, level II neuropsychological assessment in the diagnostic and care process of the person with Parkinson's disease.

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P19

Effects of dopaminergic medication on reactive and proactive inhibitory control

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Objective: In this study, we addressed the effects of dopaminergic treatment (DT) on the two domains of motor inhibition [1], i.e., reactive (the ability to react to a stop signal) and proactive inhibition (the ability to adapt the motor strategies according to the current context flexibly) according to the stage of Parkinson's disease (PD).

Methods: We recruited cognitively unimpaired PD patients under dopaminergic treatment in the early (H&Y 1/1.5, n=20), intermediate (H&Y 2, n=20), and moderate/advanced (H&Y 2.5/3, n=20) stages and 30 age-matched healthy controls. Each participant underwent a standardized motor and cognitive assessment and stop-signal task (SST). Covariance analyses adjusted for the effect of age, sex, and UPDRS3 evaluated the differences between the performance in the SST (in terms of reactive and proactive inhibition) in DT ON and OFF and each stage of the disease as well as in comparison with controls.

Results: We found that both reactive and proactive inhibition is progressively impaired along the disease. However, the DT negatively affects reactive inhibition in the early and proactive inhibition in the intermediate PD stage. By contrast, DT does not impact motor inhibition in moderate/advanced patients.

Conclusion: In PD's early and intermediate stages, the DT negatively impacts reactive and proactive inhibition, respectively, despite improving motor symptoms. Such evidence supports the dopamine overdose hypothesis [2], which suggests that the administration of DT in the first stages of PD benefits dopamine-depleted dorsal striatal circuitries improving motor symptoms but overdose the more intact dopamine-dependent circuitries of the ventral striatum, impairing executive functions relying on it. Such findings suggest that the DT has to be titrated carefully to maximize patients' quality of life in the first stages of PD.

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P20

Visuospatial deficits are associated with Pisa syndrome but not with camptocormia in Parkinson disease

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Introduction: Pisa syndrome and camptocormia are frequent postural abnormalities (PA) associated with Parkinson disease (PD). Their pathophysiology remains largely unclear, although some small-sampled pilot studies suggest a role for cognitive deficits.

Objective: To assess the potential contribution of cognitive deficits in determining PA in patients with PD.

Methods: We performed a multicenter, case-control study to analyze the cognitive profile of PD patients with either Pisa syndrome or camptocormia as compared to matched PD patients without PA. A total of 114 PD patients from seven Italian and one German centers were enrolled: 32 with Pisa syndrome (PS+) and 25 with camptocormia (CC+) were matched - for gender, age, education, PD duration, and PD stage – with 57 patients without PA (32 PS-, and 25 CC-). Patients underwent an extensive clinical and neuropsychological assessment, evaluating five cognitive domains: memory, attention, executive functions, visuospatial abilities, language. Z-scores of each test were used to estimate a cognitive domain score, which was compared for PS+ vs PS- and CC+ vs CC- using the Mann-Whitney test.

Results: All groups were comparable for the main demographic and clinical features. PS+ showed significantly worse visuospatial performances than PS- (Z-score PS+ -1±1.1; PS- 0.5±0.9; p:0.025), while CC+ did not show any significant differences when compared to CC-. The global cognitive score, assessed by MoCA, did not significantly differ between groups, nor did the other cognitive domains scores.

Conclusion: Our findings confirm, with an adequate sample size and methodology, preliminary data on the association of worse visuospatial abilities in patients with PS compared with patients differing

only for the absence of PA. However, we did not observe the same association for CC patients. These results indicate different pathophysiological trajectories between PS and CC, suggesting a specific role of visuospatial deficits in the development of PS but not of CC.

P21

Could central fatigue in Parkinson's disease be related to an energization deficit? Evidence from the Frontal Assessment Battery

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Introduction: Central fatigue is defined as difficulty in initiating or enduring physical and mental tasks, especially those requiring conspicuous self-motivation. Pathological central fatigue in Parkinson's disease (PD) may be related to a deficit in striato-thalamo-prefrontal loops, responsible for complex cognitive elaboration, such as costs/benefits analysis and decision making [1].
Objective: To verify whether central fatigue in PD is associated with a deficit in executive functions, given its relationship with higher-level cognitive processes critically dependent on executive control.

Methods: 31 PD patients without fatigue-PDnF, 29 with fatigue-PDF and 31 controls underwent an evaluation with the Frontal Assessment Battery (FAB). All subjects were also evaluated with MMSE, PSQI, BDI, STAI Y1-2, PDQ-39. Differences between groups were analyzed by means of Kruskal-Wallis test.

Results: A significant difference between groups emerged in FAB total score ($p<0.001$) and in most of the subitems partial scores (conceptualization: $p=0.008$, verbal fluency: $p=0.006$, motor programming: $p=0.023$, sensitivity to interference: $p=0.006$, inhibitory control: $p=0.004$). After Dunn-Bonferroni corrections, while most of the aforementioned items were significantly different between controls and PD population regardless the presence of fatigue, a significant difference between PDF and PDnF emerged for verbal fluency alone ($p=0.002$). No difference emerged in environmental autonomy ($p=0.14$).

Conclusions: Our data demonstrated that central fatigue is associated to a specific impairment in phonemic verbal fluency. Fluency tasks require the generation of novel rather than learned responses, as well as ignoring distractions and efficient attentional control [2]. Both these processes rests on energization, which enables cognitive operations strictly related to internal drive mechanisms[3], whose dysfunction is believed to be crucial also in the genesis of pathological central fatigue. We argue that the alteration of the internally cued behavior could be regarded as a common phenomenon that can account for both verbal fluency lower scores and the occurrence of pathological central fatigue in PD.

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P22

Apathy Evaluation Scale - informant version in progressive supranuclear palsy: psychometric properties and clinical correlates

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Objectives: Apathy is among the most common neuropsychiatric symptoms in progressive supranuclear palsy (PSP). Different criteria, scales and tools were used to evaluate apathy in PSP and no studies have examined the ability of available instruments to detect apathetic symptoms in PSP. Aims of the present study were to (I) report the psychometric properties of the Apathy Evaluation Scale- informant version (AES-I) in PSP and (II) describe the clinical correlates of apathy in PSP patients.

Design, setting and participants: At the Center for Neurodegenerative Diseases of the University of Salerno, Italy, the AES-I was validated in 66 PSP patients diagnosed according to the Movement Disorder Society criteria. Patients underwent a clinical interview, a motor evaluation, cognitive and behavioral testing. Global cognitive status was re-valuated in a subgroup of 22 patients at 15.86±9.52 months of follow-up.

Results: The mean AES-I total score was 45.03 ± 9.78. The internal consistency was high (Cronbach's alpha = 0.891); corrected item-total correlation was >0.40 for the majority of items. Principal component analysis revealed that the three factors with the highest Eigenvalues accounted for 58.88% of the total variance. We also showed that patients with higher apathy scores at baseline present a greater cognitive worsening at follow up.

Conclusion: The AES-I is a reliable and valid tool for the assessment of apathetic symptoms in PSP. Such data are useful to standardize studies of apathy in PSP and to quantify the effectiveness of any interventions on this disabling symptom. Furthermore, higher apathy scores at diagnosis may represent a marker of worse cognitive deterioration at 1-year follow up.

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P23

Cognitive and neuropsychiatric profiles of vascular parkinsonism: a two-years longitudinal study

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Introduction: Vascular parkinsonism (VP) is a relatively frequent variant of secondary parkinsonism, typically associated with arteriosclerotic encephalopathy (AE). Nevertheless, despite their high impact on quality of life, VP cognitive profile has not been fully elucidated and little is known about VP psychiatric symptoms. Moreover, longitudinal data of VP cognitive and neuropsychiatric symptoms are lacking.

Objective: To identify specific cognitive and neuropsychiatric profiles characterizing VP and compare them to patients with vascular dementia (VD), arteriosclerotic encephalopathy without or with minimal cognitive and motor impairment (AEWCM) and healthy controls (HC), at baseline (T0), 12 (T1) and 24 months (T2).

Methods: Twenty patients with VP, 20 with VD, 20 with AEWCM and 20 HC were enrolled. All participants underwent a complete clinical, functional, neuropsychological, and neuropsychiatric assessment.

Results: Patients with VP scored significantly worse than HC at T1 and T2 in long-term verbal memory and at T2 in short-term verbal memory. VP group had increased impairment in the instrumental activities of daily living scale (IADL) at T1 and T2 respect to HC. Although no significant neuropsychiatric differences were found among groups, patients with VP exhibit higher total scores in the Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HARS) at T0, T1 and T2.

Conclusion: Verbal memory impairment found in VP is consistent with some previous studies. We hypothesize that memory deficit can be related to subclinical depressive and anxiety symptoms detected, which are known to affect memory efficiency and, more specifically, the encoding memory processes. The reduced independence in IADL in VP may depend on memory impairment and motor difficulties. Other differences may not emerge because our patients with VP are younger and more educated than patients described in the current literature. Further longitudinal studies are needed to better understand disease progression and orient the therapeutic management.

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P24

Video-oculographic biomarkers for evaluating vertical ocular dysfunction in progressive supranuclear palsy

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Background: Progressive supranuclear palsy (PSP) patients show reduced amplitude and velocity of vertical saccades, but saccadic abnormalities have also been reported in Parkinson's disease (PD). We investigated amplitude and velocity of vertical saccades in PSP and PD, to establish the best video-oculographic (VOG) parameters for PSP diagnosis.

Methods: Fifty-one PSP patients, 113 PD patients and 40 controls were enrolled. The diagnosis was performed on a clinico-radiological basis (MR Parkinsonism index [MRPI] and MRPI 2.0). We used VOG to assess the diagnostic performances of saccadic amplitude, peak velocity, and their product (AxV) in upward or downward direction and in vertical gaze (upward and downward averaged) in distinguishing PSP from PD patients. The vestibulo-ocular reflex, necessary to establish the supranuclear nature of ocular dysfunction, was evaluated clinically.

Results: PSP patients showed significantly reduced amplitude and peak velocity of ocular saccades in upward and downward directions compared to PD and healthy subjects. In PD patients, upward gaze amplitude was lower than in controls. In vertical gaze, the peak velocity showed 99.1% specificity and 54.7% sensitivity for PSP classification. The AxV product showed high specificity (94.7%) and sensitivity (84.3%) and yielded higher accuracy (91.5%) than velocity and amplitude used alone in distinguishing PSP from PD.

Conclusion: Our study demonstrates that the peak velocity of vertical saccades was a very low sensitive parameter and cannot be used alone for PSP diagnosis. A new index combining amplitude and peak velocity in vertical gaze seems the most suitable video-oculographic biomarker for differentiating PSP from PD and controls.

P25

Implementation of wearable sensors for evaluation of disease severity in progressive supranuclear palsy

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Introduction: Progressive supranuclear palsy (PSP) is an atypical parkinsonism characterized by prominent motor and postural impairments [1]. The PSP rating scale (PSPrs) is a validated tool to evaluate disease severity [2]. Recently, wearable sensors such as APDM opal technologies have been used to investigate gait and related parameters in movement disorders [3].

Objective: To explore the relationship between a gait protocol using wearable sensors and the PSPrs.

Methods: PSP patients were evaluated with the PSPrs as well as the gait protocol with wearable sensors based on 2-minute walking, sway and 360 degree turning tests. Several parameters were extracted from the sensors. A Spearman rho correlation coefficient was calculated for the relationship between PSPrs (sub- and total scores) and sensor measurements. The sensor variables showing a significant correlation with PSPrs were subsequently included as independent variables in a multiple linear regression model in order to assess the sensor ability to predict PSPrs scores. The significance level in both analyses was set at ≤ 0.05.

Results: Sixty-one evaluations from 33 patients were analyzed, with 27 patients being tested twice (at baseline and at 3-months follow-up). Gait, sway and turning parameters measured with sensors showed multiple significant correlations with the PSPrs total- and sub-scores (*rho* between ± 0.3 and 0.7; $p<0.05$). All linear regressions built thereafter were significant ($p<0.05$) with adjusted R Square always > 0.7, indicating a strong relationship between the sensor parameters and the PSPrs. The strongest relationship was observed between PSPrs total score and turning velocity and mean stance time (R Square 0.976, $p <0.001$).

Conclusion: Our clinic-based protocol evaluating gait and related parameters using wearable sensors has a strong relationship with the PSPrs. Therefore, wearable sensors could be easily introduced in clinical practice as well as in research settings as a tool to objectively evaluate disease severity in PSP.

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P26

Longitudinal change of energy expenditure, body composition and dietary habits in progressive supranuclear palsy patients

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Introduction: Progressive Supranuclear Palsy (PSP) is a neurodegenerative disease associated with postural instability and oculomotor disturbances as well as akinesia and cognitive and behavioral changes [1].
Recently we described a reduction of total daily energy expenditure in PSP possibly linked to reduced physical activity level and fat free mass [2].

Objective: Aim of this study is to describe longitudinal changes of energy expenditure, body composition and dietary habits in PSP patients.

Methods: A total of 8 PSP patients were evalueted at baseline and after a mean of 8,75 months with indirect calorimeter, bio-impedance analysis and physical activity and dietary intake questionnaries. Disease severity was evaluated with the PSP-Rating Scale (PSP-rs).

Results: No change was detected in either weight or rest energy expenditure over time ($p>0,05$). Bio-impedance analysis showed no change in fat mass and fat free mass ($p>0,05$). Dietary habits showed only minor changes over time with a tendency towards a reduction of daily calorie intake (mean 2248,28 kcal/daily to 2054,42 kcal/daily) ($p=0,07$). Physical activity level decreased significantly ($p<0,05$). Similarly, PSP-rs significantly increased over time ($p<0,05$).

Conclusions: After a mean follow up of 8 months, energy expenditure and body composition remain stable in PSP patients. As opposite, physical activity level decreases significantly likley in relation to the increase in disease severity. Calorie intake remains overall stable but with a tendency towards a reduction. As the disease worsens, mobility of patients is progressively reduced. In this short-term follow up, such changes are not associated with significant modifications in energy expenditure and body composition, possibly also related to preserved dietary habits.

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P27

Gait alteration in dystonic patients

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Introduction: Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both [1]. Preliminary evidence have suggested the presence of subclinical gait impairment in patients with cervical dystonia [2].

Objectives: To analyse the pattern of gait in patients with focal/segmental cranio-cervical dystonia and compare it with healthy controls (HC) matched for age.

Methods: Patients were evaluated with the Fahn-Marsden dystonia scale (F-M) and underwent a gait analysis using the BTS GaitLab system according to Davis Protocol in order to extract spatial and temporal gait parameters. Davis Protocol consists of four phases: anthropometric measurements, positioning of reflective markers on the patient, standing phase and walking phase. The Mann-Whitney U-Test was used to verify differences between patients and HC. A significance level of 0.05 was adopted.

Results: 8 patients (3M, 5F) with a mean disease duration of 14.5 ± 12.7 years, F-M total movement scale of 11.19 ± 5.9, F-M total disability scale of 2.25 ± 1.91, and 6 HC were enrolled. Patients performed worse than HC. Significant differences were found in cycle duration (p-value < 0,01), stance duration (p-value = 0,02), stance phase (p-value = 0,01), double support phase (p-value = 0,03) and mean velocity (p-value = 0,04).

Conclusion: We found significant differences between patients and HC in terms of gait speed, confirming a previous study [2]. We additionally found other significant differences such as increased cycle duration and stance phase, which may suggest a gait uncertainty in patients with dystonia. Additional analyses are underway to correlate demographic and clinical features of patients with their gait abnormalities.

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P28

Phenotypic description of two unreported families with ANO3 dystonia

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Background: ANO3 gene encodes for a Ca2þ-gated chloride channel. DYT24 has an adult onset and usually presents with cranio-cervical dystonia combined with tremor [1,2].

Objective: This is the phenotypic description of two families affected by hereditary dystonia associated to gene ANO3 mutation (DYT24), one with a heterozygous verisimilarly pathogenic variant (hVPV), and the other with a heterozygous variant of uncertain meaning (hVUM).

Methods: Phenomenology description (with related videos), next generation sequencing of dystonia genetic panel, multichannel EMG were performed in both families.

Results: In one family, proband was the mother, who presented a severe axial dystonia associated with tremor at the head and upper limbs, whereas her son had a cranio-cervical dystonia and head jerky movements. Genetic analysis identified a hVPV in ANO3 gene associated to PINK1 gene hVUM mutation in the mother and to PANK2 in the son. Both patients are under deep brain stimulation of internal globus pallidus with benefits. In the other family, proband is a 60 y.o. man who presented cranial dystonia and upper limbs dystonic tremor, whereas his sister shows just dystonic features of Meige syndrome. Our patients were found to be heterozygous for a *de novo* missense variant in ANO3 c.1690C>G which predicts the corresponding protein change of p. (Leu564Val) and which is absent from the GnomAD reference population database and never reported in literature. All patients are under treatment with botulinum toxin with benefits. They all reported dystonia onset before the age of 20 year. Brain MRI scan showed normal findings in all of them.

Conclusions: Dyt24 has heterogeneous clinical aspects [3,4,5], both families here reported have cranio-cervical and upper limb impairment but with different clinical presentation. Patients of the same family are similar but show significant difference with subjects of the other family.

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P29

Neuropsychological correlates of theory of mind in patients with dystonia: a preliminary study

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Introduction: Dystonia is a neurological disorder characterized by motor symptoms that can lead to severe disability and affect quality of life. Recently, great attention has been placed on neuropsychological and social cognitive impairment in idiopathic and isolated dystonia. In detail, theory of mind (ToM) refers to an individual's ability to attribute mental states, to predict and explain another person's behavior, and this ability has been poorly explored in dystonia. Indeed, only one study found that ToM abilities were impaired [1] and no study explored the neuropsychological correlates of ToM in dystonia.

Objectives: The aim of this study was to investigate the neuropsychological correlates of ToM in idiopathic dystonia.

Methods: 10 patients with adult onset of focal idiopathic dystonia (FID) and 10 healthy subjects (HCs) underwent a neuropsychological battery assessing memory, visuospatial abilities, attention, language and executive functions. ToM was assessed with the Italian versions of the Eyes Test (ET), the ToM stories and the Emotion Attribution Task Stories (EAT).

Results: Mann-Whitney U test revealed significantly lower scores in FID compared to HCs on the EAT and ToM stories. Moreover, significant correlations in patients group were found between ToM stories and TMT-A, visual search and Benton test; between EAT and the delayed recall of a short story of Anna Pesenti (SSAP) and the TMT B-A; between ET and SSAP, Token test and the Dimensional Apathy Scale (DAS).

Conclusion: These preliminary results showed worse performances in tasks assessing ToM in patients affected by FID as compared to HCs. Moreover, ToM abilities in dystonia were related to several cognitive functions and psychiatric symptoms. Specifically, when ToM material was presented within a specific visual context (stories test), patients recruited visuospatial processing and attentional resources; on the other hand, when context needed to be inferred (EAT and ET), patients relied on memory, comprehension and divided attention. Finally, a worse performance in ET task was related to more severe apathetic symptoms.

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P30

Machine learning analysis of voice in stuttering

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Background: Stuttering is a childhood-onset neurodevelopmental disorder affecting speech fluency. Given the lack of standardized acoustic analysis, stuttering is currently evaluated by means of perceptual examination with dedicated clinical scales. Advanced voice analysis techniques based on machine learning would improve the diagnostic accuracy of stuttering, as suggested by previously unreported results in movement disorders [1,2,3,4].

Objective: We aimed to detect objectively stuttering-related voice abnormalities through automatic machine learning techniques. Also, we investigated the relevance of speech-tasks as well as technological apparatus (i.e., smartphone) for the objective assessment of stuttering.

Methods: Thirty-three people with stuttering and 40 age- and gender-matched controls were recruited. Sustained emission of vowel /e/ and two sentences of the connected speech were recorded through smartphones. Voice samples were analysed using machine learning procedures to compare controls and people with stuttering.

Results: Machine learning algorithm objectively discriminated with high accuracy between controls and people with stuttering, as shown by the receiver operating characteristic (ROC) curves calculated during the sustained emission of the vowel /e/ (accuracy: 87.7; AUC: 0.934), sentence 1 (Acc.: 83.6; AUC: 0.906) and finally, sentence 2 (Acc.: 81.1; AUC: 0.881).

Conclusions: Machine learning-based analysis of human voice through smartphone represents a reliable tool for the automatic detection of stuttering-related changes of voice features in patients with stuttering. Future studies would disclose whether machine learning analysis here proposed would help clinicians in the objective diagnosis of developmental disorders of speech, including stuttering.

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P31

The impact of orthostatic hypotension on non-motor symptoms of Vascular Parkinsonism

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Introduction: Vascular Parkinsonism (VP) is a secondary parkinsonism typically associated with arteriosclerotic encephalopathy. Several clinical features characterized VP including motor and non-motor symptoms such as impairment of attention, executive function, and verbal memory, depressive disorder, apathy, sleep disorders, gastrointestinal dysfunction and orthostatic hypotension (OH). Although OH occurs in up to 26% patients with VP, its impact on other non-motor symptoms in patients with VP is still unknown.

Objective: The aim of our study was to assess the impact of OH on other non-motor symptoms in patients with VP with OH (OH+) and in patients with VP without OH (OH-).

Methods: The study included 11 patients with VP (OH+) and 11 patients without VP (OH-). All subjects underwent a complete clinical, neuropsychiatric and neuropsychological assessment. Clinical evaluation included full neurological examination, the Non-Motor Symptoms Scale (NMSS), to assess non-motor symptoms, and a standard Tilt-test protocol. Neuropsychiatric evaluation assessed: depression, anxiety, apathy, anhedonia and alexithymia. Neuropsychological battery included evaluation of: global index of cognitive impairment, short- and long-term verbal memory, long-term visual-spatial memory, immediate visual memory, language abilities, complex constructional praxis, attention and executive functions.

Results: The result of NMSS indicated that patients with VP (OH+) experienced more "excessive sweating" (Domain 9, item 30) than VP (OH-) (36,40% vs. 0,0%; p=0.027). No significant neuropsychiatric and neuropsychological differences were found between groups.

Conclusion: Our results suggest that patients with VP (OH+) have excessive sweating. If this relationship is causative or associative remains unclear. Possible explanations are that excessive sweating is driven by hypovolemia, one cause of OH, or that OH and excessive sweating are both consequences of autonomic nervous system dysfunction. We hypothesize that neuropsychiatric symptoms and neuropsychological deficits may not emerge in patients with VP (OH+) because compensatory mechanisms of cerebral vasoregulation and homeostatic autoregulation in VP may be already impaired.

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P32

Hyperglycemic-induced hemichorea-hemiballismus responsive to tetrabenazine: a case report

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Content: Hemichorea–hemiballismus is a continuous, involuntary, random movement involving proximal and/or distal muscles on one side of the body (rarely the face) [1]. It is usually associated with structural brain lesions, but can occur with metabolic abnormalities, in particular during nonketotic hyperglycemia [2]. The most cases of hyperglycemic-induced hemichorea–hemiballismus (HIHH) resolve in some days with return to euglycemic state, but in some cases it can persist [3,4]. Chronic cases have slight or incomplete response to various medical treatments (neuroleptic drugs, benzodiazepines, phenobarbital) [5]. We reported a 91 year-old woman with new-onset diabetes mellitus who presented with the sudden onset of marked right hemichorea–hemiballismus. We found characteristic brain imaging (in the contralateral basal ganglia a little hyperdensity on brain CT scan and increased signal intensity on T1W MRI). The symptoms did not respond to benzodiazepine, phenobarbital, haloperidol, the patient was unable to walk, feed and rest, she developed traumatic skin lesions and (as side effect) mouth tardive diskinesia. We discontinued neuroleptic drugs and inserted low doses of tetrabenazine (25 mg os three times a day). We observed a good drug tolerance and a good of symptom's improvement: the involuntary movements are markedly reduced and the patient can bring food to the mouth by herself, can write and can walk with modest assistance.

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P33

Beyond the CAG triplet number: exploring potential predictors of delayed age of onset in Huntington's disease

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Objective: Huntington's disease (HD) is a genetic neurodegenerative disease characterized by cognitive, motor and psychiatric dysfunction. It is caused by an expansion of the trinucleotide repeat sequence cytosine-adenine-guanine (CAG) in the Huntington gene on chromosome 4. Onset typically occurs in the fourth or fifth decade, ranging from childhood to late adulthood. The CAG triplet number is generally inversely proportional to the age of onset, but the repeat number only accounts for ~70% of the variability in age of onsetSeveral studies demonstrated the impact of genetic modifiers on the age of disease onset [1,2]. In addition to genetics, we also explored the demographic, anamnestic and socio-environmental factors that can affect the age of onset, to help us understand the non-genetic variability of the age of onset in HD.

Methods: We analyzed the retrospective data of the ENROLL-HD global registry study [3], particularly focusing on the continuum of ages, to include sociodemographic, genetic and anamnestic psychobehavioral variables in a multivariate regression model aimed at identifying the potential predictors of age of motor onset (n=5053). We ran the same regression model in the sample of subjects with the same number of triplets (41 CAG, n=593) and in the sample whose family history was absent/unknown (n=630).

Results: Patients with delayed onset more frequently have unknown/missing family history, are married or widowed, live in larger urbanized contexts and have a lower educational level. Individuals with earlier onset more frequently develop psychobehavioral symptoms.

Conclusions: The HD gene was considered the epitome of genetic determinism in the past. Our results are consistent with recent evidence that other factors might modulate its impact. These findings allow characterizing the determinants of the age of onset beyond the CAG expansions and provide valuable information for stratifying patients' for future clinical trial designs.

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P34

JAK2-mutated essential thrombocythemia-associated chorea: a case report

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Introduction: The variant $JAK2^{V617F}$ is the most common somatic mutation associated with myeloproliferative disorders, such as polycythemia vera, essential thrombocythemia and primary myelofibrosis. While chorea is a well-known neurological complication of polycythemia vera, to date, only two cases of chorea associated with $JAK2^{V617F}$-positive essential thrombocythemia have been described. In addition, its pathophysiology remains unclear.

Objective: To report a case of $JAK2^{V617F}$-positive essential thrombocythemia-related chorea.

Methods: A 61-year-old woman was admitted to our department with a three-months history of slowly progressive chorea involving oromandibular district, left upper limb and ipsilateral foot and toes. Five years before, the patient was diagnosed with $JAK2^{V617F}$-mutation essential thrombocytemia. She was treated with hydroxyurea 500mg OD. Of interest, this treatment was interrupted right before the neurological symptoms onset. At the admission, blood cell count showed platelet 816×10^3/mL, brain MRI showed chronic vascular infarction in the right caudate nucleus, with no evidence of acute lesions. Hydrossyurea was reintroduced increasing the dosage up to 1000mg OD, together with tetrabenazine, 12.5mg twice daily, with clinical improvement. At follow-up, nine months later, her neurological examination was substantially improved, and platelet count normalized.

Results: Autoantibodies panel including ENA, ANA, ANCA, anti-gliadin, anti-cardiolipin antibodies, anti-beta-2-glycoprotein and lupus anticoagulant resulted negative. EEG detected slow-wave activity of non-specific meaning. Brain MRI showed right caudate nucleus ischemic chronic lesion.

Conclusions: Current literature suggests that hyperviscosity and venous stasis may alter metabolic turnover of neurotransmitters in the basal ganglia, (i.e. dopamine and serotonin) thereby causing adaptive changes in local receptor expression. In our case, we hypothesize that withdrawal of hydroxyurea determined the increase in platelet count, blood viscosity and the consequent caudate infarction. However, the subacute presentation of chorea, its gradual progression, together with the impossibility to establish a temporal correlation with the ischemic lesion, rather suggest a re-arrangement at circuit level, causing the symptom onset.

P35

Action observation and motor imagery improve motor imagery abilities in patients with Parkinson's disease: a functional MRI study

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Introduction: Motor imagery (MI) is a recognized motor learning skill that could be impaired in patients with Parkinson's disease (PD).

Objective: To assess MI ability changes and brain functional reorganization after 6 weeks of action observation training (AOT) and MI associated with increasingly difficult gait/balance exercises in PD patients with postural instability and gait disorders (PD-PIGD) relative to gait/balance training alone.

Methods: Twenty-two PD-PIGD patients were randomized into 2 groups: the DUAL-TASK+AOT-MI group performed 6 weeks of gait/balance exercises including dual-tasks combined with AOT and MI; DUAL-TASK group performed the same exercises combined with watching landscape videos. MI was assessed using the Kinaesthetic and Visual Imagery Questionnaire (KVIQ). A group of 24 healthy controls was also included. All the subjects performed brain MRI including a MI fMRI-task: subjects were asked to watch first-person perspective videos representing challenge gait/balance tasks, identify themselves in the proposed environment and mentally simulate to move themselves in each condition.

Results: At baseline, during MI task, PD-PIGD showed reduced activity of pre/post-central gyri, temporal areas, motor and cognitive cerebellar areas and an increased activity of the parahippocampal gyri relative to controls. After training DUAL-TASK+AOT-MI group showed improvement in the KVIQ score together with increased activity of cerebellar lobule IX, anterior cingulate and fronto-temporal areas and a reduced recruitment of cerebellar lobule VI and crus I. The KVIQ improvements correlated with the increased activity of cerebellar lobule IX and anterior cingulate, and with the reduced activity of crus I.

Conclusions: PD-PIGD patients showed an altered recruitment of brain areas belonging to the mirror neuron system and related to sensorimotor functions. A motor-learning training including AOT and MI can improve MI abilities in PD-PIGD patients, promoting the functional plasticity of brain areas involved in MI processes and gait/balance control.

P36

The role of [123I]-FP-CIT in differential diagnosis between CANVAS and MSA-C: an useful tool in clinical practice?

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Introduction: CANVAS (Cerebellar Ataxia, Neuropathy, Vestibulare Areflexia Syndrome) is a rare adult-onset neurodegenerative disorder usually due to a pathogenic AAGGG expansion in the RFC1 gene (cr. 4). One-third of patients present with dysautonomia, which can lead to a Multisystem atrophy type C (MSA-C)-like phenotype [1].

Objective: We studied nine Italian late-onset ataxia patients, observed at the Neurological Unit of the Federico II University, harboring the homozygous AAGGG expansion in RFC1 to clarify whether [123I]-FP-CIT is a valuable tool to differentiate CANVAS and MSA-C patients.

Methods: Genomic DNA from peripheral blood leukocytes were tested by standard PCR with primers flanking the CANVAS locus. Clinical features were estimated using the Scale for the Assessment and Rating of Ataxia (SARA) and investigations included MRI, DATscan with I-123-Ioflupane, FDG-PET.

Results: Cerebellar atrophy was present in all but one patients and it was associated with pons atrophy in one. [123I]-FP-CIT was abnormal, with a mild to moderate decrease of tracer uptake, in three tested patients without parkinsonian features. There was no statistically relevant difference in [123I]-FP-CIT findings between CANVAS and MSA-C patients.

Conclusion: An abnormal [123I]-FP-CIT does not seem to contribute to differential diagnosis between CANVAS and MSA-C: genetic testing for CANVAS expansions is still a fundamental diagnostic tool in patients with late-onset ataxia.

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P37

Cortical thickness distinguishes idiopathic normal-pressure hydrocephalus from progressive supranuclear palsy: a machine learning approach

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Background: Progressive supranuclear palsy (PSP) and idiopathic normal pressure hydrocephalus (iNPH) share several clinical and radiological features, making the differential diagnosis challenging.

Objective: In this study, we aim to differentiate between these two diseases using a machine learning approach based on cortical thickness and volumetric data.

Methods: Twenty-three iNPH patients, 50 PSP patients and 55 control subjects were enrolled. All participants underwent a brain 3T-MRI, and cortical thickness and volumes were extracted using Freesurfer 6 on T1-weighted images and compared among groups. Finally, the performance of a machine learning approach with random forest using the extracted cortical features was investigated to differentiate between iNPH and PSP patients.

Results: iNPH patients showed cortical thinning and volume loss in the frontal lobe, temporal lobe and cingulate cortex, and thickening in the superior parietal gyrus in comparison with controls and PSP patients. PSP patients only showed mild thickness and volume reduction in the frontal lobe, compared to control subjects. Random Forest algorithm distinguished iNPH patients from controls with AUC of 0.96 and from PSP patients with AUC of 0.95, while a lower performance (AUC 0.76) was reached in distinguishing PSP from controls.

Conclusion: This study demonstrated a more severe and widespread cortical involvement in iNPH than in PSP, possibly due to the marked lateral ventricular enlargement which characterizes iNPH. A machine learning model using thickness and volumetric data led to accurate differentiation between iNPH and PSP patients, which may help clinicians in the differential diagnosis and in the selection of patients for shunt procedures.

P38

Neuroimaging and behavioral abnormalities in progressive supranuclear palsy

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Introduction: Progressive supranuclear palsy (PSP) is an atypical parkinsonism often complicated by neuropsychiatric symptoms, with a high prevalence of impulsivity and apathy [1,2]. Currently, little is known about possible correlations between these aspects and cerebral morphological measurements, specially when it comes to subcortical structures.

Objective: To explore the relationship between behavioral abnormalities and brain measurements in PSP patients.

Methods: PSP was diagnosed according to the Movement Disorder Society criteria [3]. 54 patients went through Neuropsychiatric Inventory Questionnaire (NPI) and 3-Tesla magnetic resonance imaging (MRI). Regions of interest were identified with the Desikan-Killiany cortical atlas [5]. Computed cerebral measurements were thickness, area and volume. Correlations between NPI and imaging output were calculated with Spearman's Rho. Post-hoc comparisons were run with Bonferroni test. The significance level was set at ≤ 0.05.

Results: A moderate correlation was found between severity of apathy and left pallidum volumes (rho (52) = -0,688892081; p = 0,002). Smaller pallidum volumes were associated with more severe apathy.

Conclusions: Our data showed a possible link between apathy and atrophy of subcortical structures in PSP patients. These results are further supported by prior studies concerning the role of globus pallidus in the regulation of motivation and reward [6]. In fact, it has already been proved that globus pallidus lesions may determine a severe apathy syndrome, either isolated or in the context of the so-called pallidal dementia [7].
Further studies are warranted to better explain the role of basal ganglia in behavioral manifestations of PSP.

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P39

Diagnostic and prognostic role of thalamic volume in progressive supranuclear palsy

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Introduction: Progressive supranuclear palsy (PSP) is an atypical parkinsonism, characterized by vertical supranuclear gaze palsy, postural instability with falls, akinesia, and cognitive dysfunction [1]. Different diagnostic MRI markers have been proposed [2,3]. Little is known about thalamic volume and its diagnostic and prognostic utility in PSP.

Objectives: to verify if 1) thalamic volumes and subsections are smaller in PSP patients compared to Parkinson's disease (PD) and healty controls (HC); 2) regional thalamic volumes can predict the evolution of disease according to specific milestones (loss of unaided gait, wheelchair dependance, dementia, unintelligible speech).

Methods: Thalamic volumes were calculated according to Johansen-Berg atlas [4]. ANCOVA was used to detect differences among thalamic volumes of PSP, PD and HC, adjusted for age and total brain volume. Cox regression analyses were used to measure the effect of thalamic volumes on disease milestones. The significance level for both analyses was set at $\leq 0,05$.

Results: Thirty-three PSP, 33 PD and 33 HC were enrolled. Data on disease milestones were available only for 18 PSP. Thalamic volumes were significantly smaller in PSP than in PD and HC ($F= 26, 978$, $p< 0,01$). On the other hand, thalamic volumes could not predict the evolution towards specific disease milestones ($p>0,05$).

Conclusions: Thalamic volumes may be useful to distinguish PSP from PD and HC. These data confirm previous studies [5,6] and further reinforce the potential utility of new MRI diagnostic markers. Survival analyses regarding disease milestones did not show any significance, but were limited by the small sample size. Therefore, further studies are waranted to better define the role of thalamus atrophy in PSP.

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P40

Tremor dominant vs non-tremor early Parkinson's disease: differences in dopamine transporter imaging

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Introduction: Dopamine active transporter with single-photon emission tomography (SPECT) is a reliable tool in the diagnose of Parkinson's disease (PD), whereas his association with clinical features and his role as a prognostic value of disease is still debated [1]. Considering clinical phenotypes of PD, a supposed correlation of striatal dopamine uptake with bradykinesia but not with tremor may indicate different pathophysiology for these extrapyramidal signs.

Objective: The aim of this study was to evaluate the relationship between the two main clinical motor phenotypes of PD and nigrostriatal degeneration investigated through 123I-FP-CIT SPECT.

Methods: We selected 35 patients (17/18 F/M, mean age 60±8,7) with a diagnosis of idiopathic PD (H&Y 1 or 2; disease duration less than 36 months). We excluded any subject with cognitive impairment or suspect of atypical Parkinsonism. Patients were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) motor score and H&Y staging and were then subtyped into 17 tremor-dominant (TD) and 18 non-tremor (NT) PD patients. Semi-quantitative SPECT analysis of ipsilateral and contralateral regions of putamen and caudate were taken into consideration. We used Student t test to compare the subgroups.

Results: Tremor dominant group and non-tremor patients were similar in matter of age, gender and clinical variables (UPDRS III, H&Y, disease duration). TD and NT groups presented a similar reduction of 123I-FP-CIT density in controlateral putamen; however, TD group showed lower reduction of radioligand in contralateral and ipsilateral caudate (p=0,018; p=0,003) and ipsilateral putamen (p=0,01) compared to NT patients.

Conclusions: Our results, showing patients with tremor having less severe dopaminergic defect compared to patients without tremor, consist with the hypothesis that tremor in PD is generated by mixed mechanism, besides nigrostriatal degeneration. The similar contralateral putamen degeneration observed in both groups, may be related to compensatory mechanism.

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P41

Iron deposition within thalamic subregions is related to cognitive dysfunctions in early drug-naïve Parkinson's disease patients with mild cognitive impairment

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Introduction: Iron deposition using Quantitative Susceptibility Mapping (QSM) has been reported in several cortical and subcortical areas within the dopaminergic pathways in patients with Parkinson's disease (PD), and a relationship with cognitive decline has been proposed. Mild cognitive impairment (MCI) is a common nonmotor symptom in PD and it is considered a risk factor for future development of dementia.

Objectives: In this study, we aimed at o exploring the QSM signature underling MCI in early drug-naïve PD patients, focusing on several subcortical areas, and particularly on the thalamic subregions.

Methods: 3T MRI images of 59 drug-naïve PD patients (20 PD-MCI and 39 PD-noMCI), were analyzed and compared. MDS Task Force Level II diagnostic criteria were applied to determine the presence of MCI. QSM values were extracted from several subcortical deep gray matter nuclei and 16 thalamic subregions. A partial correlation analyses were run between MRI metrics and clinical data. Finally, a ROC curve was performed to test the ability of QSM values in distinguishing PD-MCI from PD-noMCI.

Results: Compared PD-noMCI, PD-MCI patients showed higher susceptibility values in right subthalamic nucleus, in bilateral inferior pulvinar and in bilateral ventral posterolateral nuclei of thalamus Moreover, higher susceptibility values in the thalamus correlated with worse motor/cognitive severity and quality of life in patients. The ROC curve analysis showed that QSM values extracted from left inferior pulvinar and right ventral posterolateral nuclei of thalamus could significantly and accurately identify the presence of MCI in drug-naïve PD.

Conclusions: This study provides evidences of higher iron deposition within lateral and posterior regions of thalamic nuclei in drug-naïve PD patients with MCI patients compared to those without. We hypothesize that these findings may reflect the presence of more diffuse neuropathological changes occurring at the disease onset, potentially leading to altered cognitive processing and sensorial perception/integration in PD patients

P42

Altered functional connectivity of the subthalamic nucleus in Parkinson's disease: focus on candidates for deep brain stimulation

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Introduction: It is not yet clear why the therapeutic benefits of deep brain stimulation (DBS) still vary among Parkinson's disease (PD) patients. To date, the idea that effectiveness of DBS is related to connectivity dysfunction of the site of the stimulation with other brain regions is raising.

Objective: To investigate the resting-state functional connectivity (RS-FC) of the subthalamic nucleus (STN), the most frequently used DBS target for PD, in different PD phenotypes.

Methods: Clinical data and resting-state fMRI were acquired from 60 PD patients and 60 age- and sex-matched healthy control subjects within an ongoing longitudinal project. PD patients were divided into two groups: 19 patients eligible for DBS (PD-DBS) and 41 not candidate for DBS (PD-noDBS). Bilateral STN were selected as regions of interest and a seed-based connectivity analysis was assessed in PD groups and healthy controls.

Results: PD-DBS showed a reduced connectivity between bilateral STN and bilateral sensorimotor areas relative to both controls and PD-noDBS patients. On the contrary, PD-DBS patients showed an increased connectivity between bilateral STN and globus pallidus, putamen and thalamus bilaterally compared to healthy controls. Similar patterns were found when PD-noDBS patients were compared to controls (albeit with lower connectivity levels than PD-DBS patients). We hypothesize that candidates for DBS showed an increased connectivity between STN and globus pallidus/thalamus, which in turn may provide a decreased connectivity with sensorimotor areas relative to patients not eligible for DBS.

Conclusions: Our results suggest that functional connectivity of deep nuclei changes among PD phenotypes and confirm an important role of functional MRI as tool for selection of candidates for DBS. The idea that STN-DBS works by modulating and restoring functional connectivity between basal ganglia and sensorimotor areas is further corroborated.

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Brain functional connectivity changes induced by neurosurgical thalamotomy for tremor in PD

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Introduction: Neurosurgical thalamotomy has proved highly effective for treating medication-resistant tremor related to Parkinson's disease (PD) targeting the thalamic ventral intermediate nucleus (Vim) involved in the dentate-ponto-cerebello-thalamo-cortical pathway.

Objective: To test whether resting-state functional connectivity (rs-FC) between Vim and the rest of the brain was modulated by thalamotomy, and whether such changes correlated with individual clinical outcomes.

Methods: An observational clinical and resting-state magnetic resonance imaging (rs-fMRI) in a single subject with tremor-dominant PD who underwent Gamma knife (GKRS) Vim thalamotomy was carried out. The patient was assessed by clinical, wearable motion sensors and rs-fMRI evaluation before treatment and at 3, 6 and 12 months after surgery. Ten age- and sex-matched controls were also enrolled. Targeted left Vim was selected as region of interest and a seed-based rs-fMRI connectivity analysis was performed in PD patient and controls at baseline and over time. 1-year trend of progression of brain network changes was evaluated in PD patient and compared to controls. Correlations among functional measures and both clinical and motion sensors data were tested.

Results: A 76-year-old right-handed woman with a 13-year history of PD was deemed to be a candidate for GKRS left Vim thalamotomy for treatment of refractory tremor in the dominant hand. Seed-based analysis showed a significantly increased FC between left Vim and left visual areas relative to controls before treatment. Over 1 year, PD patient showed a progressive decreased FC between left Vim and visual cortex, mainly after 6 months from GKRS. At 12 months after treatment, a normalization of aberrant pre-therapeutic FC between left Vim and visual areas was obtained. These FC changes over the follow-up were positively related to progressive tremor improvement over time.

Conclusions: Our findings converged towards parts of the extrastriate visual system as being involved in tremor generation and further arrest after thalamotomy.

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Quantitative dopamine transporter imaging assessment in Parkinson's disease (PD) patients carrying GBA gene mutations compared with Idiopathic PD patients: a case-control study

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Background: Mutations in the glucocerebrosidase (GBA) gene are the single largest risk factor for development of Parkinson's Disease (PD) [1]. Compared to idiopathic PD (I-PD), GBA-PD is characterized by earlier onset, worse motor impairment, higher risk of cognitive decline and depression, more rapid progression, and decreased survival [2]. However, even if clinical differences have been found, data about possible differences of dopaminergic imaging studies is still lacking.

Objectives: To compare single photon emission computed tomography (SPECT) with Ioflupane I123 injection quantitative parameters from two homogenous cohorts of GBA-PD and I-PD patients and to correlate them with clinical variables.

Methods: This case-control study included two homogenous cohorts of GBA-PD and I-PD patients. All patients have been previously screened for the presence of pathogenic LRKK2, GBA, SNCA and PARKIN genes mutations. Each GBA-PD patient has been matched with a 1:1 pairing method with an I-PD subject according to sex, age, age at disease onset, and comorbidities. For each patient the following clinical variables have been collected: Charlson Comorbidity Index (CCI), Levodopa Equivalent Daily Dose (LEDD), motor phenotype (Postural Instability and Gait Disorders [PIGD] or tremor phenotype), Hoehn and Yahr (H&Y) staging, most affected side, disease duration. All patients previously underwent single photon emission computed tomography (SPECT) with Ioflupane I123 injection at the time of PD diagnosis. Quantitative volumetric data were extrapolated from [123I]-FP-CIT using the DatQuant software. The following quantitative measures were calculated: bilateral specific binding ratio (SBR) for Striatum, Caudate, Putamen (anterior, posterior, and global); putamen and caudate asymmetries; putamen/caudate ratios and SBR in the most affected and least affected putamen and caudate nuclei. Mann Whitney test was performed to compare the two groups while Spearman rank correlation test was performed in each group to find correlations between clinical and DatQuant variables. Significant p-value has been considered at 0.05.

Results: 50 PD patients were included in the analysis (30 males, mean age: 65.18 years; mean disease duration: 6.92 years; mean H&Y: 2.33; mean LEDD: 688.06 mg; mean CCI: 2.78) including 25 GBA-PD that were matched with 25 I-PD. The two cohorts (GBA PD and I-PD) were superimposable in terms of sex, age at disease onset, disease duration, CCI, motor phenotype, H&Y stage and side of

disease onset. In terms of comparison between the two groups, we have identified a significant statistical difference in terms of SBR of the most affected anterior putamen (P=0.028) and SBR of the left caudate (P=0.043). Regarding the GBA-PD cohort, we found a negative correlation between the SBR of the most affected posterior putamen and H&Y stage (C=-0.568, P=0.003) meaning that patients whit a lower uptake in this region at diagnosis showed a higher disease severity after a mean six-year follow-up. Concerning the I-PD cohort we found a negative correlation between the SBR of the most affected caudate and LEDD (C=-0.460, P=0.021) meaning that patients whit a lower uptake in this region at diagnosis showed a higher total dosage of dopaminergic medications after a mean six-year follow-up.

Conclusions: This comparison analysis has underlined subtle significant differences in quantitative DaTquant parameters between two homogeneous cohort of GBA-PD and I-PD at PD diagnosis suggesting that the nigrostriatal system denervation may differ in GBA-PD especially in the anterior putamen. Furthermore, in the GBA-PD cohort the SBR of the posterior putamen at time of diagnosis has been confirmed as a potential indicator for evaluating the severity of the disease [3].

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P45

Supplementary motor area functional connectivity in drug-naïve Parkinson's disease patients with fatigue

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Introduction: Fatigue is a common and disabling nonmotor manifestation in patients with Parkinson's disease (PD), and the supplementary motor area (SMA) has been implicated in its pathophysiology. SMA is usually divided in its rostro-caudal axis, with the rostral (pre-) SMA playing a major role in motor planning, and the caudal (proper) SMA related to movement execution.

Aims: To investigate brain functional connectivity (FC) of SMA subregions in early, drug-naïve PD patients and its correlation with fatigue.

Methods: Seventeen PD patients affected by fatigue, 18 without fatigue, and 16 matched healthy controls were recruited. Parkinson Fatigue Scale (PFS) was used for fatigue screening (cut-off > 3.3 points) and severity rating. Seed-based resting-state functional MRI was used to compare the FC from bilateral SMA subregions to the whole brain. Voxel-based morphometry analysis was also employed to test whether FC results were related to brain structural differences. Linear correlations were run between imaging and behavioural data.

Results: PD-related fatigue was associated with an increased FC between the left pre-SMA and the left postcentral gyrus as well as a decreased FC between the left SMA proper and the left middle frontal gyrus ($ps < 0.01$). These patterns of FC were tightly correlated with PFS scores (Pearson's $rs < 0.01$). No structural brain changes were observed.

Conclusions: In early PD, altered FC of both SMA subregions might play a crucial role in fatigue pathophysiology. The altered FC of the pre-SMA might underlie a poor attenuation of sensory signals from the somatosensory systems to higher order motor system, whereas the altered FC of the SMA proper might be associated to poor explicit contingency awareness causing an overgeneralization of perceived physical effort load. These results offer new insights into the mechanisms responsible for fatigue in PD and possible targets for neuromodulation strategies oriented to modulate the SMA activity.

P46

Neuroimaging correlates of tremor and bradykinesia in patients with essential tremor

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Introduction: Essential tremor (ET) is a neurological condition characterized by postural and kinetic tremor of the upper limbs. Moreover, it has been recently pointed out that bradykinesia may be a relatively common motor feature in ET. Despite the well-known role of the cerebellum in ET pathophysiology, the possible involvement of other brain areas remains unclear.

Aims: To investigate structural damage and resting-state functional alteration of the cerebral cortex, basal ganglia, and the cerebellum in ET. Moreover, we aimed to assess possible correlations between magnetic resonance imaging (MRI) findings and bradykinesia.

Methods: Twenty patients with ET and 17 healthy subjects (HS) underwent multimodal 3T-MRI, including 3D-T1 and blood oxygen-level dependent (BOLD) sequences at rest. MRI structural analysis was performed on 3D-T1 images. A seed-based analysis was performed to study resting-state functional connectivity (rsFC) of the dentate nucleus and globus pallidus. Postural and kinetic tremor and bradykinesia during repetitive finger tapping were kinematically recorded via an optoelectronic system. We then analysed: tremor amplitude (GRMS^2) and frequency (Hz) and various movement parameters, e.g., movement velocity and amplitude and sequence effect. Finally, we assessed possible correlations between neuroimaging, clinical scores and kinematic parameters.

Results: Compared to HS, ET patients showed a higher dentate FC with cerebellum, and a lower FC with precentral and frontal areas. Furthermore, ET patients showed a higher pallidal FC with cerebellum and sensorimotor areas, and a lower FC with crus II and superior frontal gyrus. Confirming previous findings, ET patients showed lower movement velocity of finger tapping, compared to HS. Pallidal and dentate rsFC negatively correlated with tremor severity, however, they both positively correlated with movement velocity during finger tapping.

Conclusion: We here provided novel pathophysiological information in ET. The data suggest a role of both basal ganglia and cerebellar nuclei in generating either postural tremor or bradykinesia in ET.

P47

Asymmetry of bradykinesia features in Parkinson's and interhemispheric inhibition imbalance

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Introduction: Bradykinesia and other motor symptoms in Parkinson's disease (PD) are predominantly asymmetric [1,3]. An asymmetrical reorganization and an altered connectivity between the two primary motor cortices (M1) have previously been demonstrated in PD [1,2,3,4]. Whether the asymmetry of motor manifestations relates to the imbalance of the inhibitory interhemispheric connections, however, is still unknown.

Aims: To investigate the relationship between the asymmetry of bradykinesia, quantified by kinematic analysis of finger tapping, and the asymmetry of the interhemispheric inhibitory connections in PD, tested by transcranial magnetic stimulation (TMS).

Methods: Twelve PD patients (1 female, 69.75±9.9 years) and 10 age- and gender-matched healthy controls (HCs) were enrolled. Objective bradykinesia measurements during finger tapping were obtained using a motion analysis system from both sides. Paired-pulse TMS was used to measure the interhemispheric inhibition (IHI) between the hand areas of the two M1, with an interstimulus interval (ISI) between the conditioning (CS) and the test stimulus (TS) of 10 ms (short-latency IHI, sIHI) and 40 ms (long-latency IHI, lIHI)[1][2][4]. Asymmetry indices (AI) were calculated for all neurophysiological data. We then tested possible relationship between kinematic and TMS data in patients.

Results: PD patient were slower than in HCs during finger tapping ($p=0.01$). In PD there was a more severe progressive reduction of movement amplitude during movement repetition, i.e., sequence effect ($p=0.04$). When testing IHI (from the most affected to the less affected hemisphere), we found a reduced sIHI in patients. The amount interhemispheric disinhibition, i.e., interhemispheric imbalance quantified by the sIHI-AI, correlated with the sequence effect of the less affected side ($p<0.001$).

Conclusions: we here provided novel evidence on the role of interhemispheric disinhibition in the pathophysiology of bradykinesia asymmetry in PD. The results support the hypothesis that the sequence effect has pathophysiology mechanisms distinct from those underlying other bradykinesia features.

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P48

Neurophysiological changes of primary motor cortex in patients with Essential Tremor-Plus

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Introduction: Essential tremor-plus (ET-plus) represents a recently introduced entity indicating ET patients with additional neurological signs of uncertain significance, including rest tremor, bradykinesia and mild cognitive impairment (MCI). The concept of ET-plus, however, is still controversial and only few studies investigated the neurophysiological mechanisms underlying this condition.

Aims: To investigate possible neurophysiological changes of the primary motor cortex (M1) and their relationship with soft signs in patients with ET-plus.

Methods: Thirteen ET-plus patients were enrolled (5 females, 70±7.97 years). Most patients had rest tremor, subtle bradykinesia, MCI and only 3 of them had impaired tandem gait. Patients were evaluated by standardized clinical scales. Objective measurements of rest tremor and bradykinesia (during finger tapping) were obtained by kinematic analysis. M1 excitability was assessed by the recordings of resting motor thresholds (RMTs), input/output curve of the motor-evoked potentials (MEPs) and using a conditioning-test paradigm for the assessment of short-interval intracortical inhibition (SICI) and short-latency afferent inhibition (SAI). Plasticity-like mechanisms were indexed according to MEPs amplitude changes after intermittent theta-burst stimulation (iTBS). Data were compared to those from 16 healthy controls (HCs). Correlations between clinical, kinematic, and neurophysiological data were assessed in patients.

Results: Compared to HCs, ET-plus patients had higher RMTs (P=0.019), indicating a lower corticospinal excitability and a lower MEPs facilitation after iTBS (P=0.032), reflecting a lower cortical plasticity. ET patients were slower than HCs during finger tapping (P=0.03). No correlations, however, was found between neurophysiological, clinic and kinematic. In particular, there was no significant relationships between neurophysiological changes of M1 and the type or severity of soft signs in patients.

Conclusion: We here provided novel information on excitability and plasticity abnormalities of M1 in patients with ET-plus. The lack of correlation between clinical and neurophysiological data suggests that various ET-plus forms do not represent entities with a specific pathophysiological background.

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Non-invasive vagus stimulation mudulates beta band activity in a patient with Parkinson's disease

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Content: Vagus nerve stimulation (VNS) is approved for epilepsy and depression and is currently under investigation in Parkinson's disease (PD) with promising results [1,2]. The mechanism of action of VNS is poorly understood, and its clinical application has been hastened by the surgical invasiveness of the technique. Non-Invasive VNS (niVNS) has similar neurophysiological putative properties, entraining ascending system such as the cholinergic, the serotoninergic and the noradrenergic ones. Herein, we present a proof-of-concept study on the neuromodulation properties of the VNS verified on a patient with advanced PD and on subthalamic nucleus (STN) local field potentials (LFPs) recorded during awake deep brain stimulation (DBS). The niVNS was delivered through the GammaCORE (left cervical niVNS, 4 cycles of 100" at 25Hz with 60" of interstimulus time). The STN LFPs were recorded and reconfigured offline on 6 bipolar montages (L01, L12, L23 and R01, R12, R23). The recording was then segmented as: reference period, inter-stimulation period, post-stimulation period (30" after the stimulation). The post-stimulation period was further segmented in 10" chunks. It was possible to record a low-beta band modulation with a reduction of 5-10% from the baseline. This was achieved progressively and lasted up to 50 seconds after the stimulation. This is the first experiment, showing a neurophysiological effect of VNS on the STN activity of a patient with PD. The STN activity modification induced by the VNS is significantly lower to that documented after dopaminergic agents or DBS but the VNS [3] (which acute stimulation seems active on gait symptoms more than on bradykinesia and rigidity) may act indirectly, on pathways that run in parallel to the nigrostriatal one or on higher structures such as the cortex. Despite the single case, uncontrolled nature of this experiment we think that further studies are warranted.

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P50

Hyper-acute changes on γ frequency functional connectivity induced by STN-DBS in a patient with advanced Parkinson's disease

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Introduction: Subthalamic nucleus deep brain stimulation (STN-DBS) is a successful and widespread surgical treatment in patients with advanced Parkinson's disease (PD) [1]. STN-DBS, in addition to rapid improvement of PD motor symptoms, can exert fast local neuromodulator activity [2]. However, short-term effects of STN-DBS on cortical functional connectivity have been scarcely explored.

Objective: In this case study, we analysed the hyper-acute changes induced on EEG cortical functional connectivity by STN-DBS in a patient with advanced PD.

Methods: We describe a 68-year-old man with diagnosis of PD in 2008, whose onset symptoms were bradykinesia in the right upper-limb. Due to worsening of PD motor complications, patient underwent bilateral STN-DBS in October 2021. We recorded 64-channels EEG data in DBS-OFF and DBS-ON during resting state. Electrophysiological assessment was performed in February 2022. Power spectral density was computed in four frequency bands (θ-α-β-γ). Source reconstruction method was used to identify brain regions activity. Functional connectivity was calculated using imaginary part of coherency in four frequency bands (θ-α-β-γ). Power spectral density and functional connectivity were compared between DBS-OFF and DBS-ON states. Analysis were made using custom-written MATLAB script and Brainstorm toolbox [3].

Results: In DBS-OFF state, power spectral density revealed greater γ-frequency activity in left channels than in right ones. Consistently, functional connectivity showed greater values in γ-frequency over the left, more affected, hemisphere compared to the contralateral. After activating STN-DBS, we recorded a hyper-acute reduction in both power spectral density and functional connectivity in γ-frequency in left hemisphere, up to similar values to the right hemisphere. No differences were observed in θ-α-β frequencies.

Conclusion: We reported a case of hyper-acute effect of STN-DBS in modulating γ-frequency functional connectivity in a patient with advanced PD. Further studies are required to confirm this observation and investigate the potential role of γ cortical connectivity reduction in adaptive DBS.

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P51

Efficacy and safety of transcranial direct current stimulation in progressive supranuclear palsy

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Introduction: Progressive Supranuclear Palsy (PSP) comprises a wide range of cognitive, behavioural and emotional deficits [1]. Since cognitive, behavioural and emotional impairment significantly contribute to worse health-related quality of life (HRQoL) and there are no efficacious treatment options, there is the need for alternative approaches. This is a randomized double blind trial testing the efficacy and safety of transcranial direct current stimulation (tDCS) in improving cognitive function PSP.

Methods: Twenty-five PSP patients were randomly assigned to two experimental conditions: anodic stimulation and sham. Anodic group received ten tDCS sessions (2 mA) on the left dorsolateral prefrontal cortex (LDLPFC) for 20 minutes for 10 consecutive days. They underwent a comprehensive motor, cognitive and behavioural assessment immediately before tDCS, after 10 days, after 45 days and after 3 months. Repeated measures ANOVA was used to analyze data.

Results: We failed to demonstrate a specific improvement of cognitive and motor functions. However, we observed a significant improvement of behavioural disturbances in the anodic group. Particularly, depression/dysphoria frequency scores of the Neuropsychiaric Inventory Questionnaire (NPI) improved in the anodic group ($p<0.05$) after 10 days of stimulation.

Discussion: Anodal LDLPFC tDCS improves depression/dysphoria frequency in PSP patients. This result confirms studies investigating the effects of tDCS on depression [2]. tDCS might represent a promising future therapeutic and rehabilitative approach in patients with PSP [3].

Conclusion: The lack of biomarkers, the difficulties of an early clinical diagnosis and the incomplete understanding of the exact pathophysiology of PSP make it difficult to define an adequate symptomatic treatment. Pharmacological therapy is largely ineffective and tDCS represents a promising treatment for PSP.

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P52

Neurophysiological assessment of juvenile parkinsonism due to primary monoamine neurotransmitter disorders

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Background: No studies have investigated voluntary movement abnormalities and their neurophysiological correlates in patients with parkinsonism due to inherited primary monoamine neurotransmitter (NT) disorders.

Methods: Nine NT disorders patients and 16 healthy controls (HCs) were enrolled. Objective measurements of repetitive finger tapping were obtained using a motion analysis system. Primary motor cortex (M1) excitability was assessed by recording the input/output (I/O) curve of motor-evoked potentials (MEPs) and using a conditioning test paradigm for short-interval intracortical inhibition (SICI) assessment. M1 plasticity-like mechanisms were indexed according to MEPs amplitude changes after the paired associative stimulation protocol. Patient values were considered abnormal if they were greater than two standard deviations from the average HCs value.

Results: Patients with aromatic amino acid decarboxylase, tyrosine hydroxylase, and 6-pyruvoyl-tetrahydropterin synthase defects showed markedly reduced velocity (5/5 patients), reduced movement amplitude, and irregular rhythm (4/5 patients). Conversely, only 1 out of 3 patients with autosomal-dominant GTPCH deficiency showed abnormal movement parameters. Interestingly, none of the patients had a progressive reduction in movement amplitude or velocity during the tapping sequence (no sequence effect). Reduced SICI was the most prominent neurophysiological abnormality in patients (5/9 patients). Finally, the I/O curve slope correlated with movement velocity and rhythm in patients.

Conclusions: We provided an objective assessment of finger tapping abnormalities in monoamine NT disorders. We also demonstrated M1 excitability changes possibly related to alterations in motor execution. Our results may contribute to a better understanding of the pathophysiology of juvenile parkinsonism due to dopamine deficiency.

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The velocity-dependent feature of rigidity in Parkinson's disease: evidence from a robot-assisted Study

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Introduction: Several authors have considered the long-latency reflexes (LLRs) as the main pathophysiological hallmark of rigidity in Parkinson's disease (PD)[1,2]. Recently, specific biomechanical components, including the neural component (NC), have been identified to contribute to the rigidity in [PD3,4]. None has previously combined the biomechanical with the neurophysiologic recordings of muscle tone. Finally, none has explored the relationship between rigidity and angular velocity of muscle stretches in PD.

Objective: The aim of this study is to measure simultaneous changes in specific biomechanical and neurophysiologic components of rigidity in PD, during robot-assisted wrist extensions, at various angular velocities.

Methods: In this study, we recruited 16 PD patients and 25 age- and sex-matched healthy subjects (HS). Participants underwent an experimental paradigm based on the assessment of spinal (i.e., short latency reflex–SLR) and supraspinal reflexes (i.e., LLRs) as well as the three components of muscle tone (i.e., NC, viscous component - VC and elastic component - EC). We use a servomotor able to induce wrist-stretches at different velocities (i.e., 50, 100, 150, 200, 236 and finally 280°/sec). Simultaneously, we recorded the EMG activity of the stretched muscles. All PD patients were evaluated in OFF therapy with L-Dopa.

Results: We found that the amplitude and the AUC of LLRs was significantly higher in PD patients than HS, for each velocity we considered. The NC was significantly higher in PD patients than HS from 200°/sec. Also, the higher the velocity, the higher the amplitude and the AUC of LLRs and the NC in PD patients. We found that all the features analyzed for the SLRs, the latency and the duration of the LLRs, the VC and the EC was comparable between HS and PD patients at all the angular velocities.

Discussion: For the first time, we demonstrated the velocity-dependent feature of the objective rigidity in PD, as shown by higher values of both NC and LLRs. We also found a positive correlation between LLRs and NC, suggesting that the overall objective rigidity in PD would share at least some neural loops underlying the LLRs.

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P54

Beyond the beta rhythm: levodopa-dependent power law exponent changes of subthalamic local field potential recordings in patients with Parkinson's disease

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Introduction: So far, the study of local field potential (LFPs) in Parkinson's disease (PD) has been provided by the linear approach, focused on the brain oscillatory rhythms evaluated as changes in power spectra within specific frequency bands. Measurements of oscillatory activity have been largely used as expression of clinical information, i.e. the exaggerated power in the beta frequency band associated to rigidity and bradykinesia [1]. However, many studies already pointed out how the background activity, expressed as aperiodic and non-oscillatory activity and typically disregarded, actually constitutes a significant part of LFP recordings, since it appears nevertheless modulated in a physiologically-relevant manner. One of the indices that better describes this aperiodic behavior is the power law exponent (PLE) already demonstrated to change with aging and recently supposed to reflect the balance between inhibition and excitation in neuronal populations.

Objective: Assessment of levodopa-dependent PLE changes of subthalamic LFP in PD patients.

Methods: We recorded LFP from the subthalamic nucleus of 22 patients before and after treatment with levodopa, and calculated the PLE (β-exponent). The parameter is defined as the slope of the regression line computed on the spectra in log-log scale. To ensure the non-influence of the periodic oscillatory components, the regression line has been identified following a peak removal operation [3].

Results: The analysis showed significant differences in the β-exponent between pre- and post-levodopa administration ($p_{value}<0.05$ estimated through the nonparametric Mann-Whitney test). Specifically, β-exponents were lower before levodopa in the low frequency bands (<30 Hz).

Discussion: Our findings are consistent with the hypothesis in literature that inversely relates the β-exponent with the excitation/inhibition ratio [4]. Higher β-exponents (steeper PSD-slopes) after levodopa suggest a reduction of the excitation exerted over the neural population generating the LFP, which agrees with the role of dopamine in inhibiting the indirect pathway postulated by the classical pathophysiological model.

Conclusion: In the linear approach, the effects induced by levodopa have usually been linked to the attenuation of the hallmark peak for PD in beta frequency band on PSD [1]. Here, through the nonlinear approach, we went beyond these periodic features. Indeed, the presence/absence of any oscillatory peak has no effect on the computation of the measure. Therefore, we conclude that the β-exponent reflects the intrinsic properties of the complex neurological system, such as the balance inhibition/excitation, and could be proposed as novel non-oscillatory marker to assess clinical status in PD patients at different stages of the disease.

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P55

Impulsivity markers in single neurons activity in ventral subthalamic neurons of parkinsonian patients

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Introduction: Parkinson's disease (PD) is a neurodegenerative disease associated with motor dysfunctions, but a large part of PD patients following dopaminergic therapy suffers from impulsive-compulsive behaviours (ICB).

Aims: Tryng to better understand neural dysfunctions underlying mpulsive-compulsive behaviours in patients affected by PD.

Methods: We previously identified ICB markers at the single neuron level in STN [1] and we localized them in the ventral area of the nucleus [2]. We extracted single unit activity from microelectrode recordings (MER) performed at rest and in med off condition during deep brainstimulation (DBS) implant surgery. Recordings were performed in 12 PD patients without ICB (ICB-, 330 neurons) and 12 PD patients with ICB (ICB+, 412 neurons).

Results: Single unit features discriminating between ICB+ and ICB- were: i) firing regularity, ii) intra-burst firing rate and the iii) beta and iv) gamma power of background unit activity. Performance of SVM decoding of ICB based on these features was up to 80% (20/24 subjects). Crucially, when decoding was based only on the regularity of ventral neurons the performance reached 90% (22/24 subjects).

Conclusions: We conclude that ICB in PD patients in med off state are associated with decreased irregularity in ventral STN neurons and that an online MER decoder could be able to identify optimal DBS spot to treat ICB. Furthermore, our results are compatible with the hypothesis that patients developing ICB after dopaminergic treatment have a more preserved baseline in ventral areas. For these patients DBS might be a preferred option from earlier stages of PD.

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P56

Combining Non-Invasive Brain Stimulation (NIBS) with speech therapy for the treatment of neurogenic dysphagia: neurophysiological outcome in Parkinson's disease (PD)

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Introduction: Neurogenic dysphagia (ND) is a swallowing impairment which can cause upper airway obstruction, malnutrition, aspiration pneumonia and, ultimately, increased mortality [2], common in Parkinson's disease (PD) [1]. Lately, therapeutic approaches have targeted sensory-motor integration processes and neuroplasticity as promising strategy for recovery [3], and transcranial direct current stimulation (tDCS) has been proposed as adjunctive treatment [4].

Objectives: To evaluate the neurophysiological effect of speech therapy plus tDCS in patients with ND in PD or atypical parkinsonism, as measured by changes in motor evoked potentials (MEPs) recorded from the transverse muscle of tongue.

Methods: Six dysphagic patients (mean age: 68.5 ± 8.36 years, 4 women) with PD and multiple system atrophy underwent anodal tDCS (anode over the vertex, reference over the right deltoid - 2 mA for 20 min) plus speech therapy (45min after tDCS, once a day, 5 days, 2 consecutive weeks), and speech therapy alone (once a day, 5 days, 4 consecutive weeks). We stimulated motor cortex to record MEPS from the transverse muscle of tongue before (T0) and after combined treatment (T1), after speech therapy alone (T2) and 6 weeks after speech therapy alone (T3) the intervention. MEPs amplitude (mV) and Total Motor Conduction Time (TMCT - ms) were considered as outcomes. The Bayesian statistic approach, which provides the level of the evidence for the effect of the treatment, was used.

Results: The model comparison via repeated-measures ANOVA revealed weak evidence for the treatment in amplitude and TMCT changes between each timepoints (always $BF_{10} > 0.33$). However, we found a tendency to increase the values of amplitude (mV, median ± IQR– T0: 2.7 ± 1.67; T1: 3.7 ± 0) and TMCT (ms, median ± IQR – T0: 7.24 ± 0.24; T1: 8.7 ± 0).

Conclusions: Our findings suggest the promising insight that combining tDCS and speech therapy could modulate lingual MEPs.

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Compassionate Mind Training for people with Parkinson's: a pilot study

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Introduction: People with Parkinson's disease (PD) can experience deficit of emotion recognition and expression that heavily affects their quality of life and the relationships with other people and their significant ones. Compassion Focused Therapy is considered to be a valid psychological approach which helps balancing and regulating the extent and expression of emotions, increasing awareness of the state of mind and ultimately building a more compassionate way of thinking about oneself and others.

Objective: This pilot study aimed to test the feasibility and effectiveness of the Compassionate Mind Training for PD patients program, an 6-week online workshop designed to train people to be more self-compassionate.

Methods: PD patients meeting the inclusion criteria were included in the study. Before the training they filled in self-administered questionnaires evaluating symptoms of anxiety, depression and quality of life. Before and at the end of the training they were administered the Self Compassion Scale and a questionnaire assessing their perception of change and their satisfaction. Patients underwent an 6-week online Compassionate Mind Training with the therapist, once a week.

Results: Twenty-four PD attended (11 male and 13 female, mean age 57.6 ±8.1, mean disease duration 8.9 ±3.36. We found significant pre/post gains in 3 subscales of the self-compassion scale: Over-identification (p= -0.197 ±0.87), Self-kindness (p= -0.20 ±0.83) and Mindfulness (p= -0.0416 ±0.81). 84% of participants perceived a significant change of energy disposal through their emotional systems; 88% considered the training useful and would continue practicing.

Conclusion: Compassion Focus therapy is feasible in people with PD, it appears to be effective at enhancing self-compassion and mindfulness.

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Mobile health technology identifies gait impairment in newly diagnosed Parkinson's disease

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Introduction: Gait alterations are heterogeneous in the early phases of Parkinson's disease thus limiting their diagnostic relevance when evaluated clinically. Mobile health technologies enable the objective evaluation of gait pattern alterations and might increase the sensitivity for these symptoms compared to standard neurological examination.

Aim of the study: Aim of the study was to evaluate patterns of gait in supervised conditions in newly diagnosed Parkinson's disease with and without clinically relevant gait alterations.

Methods: The prospective study included consecutive early PD patients with and without dopaminergic treatment, subdivided into PDs with (PD-G) and without (PD-nG) clinically evident gait alterations, respectively, and age-matched controls. Each subject underwent gait analyses in supervised normal and dual-task conditions using mobile health technology. The study evaluated gait parameters differentiating HC from both PD-G and PD-nG.

Results: Seventy-one early PD patients (including 45 drug-naïve), including 37 Normal Gait PDs and 34 Impaired Gait PDs, and forty-four age-matched controls entered the study. PD-G and PD-nG patients showed shortened mean step lengths in comparison to HCs both in single gait and dual task tests. Step time under supervised conditions had a longer duration in both simple gaits and while performing checking boxes in PD-G, while step time duration in PD-nG was longer only in dual task tests in comparison to controls. Double limb support showed longer duration only in dual task tests in both PD-G and PD-nG in comparison to HCs. The two early PD subgroup were similar in clinical and gait characteristics except for the mean value of MDS-UPDRS-III.

Conclusion: Mobile health technologies are able to identify altered gait parameters even in early PDs without clinically relevant gait alterations. Larger ongoing longitudinal studies are needed in order to evaluate gait alterations within the prodromal phases of the disease and the impact of dopaminergic medication on gait performance over-time.

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Virtual reality for rehabilitation in Parkinson's disease and atypical parkinsonisms

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Objective: To determine the potential long-term effect of Virtual Reality (VR) in improving motor and cognitive impairment in Parkinson's disease (PD) and Atypical Parkinsonisms (AP).

Design: Retrospective cohort study with 2-years follow-up.

Setting: Rehabilitation hospital.

Participants: Inpatients with extrapyramidal disorders (N=12).

Interventions: Neurorehabilitation treatment with the use of VR treadmill, 30 minutes a day, five days a week, for four weeks every year from 2019 to 2021.

Main outcome measures: UPDRS III score at entry and discharge and MMSE score.

Results: 3/12 patients were diagnosed with PD and 9/12 patients were diagnosed with AP. The UPDRS III score was 43.3 ± 5.8 at entry in 2019 vs 35 ± 4.4 at discharge in 2021 in PD (p-value 0.01, SMD 1.63); 45.6 ± 9.0 at entry in 2019 vs 34.4 ± 7.2 at discharge in 2021 in AP (p-value 0.00002, SMD 1.36). The MMSE score was 23.5 ± 2.5 in 2019 vs 23.7 ± 2.4 in 2021 in PD (p-value 0.53, SMD 0.07); 19.7 ± 3.9 in 2019 and 18.9 ± 3.9 in 2021 in AP (p-value 0.02, SMD 0.22).

Conclusions: Current literature has demonstrated the effectiveness of VR in the neurorehabilitation of motor and cognitive disorders in PD patients, but only in the short-term. Analysis of our data showed short-term and long-term benefits to the motor performance for both PD and AP patients. Despite the limited sample size, the promising results obtained encourage a continuation of the research by including other functional outcome measures, especially when considering the lack of studies on the benefits of rehabilitation in Atypical Parkinsonisms.

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The 2MWT is as informative as the 6MWT for assessing gait in Parkinson's disease

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Introduction: Parkinson's disease (PD) is one of the commonest neurodegenerative diseases in human and it is progressively debilitating [1]. According to epidemiological projections, in the next two decades there will be twice as many cases [2] and therefore it is urgent to find simple, reliable, and inexpensive methods to monitor these patients.

Objective: This study aims to investigate the validity of the 2-minute walk test (2MWT) for motor assessment of patients with PD, as an alternative to the 6-minute walk test (6MWT).

Methods: Patients (n = 62) affected by PD in their middle phase (H&Y 2-3) were studied as part of an observational study considering motor evolution of the disease during time (Clinical Trial.gov Identifier: NCT04297800). Among different assessments, patients performed the 6MWT while wearing an inertial sensor (G-walk ®) around their waist; data for 2MWT were pulled out from the records of this device.

Results: Initial data on baseline assessment of 43(69.3%) patients were considered. The mean walking distance for the 2MWT was 111.6 meters (range 67.20-146.2) and for the 6MWT 327.5 meters (range 80.60-438.6). The distance walked in the 2MWT was highly correlated to the distance walked in the 6MWT ($r = 0.89$, $p < 0.001$). There was no significant difference in walking mean speed between 2MWT and 6 MWT (1.37 VS 1.37 m/s, p=0.734).

Conclusions: Beyond the absolute values reflecting the algorithm underlying the accelometric data processing software, these results are consistent across patients and should be considered for reproducibility. Despite the limited number of analysis respect the overall sample, the 2MWT appear to be a workable alternative to the 6MWT for describing gait motor characteristics in patients with PD and would save considerable time for clinical evaluation (248 minutes only for the assessments considered in this study at baseline).

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A wearable biofeedback device to improve gait pattern in people with Parkinson's disease: a proof of concept study

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Background: The gait of people with PD is characterized by several disturbances, partially amendable by clinical rehabilitation approaches (1). Wearable biofeedback devices can be used in neurorehabilitation as valuable instruments to improve the effects of interventions (1).The purpose of this study was to verify the effectiveness, usability, and safety of a wearable biofeedback device in improving the gait patterns of people with Parkinson's Disease (2). The device extracts gait features in real-time and delivers a vibrotactile stimulus at the user's waist synchronously with specific gait phases.

Methods: Experimental procedures included a pre-training (pre-trn) and the post-training (post-trn) assessments and three training sessions to familiarize with the device. During the pre-trn and the post-trn assessments, a 10-meter walking test (10mWT) within a gait analysis laboratory and a two-minute walk test (2MWT) have been performed. Gait trials were executed with (bf) and without (no-bf) the biofeedback and gait performances were compared at various time points to evaluate the total effect (ΔTT; post-trn_Bf - pre-trn_no-Bf), training effect (ΔTE; post-trn_no-Bf - pre-trn_no-Bf), immediate effect before the training (ΔIE; pre-trn_Bf - pre-trn_no-Bf) and after the training (ΔIE; post-trn_Bf - post-trn_no-Bf). The vertical ground reaction force (vGRF), feet's kinematic and spatio-temporal gait parameters were analyzed.

Results: Preliminary results of one subject (Age=72 years; H&Y=3) showed improvements in gait speed (ΔTT=0.32 m/sec; ΔTE=0.25 m/sec), step length (ΔTT=0.26 m; ΔTE=0.13 m), feet's kinematic, and the vGRF during the 10mWT. The subject improved the distance walked (ΔTT=25.5 m; ΔTE=21.5 m) and decreased the double-support phase (ΔTT= -4%; ΔTE= -2.2%) during the 2MWT. Improvements in distance walked and cadence were detected at pre-trn and at post-trn as IE of the vibrotactile biofeedback.

Conclusions: A short training period using the vibrotactile stimulus seems to improve the gait pattern of the subject and the device seems to be usable and safe for the user.

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Can we boost motor imagery to improve freezing of gait in patients with Parkinson disease? A pilot study

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Content: Motor Imagery (MI) is a self-generated process to activate the sensory-motor system in absence of actual movement. Increasing evidence suggests that MI can be effective in improving motor performance. Although in Parkinson's disease (PD) authors indicate a substantially normal efficiency of MI, in PD patients with freezing of gait (FOG), the MI effects are not assured. Indeed, executive resources are needed to activate MI process, like conscious elaboration and monitoring, that might be not effective in PD patients with FOG.
The aim of our research is to evaluate the priming effect of visual, auditory and cognitive tasks as boosters of the MI process in patients with PD and FOG.
19 PD with FOG attended 4 MI training sessions (one a week) in 4 different conditions, assigned in a random order. Sessions consisted of Motor Imagery training preceded or not by one of three booster tasks (1. Action observation (AO), 2. Attention task, 3. Auditory observation) and followed by motor execution. The training was focused on two motor tasks: gait initiation (GI) and turning (TU). Before and after each session, the motor performances were assessed with inertial sensors. At the beginning and the end of each session, MI ability measures - MI questionnaire (GIQ) – and FOG severity (FOG-Q) were assessed.
Overall, the results showed an improvement in MI capability (GIQ score; $p<0.05$) and FOG severity ($p<0.05$). GI task showed a reduced variability in first step length and APA execution ($p<0.05$); TU showed a reduced number of steps ($p<0.05$) and angle ($p<0.05$). When we analysed differences among the "booster" tasks, we found that AO was superior in enhancing turning performance.
These preliminary results show that boosting MI could be feasible to improve MI ability and reduce FOG, and that AO seems to better enhance the MI effect on movements.

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Rehabilitation treatment of micrographs in individuals with Parkinson's disease: outcome research

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Introduction: Micrography is one of the most common effects of Parkinson's disease and can be defined as "an impairment of the fine motor skills of the hand which mainly occur with a progressive or stable reduction in the writing width (1,2)". The exact prevalence of micrography is not yet clearly defined in the literature, ranging from 9 to 72% incidence (3-6); despite this, it is globally recognized as one of the first symptoms of Parkinson's disease, which can be used as a reliable criterion for early diagnosis.

Objective: The aim of this study is to evaluate the effectiveness of a rehabilitation treatment for the improvement of micrography in individuals with Parkinson's disease through an outcome research.

Methods: The program will be administered on an outpatient basis at the Policlinico Umberto I (Rome), where a minimum of 10 patients with a diagnosis of Parkinson's disease and a Hoehn & Yahr scale score from 1 to 3 will be recruited.
The intervention will last 9 weeks (two weekly treatments) and the sample will be evaluated in three times: pre-treatment (t0), post-treatment (t1) and 1 month after the end of treatment (t2).
For the evaluation of the intervention, the following will be used as outcome measures: the Jebsen Tajlor Hand Function test, Parkinson Disease Questionnaire-39 and the measurement of the size of the letters.

Results: 15 patients, who met the inclusion requirements, were recruited. The pre and post treatment evaluations showed statistically significant data for all the outcome measures used with a $p < 0.05$. Significant data were also obtained in the evaluation of the size of the handwriting for all follow-ups.

Conclusions: Our study has shown that rehabilitation treatment for micrography in Parkinson's disease is effective in reducing writing times and improving letter size.

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Motor resonance during movement observation in Parkinson's disease assessed by functional near-infrared spectroscopy-EEG corecording

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Introduction: The mirror neuron system (MNS) includes a group of neurons that discharge both when a movement is executed and observed [1]. Recent studies have shown that subtalamic nucleus might be involved in mirror circuit activity [2]. The Mu-rhythm event-related desynchronization (ERD) during observed movement has been suggested to be an indicator of MNS activity; it can be impaired in PD, even at the early stages of the disease [3].

Objectives: To investigate changes in oxy- and deoxyhemoglobin concentration and EEG activity in motor cortical areas at rest and during movement observation and execution, in PD patients and healthy subjects.

Materials and Methods: We enrolled 21 healthy subjects and 21 PD patients, all right-handed. Inclusion criteria for PD patients were age between 40 and 80 years, MMSE>23, absence of significant visual deficits and diagnosis of Idiopathic PD at Hoehn-Yahr stage I-II. FNIRS-EEG were co-recorded using 20 fNIRS measurement channels on motor areas and a 61 scalp electrodes EEG. During the observation session participants were asked only to observe videos in which a woman grasped a flat object or a sharp tip object. During the execution session participants had to tap a bar on the keyboard when the agent touched the object on the watched video.

Results: In parkinsonian patients' motor cortex two different patterns were noted: hypermetabolism with desynchronization during observation of grabbing flat object and hypometabolism with hypersynchronization during observation of grabbing sharp tip object. The control group, on the contrary, exhibited a specular activation pattern. We found significantly higher mean levels of oxyhemoglobin in PD patients during the resting state but no differences between the two groups in touch detection time during the execution session.

Conclusions: Training techniques such as action observation and motor imagery have recently gained attention as a promising rehabilitation tool for patients with neurological disorders [4]. Motor resonance mechanisms could compensate the abnormal motor planning in early PD, supporting specific rehabilitation strategies.

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P65

ParkInCammino - Wearable sensor analysis trial in a Parkisonian cohort selected for the Santiago Trail.

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Background: The impact of Physical activity on gait disturbances in Parkinson's disease is still theme of debate.
The application of mobile health technology enables the evaluation of several walk parameters of in different conditions, both in a context of performance and in the activities of daily life.

Objective: To investigate if the combination of physical activity and the challenge of a six-days long-distance trail could improve the gait parameters in Parkinson's disease and controls.

Methods: Twenty-two subjects including 11 patients and their caregivers were selected and underwent an extensive motor and non-motor assessment and MHT evaluation. Each patient started an intensive training for three months before taking part to a 6-days intensive trail (Santiago de Compostela Portuguese 85 Km Trial). Each subject underwent an evaluation at baseline, T1 (before Long-trail) and T2 (after the long trail).

Results: Patients showed a significant improvement in several motor and non- motor variables, including behavioral and quality of life measures. Patients but no controls showed an improvement of several gait parameters in supervised conditions, namely stance time, double limb support from baseline to T1 and to T2, whereas no changes in turning and postural instability were detected.

Conclusions: The study confirms the impact of physical activity on gait parameters in PD patients. Larger multicenter cohorts are needed in order to evaluate the long-term impact of trail experiences in PD patients.

P66

Digital inclusion and literacy in Parkinson's disease

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Introduction: COVID-19 pandemic has boosted the use of telemedicine [1,2,3]. However, this has highlighted the presence of a "*digital divide*" between those who can or cannot access and use digital devices, further spurring government strategies to implement higher "*digital inclusion*". Although literature suggests Parkinson's disease (PD) patients are leaning to this transition [4], no study ever assessed their level of digital inclusion.

Objectives: (1) To compare digital inclusion and literacy in PD-patients and controls and (2) to determine the influence of clinical factors on digital inclusion.

Methods: A modified version of the Internet Skills Scale (ISS) evaluating three main domains (operational, information navigation, and mobile) [5] was administered to PD patients from five Italian centers. Clinical (MDS-UPDRS-III [6], Hoen & Yahr [7], presence of depression and cognitive decline) and demographic informations (age, sex, education, job status, family income, housing context) were concomitantly registered.
We used Mann-Whitney U-Test for group-differences and linear regression model to determine the predictive value of age-corrected MDS-UPDRSIII and HY on ISS score.

Results: 270 PD patients and 49 matched controls were enrolled; no significant differences were found regarding age, sex and ISS global score. Significant differences emerged in the "Information Navigation" domain (p=0,006).
In PD, possible/mild cognitive decline was associated with worse ISS performance (p=0,035) and fewer Information Navigation (p=0,025) and Operational (p=0,035) skills. No significant differences were found comparing patients divided by presence of depression/apathy.
Age-corrected MDS-UPDRSIII and H&Y predicted ISS-score (for both p<0.001).

Conclusions: Although digital skills are not reduced in PD in general, patients perform worse in the Information Navigation subdomain, possibly due to cognitive dysfunction. Their digital performances however worsen with increasing disease severity, which would hamper the use of telemedicine when more needed.

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P67

mGlu3 receptors in Parkinson's disease as a candidate target for neuroprotective therapy: evidence from preclinical studies to human genetic

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Background: Type-3 metabotropic glutamate (mGlu3) receptors exert pleiotropic functions in the CNS [1]. Presynaptic mGlu3 receptors inhibit glutamate release, whereas postsynaptic mGlu3 receptors boost mGlu5 receptors signaling [2]. Activation of mGlu3 receptors in astrocytes stimulates the production of GDNF and TGF-β and drives microglia towards an anti-inflammatory phenotype [3,4].

Methods: WT and mGlu3-/- mice were chronically treated with MPTP (20 or 10 mg/kg, s.c., every other day). We analyzed dopamine (DA), DOPAC and HVA levels in the striatum at 10, 15 and 30 days through HPLC detection. We assessed nigro-striatal degeneration by immunohistochemical analysis of Tyrosine Hydroxylas in Substantia Nigra pars compacta (SNpc). We evaluated microglia phenotype in the striatum, the release of neutrophic factors and glial reaction. We are also examining the association between polymorphic variants of GRM3 (rs12704290, rs13242038, rs1468412, rs1527768, rs187993, rs1989796, rs2228595, rs2237562, rs2282966, rs2299225, rs274622, rs6465084, rs724226, rs802457, rs906415, and rs917071) or GRM5 (rs60954128 and rs3824927) and PD in a large cohort of patients.

Results: Chronic administration of MPTP in WT and mGlu3-/- mice caused a substantial drop in DA, DOPAC and HVA levels in the striatum. At 10 and 30 days, the DA loss was significantly greater in mGlu3-/- mice treated with 10 or 20 mg/kg respectively, as compared to their WT counterparts. mGlu3 receptor may have an anti-inflammatory activity, because of in mGlu3-/- mice microglia M2 is less represented. These mice also showed lower levels of neurotrophic factors and a greater glial reaction. Moreover, ad interim analysis suggests an association between the GRM3 and GRM5 variants, PD and dyskinesias.

Conclusion: These findings suggest that mGlu3 receptors might shape the balance between neurodegeneration and neuroprotection in PD and might be targeted by therapeutic intervention.

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P68

Technological assessment of handwriting and finger tapping in subjects with Parkinson's disease

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Introduction: People with Parkinson's disease (PD) often complain difficulties in repetitive hand movements and handwriting. Micrographia, defined as a reduction of handwriting speed and amplitude, is a common sign of PD.

Objective: To assess handwriting and finger tapping abilities in PD relative to healthy controls using new technological devices and software.

Methods: Ten PD and 15 age/sex-matched healthy controls underwent handwriting and finger tapping assessments. Three electromagnetic sensors placed on first and second fingertips and on the back of the right hand were used to evaluate finger tapping amplitude and speed. We developed handwriting tests consisting of pre-writing tasks such as drawing repetitive cursive loops as ample and fast as possible and colouring a figure as much as possible in a given time. Handwriting tests were performed on the touchscreen of a tablet using a touch stylus pen.

Results: Relative to healthy controls, PD patients showed reduced handwriting amplitude and speed ($p<0.05$). During finger tapping, patients with PD showed decreased movement amplitude and speed and a higher tendency to reduce them during the repetition of movements compared to healthy controls ($p<0.05$). The ability to colour the figure and to perform ample and rapid finger movements correlated with a better performance at the UPDRS-III both on and off medication ($r>0.65$; $p<0.05$).

Conclusions: As expected, patients showed reduced handwriting and tapping abilities relative to healthy controls. Interestingly, handwriting and finger tapping outcomes obtained through technological devices correlated with the motor performance assessed with clinical scales. This study showed that technological devices with customized software can provide quantitative measures of handwriting and bradykinesia that can be used in future studies to assess the effect of hand abilities rehabilitation in PD.

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Puglia Parkinson Network: a clinical governance tool

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Introduction: Parkinson's disease (PD) is a chronic and progressive disorder characterized by motor and non-motor symptoms. It decreases the quality of life of both patients and their caregivers and places a heavy economic burden on society. PD affected 1-2 per 1000 of the population at any time, with a prevalence of 200-350/100.000 and an estimated incidence of 5-21/100.000/years.

Methods: PD patients' management requires a multidisciplinary approach. According to the National Chronicity Plan, approved by the State-Regions conference in September 2016, the care of patients with chronic diseases, such as PD, must be guaranteed through a network of care, including all specialists operating in territorial departments and in hospitals. For this aim, a dedicated board of the Puglia region has built a care network, which provides three levels of assistance organized according to a mixed model, internodal and hub-spoke. The Puglia Parkinson Network (PPN) provides specialized territorial departments' identification, managed by neurologists expert in movement disorders, which represent peripheral strategic points where the PD patients can refer to. The PPN network uses an informatic tool that allows to share all patients' information. At the first evaluation, patient's clinical data (history, neurological examination, diagnosis, Hoehn and Yahr score, UPDRS score, pharmacological treatment…) are collected. The above clinical data could be updated at every follow-up visit. Since March 2021, about 2000 patients were recruited. The PPN's digital tool can manage and monitor PD patients care, connecting general practitioners and neurologists, ensuring the systematization and digitalization of all care processes. Finally, the informatic tool allows the collection of clinical data that can be used for healthcare and scientific research in the epidemiological field.

Conclusions: PPN and its digital tool are a novel model for integrated diagnostic-therapeutic pathway, allowing multidisciplinary approach and sharing PD patients' data on a regional basis.

P70

Gut microbiome alterations in alpha-synucleinopathies

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Background: Microbiome alterations have been found in Parkinson (PD) and Alzheimer's disease and might impact on brain vulnerability within the spectrum of Lewy body disorders. Aim of the study was to evaluate shared and divergent microbiome alterations in PD and dementia with Lewy bodies (DLB) compared to age-matched controls.
Method: Seventy-seven subjects including 28 PD, 21 DLB matched for age and disease duration and 24 age-matched controls entered the study. Each subject underwent an extensive clinical evaluation including motor, cognitive and dietary assessment and underwent stool and blood collection. Stool DNA was amplified using primers targeting the V3-V4 region of the bacterial 16S rRNA gene. Sequencing was performed according to the 16S-protocol on MiSeq (Illumina). Ecological measures as beta diversity, the similarity or difference in microbiota composition between individuals, as well as taxonomic abundance were computed with the free software package QIIME 2.

Result: Compared to HC, DLB and PD patients exhibited a shift in the abundance of the phylum Synergistetes (in DLB increased by 3.5 times than HC) and Actinobacteria (in PD increased by 1.5 times than HC). At genus level, DLB patients exhibited decreased abundance of *Clostridium sensu stricto 1, Fusicatenibacter, Lachnospiraceae ND3007 group, Rikenellaceae RC9 gut group and Ruminiclostridium 6* than HC as well as less Fusicatenibacter and Lactobacillus than PD (Linear discriminant analysis effect size (LEfSe), $P<0.046$).

Conclusion: PD and DLB are accompanied by specific alterations in the abundance of specific gut microbes. Further analyses are needed in order to understand whether differences in gut microbiota composition between PD and DLB might explain different brain vulnerability and disease progression within the Lewy bodies spectrum.

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Substance P is increased in serum of patients with Parkinson's disease and correlates with motor disturbances

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Introduction: Substance P (SP) is a neuropeptide belonging to the family of tachykinins, which acts as neurotransmitter, neuromodulator, and neurotrophic factor in central nervous system. The expression of SP is particularly high in nervous structures critically involved in Parkinson's disease (PD) pathogenesis, including enteric nervous system, vagus nerve, autonomic centers, neocortex and limbic areas, and especially substantia nigra [1,2]. Levels of SP might thus track neurodegeneration in these systems.

*Objective: T*o measure SP levels in serum of PD patients and healthy subjects and evaluate the possible associations with clinical parameters, such to establish a potential value for SP as disease biomarker.

Methods: SP serum levels were measured in 22 PD patients and 12 age-/sex-matched healthy controls (CTRLs) by a competitive commercial ELISA kit; patients underwent comprehensive clinical assessment by Unified Parkinson's Disease Rating Scale Part III (UPDRS III), Non Motor Symptom Scale, Mini-mental State Examination, levodopa equivalent daily dose calculation. Biochemical data were compared between the groups and correlated with clinical parameters.

Results: Serum SP was significantly higher in PD patients than in CTRLs [t (32) = 4.3; P = 0.0001]. Receiver operating characteristic analysis provided an area under the curve of 0.89 (P = 0.0001). The cutoff value of 85.6 pg/mL differentiated PD from CTRLs with a sensitivity of 82% and a specificity of 83.3%. Linear regression demonstrated direct association between serum SP and UPDRS III (B = 0.84; P = 0.01), even when dopaminergic therapy was considered as covariate (B = 0.96; P = 0.025).

Conclusion: This pilot study showed that SP serum content was higher in PD patients than CTRLs, and increased proportionally to the severity of motor disturbances, suggesting a potential value either as potential biomarker or candidate therapeutic target in PD. Further studies are now needed to confirm and extend these preliminary findings.

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P72

Emotional and action verbs influence motor response in Parkinson's disease

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Background: Emotions influence motor system and the ability to react to different stimuli. Furthermore, it is known that motor resonance mechanisms are elicited by stimuli related to actions. Parkinson's disease (PD), besides manifesting with cardinal motor symptoms, presents cognitive and emotional impairment, including difficulties in recognizing and processing emotions. We hypothesise that motor response in PD may be influenced by the emotional or action content of the sentences.

Aim: To investigate whether sentences containing action or non-action verbs with or without emotional content could affect motor performance, in terms of accuracy and reaction time (RT), in PD patients.

Methods: 48 PD patients (HY 1-2) were recruited to perform a go no-go task. They were asked to recognize if the sentences appearing on a screen had an emotional content and press a button, according to the instructions given (press in response to an emotional sentence or press in response to a neutral sentence). Sentences were furtherly divided according to the type of verb (action or no-action).

Result: Statistical analysis showed that patients were more accurate in recognizing the emotional content for "action" than for "non action" sentences when the action had a positive emotional content ($p<0.001$) or neutral ($p<0.001$). Furthermore, patients responded faster when sentences had a positive valence, both when sentences had an "action" ($p=0.000$) or a "no-action" ($p=0.000$) verb.

Discussion: "Action" verbs in sentences promoted accuracy in patients' responses, likely due to embodiment mechanisms. Interestingly, negative emotional valence seems to disrupt this embodiment gain, present only in positive and neutral sentences. Furthermore, positive emotions seem to overwhelm motor resonance processes in terms of improving motor response velocity (RT) independently by "action" or "no-action" contents, differently to neutral stimuli.

Conclusion: Results indicate that basal ganglia impairments, with motor and non motor aspects in PD, are accompanied by selective modulation in processing action-related verbs with an emotional content.

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The impact of age at onset on clinical features of Parkinson's disease: a retrospective study

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Introduction: Age at onset of symptoms influences the course and long-term therapeutic response of Parkinson's disease (PD) patients. However, studies on the prevalence and initial course of symptoms in PD patients with different age at onset are scarce.

Objective: To evaluate the prevalence and progression of motor and non-motor symptoms over the first 5 years of illness in PD patients with different age at onset.

Methods: We retrospectively collected data on motor, non-motor and therapeutic features along the first 5 years of illness in 82 PD patients referring to our PD Center. Subjects evaluated at the time of diagnosis (T0) and followed-up for 5 years (T1) were included. They were divided into 3 groups according to the age at onset of motor symptoms as follows: ≤55 years old (29 patients, group A), 56-69 years old (20 patients, group B), and ≥70 years old (33 patients, group C). Motor symptoms were evaluated by the MDS-UPDRS-III scale, non-motor features by the NMSS and therapeutic regimen was expressed as LEDD.

Results: At T0, gastro-intestinal symptoms were significantly more frequent in group B patients (35%, p=0.01). At T1, postural instability (36%, p=0.008) gait disturbances (73%, p=0.002), and attention/memory symptoms (33%, p=0.001) were significantly more prevalent in group C patients, whereas miscellaneous symptoms domain was more frequent in group B patients (65%, p=0.001).

In the whole population, there were significant increases of prevalence of gait disorders (p=0.001), postural instability (p=0.001) and several NMSS domains between T0 and T1. Within group analysis showed that gait disorders significantly increased in B (p=0.031) and C (p=0.001) groups, and postural instability significantly increased in group C solely (p=0.004).

Conclusion: Our results suggest that PD patients with different age at onset may have a different motor and non-motor feature prevalence and progression in the first 5 years.

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Correlation between olfactory disorder and cognitive function in Parkinson's disease patients

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Introduction: Parkinson's disease (PD) is a neurodegenerative disorder associated with motor symptoms such as bradykinesia, rigidity, tremor and postural instability. Moreover, PD is usually associated with non-motor symptoms (NMSs) such as olfactory dysfunction, sleep disorders, autonomic dysregulation and neuropsychiatric symptoms, like cognitive impairment, apathy, and anxiety [1]. Associations between olfactory dysfunction and cognitive impairment in PD patients are yet to be elucidated. The aim of the study was to evaluate correlations between the role of each single cognitive domain and the olfactory function in PD patients.

Methods: One hundred eighty-two patients (105 men and 77 women with a mean age of 70.2 ± 9.3) were recruited. Patients with cognitive impairment were excluded. Olfactory function was assessed with the Sniffin' Sticks Extended Test (SSET) which evaluated Olfactory Threshold (OT), Discrimination (OD), Identification (OI) and their sum Threshold-Discrimination-Identification (TDI) scores [2]. The cognitive ability was evaluated by the Montreal Cognitive Assessment (MoCA). Significant correlations between the role of each single cognitive domain and the olfactory function in PD patients were calculated.

Results: Significant correlation was observed between odor threshold versus naming ($r = 0.183$, $p<0.05$) and attention ($r = 0.225$, $p<0.01$), as well as between odor discrimination versus executive function ($r = 0.164$, $p<0.05$) and abstraction ($r = 0.188$, $p<0.05$).

Conclusion: The impairment of executive domain, abstraction and attention were significantly associated to worst scores in olfactory functions suggesting common pathways between cognitive decline and olfactory dysfunction in PD. Specific cognitive impairment in single domain were also related to particular subtests, suggesting distinctive patterns related to different type of odor dysfunctions.

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P75

Plasma biomarkers of disease progression in Parkinson's disease

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Introduction: Plasma neurofilament light chain (NfL) has been identified as one of the most promising biomarkers for predicting disease progression in several conditions, including Parkinson's disease. Recent studies reported the utility of plasma phospho-tau, beta-amyloid and glial fibrillary acid protein (GFAP) for diagnostic and prognostic purposes of Alzheimer's disease and other neurodegenerative conditions. In this study, we evaluated the ability of a panel of plasma biomarkers to predict disease progression in PD patients.

Methods: We measured plasma p-tau181, p-tau231, Aβ40, Aβ42, GFAP and NfL using Single molecule array (Simoa) assays in healthy controls (HC) and consecutive PD patients who underwent an extensive motor and non-motor assessment at baseline and two to five years of follow-up. Differences in biomarkers level between PD and HC were evaluated adjusting for the effect of age and sex. In PD patients, the correlation between plasma biomarkers and motor scores at baseline and at follow-up were evaluated using partial correlation analyses. Linear regression and Cox regression analyses were applied to evaluate the best combination of biomarkers able to predict motor progression and disability milestones adjusting for the effect of age, sex disease duration and baseline severity.

Results: One hundred seventy PD and 106 HC entered the analyses. PD patients exhibited higher p-tau181, p-tau231 and lower Aβ42 compared with HC but similar NfL, GFAP and Aβ40 levels. All

biomarkers correlated with age and disease duration, whereas NfL, GFAP and ptau181 additionally correlated with baseline motor severity. At follow-up, NfL emerged as best predictor of motor progression (linear regression analyses).

Conclusion: The present findings confirm plasma NfL as the best predictor of motor progression in PD in comparison with other plasma biomarkers. Larger on-going studies with longitudinal plasma assessment are needed to evaluate the potential value of other biomarkers for identifying co-pathologies or defying subtypes of disease suitable of different intervention strategies.

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Effects of opicapone in Parkinson's disease as assessed by kinematic techniques

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Background: By increasing L-dopa bioavailability, catechol-O-methyl transferase inhibitors are currently used as first-line add-on therapy to L-dopa to treat end-of-dose motor fluctuations in the advanced stages of Parkinson's disease (PD). In this study, we aimed to objectively investigate the effects of Opicapone on bradykinesia in PD by kinematic analysis.

Methods: We studied 13 patients with PD (mean age ± one standard deviation: 69.0 ± 7.4 years) and motor fluctuations (mean disease duration ± one standard deviation: 9.8 ± 4.4 years) being treated with dopaminergic drugs. Bradykinesia was measured by recording repetitive finger movements (finger tapping). All the patients were tested in two separate and randomized experimental sessions (with and without Opicapone), at least one week apart. In each session, patients were clinically and kinematically assessed before and after their usual morning dose of L-dopa (and the motor performance was followed up to 3.30 hours after L-dopa intake). The data were analyzed by analysis of variance (ANOVA) using the withing group factor SIDE (two levels: more vs. less affected), SESSION (two levels: without vs. with Opicapone), and TIME POINT of analysis (four levels: baseline, 30 min, 1 hour and 30 min and 3 hours and 30 min after L-dopa intake).

Results: Movement velocity during finger tapping was lower in PD patients without opicapone than in patients with opicapone [F (1, 12) =9.11, P=0.01]. When tested without opicapone, PD patients also had a lower movement amplitude than in the assessment session with opicapone [F (1, 12) = 4.91, P=0.04]. opicapone intake, however, did not modify the sequence effect in patients. Finally, as expected, we also observed velocity and amplitude improvement related to L-dopa ($P<0.05$ for both parameters) while the sequence effect did not change.

Conclusions: We here provided the first objective assessment of the effects of opicapone on bradykinesia in PD. The study results confirm that bradykinesia features (i.e., velocity, amplitude, and sequence effect) have different sensitivity to change after administration of dopaminergic drugs.

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Decrease of Levodopa Equivalent Daily Dose in Parkinson Disease Patients Treated with Safinamide: a Three-Years' Retrospective Study

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Introduction: Safinamide is a reversible monoaminoxidase B inhibitor used in the treatment of motor and non-motor fluctuations in Parkinson's disease (PD). A previous retrospective study demonstrated a significant reduction of levodopa equivalent daily dose (LEDD) in patients treated with safinamide after one year of follow-u [1]. In this retrospective study, we aim to evaluate whether total LEDD reduction persists even after 3 years of follow-up and if there is a possible correlation with clinical phenotype.

Material and methods: Twenty-eight PD patients were evaluated at different time points: at the time of Safinamide prescription (T0), after one (T1), two (T2), and three years (T3). We collected data about clinical phenotype, disease duration, mean daily dose of LD, and LEDD of other PD drugs.

Results: We stratified the patients depending on clinical phenotype and disease duration (0-6 years or more than 7 years). The repeated-measures ANOVA showed in the akinetic-rigid group (9 patients) a significant constant decrease of the total LEDD in the following three years (T0-T1 p=0,003; T0-T2 p=0,013; T0-T3 p=0,040) with a mean decrease of 16% from baseline to T3. A slight though not significant LEDD increase was observed in patients with tremor dominant PD. Furthermore, the group with more than seven years of disease duration (15 patients) demonstrated a decreasing trend in total LEDD (-7% comparing T0 to T3) while in the other group (13 patients) we observed a growth in total LEDD (+8% comparing T0 to T3).

Conclusions: In conclusion, these results support the LD-sparing role of safinamide even 3 years after its introduction. To the best of our knowledge, our study also highlights for the first time that this benefit is more relevant in PD patients with an akinetic-rigid phenotype and longer disease duration.

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Use of safinamide and non-motor fluctuations in Parkinson's disease

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Introduction: Safinamide is a monoamine oxidase B inhibitor used as an adjunct treatment of motor symptoms in Parkinson disease (PD). Some studies suggested its role in ameliorating non-motor symptoms such as pain, mood and sleep. However, its use in patients with non-motor symptom fluctuations has not been well investigated so far.

Objective: To observe the use of safinamide in PD patients with motor and non-motor symptoms (static and fluctuating).

Methods: In this cross-sectional study, non-motor symptom (static and fluctuating) scores from 30 PD candidates for device-aided therapies due to the suboptimal control of motor fluctuations were analyzed by means of the newly validated Non-Motor Fluctuation Assessment (NoMoFA) Questionnaire. NoMoFA is an assessment tool that facilitates the identification and quantification of severity of both static and fluctuating non-motor symptoms in PD, validated in 2021 and promoted by the MDS. The following demographic and clinical variables were also considered: age, disease duration, Hoehn & Yahr PD stage (HY), and levodopa equivalent daily dose (LEDD). Mann-Withney and logistic regression analysis were performed.

Results: 13/30 patients were treated with safinamide 100 mg (Saf+), no patients were treated with safinamide 50 mg. Age, disease duration, HY, and LEDD did not differ significantly between Saf+ and patients not treated with safinamide (Saf-). The static score of non-motor symptoms did not differ between Saf+ and Saf- (6.6±4 Saf+ vs. 7.1±5.8 Saf-; p:0.742), while the total non-motor fluctuation score was significantly higher in Saf+ (12.5±5.5 Saf+ vs. 7.8±5.7 Saf-; p:0.017). The logistic regression analysis confirmed the data, with safinamide use being associated with a higher non-motor fluctuation score (OR 1.228; p:0.028), after covariation for LEDD, age, disease stage and disease duration.

Conclusions: Our results support the perception of safinamide as a drug useful for non-motor symptoms in PD, especially when fluctuating, as most patients treated with Safinamide were those showing the higher score of non-motor symptom fluctuations. Longitudinal studies using NoMoFa are warranted to confirm the real efficacy of safinamide in reducing non-motor fluctuations.

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Safinamide adherence: the experience of the Movement Disorder Unit of Trieste

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Introduction: Safinamide is the latest monoamine oxydase -B inhibitor approved for the treatment of Parkinson's disease (PD). It is recommended in patients with motor fluctuations, as add-on therapy. Randomized-controlled trials and real life observational studies, showed that safinamide is safe and well tolerated. The present study describes the adherence to the treatment in the cohort of patients referred to the Movement Disorders Unit of the Neurology Department of Trieste.

Methods: A total of 600 patients has been evaluated. Upon them, patients who had received safinamide at any time between January 2016 and October 2021, have been enrolled. The following clinical data were collected: sex, age, disease duration, concomitant therapies, safinamide dose, treatment duration or discontinuation and, eventually, reason for discontinuation.

Results: Safinamide was recommended in 99 patients. 47 patients (50.5%) were still in treatment with safinamide at the end of the observation period, 13 of them for more than 4 years. In 46 patients (49.5%) the drug was discontinued, and this happen during the first year in 25 subjects. The reason for discontinuation were: side effects (48%), disease progression (22%), lack of efficacy (17%) and death (13%). Dyskinesias and hallucinations were the side effects most frequently associated with drug discontinuation. Patients with short disease duration (7.8 years) and simple therapeutic scheme (l-dopa alone) were more likely to maintain treatment. The adherence reached 60% in patients who were switched to safinamide from a different I-MAOB.

Conclusion: Our real-life study confirmed that safinamide is well tolerated in more than half of patients. For those that dropped out the treatment, the main reasons were the drug's side effects. The highest compliance to the medication is more likely to be evinced in patients affected by a less advanced form of the disease and following a lighter therapeutic scheme.

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Non-motor symptoms burden in motor-fluctuating patients with Parkinson's disease may be alleviated by safinamide: the VALE-SAFI study

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Objective: The present study aimed to explore the effect of safinamide treatment on NMS and quality of life in motor-fluctuating PD patients.

Background: Parkinson's disease (PD) is characterized by motor symptoms often experienced in concomitance with non-motor symptoms (NMS), including depression, apathy, pain, sleep disorders, and urinary dysfunction.

Methods: VALE-SAFI is an observational single-centre study in fluctuating PD patients starting safinamide treatment. The effects of safinamide on NMS, sleep, fatigue, depression and pain were assessed through validated scales. Changes in the scales from baseline (T0) to 6-month follow-up (T1) were analysed.

Results: 60 PD patients (66.67% males) were enrolled at baseline. and 45 patients completed the 6-month follow-up. PD patients improved motor symptoms at follow-up, with the significant reduction of motor fluctuations. The global score of the NMS Scale significantly decreased between baseline and the follow-up. Regarding pain domains, patients' reported a significant improvement in discolouration and oedema/swelling. Further, a significant improvement was observed from baseline to follow-up in sleep quality measured through the Pittsburgh Sleep Quality Index, while no changes were documented in daytime sleepiness. No differences were found in depression and fatigue between baseline and follow-up. Finally, the patient's perception of the impact of PD on functioning and well-being decreased from baseline to follow-up.

Conclusions: The present findings confirmed the positive effect of safinamide on both motor and non-motor symptoms, improving also the quality of life of PD patients. Furthermore, these data support the beneficial effects of safinamide on pain and mood, as well as on sleep quality and continuity.

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Safinamide use in clinical practice across Italy: a sub-analysis of SYNAPSES Study in Parkinson's disease patients

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Introduction: Safinamide modulates both dopaminergic and glutamatergic systems with positive effects on motor and nonmotor symptoms of Parkinson's disease (PD). The drug utilization study SYNAPSES was designed to investigate the use of safinamide in routine clinical practice, as recommended by the European Medicines Agency.

Objective: To describe the occurrence of adverse events in PD patients treated with safinamide in real-life conditions.

Methods: The SYNAPSES study is a multi-country, multi-center, retrospective-prospective cohort observational study, involving Belgium, Germany, Italy, Spain, Switzerland and United Kingdom.
Italy enrolled 616/1610 patients in 52 centers. Patients received for the first time a treatment with safinamide at enrollment visit or in the previous 4 months, were enrolled in 24 months and were followed up for 12 months, with intermediate evaluations after 4 (+/-1) months, 8 (+/-1) months, and 12 (+/-1) months from the start of treatment with safinamide. The aim of the "global" study was to describe the occurrence of adverse events in patients treated with safinamide in a real-life setting during 1 year. Some subgroups of interest were evaluated too, such as patients >75 years, those with relevant concomitant conditions and those suffering from psychiatric conditions.

Results: Of the 616 patients enrolled, 86.0% were evaluable at 12 months, with 23,3% being >75 years, 42,4% with psychiatric conditions and 67,7% with relevant comorbidities.
Safinamide was effective on fluctuations and motor symptoms measured through UPDRS III and IV, and on UPDRS total score, without safety issues in none of the subgroups considered.

Conclusion: The SYNAPSES data related to Italian patients confirms the good safety profile of safinamide even in special groups of patients. Motor complications and motor scores improved with clinically significant results in the UPDRS scale maintained in the long-term.

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Chronic therapy with amantadine and eye keratopathy relief: observation study in a cohort of patients suffering from Parkinson's disease

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Introduction: Amantadine, initially approved as an antiviral drug, is commonly used for the treatment of dyskinesias in Parkinson's disease (PD). Several studies have found that the amantadine use is rarely associated with a dose-dependent keratopathy. Withdrawal of amantadine in most cases involves a complete clinical regression with the disappearance of corneal edema, although at the ultrastructural level endothelial alterations may persist.

Objective: The objective of our study is to evaluate the effects of amantadine on the cornea in a population of patients with PD on combined therapy including amantadine.

Methods: We selected 76 patients with Parkinson's disease related to Parkinson Unit of AOU Careggi, 51 taking amantadine, and 25 subjects not taking amantadine as control group. All subjects underwent an eye examination including visual acuity assessment, tonometry, endothelial count, tomo-topography, corneal densitometry, and in vivo confocal microscopy (IVCM). The study excluded patients with history of trauma or eye surgery, use of topical eye medications, contact lenses or suffering from glaucoma.

Results: Among the 51 patients selected, 29 meet the criteria for inclusion (F/M=14/15). Of these patients the average age at the evalutation was 67.6±10.2 years with diagnosis of PD between 29 and 81 years. Average duration of therapy with amantadine was 4.2 years (range 1 to 11 years). Amantadine daily dosage was: 100 mg (N=8), 150 mg (N=1), 200 mg (N=16), 300 mg (N=3). About 30 % of patients showed corneal hyperrefective deposits mainly located at the endothelial level with a pleomorphism and polymegatism detected by the IVCM.

Conclusions: The data collected in our ongoing study show that corneal amantadine toxicity could be related to dose and duration of therapy. Further studies are warrented to assess the possible effect of treatment discontinuation and the long term influence on corneal endothelial cells.

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Opicapone for the treatment of Parkinson's disease: a real-world observational study

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Introduction: Opicapone is a catechol-O-methyl-transferase inhibitor (iCOMT) approved by the European Medicines Agency in 2016 as adjunctive therapy to preparations of levodopa combined with DOPA decarboxylase inhibitors in patients with Parkinson's disease (PD) and end-of-dose motor fluctuations.

Objective: To explore safety and efficacy of opicapone in a real-life, single-center, observational study.

Methods: In PD patients with motor fluctuations, we assessed motor score of the Unified Parkinson's Disease Rating Scale (UPDRS III), levodopa equivalent daily dose (LEDD), and daily off-time at baseline and 12 months after the introduction of opicapone 50 mg once daily. We also evaluated the Clinical Global Impression-Improvement (CGI-I) at 12-month follow-up.

Results: We evaluated 185 PD patients who started opicapone treatment from October 2018. Sixty patients were not further analyzed due to a missing follow-up in 25 patients (14%) or opicapone discontinuation given the lack of efficacy in 18 patients (10%) or a poor tolerability in 17 patients (9%). One hundred twenty-five patients (68%) continued opicapone at 12-month follow-up (68 males; mean age: 68.1±9.7 years; mean disease duration: 9.9±4.2 years; mean baseline UPDRS-III score: 25.6±14.2). These patients were categorized at baseline as ‘entacapone switchers’ (56%) or ‘opicapone as first iCOMT’ (43%). Most patients (71%) showed improvement at CGI-I, decrease in daily off-time (from 4.6 hours at baseline to 3 hours at follow-up), LEDD reduction (from 908 mg at baseline to 807 mg at follow-up). Notably, in 5 patients undergoing levodopa-carbidopa intestinal gel (LCIG) infusion therapy, the introduction of opicapone led to a decrease in LCIG daily dose (20% mean reduction) and numbers of LCIG extra-doses in the afternoon.

Conclusions: Opicapone is safe and effective for the management of motor fluctuations in most PD patients. Opicapone as add-on therapy to LCIG could reduce the LCIG daily dose and potentially the costs associated with this advanced therapy.

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Sex differences in levodopa pharmacokinetics in levodopa-naïve patients with Parkinson's disease

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Introduction: Levodopa (LD) is the most effective drug in the treatment of Parkinson's disease (PD) [1]. Women seem more prone to develop LD prolonged use related complications, such as motor/non motor fluctuations (MNMF) and dyskinesias (DYS) [2]. Nonetheless, there is a paucity of prospective studies examining gender-related predictors of MNMF and DYS. Among several factors, which concur with a very complex scenario, changes in LD pharmacokinetics influence the drug effectiveness.

Objective: To assess gender-related differences in LD pharmacokinetics in PD patients at their first ever intake of LD.

Methods: This multicentric study enrolled LD-naïve PD patients who received a single dose of LD/benserazide (100/25 mg) formulation. To measure plasma LD concentrations and pharmacokinetic parameters (AUC, Cmax, Tmax, t1/2), fasting blood samples were collected before drug intake and then at 8 time points until 260 minutes. LD concentrations were measured by ultra-high performance liquid chromatography coupled with mass spectrometry. Multiple linear regression analyses were performed to identify the predictors of the parameters.

Results: 35 patients (16 women and 19 men) were consecutively enrolled. AUC and Cmax were significantly higher in women than men ($p=0.0006$ and $p=0.0014$, respectively). No statistically significant difference was found regarding Tmax and t1/2. Multiple linear regression analyses revealed that female sex ($p <0.0001$) and BMI ($p= 0.014$) significantly predicted AUC. Only female sex significantly predicted Cmax ($p =0.001$). Moreover, only BMI significantly predicted t1/2 ($p =0.017$). Stratifying by gender, BMI was confirmed to significantly predict t1/2 in women ($p =0.027$), but not in men.

Conclusions: This study provides novel insights on gender differences in LD pharmacokinetics, possibly contributing to the later development of motor complications and dyskinesia in PD.

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P85

Impact of safinamide in Parkinson's disease: real-life findings from the HELP network

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Background: Several pharmacological strategies have been proposed for the treatment of motor fluctuations for motor fluctuations in Parkinson's disease (PD). Still the short and long-term of safinamide and other treatments in real-life scenario is theme of debate.

Objective: To evaluate the short and long-term impact of safinamide in Parkinson's disease in real life multicenter setting.

Methods: Data collected from digital platform from multicenter study were collected. PD patients consecutively enrolled with motor fluctuations who underwent safinamide treatment were selected and motor/non- motor assessment was evaluated before and after treatment in short term and long-term.

Results: Six-hundred-forty-nine patients were included in the network- of them, 313 presented motor fluctuations and 178 were treated with safinamide (Mean age 68.7 ± 8., mean disease duration8.1 ± 5.8, mean UPDRS-III 24.2 ± 14.8 in ON). Follow-up data were available for 112 and 89 subjects for short and long-term evaluation.
The improvement in global motor function and its impact in activities of daily living was significant at 3,6, 12 and 24 months. Longer response was associated with shorter onset of motor complication, independently from age, sex and disease severity.

Conclusions: Safinamide showed long-term benefit for motor complications in Parkinson's disease. Further studies are needed in order to confirm the association with early fluctuations with longer treatment benefit.

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Clinical-biochemical profile of *de novo* Parkinson's disease with constipation

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Introduction: Prodromal constipation (PC) at Parkinson's disease (PD) onset suggests an early degeneration of the enteric nervous system. Presenting phenotype, biochemical signature, and clinical progression of PD patients with PC (PD+PC) may theoretically differ from those without (PDwoPC), as a consequence of distinct neurodegenerative trajectories [1–3].

Objective: We compared the clinical-biochemical profile of *de novo* PD patients with and without PC, and the respective mid-term progression, to establish the grouping effect of PC.

Methods: Baseline parameters, including Hoehn and Yhar stage (HY), MDS-UPDRS-pars III, Non-Motor Symptoms Scale (NMSS), MMSE, levodopa equivalent daily dose (LEDD), were assessed in n=57 *de novo* PD+PC patients and n=73 *de novo* PDwoPC. Baseline CSF biomarkers (α-synuclein, amyloid and tau peptides, lactate, CSF/serum albumin ratio or AR) were also examined into a smaller sample and in controls (n=46). Clinical progression was estimated by comparing HY and LEDD change 2.06±1.35 years from diagnosis.

Results: At onset, PD+PC patients had higher HY ($p<0.001$) and MDS-UPDRS-pars III scores ($p=0.004$), and higher CSF AR ($p=0.045$). PDwoPC had higher Non-Motor Symptoms Scale domain-2 score ($p=0.018$), and lower CSF α-synuclein level ($p=0.003$). At follow-up, PD+PC had greater LEDD ($p=0.004$).

Conclusions: PC identifies a group of *de novo* patients with more severe motor impairment at onset, biochemical signature suggestive of blood brain barrier disruption, and greater dopaminergic requirement at mid-term; conversely, PDwoPC *de novo* patients complain with major fatigue at onset and exhibit more pronounced synucleinopathy. PC may thus mark distinct patterns of clinic-pathological progression in PD.

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Turning during single- and dual-task in patients with Parkinson's disease

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Introduction: Successful turning depends on correct intersegmental coordination. This means that the head starts with the movement, followed by trunk and feet [1]. In PD, this sequence is often affected, and the body segments turn *en bloc* [2]. As gait and balance parameters in PD are affected by DT and turns are often a problem for PD patients [3,4], this study investigated intersegmental body coordination and kinematics during turning in ST and DT in PD patients.

Objective: To investigate turning features in single (ST) and dual task (DT) in Parkinson's disease (PD) patients.

Methods: Twenty-two PD patients and 22 age- and sex-matched controls (CO) performed 3 walking tasks involving 180° turns: walking up and down a 5-meter distance alone and while performing a reaction time task and a numerical Stroop test (both smartphone-based). The following parameters were extracted through a motion capture system: turn duration (TD), number of steps (NS), mean (MAV) and peak (PAV) angular velocity. Sternum turning onset latency (TOL) relative to head and the maximum angle between these two body segments (MA).

Results: In DT compared to ST, TD and NS were larger, and MAV and PAV were smaller for both body segments in both groups. However, PD patients turned more slowly and with a lower PAV than CO. During ST, compared to CO, PD patients showed a more *en bloc* turning in terms of TOL. In both groups MA was smaller in DT compared to ST but no difference was found between the two groups. During DT, sternum started before head in PD patients, whereas the sequence is still preserved in CO.

Conclusions: PD patients turn more en bloc than controls in ST and loose intersegmental body coordination during DT conditions. These results could explain, at least partly, increased balance deficits and risk of falls during turning in PD.

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Risk factors associated with Parkinson's Disease: a case-control study

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Introduction: With the increased life expectancy worldwide, the number of Parkinson's disease (PD) patients is expected to increase by more than 50 % by 2030 [1]. The high percentage of non-genetic forms sees environmental factors as important etiological hypotheses [2].

Objective: To investigate exposure to various environmental factors with the aim of highlighting possible new associations with the onset of PD.

Methods: We enrolled 264 PD patients and 277 healthy controls from three clinical centers, between 2016 and 2018, and conducted a questionnaire-based case-control study. We assessed demographic characteristics, place of residence, comorbidities, marital status, occupation, hobbies, sports activity, smoke-alcohol consumption, and diet.
Controls were matched with cases for age, sex, and province of residence. Statistical analyses were conducted using the t-test for continuous variables and the chi-square test for categorical ones.

Results: There was no significant difference regarding marital status and demographic characteristics between cases and controls. Gynecological conditions and previous appendicectomy were significantly more frequent among controls (p=0.044 and p=0.00001, respectively). Occupational exposure to solvents (p=0.049) and metals and metal fumes (p=0.002), and recreational exposure to solvents (p=0.02), pesticides (0.024) and glues (p=0.038), was higher among cases. Overall, there was a statistically significant difference in sport activity (p=0.027) and in activities performed outdoors (p=0.016), with higher prevalence in the controls group. Controls were active smokers in greater numbers than cases at the time of the questionnaire, with a statistically significant difference (p=0.0009), while no significant differences were found in alcohol consumption. In the dietary regime survey the only difference was in cereal consumption (p=0.0018), which was greater among controls.

Conclusion: Our findings highlight the possible relevant role of environmental and lifestyle factors in the development of Parkinson's disease. In view of the increasing prevalence of the disease, it is important to carefully consider every possibility of prevention and early diagnosis.

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Caregiver's burden in cardiovascular dysautonomia associated with Parkinson's Disease

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Introduction: Cardiovascular autonomic neuropathy (cAN) is one of the most common disabling and frequently unrecognized features of Parkinson's disease (PD), with an estimated prevalence of at least 30-50% [1,2,3]. However, its impact on caregivers' burden has been scarcely investigated.

Objective: We sought to estimate the impact of cAN on informal caregivers of patients with PD, defined as individuals providing regular care to a friend, partner, or family member with PD, and to evaluate the mutual relationship between caregivers' burden and patient health-related quality of life (HRQoL).

Methods: We enrolled 36 consecutive PD patients and their caregivers. Patients underwent a detailed motor, autonomic, cognitive, and functional assessment. Caregivers were assessed by means of the Zarit Burden Interview (ZBI). Differences in caregivers' burden and strength of association between caregivers' burden, cAN severity, and patients' HRQoL were assessed using ANCOVA, logistic regression, and linear regression analyses. Analyses were adjusted for patients' and caregivers' age, PD duration, PD motor and cognitive disability.

Results: cAN+ patients showed a significantly higher impairment in non-motor and motor experience of daily living, lower MoCA scores, and worse HRQoL. Moderate-severe caregiver burden was reported in 41.7% of PDcAN+ vs. 8.7% of PDcAN- ($p<0.001$). The ZBI score was increased in PDcAN+ vs. PDcAN- (31.48±3.36 vs. 15.23±2.31; $p<0.001$), with 10-fold higher odds ($p=0.012$) of moderate-severe caregiver burden in PDcAN+, even after adjusting for potential confounders, such as patient's age, disease duration, cognition, motor disability, and caregiver's age. The ZBI score correlated with cAN severity ($p=0.005$), global autonomic impairment ($p=0.012$), and HRQoL impairment ($p<0.001$).

Conclusion: These results highlight the significant impact of cAN on PD caregivers, with caregivers' distress possibly reflecting on the patient's quality of life, therefore affecting the wellbeing of both. Our findings underline the need for targeted interventions addressing this frequently overlooked and insufficiently treated source of disability in PD.

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P90

Autonomic nervous system impairment and impulsive compulsive behaviours in Parkinson's Disease

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Objective: Aim of the present study was to evaluate the relationship between impulsivity, impulsive compulsive behaviors (ICB) and autonomic nervous system dysfunction in people with Parkinson's disease (PD) using a structured clinical assessment and objective measures of autonomic functions and autonomic reactivity.

Background: Increased impulsivity and ICB are common in PD. A recent study has showed that PD patients who develop ICB over the course of the disease have more pronounced autonomic impairment.

Methods: Thirty consecutive patients with PD were included, 14 with and 16 without ICB. They underwent an extensive clinical evaluation of motor and non-motor symptoms including autonomic dysfunction, behavioral disorders, and neuropsychiatric symptoms. Objective autonomic assessment included recording of blood pressure, heart rate and heart rate variability (HRV) over six consecutive minutes at rest and after orthostatic challenge. Patients were evaluated both OFF and ON levodopa.

Results: A repeated measured analysis of variance (ANOVA) was conducted with medication (ON and OFF levodopa) and position (sitting versus standing) as within factor and group (ICB versus no-ICB) as between factors. We found a significant interaction position*medication ($F(1,25)=5,26$; $p=0,030$) and a trend toward significant effect of the interaction between medication and group ($F(1,25)=3,58$; $p=0,070$).
Indeed, ON levodopa there was an increase in the LF/HF ratio among ICB patients when sitting as compared to OFF levodopa ($p=0,002$), while the opposite effect was obtained in patients without ICB ($p=0,047$).
We did not find any significant correlation between heart rate variability parameters in sitting position and autonomic dysfunction scores, nor any differences in autonomic sub scores between the two groups.

Conclusions: Our results suggest that ICB patients show an increase in sympathetic tone when on levodopa compared to patients without ICB.
This is the first study to show that levodopa increases the LF/HF ratio in PD subject with ICB as measured by HRV and has an opposite effect in patients without this condition.

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Orthostatic hypotension in Parkinson's disease: is there a role for the locus coeruleus?

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Introduction: Orthostatic hypotension (OH) is a common and debilitating non-motor symptom in Parkinson's disease (PD) but the mechanisms underlying its development remain largely elusive. Peripheral and central noradrenergic denervation are both likely to play a key role[1]. Locus coeruleus (LC) is the main noradrenergic nucleus of the brain and its early degeneration in PD has been put in relation with a variety of non-motor symptoms, including OH, but with inconsistent results[2-4].

Objective: To test whether degeneration of the LC is associated with OH in PD.

Methods: A total of 21 cognitively intact PD patients and 52 age matched healthy volunteers (HC) underwent 3T magnetic resonance (MRI) with specific neuromelanin-sensitive FSE T1-weighted sequences for LC. For each subject, a template space-based LC-MRI was used to calculate LC signal intensity (LC ratio) and the estimated number of voxels (nVOX) belonging to LC[5,6]. In a case-control study we compared the two MRI-LC parameters in 11 PD patients with OH (OH+) versus 10 without OH (OH-) (matched for sex, age and disease duration) using Kruskal Wallis test. We also tested for correlations between subject's LC-MRI parameters and orthostatic drop in systolic blood pressure.

Results: PD with and without OH did not differ significantly based on demographics and clinical characteristics (LEDD, UPDRS-III, MoCA, HAM-A, HDRS, RBD and SCOPA-AUT scales), except for blood pressure measurements. Both LC ratio and nVOX were significantly lower in PD compared to HC, while no differences were observed between PD OH+ and PD OH-. Additionally, no correlation was found between the MRI-LC parameters and the orthostatic drop in systolic blood pressure or the clinical severity of autonomic symptoms (SCOPA-AUT score).

Conclusions: Our results failed to indicate that the LC MRI parameters were associated with the presence of OH in PD but confirmed a marked alteration of LC signal in PD patients.

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The indirect impact of COVID-19 on major clinical outcomes of people with Parkinson's disease or parkinsonism: a cohort study

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Background: The indirect impact of the COVID-19 epidemic on Major Clinical Outcomes (MCO) of people with Parkinson's disease (PD) or other parkinsonism is unknown.

Objectives: The study aimed to (1) describe changes in Health Care Services (HCS) during the first epidemic wave in people with PD or parkinsonism; (2) compare the occurrence of hospitalization for any PD-related MCO in 2020 with 2019; (3) investigate the factors, including changes in HCS, associated with MCO and death.

Methods: All HCS of the province of Bologna and MCO were assessed through a record linkage study (ParkLink Bologna). The same analyses were performed in a cohort of controls matched for age, sex, district of residence, and comorbidities (ratio 1:10).

Results: A cohort of subjects with PD (759) or parkinsonism (192) was included together with a cohort of controls (9,226). All indicators of HCS dropped at least below 50% during the lockdown period in all cohorts, mostly impacting physiotherapy in people with PD (−93%, 95% CI 88–96%). Compared to 2019, a three-fold risk of major injuries (RR 3.0, 95% CI 1.5–6.2) and infections (RR 3.3, 95% CI 1.5–7.2), excluding COVID-19, was observed in people with PD in 2020. Furthermore, in people with PD decreased physiotherapy was associated with the occurrence of at least one MCO (OR 3.3, 95% CI 1.1–9.8) and the experience of at least one MCO was the strongest risk factor for death (OR 30.4, 95% CI 11.1–83.4).

Conclusions: During the first COVID-19 epidemic wave, HCS were drastically reduced in a province of northern Italy, regardless of the disease condition. However, compared to 2019, in 2020, only people with PD had a higher risk of MCO, which were associated with higher mortality. Strategies to maintain physical activity in people with PD should be implemented in possible future health emergencies.

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Screening performances of an abbreviated UPSIT Italian version in Parkinson's disease diagnosis

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Introduction: Hyposmia is a frequent finding in Parkinson's disease (PD), usually tested through the University of Pennsylvania Smell Identification Test (UPSIT). Our study stems from a secondary analysis from our previous work validating the culturally adapted version of the 40-item UPSIT smell test for the Italian population [1], and is aimed at providing a briefer version of this test, able to discriminate between PD patients and healthy subjects (HS).

Materials and methods: We assessed the diagnostic performance of each UPSIT item through several univariate (Fisher's $\chi 2$, Odds Ratio, Area Under the Receiver Operating Characteristic-AUCROC-curve) and multivariate (machine-learning-based: Logistic Regression and Linear Discriminant Analysis) statistical approaches. Secondly, we selected the best-discriminating 8 items by which we trained a Partial-Least-Square Discriminant Analysis (PLS-DA) and a Decision Tree (DT) model aimed at class (PD vs. HS) prediction.

Results: The 8 selected items were coconut, apple, lilac, banana, watermelon, clove, motor oil, orange. Class predictions of PLS-DA and DT models performed better with the 8-item version when compared to the full 40-item version. Moreover, an AUC-ROC curve built with the selected odors showed the best performance (sensitivity 86.8%, specificity 82%) in predicting the PD condition at a cut-off point of ≤ 6. These performances were higher to those previously calculated for the 40-item UPSIT test (sensitivity 82% and specificity 88.2 % with a cut-off point of ≤ 21).

Conclusions: Our selection contains one odor (i.e., apple) which is Italian-specific, pointing out the need for cultural adaptation of smell testing; conversely, some of our selected best discriminating odors (namely, banana, orange, clove, coconut, motor oil) are in common with existing brief smell test versions validated on PD patients of other cultures, supporting the view that disease-specific odor patterns may exist. Further testing is needed to validate results on an independent cohort and to assess the PD-specificity of our odor subset.

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CSF biomarkers profile of patients with Parkinson's disease treated with different MAO-B inhibitors in add-on

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Introduction: Monoamino oxidase type B inhibitors (iMAO-Bs) are a group of widely-used antiparkinsonian agents which showed, at experimental level, neuroprotective properties in Parkinson's disease (PD) models. However, human-based proofs that iMAO-Bs exert neuroprotection are very limited and not completely univocal. Because of the proximity with the brain, cerebrospinal fluid (CSF) mirrors pathological changes occurring in neurodegenerative diseases, allowing tracking molecular events by the measurement of neurodegeneration-related peptides levels.

Objective: Analyse the CSF profile of classical neurodegeration-related biomarkers in PD patients chronically treated with different iMAO-Bs to identify biochemical signatures suggestive of potential neuroprotective effects.

Methods: The study involved 35 PD patients in add-on therapy with iMAO-Bs for at least one year (n=13 rasagiline, n=9 selegiline, n=13 safinamide). Levels of amyloid-β-42 (Aβ42), amyloid-β-40 (Aβ40), total and 181-phosphorilated tau (t-tau and p-tau) and lactate were measured following standard procedures. Aβ42/ Aβ40 ratio was also calculated. MDS-UPDRS part III, MoCA scores and levodopa equivalent daily dose (LEDD) were collected for each patient. Clinical and biochemical parameters were compared among the groups.

Results: No differences resulted in demographics and clinical parameters among patients under different iMAO-Bs. CSF t-tau, p-tau and lactate levels, instead, significantly differed. Post hoc analysis with Bonferroni correction and pairwise comparison revealed that patients under selegiline had higher levels of CSF t-tau (p=0,001), p-tau (p=0,019) and lactate levels (p=0,028) when compared to those under safinamide, and higher levels of CSF t-tau (p=0,005) and p-tau (p=0,030) when compared to those under rasagiline.

Conclusion: This pilot study showed that distinct iMAO-Bs could be associated to different profiles of CSF neurodegeneration-related biomarkers in PD. In particular, we found lower levels of tau proteins and lactate in patients under rasagiline and safinamide, compared to those under selegiline, which may depend on the respective pharmacological properties of each drug. Future studies are now needed to confirm and extend these preliminary findings.

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Acute worsening of Parkinson's disease symptoms after Sars-CoV-2 mRNA booster vaccination: two case reports

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Introduction: Several neurological complications following SARS-Cov-2 vaccination are described, although without a clear causal relationship [1], with few cases of Parkinson's Disease (PD) symptoms worsening, and new onset of movement disorders in non-parkinsonian patients. Some vaccine-related inflammatory response might trigger a temporary alteration of the basal ganglia activity.

Case report: We describe two cases of PD patients treated with device-aided therapy who developed parkinsonian symptoms worsening after receiving the third mRNA vaccine dose (booster) for Sars-Cov2.
The first patient is a 46-year-old man with 9-year PD history, implanted with bilateral Subthalamic Deep Brain Stimulation (STN-DBS) from 2019. Transient worsening of motor and non-motor symptoms occurred the same night after mRNA-1273 booster, which did not respond to medical therapy modification. His symptoms improved after bilateral increase of stimulation intensity. The patient achieved a good wearing-off control in the following days, and went back to his usual therapeutic regimen: mild dyskinesia resolved after restoring previous stimulation settings.
The second patient is a 55-year-old man with 13-year PD history, treated with levodopa-carbidopa intestinal gel (LCIG) infusion from 2021, who experienced severe worsening of dyskinesia from the same night he underwent BNT162b2 booster. We chose to reduce his continuous dose of LCIG, obtaining only partial reduction and re-emergence of OFF periods. Dyskinesia disappeared five days later: previous dose was restored, with good control of OFF periods and only mild, non-disabling, dyskinesia increase.

Conclusion: Our reports and other from literature recovered completely after a few days of parkinsonian therapy modification, symptomatic treatment, or even spontaneously, underlining the transient and benign nature of these possible side effects [1]. Patients should be reassured about these complications, manageable through a prompt evaluation by their reference neurologist, and encouraged to receive COVID-19 vaccines and boosters, highly recommended to prevent the risk of for a worse SARS-CoV-2 infection outcome [2,3].

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P96

Temporal stability of gut microbiota composition in relation to clinical features in Parkinson's disease

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Introduction: The concept of "gut–brain axis" was first introduced in the late 2000s [1] and later reviewed to include the role of the gut microbiota, turning it into the "microbiota–gut–brain axis". In the last years, several studies focused on the specific role of altered gut microbiota in PD [2]. Most of them, however, did not analyse the modifications of the gut microbiota composition over time.

Objective: We aim to investigate the composition of gut microbiota and clinical features of the disease in our study population over a period of 14 months.

Methods: We compared gut microbiota composition in 18 PD patients and 13 healthy controls (HC) at baseline and 1 year later. PD patients and HC underwent a faecal sampling at baseline and one year later for 16S rRNA amplicons analysis. PD patients also underwent clinical examinations, performed using Hoehn & Yahr (H&Y) staging scale and Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS) part III at baseline and at the follow-up visit.

Results: Results demonstrated stability in microbiota composition in both groups over a period of 14 months: both the number of species (alfa diversity) and the structure of gut microbiota community (beta diversity) did not undergo significant modifications. Differences in microbiota composition between PD patients and HC remained stable over time. Moreover, clinical features of the disease evaluated through clinical scales remained unchanged.

Conclusion: Our findings highlight microbiota stability over time. Consistently, PD patients did not show any clinical progression. In our opinion, these results may reinforce the idea of a correlation between clinical and microbiota stability over time, supporting the pathogenic role of gut microbiota change in PD patients. These results may open the scenario to more extensive longitudinal evaluations with a larger PD patient population at different stages of the disease.

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P97

Axial symptom resistance to levodopa in Parkinson's disease: a study of patients treated with continuous infusion of levodopa-carbidopa intestinal gel

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Background: The treatment of freezing gait (FoG) and other axial symptoms of Parkinson's disease (PD) is currently an unresolved challenge for clinicians. While these symptoms appear to be unresponsive to levodopa, there are no systematic evaluations of axial symptoms at progressively increasing doses of levodopa. We sought to analyze the response to high levodopa doses of FoG, posture, gait parameters, and speech occurring in a daily-ON therapeutic condition.

Methods: We performed an interventional study in PD patients treated with continuous infusion of levodopa/carbidopa-intestinal gel (LCIG) presenting FoG in daily-ON condition. Subjects were evaluated by quantitative outcome measures at their usual LCIG infusion rate (T1), and one hour after 1.5x (T2) and 2x (T3) increase of the LCIG infusion rate. Two blinded raters evaluated the number of FoG episodes (primary outcome), posture, speech, and gait parameters. We also analyzed any changes in motor symptoms, dyskinesia, and plasma levodopa concentrations.

Results: We enrolled sixteen patients (mean age of 69±9.4 years) treated with LCIG for a mean of 2.2±2.1 years. FoG improved in 83.3% of patients and the number of FoG episodes significantly decreased (mean 2.3 at T1, 1.7 at T2, 1.2 at T3; p:0.013). Posture and speech parameters did not significantly change; stride length, turn duration, and turn velocitysignificantly improved (p: 0.049; p: 0.001; p: 0.024) after doubling the levodopa dose.

Conclusions: Increasing the dose of levodopa dose acutely may improve 'dopa-resistant' FoG and gait parameters PD patients presenting optimal control of motor symptoms and fluctuation in the absence of significant dyskinesia worsening.

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MRgFUS thalamotomy may spare dopaminergic therapy in early-stage tremor-dominant PD: a pilot study

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Introduction: MRgFUS thalamotomy is a safe and effective procedure for drug-resistant tremor in Parkinson's daisease patients.

Objectives: The primary objective of this study was to demonstrate that MRgFUS VIM thalamotomy in early-stage tremor-dominant PD patients may prevent an increase in dopaminergic medication 6 months after treatment, compared to a matched control sample of PD patients on standard medical therapy alone.

Methods: We selected patients with early-stage PD who underwent MRgFUS VIM thalamotomy (PD-FUS) and patients treated with only standard dopaminergic therapy (PD-ODT) with a 1:2 ratio. We collected demographical, clinical data and adverse events at baseline, 6-months, and 12-months after thalamotomy.

Results: We included 10 patients in the PD-FUS group and 20 patients in the PD-ODT group. We found a significant increase in total LEDD and LEDD of levodopa plus MAOB-I in the PD-ODT group 6 months after the procedure.

Conclusions: In early-stage tremor dominant PD patients, MRgFUS thalamotomy may be useful to reduce tremor and avoid the need to increase dopaminergic medications.

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Assessment of cognitive outcomes in patients undergoing magnetic resonance imaging-guided focused ultrasound thalamotomy (MRgFUS): long-term safety and efficacy

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Introduction: Data about cognitive changes in patients with Essential Tremor (ET) and Parkinson's disease (PD) treated with Magnetic Resonance Imaging-guided Focused Ultrasound (MRgFUS) are controversial.

Objective: Our aim was to assess cognitive changes associated with the procedure.

Methods: In this prospective study, patients consecutively undergoing MRgFUS were assessed through a comprehensive neuropsychological battery [(Montreal Cognitive Assessment (MOCA), Frontal Assessment Battery (FAB), Verbal and Semantic Fluency Test, Mini-mental State Examination (MMSE), Rey Auditory Verbal Learning Test (RAVLT), Raven's progressive Matrices, Beck Depression Inventory-II (BDI-II), Hamilton Anxiety Rating Scale (HAM-A), Quality of Life in Essential Tremor Questionnaire (QUEST) and PD Questionnaire-8 (PDQ-8)] before and three and six months following the treatment. Data were analyzed with paired T-Test or Wilcoxon signed-rank tests and verified with Bonferroni's correction (0,05/3). A p value < ,016 was considered significant.

Results: Thirty patients (mean age 66,57±10,39, mean disease duration 9,96±5,53) with ET (n=18) and PD-related tremor (n=12) were included. At three months, an improvement in anxiety (HAM-A 5.47±4.64 Vs 2.23±3.42, p ,001), quality of life (QUEST 33.11±11.19 Vs 7.56±6.78, p < 001, PDQ-8 7.08±4.54 Vs 2.50±2.27, p ,005, mnestic functions (RAVLT: Immediately re-enactment 31.82±7.75 Vs 34.53±7.71, p ,014; RAVLT: Deferred re-enactment 5.32±3.16 Vs 6.28±2.26, p ,012), verbal fluency (Semantic Fluency 9.74±2.68 Vs 11.75±4.87, p ,005) and in the overall cognitive status (MOCA 23.73±4.05 Vs 25.07±3.03, p ,010) was observed. Anxious feelings (HAM-A 5.47±4.64 Vs 2.93±4.21, p ,004) as well quality of life [(QUEST 33.11±11.19 Vs 3.56±5.25, p < 001), (PDQ-8 7,08±4,54 Vs 1,33±1,49, p ,003)] and overall cognitive functions (MMSE 26,60±3,60 Vs 28,21±1,74, p ,013) also were improved at six months. No changes were detected in others cognitive domains.

Conclusions: Our study takes a step toward in endorsing the neuropsychological safety of MRgFUS, with a view to consider possible bilateral treatments, to date unapproved yet.

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Menstrual-related fluctuations in an early-onset Parkinson's disease patient treated with STN-DBS: correlation with local field potentials

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Introduction: It is known that sex hormones may influence motor function in Parkinson's disease (PD) patients, even though contradictory findings have been reported [1].

Objective: To describe the case of a PD patient who reported menstrual-related fluctuations of her motor symptoms and provide a correlation between objective evaluation and spectral analysis of local field potentials (LFPs).

Methods: This 21-years-old lady, harboring a homozygous mutation c.G859A in the *Parkin* gene, was treated with deep brain stimulation of bilateral subthalamic nucleus (STN-DBS) at age 20 reporting global clinical benefit after surgery. Nonetheless, she described troublesome changes in motor function in different phases of the menstrual cycle. She was thus enrolled in a study involving weekly examinations for a whole month. Serum levels of estradiol, progesterone, FSH, and LH were obtained. Objective evaluation was performed through the MDS-UPDRS III in different conditions (stim-off/med-off, stim-on/med-off, stim-on/med-on) and LFP spectral analysis was conducted using a sensing-enabled neurostimulator.

Results: In the late follicular phase (17b-estradiol=231 pg/mL) and in the luteal phase (17b-estradiol=155 pg/mL, progesterone=11.36 ng/mL), the clinical improvement in stim-on/med-off compared to stim-off/med-off reached its lowest values (10% and 7% respectively, highest benefit=48%). Decreased improvement in stim-on/med-on compared to stim-off/med-off (45% and 34%, highest benefit=70%) was observed as well. The suppression of beta activity was similarly affected by hormonal changes, as in the luteal phase both the stimulation alone and the combined effect of stimulation and dopaminergic therapy decreased beta activity respectively by 23% (highest suppression=42%) and 18% (highest suppression=44%). The percentage of beta activity reduction in stim-on/med-on from stim-off/med-off was predicted by serum levels of FSH (beta=0.994, P=0.006) and progesterone (beta= - 0.992, P=0.008), but not estradiol.

Conclusions: This study provides novel insights into the role of sex hormones in motor fluctuations of PD patients and their effect on the modulation of LFP activity.

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P101

Dysphagia as a poor outcome predictor in advanced Parkinson's disease patients treated with levodopa-carbidopa intestinal gel: a retrospective study

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Introduction: Dysphagia frequently occurs in advanced and late stages of Parkinson's disease (PD), and represent a significant risk factor for malnutrition and aspiration pneumonia. Some studies have highlighted the pivotal role of dysphagia in predicting disease progression; however, no one involved advanced PD patients treated with levodopa-carbidopa intestinal gel (LCIG).

Objective: To evaluate the impact of dysphagia on poor outcome measures in advanced PD patients under LCIG treatment.

Methods: We retrospectively collected records of 32 PD patients referring to our Movement Disorder Center who had started LCIG treatment between 2012 and 2022. The following records were collected: (I) demographic and clinical features; (II) detailed pharmacological therapy including LCIG dosage and total LEDD; (III) presence of dysphagia evaluated with a score >1 in UPDRS-2.3. We considered a primary composed endpoint, including the outcomes of "death", "HY=5," and "hospitalization". Secondary endpoints were the outcomes of "death" and "HY=5".

Results: There were 17 dysphagic (53%), and 15 non-dysphagic patients (47%). These groups were similar in terms of age, gender, disease duration, age and H&Y score at the time of LCIG implantation, treatment duration with LCIG, cognitive impairment, visual hallucinations. 10/17 dysphagic patients (59%) and 2/15 non-dysphagic patients (13%) met the primary endpoint ($p = 0.022$, LogOR 2.228). 8/17 dysphagic patients (47%) and 1/15 non-dysphagic patients (7%) met the secondary endpoint of "death" ($p = 0.032$, LogOR 2.521). 7/17 dysphagic patients (41%) and 1/15 non-dysphagic patients (7%) met the secondary endpoint of "H&Y=5" ($p = 0.066$, LogOR 4.529). 5/7 dysphagic patients (71%) who present H&Y=5, have presented an H&Y score <5 before the occurrence of dysphagia.

Conclusion: Our study demonstrates that dysphagia represents a poor outcome predictor in terms of occurrence of death, high functional impairment, and hospitalization in advanced PD patients treated with LCIG, highlighting the importance of prioritizing its management.

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Duodenal levodopa infusion in advanced Parkinson's disease: a 5-year retrospective study

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Background: Duodenal Levodopa Infusion (DLI) is a diffuse treatment for patients with advanced Parkinson's disease (APD),[1] that provides continuous levodopa stimulation by means of a percutaneous endoscopic gastrostomy with a jejunal extension tube (PEG-J) connected to a portable infusion pump.

Aim and Methods: The aim of the study is to investigate the long-term[2] motor outcome and safety of DLI in patients with APD. We retrospectively identified all patients treated with DLI from October 2009 to January 2020 at the Center for Movement Disorders of Perugia Hospital.[3] Patients demographics and clinical features, including MDS-UPDRS III score, PEG-J procedures, causes for any discontinuation, reported complications and mortality were collected.

Results: The study included 30 APD patients (median age 72±5.6 years; mean disease duration 17.2±5.7 years). Mean treatment duration was 35.6±30.6 months. Overall, 156 PEG-J procedures were performed. One patient discontinued treatment after 6 months, due to peripheral neuropathy. Six patients died for causes not related to DLI, during the first 4 years of treatment. The rate of reported complications increased during the first four years of treatment. Specifically, after 2 years, the rates of complication diverged, being device-related complications more frequent (0.8±0.4) than stoma related complications (0.4±0.5). Device-related complications remain the most frequently reported for the whole follow-up period. MDS-UPDRS III score also increased over time, reaching the peak after the first five years of treatment.

Conclusion: A continue follow-up up to 5 years of treatment with DLI can reduce the rate of complications and provide a better control on motor symptoms.

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Levodopa-carbidopa intestinal gel efficacy on freezing of gait and other features of gait: preliminary results from a 6-months prospective study

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Introduction: Levodopa-carbidopa intestinal gel (LCIG) showed some benefit on Freezing of Gait (FoG) and gait difficulties in advanced Parkinson's disease (PD), also in cases refractory to oral dopaminergic therapy [1,2]. As these assessments were primarily conducted by means of expert-delivered rating scales and patient judgment of severity of symptoms, there is a need of implementation by use of objective, observer-independent outcome measures.

Objective: To assess the efficacy of LCIG on FoG and spatiotemporal gait parameters by means of New Freezing of Gait Questionnaire (NFoG -Q), confirmed by technology objective measurement with APDM Mobility Lab™ motion sensors.

Methods: This is an observational open-label study enrolling patients screened as candidates for LCIG therapy, currently including 9 patients with several episodes of FoG a day in the month preceding the baseline evaluation. Assessment by sensors was first performed at baseline, before percutaneous endoscopic gastrojejunostomy implant, in the OFF and best-ON oral antiparkinsonian therapy condition, and repeated 3 and 6 months after starting LCIG therapy, during daily-ON condition.

Results: 5 of 9 patients have currently completed the 6-month follow-up, with a significant improvement at the NFOG-Q (from 15,8±4,2 to 10,6±6,1, p=0,013). The motion sensors confirm the improvement from baseline best-ON to 6 months daily-ON: a trend is valuable at the Two-minute walking test for gait speed and step duration (increase) and double support (reduction), at the Timed up and go test for duration (reduction), at the 360 degrees Turn Test for Turn angle (increase), and at the Sway test for Sway area (reduction).

Conclusion: Preliminary results from motion sensors suggest an improvement of gait features after LCIG start, confirmed by patients' subjective impression. The lack of response at three months could indicate the need for a longer time to induce synaptic plasticity processes within neuronal networks implicated in the genesis of the symptom [3].

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Polyneuropathy in levodopa-carbidopa intestinal gel infusion therapy

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Background: Levodopa-carbidopa intestinal gel (LCIG) is an effective treatment for advanced Parkinson's disease (PD). The benefits of LCIG are uneven among patients, with some discontinuing treatment due to device-related complications, disease progression (comorbidities/dementia), polyneuropathy, troublesome dyskinesias, and caregiver and/or patient dissatisfaction [1,2].

Object: Rate of polyneuropathy-related LCIG with Vitamin-B-complex and folate supplementation.

Methods: Information on neurological, medication, and LCIG implant history were extracted from the medical records of 52 patients treated with LCIG between 2010 and 2020 in Ferrara. Data on electroneurography-electromyography (ENG-EMG) at baseline and during follow-up (up to 12 years) were used to detect the rate of polyneuropathy occurring during treatment and its relationship to LCIG discontinuation.

Results: Of 52 patients (mean-age 72,1±6,2; disease-duration-months 234,1±88,5; mean-months-on-LCIG-therapy 54,9±30,5), twenty-two (42,3%) discontinued the treatment: 36,4% (8 patients) for late stage-dementia and/or psychosis, 27,2% for device-related complications, 27,2% for comorbidities, 9,1% for narrow therapeutic window, one for troublesome-dyskinesia, and one for polyneuropathy. Patients who discontinued treatment had a significance longer PD duration (271,6±85,1 vs 206,5±81,6 months; *p-value* <0,01) without differences in LCIG duration treatment (54,0±35,6 vs 55,62±26,7), continuous dose (3,3±1,1 vs 3,4±0,9), and age (69,2±6,8 vs 71,2±5,9) . At baseline 19,2% showed sensory/motor axonal polyneuropathy; during follow-up the rate reached 23,4% (*ns* p=0.14). However, only one patient, who had already toxic polyneuropathy at baseline, had severe sensory-motor axonal neuropathy, leading to discontinuation of LCIG after 8 months.
All patients received treatment with VitB-complex and folate after implantation (4,3±6,4 months), with no difference in treatment initiation (*ns* p=0.07).

Conclusion: In our patient cohort, one patient, who had polyneuropathy before LCIG, discontinued treatment for worsening polyneuropathy. In long-term follow-up (12 yrs), we do not have another case of polyneuropathy that led to discontinuation. We confirm that vitamin intake and proper EMG-ENG/clinical follow-up can reduce the rate of polyneuropathy in LCIG-treated patients and, consequently, the treatment discontinuation [3].

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Effects of adaptive deep brain stimulation on attention in patients with Parkinson's disease

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Introduction: Adaptative Deep Brain Stimulation (aDBS) is a recent development of DBS in which the stimulation is modulated according to the clinical state of the patients [1].
However, before aDBS comes into clinical practice it is necessary to prove its safety and efficacy.

Objectives: The main objective of this study is to assess the side effects of aDBS on attentive functions using a simple reaction times task (RTs) during an 8-hours session also considering effects of levodopa medication.

Methods: 16 patients with PD [(mean±SD) age 58±8; UPDRS 31 ± 9; 4 Female] implanted with electrodes in the bilateral STN were enrolled in the study. The experiment was conducted 6 days after surgery and patients were stimulated with an external aDBS device. Patients were evaluated with a simple RTs task four time throughout the 8 hours in correspondence to "on aDBS-on medication" condition (T0, T2) and to "on aDBS-off medication" condition (T1, T3). We calculated mean RTs between T0 and T2 (on-on condition) and between T1 and T3 (on-off condition) to compare the effects of aDBS when medication was in on VS off state.

Results: Paired sample T-tests showed no RTs differences between the mean RTs in 'on-on' conditions and RTs in 'on-off' conditions t(16) = - 1,34 p = 0,198. [on-on Mean ± S.D. VS on-off Mean ± S.D. (456,06 ± 93,84; 479,78 ± 129,35)]

Conclusions: RTs are a reliable method to assess the effectiveness of DBS [2], to date no difference between conventional DBS and aDBS in RTs has been found in parkinsonian monkeys [3].
In our study, we showed that the pharmacological off-state had no effects in slowing RTs when aDBS was on, suggesting that aDBS could be effective even during pharmacological off-state without psychomotor or attention side effects.

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Sleep modulation in Parkinson's disease patients with deep brain stimulation: the role of frequency variations

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Introduction: Deep Brain Stimulation (DBS) is an effective treatment for motor symptom in Parkinson's disease(PD). Low frequencies stimulation of Subthalamic Nucleus (STN) probably improve gait disorders for an involvement of the Peduncolo-Pontine Nucleus (PPN). The aim of our study was to investigate the differences between low (60Hz) versus high (130hz) frequencies of STN DBS in PD patients (PD-DBS) in sleep parameters. We also explored differences in sleep parameters between PD-DBS and PD patients with only medical treatment (PD-MED) and healthy controls (HC).

Matherial and Methods: PD-DBS, PD-MED non demented patients and HC were recruited. All subjects underwent a full night laboratory polysomnography, while PD-DBS performed two recordings in different non consecutive days: a night with 60Hz frequency of stimulation, one night with 130Hz frequency of stimulation. Sleep conventional macrostructure and microstructure analysis was performed. Motor symptoms were evaluated with validated scale and with a wrist Actigraphy.

Results: In our study 10 PD-DBS patients, 10 PD-MED and 10 HC were enrolled. PD-DBS patients presented increased REM sleep during 60Hz stimulation compared to 130Hz. NREM sleep (macrostructure and microstructure) was not significantly modified in the two stimulation conditions. Tremor was significantly higher at 60Hz frequency of stimulation than 130Hz. When the three groups were compared PD-MED presented a significant lower number of REM periods and a trend towards significant of lower REM percentage than HC; PD-DBS patients when stimulated with 60Hz showed REM percentage and number of REM periods higher than PD-MED and with values similar than HC.

Conclusion: Low frequencies stimulation of STN could increase REM sleep, suggesting a possible involvement of PPN. STN stimulation at 60Hz seems to not cause modification of NREM sleep and microstructure of sleep, while DBS shows globally a modulation effect on sleep improving sleep parameters compared to PD-MED patients.

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Asymmetry and side concordance of rest tremor and bradykinesia in patients with essential tremor

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Introduction: Subtle parkinsonian signs, i.e., rest tremor and bradykinesia (movement slowness), can occur in patients with essential tremor (ET) [1] and can be considered soft signs for the definition of ET-plus [2].

Objective: To investigate in a broad sample of ET patients the clinical and kinematic features of rest tremor and bradykinesia with particular attention to their body distribution and side concordance.

Methods: Eighty ET patients were enrolled. Upper limb action (postural and kinetic) tremor, rest tremor, and bradykinesia during finger tapping, were assessed by using standardized clinical scales and a kinematic system for movement analysis. We then investigated tremor asymmetry and side concordance between motor symptoms in ET patients.

Results: Thirty-one out of 80 patients (38.75%) had clinically detectable upper limb rest tremor. In 21 of them (67.74%), rest tremor was clearly asymmetric. In patients with rest tremor, the kinematic analysis of finger tapping revealed an asymmetry of the movement velocity in 17 cases (54.84%). However, in most patients (10 out of 17, 58.82%), there was no side concordance between rest tremor and bradykinesia. Conversely, in our sample, we observed a side concordance between asymmetric postural tremor amplitude and bradykinesia in a high percentage of cases (9/11 patients, 81.82%: $p=0.01$).

Conclusions: Rest tremor and bradykinesia are relatively frequent features in patients with a clinical diagnosis of ET. Our findings suggest that rest tremor and subtle bradykinesia (movement slowness) in ET possibly reflect different pathophysiological mechanisms [3]. Conversely, the side concordance between postural tremor and bradykinesia in ET suggests that these two motor alterations may have a common pathophysiological basis, possibly reflecting the prominent cerebellar involvement in this condition.

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P108

Basal ganglia lesion due to diabetic striatopathy can result in a different threshold for drug induced movement disorders

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Background and objectives: Diagnosis of Diabetic striatopathy (DS) is based on both clinical assessment and striatal hyperintensity on T1-weighted MRI [1]. Here we report two patients with acute DS who have developed early contralateral parkinsonism following treatment with dopamine-depletors.

Results: An 81-year-old male patient and a 71-year-old woman with type II diabetes mellitus in poor glycemic compensation were admitted to our department for the acute onset of left upper and lower limb choreic involuntary movements. The man began to complain of the insidious appearance of choreic left arm movements after 20 days from insulin withdrawal; in the second case no therapeutic switch had been made. On admission their Glycated Hemoglobin level was 76 and 105 mmol/mol (standard value 20-42), respectively. T1-weighted brain MRI showed area of altered signal in the right putaminal region in both patients [2]. [123I]-FP-CIT was performed in case 2 and showed a slight but non-significant reduction of the radiotracer uptake in the right putamen. Treatment with Haloperidol was started up to 2-3 mg/day [3] with a good response within a few weeks. After 2 months they both complained of clumsiness with the right upper limb and a tendency to crawl the homolateral foot on the ground. On neurological examination a right-sided marked bradykinesia with moderate rigidity was noted. Therapy with Haloperidol had been gradually reduced until suspended, with marked improvement of the hypokinetic disorder.

Conclusions: It's quite unusual for DS to happen during a therapeutic switch as in our first patient, infact there are no cases described in the literature. We could therefore hypothesize a different susceptibility of basal ganglia to the effect of dopamine-depletors: a structural damage of the striatal pathway could result in higher threshold, making drug effective against the hyperkinetic disorder. Iatrogenic parkinsonism relative risk is usually related to the duration of treatment with neuroleptic drugs [4]; in our patients instead, a lower threshold in the healthy basal ganglia side caused the early appearance of parkinsonism.

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P109

Leg restlessness and hyperparathyroidism in Parkinson's disease: a further cue to RLS pathogenesis?

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Introduction: Leg restlessness is frequent in Parkinson's disease (PD) and a key symptom of restless leg syndrome (RLS), whose pathogenesis is still debated. The latter has been associated with dopaminergic impairment and with other conditions such as renal insufficiency. PD patients frequently report low levels of vitamin D, which have been related to poor quality of sleep but not specifically to RLS [1]. Our aim was to investigate the potential association between vitamin D and PTH metabolism with leg restlessness in PD.

Methods: 50 PD patients were investigated with motor and non-motor scales and stratified according to the presence of leg restlessness at NMSQ. Serum levels of vitamin D, PTH, calcium, and phosphate, data on supplementations, and calcium intake were also obtained.

Results: In our sample, 36% of patients reported leg restlessness. Almost 80% had low vitamin D, while secondary hyperparathyroidism was diagnosed in 21 subjects (45%). Leg restlessness was significantly associated with worse motor symptoms and quality of sleep. Moreover, it was associated with hyperparathyroidism (OR 3.48) and with PTH levels, independently of vitamin D, calcium/phosphate levels, and motor status (multivariate model, p=0.02).

Conclusions: A relationship between PTH metabolism and parkinsonism has been anecdotally reported [2]. Here for the first time, an intriguing relationship between PTH and leg restlessness in PD was observed. PTH has a putative role in nociceptive modulation, moreover recent literature documented a link between hyperparathyroidism and RLS in patients with renal insufficiency (secondary hyperparathyroidism) [3]. Herein, the presence of secondary hyperparathyroidism - possibly caused by low vitamin D - relates independently to the presence of leg restlessness, adding PTH to the non-dopaminergic landscape of non-motor symptoms in PD.

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P110

A case of abdominal myoclonus secondary to spinal cord stimulation

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Introduction: Myoclonus is defined as brief, rapid involuntary movements caused by muscular contractions. Abdominal myoclonus (AM) is a rare form of spinal segmental myoclonus whose aetiology may include functional or structural lesions of the spinal cord, causing abnormal rearrangement of the spinal circuitry [1].

Objective: To describe a case of acute/subacute onset AM due to spinal cord stimulator (SCS).

Methods: Retrospective examination of medical charts and report of a single case of AM.

Case presentation: A 78-year-old man was admitted for acute/subacute onset of AM. Patient had seven years-long history of Parkinson's disease (treated with pramipexole 1.05 mg/die) and previous spinal surgery for severe spondylosis. Because of a severe low back pain syndrome, he was implanted either with a spinal cord stimulator (SCS) (leads placed at T7 level), or an intrathecal morphine delivery system (providing 1.5 mg/die), five and one year earlier respectively. Neurological examination showed AM, exaggerated in supine position; sensory stimuli and distraction tasks, did not affect AM. Besides parkinsonian syndrome, no further focal signs emerged. Spinal RX showed the correct leads placement. Video EEG polygraphy excluded focal epileptic activity. Patient was initially treated with clonazepam (up to 2 mg/die) and gabapentin (up to 900 mg/die), with no significant improvement (pramipexole was continued). Of relevance, AM presented a sudden increase in amplitude and intensity during a recharge session of the SCS. Turning-off the SCS, the AM completely resolved in few minutes, without reappearing in the successive six months.

Conclusions: This case indicates that AM can be secondary to SCS. Muscle spasms are reported in literature as rare side effects [2][3] of SCS implantation, probably due to the spinal anterior horn cells hyperexcitability. Here, we observed a direct time correlation between AM worsening and SCS recharge first, and the complete resolution of AM after switching-off of the device.

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P111

Kinematic analysis of mild bradykinesia features in frail elderly people

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Introduction: Mild Parkinsonian signs, including bradykinesia, commonly occur in elderly people with a prevalence ranging from 15% to 95% [1].

Objective: To kinematically characterize the possible bradykinesia features in elderly people in relation to their overall frailty.

Methods: We enrolled 41 healthy subjects (25 F, mean age ± 1 SD: 63.9±8.91, range 46-83 years). The kinematic analysis of bradykinesia included repetitive finger-tapping analysis. We measured the number of movements, as well as rhythm (coefficient of variation - CV), amplitude, velocity, and amplitude decrement (sequence effect) of repetitive movements. Along with demographic and clinical data collection, including the Mini-Mental State Examination (MMSE) and the Frontal Assessment Battery (FAB), we evaluated the frailty status of all participants using a 40-item Frailty Index (FI). The possible relationships between demographic and clinical data and kinematic movement features were assessed by Spearman's correlation test.

Results: First, we found a significant positive correlation between the CV and the FI ($r= 0.42$, $p<0.01$), i.e. the higher the CV (more altered movement rhythm) the higher the subject frailty. Second, we found that the sequence effect positively correlated with the age of subjects ($r=-0.34$, $p<0.05$), i.e. the greater the sequence effect during finger-tapping, the older the subject.

Discussion: The kinematic analysis of finger tapping allows an objective assessment of bradykinesia features in frail elderly people. The correlation between altered movement rhythm and the overall frailty of the subject possibly reflects a frontal dysfunction (given previous studies suggesting a relationship between altered movement rhythm and executive dysfunction as well as between executive dysfunction and frailty). The correlation between the sequence effect and the age of the subject possibly reflects altered network dynamic and synaptic plasticity alterations primarily due to aging.

Conclusions: The preliminary data emphasize the importance of the quantitative assessment of bradykinesia features in the frail elderly population, which are possibly underestimated and likely reflect distinct pathophysiological mechanisms. The present results require confirmation on a larger sample of healthy subjects.

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P112

CAWEDD (Cerebellar Ataxia With Evidence of Dopaminergic Deficit): CANVAS is the last on the list

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Introduction: Cerebellar Ataxia, Neuropathy and Vestibular Areflexia Syndrome (CANVAS) is caused by biallelic intronic AAGGG repeat expansions in the *RFC1* gene, and is the major cause of late-onset hereditary ataxia. *RFC1* expansions are also responsible for a significant percentage of "idiopathic" sensory neuropathy, without ataxia. Nigrostriatal degeneration at [123I]-FP-CIT is a typical finding of MSA-C, but has also been reported in a number of hereditary ataxias such as SCA2, 3, 6, 17, 31, SPG7, and AOA1, with or without parkinsonism. Interestingly, biallelic *RFC1* expansion has been reported in patients with Parkinson's disease and without ataxia as well as in cases with MSA-C.

Objective: We present two patients with CANVAS who showed DAT evidence of nigrostriatal degeneration. The aim is to provide further evidence of dopaminergic deficit in hereditary cerebellar ataxias, by adding to the list the one thought to be the most frequent.

Methods: We performed clinical evaluation, ENG/EMG, brain MRI, [123I]-FP-CIT, and genetic investigation of *RFC1* expanded alleles.

Results: Both patients carried biallelic intronic AAGGG repeat expansions in *RFC1* and showed slowly progressive ataxia associated with cerebellar atrophy and axonal sensory neuropathy. Interestingly, [123I]-FP-CIT revealed nigrostriatal degeneration despite the absence of parkinsonism.

Discussion: CANVAS represents the latest member of a large group of pathologies grouped under the umbrella of CAWEDD (Cerebellar Ataxia With Evidence of Dopaminergic Deficit). The pathophysiological mechanisms underlying loss of dopaminergic neurons in cerebellar ataxia is not clear. Intriguingly, cerebellar dysfunction seems to be protective towards parkinsonism despite presence of nigrostriatal denervation: subthalamic nucleus lesion, observed in SCA2 and SCA3, may counteract the effects of the nigrostriatal depletion and therefore explain the lack of clinical parkinsonism; however, disruption of the cerebellum may be itself the principal mechanism preventing and/or compensating the motor effects of striatal denervation in patients with ataxia. We suggest to consider *RFC1*-related diseases in late onset cases where ataxia combines with [123I]-FP-CIT abnormalities.

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Hypermobile spectrum disorders symptoms in patients with functional neurological disorders and autism spectrum disorders : a preliminary study

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Introduction: Functional Neurological Disorders (FND) and Autism Spectrum Disorders (ASD) share some common features in terms of alexithymia, sensory sensitivity and interoceptive issues [1]. Recent evidence shows that both present symptoms compatible with hypermobile Ehlers-Danlos Syndrome and Hypermobile Spectrum Disorders (hEDS/HSD), a heterogeneous group of heritable connective tissue disorders.
Objectives: To compare the prevalence of hEDS/HSD in patients with FND and individuals with High-Functioning ASD (HF-ASD).

Methods: Twenty patients with FND and twenty-seven individuals with HF-ASD were recruited at the tertiary level outpatient clinic of ASST Santi Paolo e Carlo, Presidio San Paolo (Milano, Italy); diagnosis of FND was made according to DSM-5 diagnostic criteria by a neurologist and a psychiatrist. Twenty-six neurotypical healthy controls (HN) were recruited amongst hospital staff and acquaintances. Participants completed the Self-reported screening questionnaire for the assessment of Joint Hypermobility Syndrome (SQ-CH) [2], a seven-item instrument including the Hakim and Grahame's five criteria and two additional ones. Correlation between the instrument and the widely used Beighton's criteria is high ($r = 0.9$; $p < 0.001$).

Results: 55% of the patients with FND, 44.4% of the individuals with HF-ASD and 30.8% of HN scored above the cut-off at the SQ-CH. SQ-CH scores of both FND and HF-ASD groups were significantly higher than the HN group ($p=0.039$ and $p=0.043$ respectively); no difference emerged between FND and HF-ASD ($p>0.05$).

Conclusions: Both individuals with HF-ASD and patients with FND present hEDS/HSD-related symptoms in a higher number than the general population. Imputable mechanisms include (1) overwhelming of executive functions with consequent motor competence impairment for HF-ASD patients, and (2) exacerbation of FND symptoms by physical injury and chronic pain due to abnormal range of joint mobility. Moreover, it is postulated that the amygdala and the anterior cingulate cortex circuitry are responsible for the imbalances at the proprioceptive, interoceptive, and emotional levels.

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P114

Prevalence and features of non-motor symptoms in Wilson's disease

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Introduction: Wilson's disease (WD) is an autosomal recessive disorder caused by excessive copper deposition in liver, brain and other organs [1,2]. The clinical picture is characterized by hepatic, psychiatric and neurological dysfunction. Movement disorders are the core neurological features, although non-motor symptoms (NMS), as cognitive/affective, autonomic and sleep disorders, may occur over time [2,4]. We aimed to assess the frequency of NMS in WD patients compared with healthy subjects.

Methods: Twenty-seven patients affected with genetically proven WD (12 F, 15 M) and 35 healthy controls (Ctrl; 17 F, 18 M), comparable for age and education, were enrolled. Eighteen patients presented with the neurological form of the disease (NV) and nine with the non-neurological variant (NNV) [3]. NMS were assessed in all subjects by the following clinical scales: Mini-Mental State Examination (MMSE), Non-Motor Symptoms Scale (NMSS), SCOPA-AUT Questionnaire, Apathy Evaluation Scale (AES), Beck Depression Inventory (BDI), Epworth Sleepiness Scale (ESS), Restless Legs Syndrome Rating Scale (RLSRS), REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease (QUIP-RS).

Results: We found that the patients showed more severe and frequent NMS and daytime sleepiness, and lower MMSE than Ctrl. In comparison to healthy subjects, NV subjects showed statistically significant higher ESS, NMSS, and RLSRS scores, and a lower MMSE score. Subtle and subclinical extrapyramidal/pyramidal signs and brain MRI signal abnormalities were detected in patients considered as asymptomatic for neurological disturbances.

Conclusions: NMS are common among WD patient, in particular those with NV, likely due to the widespread pathological changes throughout the central nervous system.

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A case of functional lingual tremor-like dyskinesia after COVID-19 vaccine

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Introduction: COVID-19 vaccination program is currently involving billions of people worldwide and the presumed side effects of the vaccine are under the scrutiny of the scientific community. Among others, functional neurological symptoms (FNS) have been reported [1,2].

Objective: To describe the case of a patient who presented functional tremor-like dyskinesia of the tongue 3 days after the vaccination against COVID-19 (Moderna-Spikevax).

Methods: AM, a 20 years old Italian female, suddenly developed a lingual dyskinesia, then replaced by lingual tremor, increasing when she was in tension. EEG and MRI appeared without alteration; neurological examination described only a variable tremor-like movement of the tongue, partially reduced by distracting maneuvers; psychiatric examination showed initial insomnia, anxiety symptoms and depressed mood during the previous year. Final diagnosis was a functional dyskinesia of the tongue, precipitated by COVID-19 vaccine, in the context of a probable adjustment disorder with mixed anxiety and depressed mood. A follow-up in a tertiary level specialized clinic for FNS, with psychiatric and psychotherapeutic input, was recommended. At the following evaluations, the lingual symptomatology appeared stabilized, but the anxiety and depressed mood persisted; hence, sertraline 50mg/die was recommended.

Conclusions: The precipitating factors for the development of FNS after COVID-19 vaccination are likely to be ascribed to expectations, beliefs, arousal, and emotional processing, especially in people whit biological, social, and/or psychological predisposition [1]. This issue should be dealt on two levels: primary and secondary prevention. First, it would be useful to share vaccine safety data with recipients, to allay their excessive emotional involvement and anxiety; second, prevent the misdiagnosis of FND should be a goal of scientific literature. This could be achieved by studying and acknowledging FND as a possible side effect of the COVID-19 vaccine, in order to be able to promptly recognize the nature of the symptom and to investigate it with adequate examination.

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Socio-cognitive deficits in spinocerebellar ataxia SCA2

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Introduction: The idea that regarded the cerebellum as a control center for movement and related behaviors has been revised. Recent studies show how involved it is in the control of functions defined as "non-motor", including cognitive functions, emotions, and social cognition and mentalization [1,2]. The areas that modulate these abilities reside in the posterior part of the cerebellum (regions called Crus I and II), and have projections towards the dorsomedial prefrontal cortex (dmPFC), the temporo-parietal junction (TPJ) and the precuneus [3]. One of the main tasks of this complex network is to regulate social behavior, and due to Its extension, It might also account for the disfunction of other cognitive abilities such as attention, language, memory and executive functions [4].

Objective and methods: Aim of this study is to investigate through neuropsychological tools what are the consequences of the malfunctioning of this network in terms of social cognition and mentalization ability in patients with spinocerebellar ataxia (SCA2 subtype), under treatment at the AOU Maggiore della Carità in Novara. The neuropsychological battery includes screening tests for global cognitive functioning and specific tests for each domains (attention, memory, language, executive functions). Mentalization skills and social cognition were assessed by “Reading the mind in the eyes” test and “Faux pas” test. We also monitored the possible presence of anxious, depressive and apathy states.

Results: An initial analysis of the data reveals a difficulty in the tasks of recognizing the expressions and emotional state of others, and a worse performance as regards executive functions and memory.

Conclusion: In conclusion, knowing and understanding the difficulties of specific cognitive functions and social cognition/mentalization could help to better manage patients and caregivers. It also help to set up preventive treatments (cognitive stimulation and enhancement of mentalization skills). Finally, it might represent a sort of preclinical marker of the disease.

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Pure autonomic failure: which markers of phenoconversion to central alpha-synucleinopathies? A clinical case

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Introduction: Pure autonomic failure (PAF) is a neurodegenerative disorder of the autonomic nervous system characterized by peripheral deposition of a-synuclein in autonomic ganglia and nerves. However, patients with PAF may progress into other synucleinopathies with CNS involvement.

Clinical case: A 48 years-old women developed hortostatic hypotension (OH) with frequent syncope. She was seen at our clinic, at the age of 58. Autonomic testing showed neurogenic OH and anhidrosis. Supine plasma norephinephrine levels were <25pg/ml and HR was 68bpm. Constipation, urinary urgency, loss of smell and a history of RBD were referred. Neurological examination and [123I]-FP-CIT
were normal, whereas 123-I MIBG demonstrated a cardiac denervation. A diagnosis of PAF was made. The patient underwent to follow-up visits every 4 months. Five years later, she developed mild generalized bradykinesia, hypomimia and difficulty performing fine movements mainly on left hand. A [123I]-FP-CIT was repeated demonstrating presynaptic dopaminergic deficit in both putamen and in both caudate nuclei (right>left). Levodopa and rasagiline were started with good response on motor symptoms (UPDRS 11vs23).

D*iscussion:* The age of the onset of autonomic failure in our patient was 48 years and the time of phenoconversion to diffuse synucleinopathy was 15 years. It has been suggested that the early onset of autonomic failure (before the age of 50) makes phenoconversion to MSA more likely than PD/DLB (mid-60s) and that the time of phenoconversion to MSA is about 5y compared to PD/DLB, which is expected to be 9.5y. The combination of olfactory dysfunction, RBD and cardiac denervation is considered a predictor of phenoconversion to PD. Furthermore, plasma norepinephrine levels<110 pg/ml and HR<70 bpm are more associated with patients maintaining the PAF phenotype [1]. Our patient presented with a combination of these signs and symptoms. The coexistence of different prognostic markers should suggest careful clinical follow-up of patients with PAF.

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P118

Tremor syndromes in the elderly: three cases

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Introduction and objective: We report three patients who presented a late onset, slowly progressive tremor syndrome associate to mild parkinsonian, cerebellar and psychiatric features.

PATIENT 1: 82 years old man who presented with gait and balance disturbances associated with bilateral hand tremor, with onset 2 years ago. On examination, we can appreciate mild cerebellar ataxia, dysmetria of left arm and intentional tremor of both hands.

PATIENT 2: 63 years old man who reports tremor of both hands, mild depressive symptoms and behavioral issues which started ten years ago. On examination, he showed bilateral rest and action tremor, mild clumsiness on finger tapping and difficulty in tandem gait walking.

PATIENT 3: 60 years old woman generalized tremor syndrome, which started 8 years ago. On examination, she showed mild bradykinesia in finger tapping bilaterally and rest and action tremor on the four limbs, head and chin. She also reported anxiety and mild depression.

Methods: The patients underwent Brain MRI, routine laboratory testing, neuropsychological assessment and FMR1 gene PCR analysis.

Results: Laboratory workout showed normal findings. Neuropsychological and behavioral assessment of patient 2 reported a control disorder and decrease of motivation without cognitive issues. Brain imaging of patient 1 and 2 showed diffuse cerebellar atrophy and hyperintensity of middle cerebellar peduncles. MRI of patient 3 showed diffuse supratentorial atrophy associated with white matter hyperintensity. Therefore, they underwent genetic testing for Fragile X-associated tremor/ataxia syndrome (FXTAS), that revealed a CGG expansion in the permutation range in FMR1 gene (respectively 88, 106 and 100 CGG repeats).

Conclusion: Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late onset neurodegenerative disorder characterized by progressive ataxia, tremor, cognitive involvement, neuropathy, and autonomic dysfunction. The diagnosis should be considered in elderly patient who present these clinical features with or without family history for Fragile X syndrome (FXS). Brain MRI can provide an important support for diagnosis that must be confirmed by genetic test.

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STN-DBS does not increase the risk of sialorrhea in patients with advanced Parkinson's disease

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Background: Sialorrhea is a frequent and disabling symptom in patients with Parkinson's disease (PD) [1]. To date, no study has been specifically designed to test the effects of deep brain stimulation (DBS) on sialorrhea in PD.

Objective: We aimed to evaluate the effect of STN-DBS on the development of sialorrhea in PD patients, assessing its incidence rate and risk factors in the long-term follow-up.

Methods: Sialorrhea development was retrospectively evaluated in two groups of STN-DBS and medically managed PD patients. Risk factors for sialorrhea were evaluated collecting demographic and clinical data.

Results: A total of 132 patients (88 with DBS and 44 on medical treatment) were included. The demographic and clinical variables, including sialorrhea, were similarly distributed between the two groups. Throughout the follow-up period [mean 7.9 years for the DBS group and 4.6 years for the control group], 24 DBS patients and 7 controls developed new onset sialorrhea. Sialorrhea incidence did not differ between the STN-DBS and the control groups: 49.2 and 43.7 per 1,000 person-years of observation respectively ($p = 0.8$). Male sex [hazard ratio (HR) 1.6, $p = 0.006$], Hoehn and Yahr (HY) stage (HR 2.6, $p = 0.006$), and dysphagia (HR 3.5, $p = 0.002$) were independent risk factors for sialorrhea. Interestingly, STN-DBS did not significantly increase the risk of developing sialorrhea (HR 1.4, $p = 0.3$). Comparing DBS patients with and without new onset sialorrhea, no difference was found for stimulation parameters.

*Conclusions***:** In our cohort, the risk factors for sialorrhea were male sex, HY stage, and dysphagia, as previously described in literature [2]. The present study shows that STN-DBS does not increase the risk of developing sialorrhea in the long term follow-up, suggesting that sialorrhea is a consequence of the underlying neurodegenerative disease, regardless of DBS.

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P120

Long-term effects of bilateral STN-DBS on speech in Parkinson's disease patients

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Introduction: Speech alterations are very common and disabling in Parkinson's disease (PD) patients. However, mixed results have been reported regarding the effects of bilateral Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) on speech.

Objective: To evaluate the long-term effects of bilateral STN-DBS on speech in a cohort of advanced PD patients.

Methods: This observational study included 25 consecutive advanced PD patients treated with bilateral STN-DBS. Demographic, neuroimaging, and clinical variables were collected. Each patient underwent a neurological evaluation (performed using UPDRS part III score and subscores) and a perceptual-acoustic analysis of speech in OFF- and ON-therapy conditions before surgery. All patients have been reevaluated in the long-term in different stimulation and drug conditions (on-stimulation/off-medication; off-stimulation/off-medication; on-stimulation/on-medication). The primary outcome was the percentage change of speech intelligibility obtained by comparing postoperative on-stimulation/off-medication condition with preoperative off-medication condition. Based on the presence/absence of postoperative worsening of speech intelligibility, patients were divided into two groups ("stable" vs "worsened") that were compared to find significant differences in demographic, clinical and speech variables.

Results: 25 PD patients treated with bilateral STN-DBS with a mean five-year follow-up were included. In the long-term, speech intelligibility did not worsen if compared with preoperative values. STN-DBS led to a significant improvement of speech intelligibility ($p<0.005$) in the postoperative assessment by comparing the on-stimulation/off-medication and off-stimulation/off-medication conditions. Patients included in the "worsened" subgroup (n=9) showed: greater PD motor severity before surgery; postoperative worse speech intelligibility, higher shimmer of sustained phonation and lower intensity of both spontaneous speech and sustained phonation.

Conclusions: Our results highlight the possible long-term beneficial effects of bilateral STN-DBS on speech intelligibility in advanced PD patients. The identification of PD clinical characteristics associated with long-term worsening of speech after surgery may allow to improve the prognostic accuracy and to employ early speech interventions.

P121

Impact of GBA variants on deep brain stimulation clinical outcome in Parkinson's disease patients

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Background: Deep brain stimulation (DBS) has become a routine treatment option for improving quality of life in Parkinson disease (PD). Although longstanding DBS in PD patients can impair cognition with a negative impact on verbal fluency, the occurrence of dementia is not higher compared to general PD population. GBA heterozygous variants are a well-known risk factor for PD and result in earlier disease onset and more malignant phenotype compared to non-carriers. Yet, how this genetic factor could influence the long-term outcome of DBS remains unclear.

Aims: To evaluate the prognostic role of GBA variants on the clinical outcome of DBS in PD patients.

Methods: We retrospectively analysed genetic and clinical data from our cohort of DBS-PD patients upon stratification for the presence/absence of *GBA*variants. All patients underwent pre-DBS evaluation and had a regular follow-up visit after surgery. Clinical assessment included: MDS-UPDRS in both ON and OFF state, cognitive evaluation and levodopa equivalent daily dose (LEDD).

Results: 84 DBS-PD patients were genotyped, of whom 16 carried GBA variants (9F/7M, disease duration 13,9±5.8 yrs; target DBS: 13 STN/3 GPI). Among GBA-PD, 7 had severe variants, 4 mild variants, 5 risk alleles. After surgery, all GBA-PD showed persistent motor improvement, with satisfactory control of motor fluctuations and dyskinesias. LEDD was also significantly reduced by 30%. Four patients developed postural instability; five patients, all with disease duration >10 years manifested dementia within 5 years from surgery.

Conclusion: This study addresses the impact of GBA variants on the clinical outcome of DBS. Although preliminary, our data suggest that GBA mutations do not seem to negatively influence the motor and non-motor outcome of DBS patients. Future studies on larger PD cohort are needed to clarify the impact of GBA mutations on DBS outcome, as this could open new perspectives for customized DBS implantation protocols and stimulation paradigms.

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Long-term subthalamic deep brain stimulation outcome in a Parkinson's disease patient associated with PRKN gene deletion

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Introduction: Parkinson's disease (PD) patients with Parkin gene (*PRKN*) mutations show good response to subthalamic deep brain stimulation (STN-DBS)[1]. However, different *PRKN* mutations could lead to heterogeneous long-term outcomes. To date, no STN-DBS follow-up longer than 5 years are reported.

Objectives: To report the 15-year follow-up after STN-DBS of a PD patient presenting a compound heterozygous deletion of exons 3 and 11 of the *PRKN* gene.

Case report: In 1994, a 39 years-old male was diagnosed with PD after the onset of resting tremor; levodopa was started, and during the following ten years he reported good motor symptoms control, with only mild modification of levodopa intake and pramipexole introduction. In 2005 he developed disabling motor fluctuations and dyskinesia; entacapone was started, but immediately interrupted for visual hallucinations. The genetic diagnosis was made in 2006. In 2007 he underwent bilateral STN-DBS, with a marked improvement of motor symptoms and fluctuations. After six years, he reported mild motor fluctuations, improved after stimulation and treatment modifications. After ten years he showed diphasic dyskinesias, feet dystonia, postural instability, and gambling (disappeared after pramipexole discontinuation). Since 2018 he showed a single-domain MCI. In April 2022 (15 years after STN-DBS) motor symptoms/fluctuations are still well controlled with levodopa 1200 mg/day, and stimulation set at 3.3 V, 60 usec, 130 Hz bilaterally. MDS-UPDRS-I-II-III-IV scores are 21-18-30-8, respectively. He reports mild dysphagia, orthostatic hypotension; MoCA score is 26/30.

Conclusion: More than 40% of *PRKN* mutations result from structural variants,[2] with the deletion of exon 3 being the most frequent mutation. We described for the first time the STN-DBS outcomes of a compound heterozygous deletion of exons 3 and 11[3], along with the longest follow-up after STN-DBS in a *PRKN*-associated PD. We confirmed good long-lasting outcomes, with marked improvement in motor symptoms/fluctuations and no significant worsening of cognitive profile.

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P123

The impact of Deep Brain Stimulation on caregiver of people with Parkinson's disease: a systematic review of qualitative studies

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Introduction: Subthalamic nucleus deep brain stimulation (STN-DBS) represents an effective treatment in Parkinson's disease patients (PDPs). However, the effects of STN-DBS on caregiver burden (CB) of PDPs caregivers are still debated.

Objective: To explore the experiences and unmet needs of PDPs caregivers after STN-DBS by performing a systematic review and meta-synthesis of collecting and aggregating qualitative studies.

Methods: We conducted a systematic review of qualitative studies whose findings were synthesized after the critical appraisal. The search comprised five electronic databases: MedLine, Embase, Cinahl, PsycINFO and Scopus. Inclusion criteria for the meta-synthesis were (a) studies on the experience of CGs of PDPs post-STN-DBS, (b) English peer-reviewed articles, (c) qualitative or mixed methods studies reporting participants' quotations. Descriptive themes and conceptual elements related to PDPs CGs experiences and unmet needs were identified by performing the meta-synthesis.

Results: After duplicates' removal, 720 titles were screened, and only eight articles met the inclusion criteria. Three main categories (and related subcategories) were identified through the meta-synthesis: i) pre-STN-DBS: the starting situation characterized by the impact of PD on everyday life, the limitations to CGs' socialization and autonomy, and the CGs' effort in stepping aside for love and care activities; ii) post STN-DBS: signifying treatment-related changes with the feeling of being unprepared for changes (involving neurologists and professionals' communication), the fear and concern due to partners' behavioural changes, and the struggling to find an etiological explanation for those changes; iii) post STN-DBS: reconfiguring as caregiver and partner.

Conclusions: This meta-synthesis clarifies the meanings given by, and unmet needs of, caregivers of PDPs that underwent STN-DBS dismissing the idea of the unchanging symbiosis between caregivers and PDPs. STN-DBS treatment challenges the caregivers-patients relationship, according to the caregivers. Caregivers adequately supported from a psycho-social perspective will be able to accommodate a new role that is constantly to re-define.

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Globus pallidus internus-deep brain stimulation in Huntington's disease: a case report

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Introduction. Deep brain stimulation (DBS) of the internal globus pallidus (GPi) has been proposed for the treatment of drug-resistant chorea in selected patients affected by Huntington's disease (HD), but long-term efficacy and optimal stimulation protocols are not yet well established.

Case presentation. We report the case of a 61 y.o. man with 20-year history of genetically confirmed HD. He presented severe and disabling axial and limbs chorea associated to mild bradykinesia. Pharmacological treatments for chorea (tetrabenazine, haloperidol, valproate, atypical antipsychotic) were ineffective or not tolerated. Pre-surgery neuropsychological assessment found out a quite well-preserved cognitive status except for moderate executive, memory and language deficits along with mild anxiety and depression. He underwent to bilateral GPi-DBS in November 2021, no post-operative motor or cognitive side effects occurred. With 130 Hz stimulation hyperkinetic movements slowly decreased, but parkinsonism, freezing of gait and unbalance, correlating with stimulation intensity and increasing frequencies, appeared. However, lower frequency and low voltage stimulation (75Hz, 1.5V) improved chorea by 42% compared to pre-surgery (from 12 to 7 according to Unified Huntington's Disease Rating Scale-chorea subscore) without affecting gait and global movement quality significantly. Therapeutic effect on chorea was objectively assessed by multichannel electromyography at various stimulation voltages. Videolaringoscopy showed an improvement of swallowing in the On-DBS state, with better bolus propulsion compared to Off-DBS. Neuropsychological assessment, repeated at 1&3 months, was not affected by surgery and DBS status, but anxiety and depression improved, allowing antidepressant reduction. Subjective motor improvement is maintained 6 months after surgery.

Discussion. GPi-DBS surgery was well tolerated by our patient, with improvement on motor function, swallowing and mood. The main stimulation challenge was finding a balance between therapeutic effect on chorea and parkinsonism, as an unavoidable side effect. This case supports the possible benefit from DBS in HD patient with predominant motor phenotype.

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Deep brain stimulation of the Dentato-Rubro-Thalamic tract in a case of post-lesional Holmes tremor: a CSD guided procedure

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Introduction: Holmes tremor (HT) is an irregular, slow-frequency (<4.5 Hz) tremor that arises as a delayed manifestation of lesions in the upper brainstem such as stroke. Thalamic deep brain stimulation (DBS), mainly ventralis intermediate nucleus (VIM) DBS, is currently adopted for the neuromodulation of tremor of various origin. However, due to inconsistent results, other targets (GPi, ZI, VOA, VOP) are currently under investigation. More recently, the constrained spherical deconvolution (CSD) based tractography, in place of the standard diffusion tensor imaging (DTI) based tractography, has been shown to characterize intra voxel diffusion behavior and therefore identify the complex architecture of the dentato-rubro-thalamic tract (DRTT) as a potential target for treating tremor [2].

Case description: A 51-year-old woman presented to our clinic with a disabling right-sided rest tremor, secondary to a left ponto-mesencephalic hemorrhage occurred 5 years before. The tremor affected mainly her upper right arm, had a slow frequency (3-4Hz) and persisted during movement. The medications she had taken until then had failed in the control of her symptoms. We therefore addressed her to an imaging and neurophysiology guided awake DBS procedure. The pre-surgical planification included advanced neuroimaging with constrained spherical deconvolution (CSD) based tractography obtained from diffusion weighted imaging (DWI) in order to identify with extreme precision the DRTT. During the operation we observed a striking improvement of the tremor, without notable side effects. A Percept PC neurostimulator with a directional (Sensight) lead was placed. The patient was then programmed aiming at a multitarget approach (caudal VIM + DRTT) leading to an almost complete tremor suppression (80%).

Discussion: To date clinical manifestations of HT have implicated the involvement of the nigrostriatal system, the cerebello-thalamo-cortical pathway and the dentate-rubro-olivary pathway. Thanks to the innovative pre-operative reconstruction of nervous pathways with CSD tractography and intraoperative visualization of the lead during awake DBS, DRTT was effectively targeted. A significant benefit on our patient's tremor was obtained, paving the way towards the use of new promising neuroimaging techniques able to target the pathways involved in the pathogenesis of HT.

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P126

Does deep brain stimulation improve patients' quality of life?

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Introduction: Deep Brain Stimulation (DBS) is a well-known surgical treatment used to reduce the motor symptoms of Parkinson's disease [1]. This treatment, by decreasing patients' dyskinesias and motor fluctuations, is known to improve their quality of life [2].

Objective: Aim of the present work is to present the ongoing validation of the Italian version of the Japanese Parkinson's Disease QoL for Device-Aided Therapy (PDQ-DAT) questionnaire, which investigates the quality of life of patients with Parkinson's disease who have undergone surgery with a therapeutic device [3].

Methods: For this purpose, we selected 10 patients from the AOU Maggiore della Carità di Novara who underwent DBS.
To test our hypotheses, all patients were given an Italian version of the already mentioned questionnaire. This questionnaire investigates, through 24 multiple-choice questions divided into 3 macro-areas (daily activities, satisfaction with the therapeutic device, psychological well-being), the presence of particular problems that could compromise the patient's quality of life. The same questionnaire was given to the patients at the time of discharge (T0) and after one month (T1), 3 months (T2) and 6 months (T3).

Results: From the analysis of the questionnaires of the first 10 patients evaluated so far, a progressive improvement in the quality of life emerged, with an average decrease of 2 points for each cluster investigated. In particular, we noticed improvements in autonomy and movement, resumption of social activity, decrease in concerns related to the device, decrease in cognitive and behavioral difficulties.

Conclusion: In conclusion, the results achieved so far, which will certainly have to be enriched, seem to demonstrate the benefits of DBS on the quality of life of patients.

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P127

Imaging-guided or clinical programming alone in directional DBS: which is better?

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Introduction: Deep brain stimulation (DBS) is a well-established surgical procedure for treatment of motor complications in advanced Parkinson's disease (PD). It is aimed at two main targets; the subthalamic nucleus (STN) and internal globus pallidus (GPi). The GUIDE™ XT is a software which reconstructs and simulates the leads' position, using computerized tomography scan on a 3D anatomical map, helping clinicians to visualize the stimulated field in order to optimize and personalize DBS parameters for each patient.

Objective: To investigate if imaging-guided programming provides an advantage in modulating DBS parameters compared with clinical programming alone.

Methods: We evaluated a cohort of 56 PD patients who underwent DBS surgery with directional leads (44 STN and 12 GPi, 38 Male and 18 Female, mean age 62 years) from 2017 to 2022. Of these, 27 were re-evaluated in OFF medication after clinical (T1) and imaging-guided programming (T2). Time span between T1 and T2 was six months. Clinical status was evaluated through the Unified Parkinson's Disease Rating Scale (UPDRS) part III and IV. We compared the two groups using the Wilcoxon matched-pairs signed rank test. A p-value of less than 0.05 was considered significant.

Results: Imaging-guided programming produced a significant clinical improvement as measured with the UPDRS scale; mean UPDRS part III scores decreased significantly between T1 and T2 (T1= 17,3±10,6; T2 15,6 ± 10,7 p=0,008). Similarly, we observed a meaningful effect on motor fluctuations measured with UPDRS part IV (T1=3,26 ±3,53; T2 =1,92± 2,2; p=0,003). There was no relevant difference of levodopa equivalent daily dose (LEDD) between T1 and T2.

Conclusion: Imaging-guided DBS programming could provide an important tool to achieve optimized and personalized stimulation and improve clinical outcomes. Prospective randomized trials are needed to better understand if DBS imaging-guided is more suitable than clinical programming alone.

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Gait patterns in patients affected by Parkinson disease with and without freezing of gait

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Introduction: Freezing of Gait (FoG) is a disabling gait disorder in patients with Parkinson Disease (PD). FoG is defined by "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk." [1]. Apart from FoG episodes, previous studies showed that PD patients with FoG display higher gait variability measures and increased asymmetry [2, 3].

Objective: To compare gait patterns in PD patients with and without self-reported FoG, in both single and dual task.

Methods: Seventy-one PD patients were consecutively enrolled and classified into freezers (FoG+) and no-freezers (FoG-), based on their answer on item 2.13 of MDS-UPDRS. All patients were assessed by Gait analysis, through BTS Bioengineering gait analysis system. Gait analysis protocol included a single task (normal gait) and two different dual tasks (a motor dual task and a cognitive dual task). A univariate statistical analysis was performed through SPSS software with Mann Whitney test on spatio-temporal gait parameters for each task in order to compare gait patterns between FoG+ and FoG-.

Results: Sixteen out of 71 PD patients were classified as FoG+, whereas 55 were classified as FoG-. As compared to FoG-, FoG+ PD patients showed increased swing variability (p-value=0.044) in single task, augmented double support phase (p-value=0.036) and reduced both mean velocity (p-value=0.042) and cycle lenght (p-value=0.040) in cognitive dual task.

Conclusions: Beyond FoG episodes, FoG+ vs FoG- PD patients showed increased measures of dynamic instability, especially in cognitive dual task. Our findings would support to employ early integrated rehabilitation strategy aimed at improving dynamic balance in FoG+ PD patients, thus reducing risk of falling.

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P129

Over 5 years for correct diagnosis. The importance of identifying NMS and the role of acute LD challenge test

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Introduction: Parkinson's disease (PD) has a heterogeneous clinical presentation, including a broad spectrum of non-motor symptoms (NMS), such as depression [1]. The diagnosis of PD is based on the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria as the presence of motor signs including their responsiveness to levodopa (LD) [2][3]. We report a case of delayed diagnosis of PD during the COVID-19 pandemic in a patient who complained of depression before the occurrence of PD motor symptoms.

Objective: The aim of this presentation is to highlight the importance of identifying NMS as key to early diagnosis of PD [4] and to reinforce the role of acute LD challenge test in diagnostic work-up of PD.

Methods: We present the case of a 65-year-old female, who complained of depressive symptoms started five years earlier with unsatisfactory response to antidepressant therapy. She came to our emergency department presenting bilateral rigidity and severe bradykinesia, progressively worsening over the last months. Before being evaluated by our team, her clinical presentation was interpreted as a psychotic-like syndrome with catatonic state. On examination she showed cogwheel rigidity bilaterally, severe bradykinesia and resting tremor (right >left). Brain MRI was unremarkable; considering the UKPDSBB criteria, we performed the acute LDCT (200/50 mg levodopa/carbidopa) and achieved an impressive improvement in motor symptoms as assessed by the UPDRS scale, passing from a score of 76 to 38 (50%). [123I]-FP-CIT imaging, carried out in the following days, confirmed bilateral nigrostriatal dysfunction (left>right).

Results: Based on the clinical and imaging findings, we made a diagnosis of PD; the patient started levodopa–benserazide, selegiline and rotigotine treatment with a significant improvement of her parkinsonian symptoms, including depression, at a three-month follow-up.

Conclusion: Despite modern algorithm and hypothetical telemedicine, a correct clinical evaluation and LDCT conserve their main utility, especially when NMS, namely a pharmaco-resistant depression, is the initial hallmark of PD.

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P130

Assessment of manual dexterity using a smartphone in subjects with Parkinson's disease

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Introduction: People with Parkinson's disease (PD) often complain difficulties in activities involving precise, ample, and rapid hand movements such as the use of a smartphone.

Objective: To assess hand dexterity abilities using a smartphone in PD relative to healthy controls using customized tests and software.

Methods: Ten PD and 15 age/sex-matched healthy controls underwent hand dexterity assessments. We assessed hand function using Manual Ability Measure (MAM-36) and the Purdue Pegboard Test (PPT). To obtain objective data on movement speed and amplitude, we developed tests involving the most commonly used gesture when using a smartphone (i.e. tap, swipe, slide). These tests were performed on the touchscreen of a smartphone and consisted in: a) alternatively tap with the thumb on two rectangles (TAP); b) perform swipe gestures to browse pages (SWIPE); c) perform thumb movements to link dots of a grid according to a defined path (Swipe-Slide Pattern - SSP).

Results: Relative to healthy controls, PD showed worse performance in the PPT, lower score in the MAM-36, reduced movement amplitude and speed in TAP, SWIPE and SSP tests and a reduced number of correct sequences in SWIPE and SSP tests ($p<0.05$). Moreover, a higher number of correct gestures during the SWIPE test correlated with a better motor performance assessed with the UPDRS-III both on and off medication ($r>0.66$; $p<0.05$).

Conclusions: As expected, PD showed reduced hand dexterity abilities. Interestingly hand dexterity objective outcome measures obtained with the smartphone correlated with the motor performance assessed with clinical scales. This study showed that technological devices can be used to assess dexterity in PD providing objective and task-specific outcome measures of hand dexterity rehabilitation in PD.

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QIAS: an evolutionary system for e new UPDRS computerized interpretation

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Introduction: Construction of an advanced computerized post-analysis system of the UPDRS test for a new interpretation based on the transformation from an exclusively quantitative test into an Analytical / Quantitative test

Objective: Given that Parkinson's disease is one of the most complex and polymorphic diseases of the nervous system in its various clinical manifestations, our working group has set itself the goal of building an innovative tool to help physicians in the management of Parkinson's disease (PD) and which is to provide specialists in the field:
• a tool for a qualitative and quantitative analysis of the disease
• a tool capable of giving an exhaustive follow-up on the progress of the disease.

Description: The starting idea was to create an innovative software able to provide a valid help to the doctor in the management of Parkinson's disease (PD).
It was therefore decided to start from the international evaluation scale of Parkinson's disease, called UPDRS, and to start by evaluating the criticality of this, also very valid, analysis tool.
The criticality in UPDRS, in our opinion, consists in the fact that it, as formulated, is an investigation tool of mere value in consideration of how much, as in the test one has an absolute vision, it is possible to have a global vision, it is possible to have an equally vision of the disease but not an overall and at the same time fragmentary vision of the various and complex facets that are inherent in Parkinson's disease. How can this be achieved?
Build automatic Parkinson's disease management software that was simple to manage and always accessible at anytime and anywhere the doctor was.
In addition, the software should have been able to have the doctor manage Parkinson's disease in less time than the paper analysis.
Given the goals we set ourselves, we were able to build software that can be used via the web through today's means of communication such as, for example, a PC, a tablet, a smartphone and so on. All this, moreover, without having the doctors need to install any application system on their machines but only having the possibility to access, through their own applications, the software installed on a remote web platform with a simple login operation.
The main features of the software are:
- Guided compilation of the UPDRS forms, transformed into electronic format for the evaluation of the PD
- Analysis and automatic generation of evaluation charts of the same, divided in turn into the various sub-areas of which the UPDRS is composed
- Comparison evaluation between cards of different dates
- Access to historical data

Software utility
For the doctor:
- Analysis tool
- Archiving system

For the team managing the program
- Data acquisition tool
- Sample data analysis tool
- Other uses

It should be noted here that the coordination team would manage in real time the analysis data provided by the doctors participating in the network in a completely anonymous way and with full respect for the privacy of both the doctors of the network that would be created and the patients they assist.

Conclusions: In conclusion, we believe that the software developed by our group, which we have called QIAS (Quality Illness Analysis System), is a very useful and truly innovative tool as, in addition to being useful for specialists who are interested in Parkinson's, it could constitute an idea forerunner for the transformation of most of the evaluation scales from quantitative to qualitative of almost all the diseases that these scales use in the various branches of medicine in general for a more rational identification and evaluation of the same.
Finally, we would like to point out that apps are being designed to be used by patients themselves on their personal application tools even from their own home to communicate at a distance to their treating doctors the inevitable transformation of the history of their diseases both in the sense of improvement and in the sense of a worsening, thus being able to be included in the broader field of telemedicine.

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An algorithm for the detection of motor symptoms and complications in patients with Parkinson's disease

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Introduction: Wearable devices have the potential to provide an objective recording of PD motor symptoms. Some of the proposed solutions are based on detection of the frequency content in the range in which pathological movements due to PD typically occur. However, this frequency range is superimposed to power spectrum of physiological movements. Therefore, solely evaluating the frequency content does not usually offer a sensible distinction between movement disorders and normal daily activity. In order to improve this, the wrist-worn tool "PD-Watch" has been proposed that evaluates the frequency data content and identifies specific movement patterns that movement disorders are typically associated with (e.g. hand tremors at rest due to PD usually occur with a supination–pronation characteristic).
Objectives: We propose to assess the extent of the contribution due to specific movement patterns identification in reducing the probability of mistaking the discrimination between movement disorders and normal daily activity.

Methods: 20 patients with PD were recruited. Data were acquired with the PD-Watch for 24 hours. Data were processed with solely frequency evaluation (Method#1) and with the evaluation of both frequency and movement patterns (Method# 2, i.e. PD-Watch algorithm). Data provided by the two methods were compared to patient diaries and to proper items of the UPDRS.

Results: Data provided by the Method#2 show a good agreement ($r2 = 0.744$, p-value: 0.0004) [1] with UPDRS scores and patient diaries. Data provided by the Method#1 overrate the presence of motor symptoms, e.g. the overall tremor duration detected during the whole day may be overstimated from 10% to around 100% with respect to UPDRS scores and patient diaries.

Conclusions: While results need to be extended with further clinical trials, the proposed algorithm on the detection of both frequency and movement pattern appears promising and suitable for supporting the evaluation of motor symptoms and complications.

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P133

The possible interplay between speech acoustic parameters and axial motor impairment in advanced Parkinson's disease patients

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Introduction: The relationship between speech parameters, axial symptoms and disease severity in Parkinson's disease (PD) patients is still unclear. Moreover, the effects of dopaminergic treatment on speech parameters are debated.

Objective: To evaluate possible correlations between axial motor features, disease severity and speech parameters in advanced PD patients and to examine chronic dopaminergic treatment effects on speech disturbances.

Methods: Retrospective data from 50 advanced PD patients in OFF- and ON-states were considered. Perceptual and acoustic analysis of spontaneous monologue and sustained phonation, including quantitative parameters and speech intelligibility rate, were performed in OFF- and ON-conditions. UPDRS part III score and subscores [Postural Instability Gait Disorder (PIGD) composite subscore] and Hoehn and Yahr scale (H&Y) were also applied. Statistical analysis was performed using Spearman correlation coefficient and Mann-Whitney test to compare groups.

Results: In ON-state PIGD subscore correlated positively with dysfluency score ($p=0.04$) and negatively with speech intelligibility rate ($p<0.01$). Patients presenting freezing of gait (FOG) had lower speech intelligibility rate compared to patients without FOG ($p=0.05$) meaning that patients with higher axial impairment after levodopa intake were more disfluent and less intelligible. In the OFF-state, H&Y score correlated negatively with maximum phonation time (MPT) of sustained phonation and speech intelligibility rate ($p=0.01$ and $p=0.04$ respectively), meaning that more severe PD patients had poorer speech quality. In the OFF- and ON-conditions, patients with speech dysfluencies had longer levodopa treatment duration than patient without speech dysfluencies (OFF:$p=0.03$; ON:$p=0.04$), regardless of levodopa equivalent dose (LED) and disease duration.

Conclusions: We confirm the possible correlation between speech and axial symptoms in advanced PD. MPT and speech intelligibility rate correlated with disease severity, suggesting their possible role as markers of disease severity. Patients with speech disfluencies had longer history of dopaminergic treatment, but not necessarily longer disease duration or higher LED than patients without disfluencies.

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Triple trouble: a man with Parkinson's disease, dural arteriovenous fistula and probable inflammatory disease of the central nervous system

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Introduction: In recent years there has been renewed interest in the role of autoimmunity in many neurological disorders such as neurodegenerative diseases and multiple sclerosis. The possible role of impaired immune response in etiopathogenesis of movement disorders such as parkinsonism or dystonia is also commented.

Objective: We present the case a 67-year-old man with a rare concomitant diagnosis of Parkinson's disease, inflammatory disease of central nervous system (CNS), and spinal arteriovenous fistula.

Methods: Since the beginning of his clinical history, the patient underwent neurological and radiological tests (physical examination, brain and spinal cord magnetic resonance imaging (MRI), Dat - SPECT and angiography).

Results: At the age of 65 the patient was diagnosed with Parkinson disease, which started with tremor in the right upper limb and micrography. After 2 years he presented difficulty in walking with weakness of the right lower limb with a subacute onset and progressively worsening course. Patient was then hospitalized, the spinal cord MRI showed characteristics suspicious for dural arteriovenous fistula in the dorsal region, confirmed by angiography. Endovascular surgery to embolize the dural fistula was performed. Incidentally the MRI study revealed previous cervical myelopathy and some lesions of the white matter of the brain. In the suspicion of inflammatory disease, blood autoantibody screening was performed, revealing positivity of antibodies to ENA and lupus anticoagulant, and absence of antibodies to myelin oligodendrocyte glycoprotein (MOG). Patient refused to perform lumbar puncture. Further diagnostic investigations are underway.

Conclusions: The patient represents a very rare case in which 3 pathologies with different etiology have occurred in the same subject. We want to underline the importance of not underestimating new symptoms in patients with diagnosis of already complex pathologies.

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Uptake of telehealth in Parkinson's disease clinical care during the COVID-19 pandemic: an Italian online survey

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Introduction: Traditionally, medical care and research in Parkinson's disease (PD) have been conducted with in-person encounters. The recent COVID-19 pandemic has profoundly impacted the delivery of in-person clinical care and clinical research.

Objective: We aimed to investigate the impact of COVID-19 on access to telehealth care, interviewing both PD patients and neurologists through an online survey.

Methods: Survey responses were collected from 1 March to 31 May 2021 through an anonymous, self-reported questionnaire, on the on line platform.

Results: The survey was completed by 197 PD patients and 42 neurologists. Alternatives to in-person visits (SMS, chat, telephone, email, video consultation) were used by 37.56% of PD patients and 88.10% of neurologists. Among the available tools, video consultation was chosen by 13.70% of PD patients and 40.48% of neurologists. Participants reported being generally satisfied with their experience. In particular, the patient-neurologist interaction appeared to be the element that most positively affected the video consultations.

Conclusions: The current results suggest a need for flexibility in conducting office visits and clinical trials in PD patients. Technology has the potential to enhance patient care and convenience, when in-person visits can be challenging.

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Driving abilities in Parkinson's disease patients with wearing-off and the impact of add-on therapies

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Introduction: Progressive impairment of motor and cognitive abilities due to Parkinson's disease (PD) can lead to an alteration of driving performances, but little is known about the determinants of impaired driving abilities and whether dopaminergic therapy can improve driving performances [1,2].

Objective: The aim of this study is to evaluate the driving skills of PD patients, the impact of wearing-off and the effect of add-on therapies on driving performances on a driving simulator. EEG data have also been collected through EEG.

Methods: Twenty patients with PD on chronic levodopa therapy and with the recent add-on therapy due to wearing-off were recruited. Driving abilities were tested through a driving simulator (City Car Driving software and logitec driving). The software simulates city roadways with traffic lights, cars, and pedestrians. An assessment of motor impairment (UPDRS), cognitive ability (MOCA) and wearing off (questionnaire) and actual driving abilities were performed [3]. Patients were then evaluated for driving performances and learning curves during their best on time (V1) and during their wearing-off time (V2) on a standardized path.

Results: Mean Hoehn and Yahr was of 2±0.5, MoCA of 25 ± 2.5, UPDRS III of 17 ± 5 and LEDD of 800±230. Add-on therapies were iMAO, Dopamine agonists, amantadine and iCOMT. Basal driving history assessment revealed driving troubles increasing with disease staging, age independently. Motor and cognitive features related to the DS score and with learning curves ($p<0.01$). Wearing off were featured by worst driving performances ($p<0.01$), iCOMT were associated with a lower degree of wearing off and higher driving performances and learning curves during the wearing off time ($p<0.05$). EEG analysis is currently ongoing.

Conclusions: PD features are associated with driving impairment. The relationship between PD and driving might be influenced by fluctuations and therapies. However, the potential negative impact of therapies (ie, somnolence, impulsivity) should also be evaluated.

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P137

Effects of altered neuropsychiatric symptoms on the gait initiation in subjects with Parkinson's Disease

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Introduction: In People with Parkinson's Disease (PwPD), impairments of Anticipatory Postural Adjustments (APA) may be related to difficulties with initiating stepping. The role of psycho-emotional and neuropsychiatric symptoms on postural control and walking is well established [1]. However, no influence of emotional visual stimuli emerged on the Center Of Pressure (COP) displacements [2].

Objective: To investigate the association between APA and the emotional disturbances during gait initiation in PwPD.

Methods: Twenty-two subjects with PD (H&Y 2-3) stood on a dynamometric platform and were asked to initiate gait in response to neutral, pleasant and unpleasant auditory stimuli. The experiment took place during the "on" state. The COP displacements during the imbalance and unloading phases were calculated from the ground reaction force data [3]. The alexithymia, anxiety and impulsiveness were respectively assessed through the Toronto Alexithymia Scale (TAS-20), the State-Trait Anxiety Inventory-Y Form (STAI-Y, TRAIT Dimension) and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease (QUIP-RS-IT). Correlation analysis was performed between the APA parameters and the clinical scales using the Spearman test.

Results: In the sagittal plane, during the imbalance phase, the COP displacement showed moderate correlations both with the STAI (rho=0.53, p=0.01) and the TAS-20 (rho=0.50, p=0.02) after the listening to the unpleasant stimuli. These associations indicate that PwPD with more severe emotional disturbances showed greater reductions of the backward movement of the COP.

Conclusions: Our results showed a significant impact of the psycho-emotional alterations on the preparatory stages of the step itself, as already hypothesized [4,5,6]. In particular, an altered understanding and regulation of emotions and increased anxious traits seem to have negative effects on the gait initiation. Consequently, it appears useful and important an early and careful assessment of all neuropsychiatric symptoms.

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Determinants of quality of life and daily mobility in Parkinson's disease: the role of fear of falling.

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Background: The fear of falling (FOF) is defined as a lasting concern about falling and can impact severely quality of life (QoL) [1]. Parkinson's Disease (PD) patients frequently manifest postural instability, recurrent falls and FOF.

Objective: We aimed to investigate the relationship between the PD clinical features, the presence of FOF and its impact on QoL. We explored whether the reduction of patient mobility - measured through a 24-hour continuous remote monitoring essay - might depend on FOF.

Methods: Fifty non-dement, PD patients were enrolled by our movement disorders outpatient clinic. The PD status and severity were assessed with UPDRS part I to IV, modified Hoehn and Yahr scale, Non Motor Symptom Questionnaire (NMSQ), Montreal Cognitive Assessment (MoCA) and Schwab & England ADL scale (ADL). The FOF presence and its severity were scored through the Fall Efficacy Scale (FES); FOF was defined as a FES score >19. Further data on freezing of gait and postural stability were collected. All patients were equipped with a smartphone with an embedded application to monitor their quantity of motion (activity index, AI) for a 24-hour period.

Results: Thirty patients (60%) reported a previous history of falling. The median FES score was 17; 19 (38%) patients reported FOF. Various motor and non-motor parameters were associated with a higher FES score. Patients with FOF had also significantly lower QoL and ADL, independently by motor and non-motor disease features. Forty-seven out 50 subjects (94%) have been investigated though a 24-hour motion monitoring tool. The FES score and the AI had a mutual direct relationship ($p=0.010$). Patients with FOF had lower AI than patients without FOF ($p = 0.025$). Both are associated to the mobility related quality of life, while FOF had a more widespread and independent association with several non-mobility related QoL issues.

Conclusions: The presented data confirm that FOF is a prevalent and pervasive condition affecting mobility and various QoL aspects of patients with PD [2]. FOF identification and treatment strategies are of critical importance in the management of PD.

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A case of ataxia with oculomotor apraxia type 2 due to a novel mutation of SETX gene: a deep clinical-instrumental phenotyping

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Introduction: Ataxia with oculomotor apraxia type 2 (AOA2) is an autosomal recessive disorder presenting with cerebellar ataxia, sensory-motor axonal neuropathy, occasional oculomotor apraxia, cerebellar atrophy on imaging and high alpha-fetoprotein (AFP) serum level. AOA2 is genetically defined by a variety of SETX coding mutations mapped to chromosome 9q34. Seldom noncoding mutations affecting RNA processing have been reported too. AOA2 diagnosis is established in patients with clinical, laboratory, and radiographic hallmarks and confirmed by identification of biallelic pathogenic variants of *SETX*.

Case presentation: A 19 years-old man came to our attention for progressive gait ataxia debuted five years earlier. His past medical history was unremarkable, except for scoliosis, while his parents were consanguineous. On neurological examination, he had bilateral horizontal gaze-evoked nystagmus with hypometric saccades and saccadic horizontal smooth pursuit, appendicular ataxia, limbs and trunk myoclonic involuntary movements with hands' dystonic postures and dance of the tendons. Video-oculography confirmed oculomotor signs suggestive of cerebellar impairment. Blood tests detected an elevated AFP level. Brain MRI showed cerebellar atrophy, while electroneuromyography revealed an axonal sensory-motor polyneuropathy.
Instrumental gait analysis showed an initial alterations both during the stance and the swing phase of the gait cycle. The protocol for balance assessment detected an impairment in the tasks with eyes closed.
In the suspicion of a pathology belonging to the autosomal recessive cerebellar ataxias (ARCA) spectrum disorder, a direct search of point mutations by second-generation sequencing was performed revealing a novel biallelic variant in SETX gene (c.6208+2dupT), which probably led to an aberrant splicing of mRNA with intron retention. Considering patient's typical AOA2 features and parental consanguinity, it is likely that this variant played a pathogenic role in our case.

Conclusion: The present case highlights a possible novel pathogenic mutation causing aberrant splicing of SETX mRNA in a patient with AOA2.

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The case of two sisters carrying GRN p.R298H mutation

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Introduction: Progranulin (*PGRN*) is a secreted glycoprotein encoded in humans by the *GRN* gene, located on chromosome 17q21. Several nonsense and missense pathogenetic *GRN* mutations have been described [1]. To date, *GRN* p.R298H mutation was only reported in two papers and its pathogenetic role is still considered to be defined [2,3].

Objective: We herein present the case of two sisters carrying a *GRN* p.R298H mutation with extremely different clinical phenotypes and family history of dementia and behavioral disorders.

Methods: Patients underwent a multidimensional assessment including neurological and neuropsychological evaluation, structural and functional imaging, and genetic screening.

Results: The older sister presented at the age of 63 with severe depression of mood and apathy. She had a rapidly progressive and markedly asymmetrical parkinsonism and dementia. At the age of 65 years, she was anarthric and she developed severe dystonias prevalent in the left side of the body and in the cephalic district. She was bedridden at the age of 66 years. She was diagnosed with corticobasal syndrome. The younger sister presented at the age of 64 with dysphonia, dyspnea and inspiratory stridor. Soon afterward, she developed urinary urgency and sporadic episodes of urinary incontinence. The only clinical feature common to both sisters is frontal cognitive dysfunction. Their father died at 52 years due to diabetic complications. Two paternal aunts were diagnosed with dementia and behavioral disorders.

Conclusions: Our cases strongly support the pathogenicity of the *GRN* p.R298H mutation, which is first detected in two members from the same family, both with clinical manifestations. Our findings suggest that this mutation may be associated with an extremely variable phenotype. This wide clinical variability among the members of the same family has been frequently reported as features of *GRN* mutations [4]. More importantly, we report the first case of an *FTD-associated* mutation manifesting with inspiratory stridor.

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Screening for Fabry's disease in a case series of Parkinson's disease patients from Southern Italy

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Introduction: Autophagy-lysosomal pathway dysfunction is involved in PD pathogenesis, causing abnormal accumulation of alpha-synuclein in Lewy bodies. Mutations in several genes encoding lysosomal enzymes have been associated with PD so far. Fabry disease (FD) is a X-linked lysosomal storage disease caused by alpha-galactosidase (α-GAL) deficiency, leading to deposition of globotriaosylceramide (Gb3) in nervous system and other organs. GLA gene variants and decreased α-GAL activity have been detected in PD patients in a few previous studies or case reports.

Objective: We aimed to assess α-GAL levels in a case series of PD patients from Campania, in Southern Italy.

Methods: One hundred forty-four unrelated subjects (88 males and 56 females) affected with PD were enrolled. Demographics data, medical and family history, and brain MRI findings were collected. α-GAL activity was measured using a fluorometric assay in males. GLA gene sequencing was performed in females and males with decreased α-GAL activity, who also underwent globotriaosylsphingosine (lyso-Gb3) levels analysis.

Results: The mean age ± SD was 67.3± 9.2 years, and mean age ± SD at onset was 58.4±10.2. The most common motor phenotype was tremor-dominant PD (n=75, 52%). Twenty-nine participants (20%) had a positive family history for PD, whereas 7 subjects (7%) reported at least one first family member suffering from cerebrovascular disease. Seventy-six patients (53%) had at least one cardiovascular risk factor and four (3%) had a past medical history of stroke or TIA. Brain MRI showed signs of cerebral small vessel disease in 58 cases (40%). α-GAL levels resulted lower than cut-off in 15 males (20.5±6.1 μmol/L/h), whereas lyso-Gb3 values were within reference range. GLA gene variants were not detected in any tested subjects.

Conclusion: Our results did not show any association between FD and PD. Further investigation is necessary to confirm these findings, including larger and more homogeneous cohorts.

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Onset of parkinsonism in a patient with Fabry'sdisease

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Introduction: Fabry disease (FD) is an X-linked lysosomal storage disorder caused by the deficient activity of alpha-galactosidase A. There is a progressive and diffuse lysosomal accumulation of glycosphingolipids in vascular endothelium, kidneys, heart, brain, skin, cornea and other tissues leading to multiorgan damage. Clinically, patients suffer of transient ischemic attacks, strokes, acroparesthesia. Brain white matter lesions are common in MR examinations. We describe the case of a patient with Fabry syndrome with the onset of extrapyramidal signs and cognitive decline.

Case description: A 62 years old male affected by Fabry disease with involvement of kidney, eyes, hear and heart, come to our neurological department for the onset of mask-like face, mild rigidity, gait instability. Family members described difficulty in recent memory, recall, spazial orientation. Neurological examination revealed postural and gait retropulsion, hyperreflexia and positive Babinski's sign and rigidity on both sides. Brain MRI disclosed multiple high signal intensities in the basal ganglia and deep white matter regions and mild upper cortical atrophy. [123I]-FP-CIT confirmed parkinsonism with a reduction of striatal caption especially in the left side. Cognitive evaluation confirmed deficit in memory, spatial orientation and recall.

Conclusion: A lot of recent reports describe the occurrence of parkinsonian signs in patients with Fabry disease [1]. Wise et al. performed an online survey and family history questionnaire to determine the prevalence of PD in 90 FD patients. Gago et al. studied the prevalence of PD in a large cohort of 229 FD patients [2]. An italian MRI-study of Russo C. et al. [3], demonstrated a nigrostriatal involvement in FD patients. All these reports support the hypothesis that there may be an increased risk of developing PD in individuals with *GLA* gene mutations. The presence of cognitive decline in our patient suggests that the brain involvement is more widespread.

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A newly implemented NGS-based methods to detect GBA variants in patients with Parkinson's disease

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Introduction: Heterozygous variants in the *GBA* gene, encoding for the lysosomal enzyme β-glucocerebrosidase, are the most common genetic risk factor for Parkinson disease (PD), accounting for 5-15% of all PD cases. Sequencing of the whole *GBA* coding region (11 exons) is a burdensome task, both employing conventional techniques such as Sanger sequencing as well as more innovative strategies such as next-generation-sequencing (NGS). In particular, the high degree of homology (96-98%) between *GBA* and its pseudogene *GBAP* often leads to recombination events that eventually produce complex alleles which are misaligned and missed by the standard NGS pipeline.

Objectives: We implemented a NGS-based technology on a selected pool of 100 PD patients, including negative and positive controls.

Methods: The NGS experiment was designed to start from a specific long-range PCR which amplifies a unique 6 kb amplicon encompassing the *GBA* gene only. This was used as template to create libraries, which were amplified using Nextera technology and then run on an Illumina MiSeq instrument. In parallel to standard bioinformatic analysis, a tailored pipeline was used, masking *GBAP* pseudogene on the reference sequence and forcing the alignment of reads against the *GBA* gene only.

Results: All known *GBA* variants were correctly called and identified using this approach; furthermore, comparing (*.bam) files obtained with standard vs forced alignment, the latter showed a significant increase in read depth and mapping quality.

Conclusion: The proposed NGS-based approach appears a reliable and valid alternative for *GBA* sequencing, holding promise to increase speed analysis and variant detection rate compared to conventional strategies.

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Genetic landscape of early-onset Parkinson's disease in Italy: results of the PARKNET multicentric study

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Background: The advent of next-generation sequencing (NGS) unraveled the genetic landscape of Parkinson's disease (PD), with a particular attention on early-onset PD (EOPD). Few studies based on the genetic screening of genes associated with PD in specific populations have been conducted so far.

Objectives: To perform an integrated genetic analysis focused on EOPD from Italy. To assess the pathogenicity of identified variants for diagnostic purposes.

Methods: Eight Italian Movement Disorders Centers shared clinical and genetic data of EOPD patients (age at onset, AO<55y) that underwent genetic analysis for diagnostic purposes with NGS panel and MLPA. A minimum common gene set of 15 genes was assessed. Stratification of collected data according to an AO less than 40y was performed (vEOPD subgroup). The identified variants were classified according to the ACMG criteria.

Results: Genetic results of 650 EOPD patients were collected (160 vEOPD, 25%). A genetic diagnosis was possible in 97 of 650 patients (15%; 42 of 160 vEOPD, 26%), where *GBA* pathogenic/likely pathogenic variants (47 of 650, 7%; 13 of 160 vEOPD, 8%) and biallelic *PRKN* pathogenic/likely pathogenic SNVs/CNVs (15 of 650, 2%; 11 of 160 vEOPD, 7%) were the most common findings.

Conclusions: In this study, genetic results from the larger Italian EOPD cohort reported so far were collected. Our findings suggest that *GBA* variants are an important genetic factor in Italian EOPD patients. Biallelic *PRKN* and *PINK1* SNVs/CNVs are more represented in EOPD patients with younger clinical onset. Our results confirm that the screening of a small gene set, including *GBA*, *LRRK2*, *PRKN*, *PINK1*, and *SNCA*, seems to be sufficient for diagnostic purposes in EOPD patients without atypical features.

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A novel mutation in two siblings with sialidosis

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Background: Progressive myoclonus epilepsies (PMEs) are a group of heterogeneous genetic diseases [1], which include sialidosis. Sialidosis is an autosomal recessive lysosomal storage disorder caused by mutations in the neuroaminidase gene (NEU1) [2]. It is classified into type 1, a milder form with later onset, and type 2, a severe form with infantile onset and dysmorphic features. PMEs clinically present with epilepsy, cognitive impairment, ataxia and myoclonus. The macular cherry-red spot is a typical finding of sialidosis [3] however rare cases not presenting this sign have been reported[4]. Pharmacological treatment in PMEs is symptomatic, often requiring a polytherapy of antiepileptic drugs. Myoclonus is often the most disabling symptom, and tend to partially respond to treatments. Perampanel, a selective non-competitive AMPA receptor antagonist, has been recently described in small cases to ameliorate myoclonus in PMEs[5,6,7,8]

Aim: We describe two siblings with different clinical presentation, both diagnosed with sialodosis type 1 caused by the same novel mutation in NEU1 gene.

Case presentation: The female sibling reported gait disturbances since the age of 40, with progressive appearance of cerebellar ataxia and nystagmus. Years later, mild face and inferior limbs myoclonus appeared, with good response to Levetiracetam. The male sibling reported severe action myoclonus since the age of 45, with progressive loss of gait, and generalized epileptic seizures. Myoclonus caused marked disability in everyday life with partial response to a polytherapy of antiepileptic drugs. Add-on treatment with Perampanel was started, with amelioration of myoclonus and reduction of life disability. Both of them presented dysarthria, dysphagia and depression but no macular cherry-red spot. In both the cases, brain MRI did not revealed abnormalities and neurophysiological tests were consistent with cortical myoclonus. Genetical analysis revealed a novel mutation in NEU1 gene (c.134C>T p.Ser45Phe) in homozygosis in both the siblings.

Conclusions: We identified the novel c.134C>T p.Ser45Phe NEU1 mutation in two siblings presenting with clinically different PME. Besides, we report beneficial effect of Perampanel for myoclonus associated with PMEs.

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Heterogeneous impact on speech and gait disorders in MYORG gene biallelic mutations: two sides of the same coin or not?

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Introduction: Primary familial brain calcification (PFBC) is a rare inherited neurodegenerative disease characterized by bilateral calcifications in the basal ganglia and other brain regions in the absence of other secondary causes of brain calcification. Affected individuals exhibit a wide range of clinical symptoms, including dystonia, parkinsonism, ataxia, cognitive impairment, and psychiatric symptoms. Pathogenic variants in KIAA1161 (MYORG) gene have been linked to an autosomal recessive form of PFBC.

Case presentation: A 54 years-old woman came to our attention for progressive gait unsteadiness, difficulty in walking with stiffness of right lower limb, subjective deterioration of cognitive performance and anxiety. Neurological examination showed bilateral asymmetrical (right>left) rigidity, bradykinesia, ataxia in the lower limbs together with gait ataxia and postural instability. Blood tests were unremarkable. Brain CT revealed extensive and symmetric calcification of basal ganglia, thalamus, midbrain, pons, and cerebellum. Brain MRI showed high-intensity T2 and FLAIR alterations corresponding to the calcified lesions. PET-FDG showed bilateral hypometabolism in temporal and cerebellar cortex; neuropsychological assessment revealed a mild dysexecutive-visual-spatial impairment. Instrumental gait analysis showed walking at reduced speed, characterized during stance by calf muscle overactivity that impaired the ankle push-off and during swing by a co-contraction of the leg muscles that impaired foot clearance. On the contrary, speech acoustic-perceptual analysis showed a well-preserved speech without ataxic, spastic, or hypokinetic components. A direct search of PFBC genes mutations by NGS was performed revealing biallelic variants in MYORG: p.(Arg441Alafs*65) (class 4 ACMG) and p.(Leu614Pro) (class 3 ACMG).

Conclusion: The deep clinical-instrumental assessment performed in this case allowed to underline the possible heterogeneous impact of MYORG mutations on the different axial functions with a less relevant involvement of speech if compared with gait and balance.

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Perampanel as a novel treatment for myoclonus in myoclonus-dystonia syndrome

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Background: Myoclonus-dystonia (MD) is a heterogeneous genetic group of disorders characterized by subcortical myoclonus and mild to moderate dystonia [1,2]. The main causative gene is the epsilon sarcoglycan gene (SGCE) but genetic background can be heterogeneus [3]. Response to medications is variable, with poor tolerability limiting their use [4].

Case presentation: We present the case of a patient with involuntary movements since childhood. Symptoms progressed gradually over the years, involving neck, shoulders and upper limbs and interfering with daily activities. She referred to a neurologist at the age of 46y, and myoclonus-dystonia was diagnosed. Genetic testing identified a novel mutation in SGCE gene (c.907delC) in heterozygosis. Her parents were dead, thus no genetic analysis was possible. However, none of her relatives reported neurological disturbances. Clinically, she presented brief myoclonic jerks predominating in the upper limbs and neck, mild at rest and elicited by action, posture and tactile stimulus. Myoclonus was accompanied by mild neck and right arm dystonia. Over time she assumed a large variety of antiepileptics without beneficial effect on myoclonus and low tolerability. Treatment with Perampanel at 4 mg/day was started, with a beneficial effect on myoclonus. No adverse events were reported.

Discussion: Perampanel is the first selective non-competitive AMPA receptor antagonist approved in add-on for focal and generalized tonic-clonic seizures. It has been used to treat myoclonus in a few patients with Progressive myoclonic epilepsies and Lance Adams syndrome with beneficial effects [5,6] but no reports are available in literature in MD. To our knowledge this is the first trial of perampanel in MD.

Conclusions: We presented the case of a patient with MD due to SGCE mutation who was treated with Perampanel with beneficial effects. We propose Perampanel as a novel treatment for myoclonus in MD.

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Parkinson and Gaucher's diseases: common risk factors and future therapeutic targets

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Introduction: Gaucher's disease is an autosomal recessive disorder due to glucocerebrosidase (*GBA*) gene mutations and it's the most common Lysosomal Storage disorder. Several genetic mutations have been described to cause inefficient production of the correctly folded glucocerebrosidase enzyme (GCcase). Many studies suggest an association between mutations in *GBA* gene and susceptibility to developing Parkinson's disease (PD), underlining lower activity of GCase in Parkinsonian patients with or without *GBA* variants.

Objective: The aim of the study is to evaluate the frequency of low GCase's activity and *GBA* mutations in a large cohort of PD patients.

Methods: A cohort of 252 PD patients was selected at the Parkinson unit of AOU Careggi in Florence. For each patient, clinical data were collected and GCase enzyme activity screen was performed through Dried Blood Spot (DBS). *GBA* gene sequencing analysis was performed on patients with low GCase activity (<5 μmol/h/L).

Results: We found 78 patients with low GCase's activity and among these 22 patients with *GBA* mutations. The most common *GBA* variants found were p.(Asn370Ser) in 32%, p.(Leu444Pro) in 9%, p.(Glu326Lys) in 9%, p.(Asp409His) in 9% and p.(Thr369Met) in 4%. In this group of patients the average age of symptoms onset was 57,9±9,3 years. The first symptom was tremor in 14 patients and rigidity in 4. Ten patients manifested cognitive impairment during follow-up visits. Forty percent (N=9) of subjects had a positive family history of PD.

Conclusions: In our cohort the proportion of PD patients with reduced GCase's activity and the one with *GBA* mutations are consistent with already published data (from 5 to 20%). *GBA* variants represent a risk factor for Parkinson's disease and particularly for the forms with dementia. The modulation of GCase activity represents a potential therapeutic target for PD in the near future.

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Monolateral blepharospasm in primary familial basal ganglia calcification

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Introduction: Il blefarospasmo è una tipica distonia focale facciale con contrazione involontaria di una o entrambe le palpebre. I sintomi includono l'ammiccamento frequente e l'irritazione dell'occhio. L'eziopatogenesi è sconosciuta sebbene molti dati indicano come causa una alterazione a livello dei gangli della base. La calcificazione familiare dei gangli della base è una condizione rara caratterizzata da mutazioni in diversi geni. Sono state descritte diverse alterazioni genetiche responsabili di questa patologia. Una mutazione del gene PDGFB (Platelet derived growth factor subunit beta) è la seconda mutazione più frequente, coinvolta nel reclutamento dei periciti, nella regolazione della barriera emato-encefalica e nell'angiogenesi. Descriviamo il raro verificarsi di blefarospasmo monolaterale in una famiglia con mutazione PDGFB e calcificazione dei gangli della base.

Descrizione del caso: Una donna di 62 anni affetta da calcificazione dei gangli della base diagnosticata da 10 anni presenta ammiccamento dell'occhio sinistro e la chiusura periodica della palpebra sinistra. Erano presenti una lieve dismetria cerebellare e un tremore intenzionale degli arti superiori bilaterali, instabilità dell'andatura con una tendenza a cadere di lato. Calcio, fosforo e altri ioni erano normali. La risonanza magnetica del cervello, con specifiche sequenze SWI (Susceptibility-wheighted images) ha rivelato una tipica calcificazione bilaterale e simmetrica dei gangli della base e del cervelletto. L'ipoparatiroidismo è stato escluso. L'analisi genetica ha mostrato la presenza di una mutazione nell'esone 4 con cambio nucleotidico 421 T>C del gene PDGFB, con una variante missens p.Cys141Arg.

Discussion: Il Blefarospasmo in pazienti con calcificazione dei gangli della base è stato descritto prima in due casi. In entrambi i casi il blefarospasmo era bilaterale. La comparsa di blefarospasmo unilaterale nel nostro paziente rappresenta la prima descrizione di questo disturbo in questa forma di alterazione genetica di calcificazione familiare dei gangli della base. I neurologi dovrebbero essere consapevoli dell'emergere del blefarospasmo associato alla mutazione del gene PDGFB e alla calcificazione familiare dei gangli della base.

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Hydrocephalus and tremor in a man with tetrasomy 48, XXXY

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Introduction: Sex chromosomal aneuploidy is the most common disorder of sex chromosomes in humans (1:400) while chromosome tetrasomies, like addition of more than one extra X and/or Y chromosome to a normal male karyotype, are very rare conditions causing syndromes characterized to varying degrees of tall stature, hypergonadotropic hypogonadism, developmental delays, cognitive impairments and behavioural disorders. Brain MRI studies showed in some of these patients nonspecific T2/Flair white matter hyperintensities, which ranged in size and degree.

Objective: We describe neurological manifestations in a 45 years old man with aneuploidy 48, XXXY.

Methods: Subject underwent serial neurological, neurosurgical and neuropsychological evaluations, brain magnetic resonance imaging (MRI), [123I]-FP-CIT-SPECT and electroencephalogram.

Results: We present the case of a man with 48, XXXY aneuploidy who manifested movement disorders. Syndromic state included exotropia, overweight, tall stature, cognitive development delay and psychiatric disorders (impulse-control disorder and mood alterations). At the age of 35 years, he manifested postural and telekinetic tremor of the four limbs and of the head; after two years progressively worsening gait, balance disorder and urinary incontinence appeared. Brain MRI showed hydrocephalic dilatation of the lateral ventricles and small non-specific hyperintense alterations in T2 sequences in the white matter mainly of the frontal lobes. Neuropsychological evaluation highlighted impairment of verbal and visuospatial memory functions, of frontal functions and of selective attention. Electroencephalogram revealed diffuse slow waves compatible with mild encephalopathy without epileptic abnormalities. The DAT-SPECT was found to be normal. On neurological evaluation ataxic walking, postural tremor and telekinetic were evident, while other extrapyramidal signs were absent. Neurosurgeons decided not to perform derivative surgery. Propranolol therapy was not tolerated for episodes of blood hypotension. However, movement disorders and brain MRI remained unchanged over the next 10 years.

Conclusions: The case described increases the knowledge about the possible neurological manifestations of 48,XXXY aneuploidy.

INDICE AUTORI

Per visualizzare i contributi

cliccare sui codici alfa-numerici

(A – B – C – D – E – F – G – H – I – J – K – L – M – N – O – P – Q – R – S – T – U – V – W – Y – Z)

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