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SOCIETÀ ITALIANA PARKINSON E DISORDINI DEL MOVIMENTO LIMPE-DISMOV ETS

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ABSTRACT

Indice generale

Comunicazioni Libere

C1

Unraveling the role of GBA1 genotype in axial signs response to subthalamic deep brain stimulation

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Introduction: Patients with Parkinson Disease (PD) carriers of pathogenic variants of GBA1 gene have higher risk of cognitive and axial motor signs deterioration. Given the high prevalence of these disturbances in GBA1 patients and the suggested detrimental effect of GBA1 mutations on cognitive outcome of STN-DBS [1,2], a definition of the course of axial motor signs after surgery in this population is of great relevance [3].

Objectives: The main aim of this study is to elucidate the potential role of GBA1 genotype as predictor of the outcome of axial motor signs in patients with PD who underwent bilateral subthalamic deep brain stimulation (STN-DBS).

Methods: This retrospective cohort study involved 10 Italian tertiary-level Movement Disorder Centres contributing to the Italian PARKNET project. Demographic and clinical data, including the UPDRS III axial subscore, were collected at baseline and one, three and five years after surgery.

Results: We selected 353 PD patients who underwent DBS surgery (75 GBA+ and 253 GBA-). 5-year follow-up data were available for 233 patients, including 43 mutated subjects. Following STN-DBS, both groups presented a comparable variation of the axial score in the on-medication condition at 1-, 3- and 5-year follow-ups, while GBA+ group showed a greater improvement of the axial score at 5-year follow-up in the off-medication condition. At the multivariable Cox regression, a higher off-medication UPDRS III score at baseline in the GBA+ group predicted a better axial outcome in the off-medication condition (HR=0.93, 95% CI 0.91-0.96). GBA1 status was not identified as a predictor of axial signs outcome.

Conclusions: GBA1 genotype does not influence the course of axial motor signs up to five years after STN-DBS, which may be considered a valid therapeutic option in this frequent genetic subgroup.

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C2

Microstructural MRI and glymphatic flow alterations in patients with isolated 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: To assess neurological, gait analysis, microstructural MRI, glymphatic flow alterations features in iRBD subjects relative to controls; to study the correlations between clinical and MRI features; and to compare sub-groups of iRBD patients.

Methods: Forty-four iRBD subjects and 52 controls underwent motor, non-motor and cognitive assessments, gait analysis and MRI evaluations. Brain microstructural alterations were studied using Tract-Based Spatial Statistic (TBSS) and Gray-matter-Based Spatial Statistics (GBSS). Diffusion-Tensor Image Along the Perivascular Space (DTI-ALPS) index was obtained for the evaluation of glymphatic flow functionality. Cluster analysis was applied to divide iRBD patients in sub-groups. ANOVA models were used to compare clinical, and MRI data. Correlations between clinical and MRI data were assessed.

Results: IRBD subjects showed worse sleep quality, a reduced manual dexterity and spatio-temporal gait parameters alterations relative to controls. iRBD showed microstructural alterations in the gray-matter of frontal and parietal lobes, and in the white-matter of brainstem and frontal lobe. iRBD showed lower DTI-ALPS index relative to controls. Correlation analyses in the iRBD group showed that worse gray matter microstructural alterations correlated with worse performance in the Nine-Hole-Peg-Test, lower peak turning velocity during Timed Up and Go test with a cognitive dual-task and worse sleep quality. Cluster analysis resulted in two clusters, with one showing generally worse clinical, neuropsychological and gait performances together with a worse DTI-ALPS index.

Conclusions: Clinical, gait analysis and MRI data collected longitudinally could be useful in the creation of predictive models for the conversion from iRBD to parkinsonisms.

References: [1] Italian Ministero della Salute (grant number RF-2018-12366746).

C3

Multidomain cognitive tele-rehabilitation for Parkinson's disease with mild-to-moderate cognitive decline

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Introduction: Cognitive decline is a non-motor symptom of Parkinson's disease (PD) that significantly impairs quality of life [1]. Cognitive stimulation (CS) has demonstrated efficacy in enhancing cognitive function in PD-related cognitive impairment [2]. However, logistical challenges, like mobility limitations, frequently restrict access to regular in-person CS programs. Telerehabilitation offers a promising, home-based alternative that uses technology to deliver personalized interventions [3].

Aim: This study aims to evaluate the efficacy of remote CS in individuals with mild-to-moderate PD-related cognitive impairment.

Methods: Forty-five PD patients were randomized into a tele-rehabilitation group (TRG, n=25) or a control group (CG, n=20). The TRG underwent daily remote CS sessions, while the CG performed traditional paper-and-pencil-based cognitive exercises. Clinical and neuropsychological assessments were conducted at baseline, immediately post-intervention, and six months post-intervention.

Results: In the TRG, participants significantly improved in executive, attentional, and visuospatial abilities, demonstrating the effectiveness of tele-rehabilitation in addressing key cognitive deficits in PD. The CG showed similar benefits associated with a significant reduction in depressive symptoms, highlighting the added benefits of social interactions in traditional approaches. The cognitive decline observed at the six-month follow-up suggests the need for sustained engagement and long-term interventions to preserve these benefits over time.

Discussion: Telerehabilitation effectively enhances cognitive domains such as attention, executive function, and visuospatial skills, presenting a feasible and accessible solution for individuals with PD and mild-to-moderate cognitive decline. Future approaches may benefit from hybrid models that combine telerehabilitation's accessibility with the psychosocial benefits of in-person interventions to maximize cognitive and emotional outcomes for PD patients.

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C4

Single-interval and rhythmic temporal prediction in cervical dystonia

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Introduction: Temporal prediction (TP) is a flexible system shaped by context, with recent research [1] showing a double dissociation in its neural basis: the basal ganglia support TP in rhythmic contexts, while the cerebellum is involved in single-interval predictions. Abnormalities of TP may offer a novel pathophysiological framework for dystonia, based on the contribution of predictive timing in sensorimotor integration mechanisms, which are impaired in dystonia [2].

Objectives: To explore TP ability in patients with cervical dystonia (CD) compared to healthy controls (HC) and to examine the relationship between TP and clinical and cognitive features of cervical dystonia.

Methods: Twenty CD and twenty HC completed a clinical assessment and a TP task. Reaction times (RTs) were measured during TP under three conditions: rhythmic (periodic stream, fully predictable target appearance), single interval (aperiodic, based on pairs of stimuli defining the target interval), and random (unpredictable target onset). RT benefit scores were calculated by subtracting RTs in the random condition from those in predictive conditions.

Results: CD patients had lower benefit scores in the single-interval condition than HC, with no difference for CD and HC in the rhythmic condition. The single-interval benefit score negatively correlated with Toronto Western Spasmodic Torticollis Rating Scale (TWTRS) severity scores.

Conclusions: CD patients exhibited a selective impairment in forming interval-based predictions, which correlates with dystonia severity; greater severity leads to the largest decline in TP performance. No differences were observed between CD and HC groups for rhythmic-based predictions. These findings support the involvement of the cerebellum in dystonia pathophysiology and highlight the cerebellum's role in the abnormal memory-based temporal prediction ability observed in CD. Such abnormalities in temporal prediction may contribute to deficits in motor planning and movement output.

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C5

The role of radiomic in differentiating PSP phenotypes using MR imaging

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Introduction: Differentiating Progressive Supranuclear Palsy-Richardson's Syndrome (PSP-RS) from others variant of PSP (vPSP) is a significant diagnostic challenge [1].

Objective: This study aimed to explore the feasibility of radiomics features extracted from T1-weighted MRI images to differentiate PSP from healthy controls (HC) and among various phenotypes.

Methods: A total of 59 participants were enrolled, including 20 HC, 19 PSP-RS, and 20 vPSP (8 cortical [vPSP_c] and 12 subcortical [vPSP_sc]). Automatic segmentation of brain structures was performed using a brain atlas. Eighty-six radiomic features (18 first-order and 68 texture) were extracted from T1-weighted MRI regions of interest (ROIs), including the 3rd and 4th ventricles, brainstem, cerebellum, and various cortical and subcortical areas (e.g., putamen, pallidum, precentral gyrus, supplementary motor cortex). Univariate statistical analysis was conducted to differentiate HC from PSP (HC vs PSP-RS and HC vs vPSP). A Kruskal-Wallis test with post hoc analysis was applied to compare PSP phenotypes (PSP-RS vs vPSP_c vs vPSP_sc).

Results: Over 50% of first-order and texture radiomic features significantly distinguished HC from PSP across most ROIs. Key regions such as the brainstem, cerebellum, cerebellar vermal lobules, precentral gyrus, pallidum, putamen, and supplementary motor cortex significantly differentiate PSP-RS from vPSP ($p<0.05$). Post-hoc analysis identified the brainstem as the region with the highest number of discriminative radiomic features for distinguishing PSP-RS from both vPSP_c and vPSP_sc ($p<0.01$).

Conclusions: Radiomic analysis demonstrated a potential role in differentiating HC from PSP and distinguishing PSP-RS from vPSP phenotypes. These findings underscore the utility of radiomics as a neuroimaging tool to aid in differential diagnosis, with significant implications for prognosis and patient stratification in clinical trials.

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C6

Gender differences in cognitive stimulation efficacy in subjects with Parkinson's disease and mild cognitive impairment

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Introduction: Cognitive stimulation (CS) is a promising treatment in people affected by Parkinson's disease (PD) associated with mild or moderate cognitive decline [1]. Sex and gender may influence treatment response in PD but no data on gender differences in CS efficacy in PD are available.

Objective: This study investigated gender differences in clinical and neuropsychological outcomes of CS treatment, delivered through both remote or face-to-face programs, in subjects with PD and mild or moderate cognitive decline.

Methods: Forty-five subjects were enrolled and divided into two groups: a tele-rehabilitation group (TRG, men = 15, women = 10) receiving a remote CS, and a control group (CG, men = 15, women = 5) undergoing conventional CS. Neuropsychological assessments were conducted at baseline, after 20 sessions of CS, and after six-months follow-up. This work was supported by the Italian Ministry of Health ("MultiPlat_Age" project, grant number: NET-2016-02361805-5) [2].

Results: After CS, men demonstrated significant improvements in attention and working memory, particularly in the TRG, as reflected in higher scores on the Digit Span backward test. Women showed enhancement in verbal memory, achieving significantly higher RAVLT immediate recall scores ($p = 0.029$), with the most significant benefits observed in the CG. Semantic verbal fluency and praxis were domains where men outperformed women, particularly in the CG.

Conclusions: Our study showed gender differences in the efficacy of CS, both in tele-rehabilitation and in traditional approaches, in subjects with PD and mild cognitive impairment. These results reinforced remote cognitive rehabilitation efficacy, especially in men, as an alternative approach for subjects with restricted access to traditional in-person CS programs, overcoming logistical and mobility difficulties that may reduce subjects' compliance. Future research should develop tailoring cognitive rehabilitative interventions in men and women to improve clinical outcomes and overall quality of life of people with PD and mild cognitive impairment.

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C7

Biomarkers of neurodegeneration: comparison between iNPH, LOVA and other neurodegeneration diseases

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Introduction: Idiopathic normal pressure hydrocephalus (iNPH) and Long Standing Overt Ventriculomegaly in Adults (LOVA) are both chronic hydrocephalus forms with clinical onset in adulthood. LOVA is considered a congenital, obstructive hydrocephalus, marked by macrocephaly and severe ventriculomegaly, while iNPH seems to involve also neurodegeneration and often overlaps with other neurodegenerative disorders. [1] CSF biomarkers may help in differential diagnosis, however, no definitive biomarker profile exists for iNPH, and there is no data on LOVA CSF biomarkers [2].

Objectives: Our study aims to analyze the CSF markers of neurodegeneration in iNPH and LOVA patients and compare this data with other neurodegenerative diseases.

Methods: We collected the CSF of iNPH (n=97), LOVA (n=20), PD (n=26), AD (n=27), VD (n=21), and FTD (n=18) patients. We detected Tau, p-tau, Ab40, and Ab42 proteins levels in CSF and obtained the Ab42/Ab40 ratio. We compared the data with the Kruskal-Wallis H test and then performed Dunn post-hoc analyses with Bonferroni's correction.

Results: Tau and p-Tau proteins in the LOVA group was significantly lower than AD, iNPH, VD, and FTD ($p<0.05$), while the AD group had a significantly higher value of Tau and p-Tau proteins than iNPH, LOVA, and PD groups ($p<0.05$) but not VD and FTD. The Ab40 protein levels in the LOVA and iNPH groups were found to be similar; however, this CSF marker is significantly lower in the LOVA group than in the PD, AD, VD, and FTD groups ($p<0.05$). The iNPH group presented a lower value than the AD and PD groups ($p<0.05$), but not different from the VD and FTD groups. There was no significant difference in the Ab42/Ab40 ratio between the different groups, except in the case of AD, where this ratio was significantly lower than in the other groups ($p <0.05$).

Conclusions: The combination of the CSF biomarkers (T-tau, p-Tau, Aβ40 and Ab42/Ab40 ratio) can be useful to make iNPH and LOVA diagnosis and to distinguish these diseases from other neurodegenerative disorders.

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C8

Gait patterns associated with unsupervised machine learning-based clinical clusters in Parkinson disease: a new approach to identify and assess disease phenotypes?

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Introduction: Parkinson's disease (PD) is increasingly recognized as a disorder that extends beyond its core diagnostic criteria, encompassing a wide range of motor and non-motor [1] symptoms and signs that variously aggregate in heterogeneous phenotypes with different clinical course [2].

Objective: To evaluate gait patterns [3] in single and dual-tasks in clinical clusters identified by unsupervised machine-learning method.

Methods: A clustering analysis through K-means algorithm was conducted on MDS-UPDRS Parts I&II [4] items scores, after excluding gait-related items, in a cohort of 105 PD patients consecutively enrolled and evaluated with gait analysis acquired in three different conditions (normal gait, and two dual-tasks). Subsequently, univariate statistical analysis (ANOVA test or Kruskal-Wallis test, as appropriate) with post-hoc analysis was carried out to evaluate the differences among groups on spatio-temporal gait variables. Significance was set a $p<0.05$.

Results: The unsupervised machine learning analysis identified two clusters of which one emerged significantly smaller versus the other one, reflecting asymmetric clustering. Based on these findings, to better refine the clustering process, a second cluster analysis was conducted, after instructing the algorithm to select three clusters: the analysis identified 44 subjects in Cluster 1, 13 subjects in Cluster 2 and 48 subjects in Cluster 3. When comparing spatio-temporal gait features among the three groups, the Cluster 2 exhibited several statistically significant differences with the other two, emerging as the phenotype with the worst gait pattern. Of note, the extent and statistical significance of gait variables differing in comparison with the other two groups increased from single-task to dual-task, peaking for cognitive dual-task.

Conclusions: An unsupervised machine learning approach on clinical variables is able to identify discrete clusters [4]. Such clusters exhibit different quantitative gait features mainly under dual task conditions. The present findings suggest that combining clinical clustering approach and quantitative gait measures may help to identify previously uncharacterized PD phenotypes, predictive of specific trajectories.

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C9

Preserved neuroplasticity in patients affected by Parkinson's disease responders to external cueing strategies

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Introduction: Neural plasticity in the primary motor cortex (M1) is impaired in Parkinson's disease (PD) [1], with a lack of LTP-like plasticity and abnormal beta-band activity in sensorimotor areas. PD patients exhibit decreased beta desynchronization during movement initiation, correlating with more severe motor symptoms [2]. However, rhythmic auditory cueing (RAC) has been shown to normalize beta activity in sensorimotor areas during gait [3]. Recent studies suggest that LTP-like plasticity in M1 may enhance beta desynchronization during movement execution [4].

Objectives: This study hypothesized that PD patients who respond to RAC (i.e., show reduced gait variability during cued gait) might have preserved LTP-like plasticity in M1, which is linked to beta activity in the sensorimotor cortex, compared to non-responders.

Methods: Eleven RAC responders (Age: 67.6 ± 7.7 years; H&Y: 2.1 ± 0.31) and ten non-responders (Age: 67.6 ± 7.8 years; H&Y: 2.1 ± 0.40) with PD were assessed. Corticospinal excitability (CSE) was measured via input/output (I/O) curves at 80%, 100%, 120%, 140%, and 160% of the resting motor threshold (RMT) before and after iTBS, a TMS protocol to induce LTP-like plasticity in M1. The area under the I/O curve (AUC) was computed.

Results: Responders exhibited increased CSE post-iTBS, reflected in significantly higher motor-evoked potentials (MEPs) at 100% ($p=0.008$), 120% ($p=0.022$), 140% ($p=0.003$), and 160% ($p=0.001$) of RMT, and increased AUC ($p=0.001$). Non-responders showed no significant post-iTBS changes. Additionally, responders demonstrated a significantly higher post-iTBS AUC ($p=0.021$) compared to non-responders, with no baseline differences between groups.

Conclusions: These findings suggest that RAC responders may retain intact neuroplastic mechanisms in M1, potentially linked to reduced abnormal beta-band activity or more efficient beta desynchronization during externally cued movements. Further investigation using non-invasive brain stimulation and neurophysiological methods is planned as part of the international 'UNITE-PD' project aiming to elucidate the neural mechanisms of cueing strategies in PD.

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C10

Concordance between imaging and clinical based STN-DBS programming improves motor outcomes of directional stimulation in Parkinson's disease.

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Background and purpose: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established treatment for advanced-stage Parkinson's disease (PD) [1]. Recent advances in STN-DBS technology introduced new tools to improve PD treatment efficacy, while increasing the complexity of clinical programming [2]. Lead localization software can be helpful in the stimulation contact selection process [3,4]. We aimed to assess the concordance between imaging-suggested (IGP) and conventional-programming (CP) selected stimulation contacts one year after surgery and its impact on motor outcomes.

Methods: Sixty-four PD patients with bilateral STN-DBS were enrolled. Lead localization was reconstructed with BrainlabTM software. For each electrode, the vertical contact level and, when applicable, the directionality predicted by visual reconstruction to be the most effective were established and compared to the stimulation parameters clinically activated one year after surgery. IGP/CP concordance ratio was calculated for both stimulation level and directional contacts. Motor outcomes were compared among groups of concordant and discordant IGP/CP programming.

Results: One year after surgery, IGP/CP concordance was 80% for active stimulation vertical contact level and 51% for directionality. No significant difference in motor outcomes was found between IGP/CP concordant and discordant patients for contact level activation, whereas patients with concordant IGP/CP active directional stimulation (c-Direction) showed superior motor outcomes at one-year follow-up than those discordant (d-Direction) (UPDRS-III stimulation-induced improvement: c-Direction=-25.66±13.74 vs d-Direction=-12.54±11.86; p=0,011).

Conclusions: Visual reconstruction software correctly predicted the most clinically effective stimulation contact levels in most patients. Imaging therefore facilitates classic STN-DBS clinical programming while assuring similar outcomes. Moreover, better motor outcomes were reached by patients with concordant IGP/CP directional parameters, suggesting that visualization can represent an added value in particular for directional stimulation programming.

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C11

Age at onset modulates sex differences in Parkinson's disease

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Background: The influence of sex on dopamine transporter (DAT) availability, motor severity, and the risk of complications in Parkinson's disease (PD) remains incompletely understood.

Objective & Methods: This retrospective study included 158 de novo PD patients who underwent [^{123}I] FP-CIT SPECT imaging at diagnosis, with a mean follow-up of six years. Patients were divided into tertiles based on age at onset. Clinical and imaging data were analyzed to: 1) evaluate differences in DAT availability between sexes with respect to age at onset; 2) compare baseline motor severity (MDS-UPDRS-III scores) and follow-up outcomes between sexes within and across age groups; and 3) assess the age-related effect of sex on the prevalence of motor complications after six years.

Results: Fifty-four patients were classified as early-onset PD (EOPD, 52.7±10.1 years), and 52 as late-onset PD (LOPD, 74.5±9.9 years). In the EOPD group, females exhibited significantly higher striatal DAT binding and lower baseline MDS-UPDRS-III scores compared to both males ($p=0.010$) and older females ($p=0.001$). This trend reversed in the LOPD group, where females showed worse motor scores compared to males of the same age, despite no significant differences in DAT binding. Motor complications were similar between sexes but more frequent in the EOPD group than in the LOPD group. Linear regression revealed a significant effect of age at onset on putamen and caudate DAT binding in females (most and least affected caudate: $p=0.001$ and $p=0.003$, respectively), whereas no significant effects were observed in males.

Conclusions: These findings highlight an age-dependent sex effect on striatal DAT availability and motor severity in PD. Younger females exhibited more preserved DAT binding and a milder motor phenotype compared to younger males and older females. This may reflect a progressive decline in DAT availability with age at onset, potentially linked to diminishing neuroprotective effects of estrogen in younger females.

C12

Exploring the relationship among cardiovascular autonomic failure, isolated REM sleep behavior disorder and Parkinson's disease: a prospective evaluation

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Introduction: Isolated REM sleep behavior disorder (iRBD) is a prodromal condition of α-synucleinopathies, including Parkinson's disease (PD). PD with RBD in the early phase (PD+RBD) is associated with more severe motor and non-motor symptoms, including cardiovascular autonomic failure (cAF). However, whether cAF is more related to RBD or to PD has to be confirmed.

Objective: To compare the prevalence and progression of cAF in iRBD and PD.

Methods: 100 early-stage (<3 years) PD (20 with RBD) [1-2], and 40 iRBD [3] were prospectively evaluated with videopolysomnography and cardiovascular reflex tests (CRTs) at baseline and after 1.85±0.60 years. Mixed-effects regression models adjusted for age and sex assessed baseline differences and longitudinal changes.

Results: At baseline iRBD (mean age 66.57±5.99 years, 17.5% female) exhibited more severe cAF than PD (62.53±8.23 years, 35.0% females), with more frequent neurogenic orthostatic hypotension (nOH – 15.0% vs 4.0%, p=0.022) and abnormal blood pressure responses to CRTs (pathological Valsalva Maneuver - VM overshoot in 47.4% vs. 18.0%, p=0.001). The prevalence and severity of autonomic failure was similar between iRBD and PD+RBD (nOH – 20%, p=0.563; pathological VM overshoot – 50.0%, p=0.708). Longitudinal data demonstrated progressive deterioration of baroreflex function, with increased prevalence of nOH in iRBD and PD+RBD (incident nOH in 4 and 3 patients respectively; yearly odds ratios - OR = 5.47 p=0.003 and 2.30 p=0.046), not significant in PD-RBD and PD as a whole (OR = 1.80 and 0.99 with, p=0.165 and 0.983 respectively). Prevalence of pathological VM overshoot increased only in PD+RBD (OR 7.83, p=0.041).

Conclusions: The neurodegenerative process underlying cAF is more closely associated with RBD than with PD phenotype. Autonomic dysfunction worsens over time predominantly in the presence of RBD, regardless of phenoconversion status, highlighting RBD as a key driver of autonomic impairment and progression.

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C13

Brain MRI findings in Primary Familial Brain Calcification: results from a single-center Italian cohort

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Introduction: PFBC (Primary Familial Brain Calcification) is a genetic neurodegenerative disorder characterized by bilateral calcification of basal ganglia, featuring movement disorders, psychiatric or cognitive disturbances. CT scan is the gold standard technique to image brain calcification, whereas the role of MRI is currently limited and no clear correlations between genetic PFBC subtypes, clinical phenotypes and radiological features are known.

Objectives: Describing MRI findings and clinical-genetic correlates in a single-center PFBC cohort.

Methods: 45 PFBC subjects and 67 matched healthy controls (HC) from the ERN-RND Center of Padua University underwent a 3T brain MRI (T1, FLAIR, SWI sequences, FreeSurfer cortical thickness analysis), genetic tests (NGS Illumina NextSeq), blood tests (exclusion of alternative diagnoses), clinical and neuropsychological evaluation.

Results: A genetic diagnosis was formulated in 29/45 patients (64.4%); 30/45 (66.6%) had neurological symptoms (movement disorders or cognitive decline, mean disease onset 44.6 years). Mean age at MRI scan was 57 years. FLAIR and SWI sequences proved sensitive in identifying brain calcifications. White matter involvement and leukopathy in both cerebrum and cerebellum were significantly associated with mild cognitive impairment (OR 5.7, p=0.02; mean MoCA 21 vs 26, p=0.004). The presence of dentate nuclei calcifications was a significant predictor of a genetic diagnosis (OR 7.3, p=0.03) and of behavioral-psychiatric symptoms (91% vs 56%, p=0.04). All MYORG mutation carriers (n=5) showed punctate calcifications in the brainstem in a region approximately corresponding to hypoglossal nerve nucleus, possibly contributing to dysarthria, typical of this genetic subtype. A statistically significant reduction in cortical thickness in the left premotor cortex was observed in PFBC ($p<0.05$) vs HC, whereas no alterations were documented in asymptomatic PFBC subjects compared to HC. Cerebellar atrophy was evident in MYORG subjects.

Conclusions: Brain MRI can be a useful tool in PFBC diagnosis; additional radiological findings may have potentially relevant genetic and prognostic correlations.

C14

Brain beta amyloid pathology impacts cognitive profile in normal pressure hydrocephalus

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Introduction: Normal Pressure Hydrocephalus (NPH) is a clinico-radiological syndrome of elderly individuals. Recent studies revealed a high rate of neurodegenerative disorders in NPH patients, showing Alzheimer or Lewy body pathologies. In literature, studies focusing on cognitive profile of NPH patients with neurodegenerative co-pathology are scanty [1,2].

Objectives: 1) To describe the neuropsychological profile at baseline and 6 months after surgery in a cohort of NPH patients; 2) to compare cognitive functions in NPH with and without brain co-pathology related to amyloid-beta deposition.

Methods: Patients underwent an inpatient standardized work up with tap-test, including instrumental and clinical evaluations, cerebrospinal fluid biomarkers analysis and a comprehensive neuropsychological assessment [3]. A multidisciplinary team selected candidates for surgery. An extensive clinical evaluation including neuropsychological re-assessment was carried six months after surgery.

Results: From 2015 to 2024, 226 (97 females) consecutive NPH patients completing the baseline evaluation were included. To date, the neuropsychological assessment at six months after surgery was performed in 100 shunted NPH patients (40 females). The cognitive profile in all individuals revealed deficits in attentive and executive functions with a significant improvement in visuo-spatial long-term memory and verbal short-term memory after surgery. Overall, 27.0% of NPH participants showed an amyloid-positive (Aβ+) status. At baseline, the comparison between Aβ+ (n=61) and Aβ- (n=165) patients revealed worst neuropsychological performances in the former group, with a greater involvement of memory abilities. In shunted patients undergoing neuropsychological assessment, differences in post-operative cognitive profile emerged between the two groups.

Conclusions: Cognitive profile in NPH patients is mainly characterized by attentive-executive deficits. Brain beta-amyloid pathology affects a significant proportion of NPH patients and contributes to a worse cognitive status at baseline. The identification of Aβ pathology should be considered in the clinical assessment of NPH patients as greater cognitive involvement could impact patient's disability and caregiver burden.

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C15

Subcutaneous foslevodopa/foscarbidopa: focus on treatment titration and starting phase

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Introduction: Continuous subcutaneous foslevodopa/foscarbidopa (FL-FC) infusion is the newest therapy for patients with Parkinson's Disease (PD) and motor fluctuations no longer controlled by oral therapy. It is a prodrug metabolized into levodopa in the subcutaneous tissue. [1,2] As demonstrated by Levodopa-carbidopa-intrajejunal-gel (LCIG) therapy, the titration and dose optimization phase of infusion therapy is pivotal for ensuring a successful long-term outcome in patients transitioning from oral therapy. We report our experience with the initiation and titration phases of subcutaneous FL-FC, comparing it to the first three months of treatment data with LCIG

Methods: We retrospectively analyzed two groups of patients: FL-FC group (n=10), and LCIG group (n=70). For each group, we collected clinical data (UPDRS-III, PDSS, and WOQ-9 scales) and the levodopa equivalent dose (LEDD) at therapy initiation (T0) and after three monthstreatment (T1), as well as the number of follow-up visits required to optimize symptoms during the first three months of infusion.

Results: At T1, all patients demonstrated similar motor improvement, reduced sleep disturbances, and an overall higher quality of life with both infusion treatments. However, we observed a significant difference in the number of follow-up visits required (median of 3.4 for FL-FC vs. 1.1 for LCIG) and in the increase in LEDD (37.55% for FL-FC vs. 6.93% for LCIG) necessary for clinical optimization at T1

Conclusion: Our data suggest that FL-FC has proved to be an effective therapy for patients with motor fluctuations not optimized by oral or intrajejunal therapy. The titration and optimization phase, however, need frequent visits and adjustment of infusion dose in the first months of treatment. The increase in LEDD compared to oral therapy was also significantly higher with FL-FC than with LCIG. Further studies are needed to explore the pharmacokinetics of subcutaneous tissue and interpatient variability, enabling better patient selection and more personalized therapy.

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C16

The natural history of body-first versus brain-first Parkinson disease subtypes

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Introduction: Several lines of evidence support the hypothesis of brain-first and body-first Parkinson disease (PD) subtypes, characterized by distinct origins of α-synuclein pathology [1]. However, data on premotor non-motor burden and motor progression to Hoehn & Yahr (H&Y) stage 3 in these subtypes remain inconsistent [2].

Objective: To analyse the natural history of body-first versus brain-first PD subtypes.

Methods: Data from 400 PD patients enrolled at a single Italian centre were analysed. All patients underwent a standardised retrospective baseline assessment of premotor and motor symptoms at onset and were prospectively followed for up to 9.7±4.9 years from motor onset. Premotor REM sleep behaviour disorder (RBD), considered a prodromal phenotype of the body-first subtype [3], was used to divide patients into two groups: 81 patients with probable premotor RBD ($PD^{preRBD+}$) and 319 patients without ($PD^{preRBD-}$).

Results: At motor onset, $PD^{preRBD+}$ patients were older than $PD^{preRBD-}$ patients (64.9 ± 8.1 vs. 61.2 ± 9.8 years, $p = 0.002$), exhibited a lower frequency of tremor (53.1% vs. 68.7%, $p = 0.008$), and more frequently presented with bilateral motor symptoms (28.4% vs. 13.5%, $p = 0.001$). $PD^{preRBD+}$ patients also reported a higher burden of premotor symptoms, including constipation, dysautonomia, hyposmia, cognitive impairment, and pain. Over the follow-up period, $PD^{preRBD+}$ patients progressed more rapidly to H&Y stage 3 (log-rank $p = 0.005$), even after adjusting for sex, years of schooling, age at motor onset, and initial motor phenotype.

Conclusions: Our results align with the hypothesis of brain-first and body-first PD subtypes, providing novel insights into their different premotor non-motor burden and motor progression trajectories.

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C17

Acute and long-term effects of deep brain stimulation on cortico-cortical functional connectivity in Parkinson's disease: a high-density EEG study

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Introduction: Deep Brain Stimulation (DBS) is an established therapy for Parkinson's disease (PD), yet its underlying mechanisms remain elusive. It was previously hypothesized that DBS may suppress hypersynchronous oscillatory activity within cortico-basal networks [1,2].

Objective: Using a network-based approach, we aimed to assess acute- and long-term (i.e., chronic) effects of DBS on cortico-cortical functional connectivity (FC) in PD patients using high-density EEG (HD-EEG).

Methods: Sixteen PD patients were evaluated before (PRE-DBS) and ≥ 6 months after DBS surgery targeting the Subthalamic Nucleus (STN) or Globus Pallidus internus (GPi). Resting-state HD-EEG was recorded using a 64-channel system following >12 hours of L-Dopa withdrawal. Postoperatively, HD-EEG was performed with DBS turned on (POST-DBS-ON) and ≈15 minutes after switching it off (POST-DBS-OFF). Symptoms were assessed using MDS-UPDRS-III and IV scales. Source reconstruction identified brain region activity based on individual brain MRIs. Cortico-cortical FC in θ, α, low-β, high-β and low-γ frequency bands was analyzed based on weighted phase-lag index. FC changes were assessed using network-based statistics.

Results: Comparing POST-DBS-ON and POST-DBS-OFF conditions (DBS acute effects), we observed reduced FC in the low-β band in a wide cortical network, which significantly correlated with acute motor symptoms improvement (MDS-UPDRS-III scores). When assessing longitudinal changes after DBS, we identified differential networks in the low- and high-β bands where the FC was significantly reduced postoperatively (POST-DBS-OFF) compared to PRE-DBS, correlating with improvements in motor complications (MDS-UPDRS-IV scores).

Conclusions: DBS induces acute and chronic changes in cortical networks that might underlie its clinical efficacy [2]. Acute changes in cortical connectivity could reflect immediate beneficial effects of DBS on abnormal β synchronization within cortico-basal circuits. Chronic DBS downregulates hypersynchronized cortico-cortical β networks, potentially contributing to the long-term reduction of motor fluctuations. These findings might reflect DBS-induced long-term effects on cortical networks, possibly underlying a plastic reorganization of cortical circuits [3].

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C18

Segmental and multifocal dystonia: two faces of the same disease?

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Background: According with the dystonia classification, segmental dystonia involves two or more contiguous body regions, while multifocal dystonia affects two or more non-contiguous regions.[1] However, there is no consensus on the precise definition of body regions, especially concerning the limbs [1,2]. The clinical characteristics of segmental and multifocal dystonia have never been systematically compared.

Objectives: To compare demographic and clinical features between segmental and multifocal dystonia.

Materials and Methods: Patients with isolated adult-onset idiopathic dystonia (IAOD) were selected from the Italian Dystonia Registry. Two models were used for analysis.
Model 1: upper limb was considered as a single body region.
Model 2: upper arm and hand were analyzed as separate body regions.

Results: Among 2100 IAOD patients, 1611 were diagnosed with focal dystonia, 465 with segmental or multifocal dystonia, and 24 with generalized dystonia.
Model 1: 334 patients were classified as having segmental dystonia, and 131 as having multifocal dystonia. No significant differences were observed in sex, age at dystonia onset, and dystonia-affected body sites between the two groups; however, blepharospasm was significantly more frequent in multifocal dystonia ($p < 0.001$), while oromandibular and lower limb dystonia were more common in segmental dystonia ($p < 0.001$).
Model 2: 248 patients were diagnosed with segmental dystonia, 169 with multifocal dystonia, and 48 were excluded due to lack of information. The segmental group showed higher age of dystonia onset 57.2±12.4 vs. 53.2±15 years; p 0.003), and women sex frequency (180 vs. 104; p 0.02). Oromandibular and laryngeal dystonia were more common in segmental dystonia ($p <0.01$), whereas cervical dystonia, upper limb and lower dystonia predominated in multifocal dystonia ($p <0.001$).

Discussion: The clinical differences between segmental and multifocal dystonia may indicate underlying pathophysiological variability. Our findings also highlight the need for consistent and standardized classification criteria.

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C19

Types of pain in multiple system atrophy

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Introduction: Eighty-seven percent of individuals with multiple system atrophy (MSA) report pain, but which pain types mostly contribute to pain burden remain unclear.

Objective: Here we estimate the prevalence of different pain types in MSA.

Methods: We analyze the prevalence of different pains according to the King's Parkinson's Disease Pain Questionnaire (KPPQ), and of further putative pain causes (i.e., coat-hanger pain, pain related to catheterization, bladder infections/spasms, pressure sores, bruises, cold hands/feet) in a cohort of MSA individuals, who answered a web-based survey in 2023. MSA individuals were matched for gender, age (±3 years), and disease duration (±2 years) with PD subjects and HCs from a King's college cohort, who had completed the KPPQ.

Results: Among 264 MSA individuals who accessed our survey, 194 are retained after data cleaning, of which 157 with completed KPPQ. Nocturnal (73%, n=114), musculoskeletal (63%, n=98), and fluctuation-related pain (62%, n=94) and, among putative MSA-specific pains, the coat-hanger pain (59%, n=91), pain related to cold-hands and feet (48%, n=75), and to bruises (44%, n=69) occurred most frequently. No differences are observed across the parkinsonian (MSA-P, n=59) and the cerebellar (MSA-C, n=75) subtype. In the matched subgroup (n=96), all pain types were more frequent in MSA compared to HCs, except for musculoskeletal pain, which was as frequent in MSA as in the HCs (63% vs 66%, p=0.722) and more common in PD than in MSA (78% vs. 63%, p=0.023). Orofacial pain was more frequently reported in MSA compared to PD (32% vs. 12%, p<0.001).

Conclusions: Both disease-related (e.g., orthostatic hypotension- related coat-hanger pain) and unrelated (e.g., musculoskeletal pain) pain types contribute to pain burden in MSA. Tailored tools are needed to screen for all possible types of pain in MSA, which may benefit from an optimized symptomatic management of core motor and non-motor features.

C20

Plasma pTau217 as a marker for Alzheimer's co-pathology in Parkinson's spectrum disorders

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Introduction: Alzheimer's disease (AD) co-pathology is common in Parkinson's spectrum disorders and independently contributes to dementia [1,2]. Plasma pTau217 has emerged as a promising blood-based biomarker for detecting AD pathology, offering a more accessible and cost-effective alternative to b-amyloid (Aβ) positron emission tomography (PET). Elevated pTau217 correlates with Aβ and tau PET, and may also help to identify AD co-pathology in Parkinson's disease (PD) patients at risk for dementia [3,4] as well as in atypical parkinsonisms [5].

Objectives: To evaluate the utility of plasma pTau217 for detecting AD co-pathology in parkinsonian disorders and its association with cognitive impairment.

Methods: The PADUA-CESNE cohort included 170 participants: 57 with PD, 4 with dementia with Lewy bodies (DLB), 28 with Progressive Supranuclear Palsy (PSP), 4 with corticobasal syndrome (CBS) patients, 51 healthy aged controls (HC) and 26 with mild cognitive deficits (MCI). All participants underwent an extensive cognitive assessment, including MoCA and MMSE, which enable to classify patients across the PD-cognitive spectrum: cognitively normal (PD-NC), with MCI (PD-MCI) or dementia (PDD/DLB). Plasma pTau217 was measured using a research-use-only Lumipulse G1200 assay (Fujirebio, Japan). A previously validated pTau217 > 0.22(ng/L) cut-off, established against Aβ-PET and accounting for 10% analytical variability, was adopted to define Aβ positivity [6].

Results: HC had lower pTau217 than PSP/CBS (p=0.005), while PD-NC showed lower levels than PD-MCI (p=0.042), PDD/DLB (p=0.049), and PSP/CBS (p=0.002). No pTau217-positive cases were observed in PD-NC. AD co-pathology positivity was highest in the MCI group (32.14%), followed by CBS/PSP (28.13%), PDD/DLB (27.27%), and PD-MCI (15.63%), with the lowest in HC (7.84%). Within the overall PD group, negative correlations were found between pTau217 and MoCA (r^2=–0.38, p=0.004) and MMSE (r^2=–0.37, p=0.006). follow-up available after opicapone initiation, revealed a significant improvement in the NMSS global score (T-test, p = 0.015), and confirmed the major effects on sleep and pain (p = 0.026).

Conclusions: pTau217 is elevated in PD patients with cognitive impairment, particularly PDD/DLB, but not in cognitively normal PD. It may serve as a reliable marker of AD co-pathology, warranting further validation with PET imaging.

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C21

Genetic etiology and its impact on GPi electrophysiology and implications for adaptive DBS in dystonia

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Introduction: Genetic forms of dystonia stem from pathogenic mutations in causative genes leading to diverse clinical manifestations [1,2]. Elevated low-frequency activity within the globus pallidus internus (GPi) has been consistently linked to dystonia [3,4]. However, the impact of the genetic etiology on GPi activity remains unclear. Understanding this relationship holds significant potential for advancing adaptive deep brain stimulation (DBS) treatments.

Objectives: Herein, we investigated the effects of genetic etiology on the GPi electrophysiology and its implications for adaptive DBS in dystonia.

Methods: We analyzed the electrophysiological properties [5] of the GPi using data from 67 MER trajectories obtained from patients with DYT-GNAL, DYT-KMT2B, DYT-SGCE, DYT-THAP1, DYT-TOR1A , DYT-VPS16, and idiopathic dystonia (iDYT) who underwent GPi-DBS surgery. The analysis focused on activity across standard frequency bands.

Results: Elevated relative power in the theta (4–8 Hz) and alpha (8–12 Hz) bands relative to baseline activity was consistently observed across dystonia forms. However, this elevation was significantly lower in the alpha band for DYT-VPS16 (3.26%, median fraction of total power) compared to iDYT (4.41%, P =0.016) and DYT-THAP1 (4.17%, P =0.039). We observed pronounced gamma activity (30–100 Hz) in DYT16 cases compared to others, but its significant correlation with baseline

BFMDRS arm scores (r_s =0.47, P =0.046) suggests this difference is linked to upper limb symptoms rather than genetic etiology. Lastly, we found that genetic etiology does not affect the spatial characteristics of GPi electrophysiology along MER trajectories.

Conclusions: Accounting the genetic etiology of dystonia as a factor in closed-loop DBS stimulation may improve clinical outcomes, while intraoperative MER-based DBS lead placement can proceed independently of the patient's underlying genetic cause. These findings align with our recent study presenting that dystonia genes converge into similar pallidal spiking patterns, with the extent of pallidal bursting serving as a potential mechanism underlying the varying responsiveness of these genes to GPi-DBS [6].

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C22

Multi-pathway salivary biomarkers predict clinical outcomes and mirror disease progression in Parkinson's disease: a follow-up study

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Introduction: Among neurodegenerative disorders, Parkinson's Disease (PD) exhibits the fastest-growing incidence worldwide [1], highlighting the urgent need for minimally invasive biomarkers. Saliva presents a promising non-invasive sample for the search of biomarkers in PD [2]. In our previous study, we investigated salivary biomarkers targeting different molecular pathways, including alpha-synuclein (a-syn) and tau pathology, autophagy (MAP-LC3b), and inflammation (TNFa), in de novo PD patients. This analysis demonstrated high accuracy in discriminating PD patients from healthy controls (HC) [3].

Objectives: Investigate longitudinal changes in salivary levels of oligomeric a-syn, total a-syn, phosphorylated-tau (p-tau), total tau, MAP-LC3b, and TNFa in PD patients. Assess whether salivary biomarkers at disease onset can predict clinical worsening over time. Correlate longitudinal changes in molecular and clinical data in PD patients.

Methods: A clinical and molecular 3.5-year follow-up (T1) was conducted on 40 PD patients of the previous PD cohort [3]. Levels of oligomeric and total a-syn, p-tau, total tau, MAP-LC3b, and TNFa were quantified using ELISA Assays. Clinical assessments at T1 included motor and non-motor symptoms scales. Statistical analyses included the Friedman test to evaluate molecular and clinical changes between T0 and T1; linear regression analysis to determine whether salivary biomarkers at T0 could predict clinical progression; Spearman's correlations to explore correlations between changes in molecular biomarkers and clinical scores.

Results: Oligomeric a-syn and MAPLC3b showed significantly lower salivary levels, while total a-syn, p-tau, total-tau and TNFa exhibited significantly higher salivary levels from T0 to T1. Oligomeric and total a-syn, total-tau and TNFa at T0 were able to predict the worsening of motor symptoms, while MAPLC3b to predict the worsening of non motor symptoms. Changes in TNFa positively correlated with worsening of global cognition and fronto-executive functions.

Conclusions: These findings support the potential of salivary biomarkers for both diagnostic and prognostic applications in PD, warranting further validation in larger cohorts.

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C23

Multicenter, randomized, double-blind, placebo-controlled trial on ambroxol in GBA-associated Parkinson's disease: preliminary clinical and pharmacokinetic findings

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Introduction: Patients with GBA-related Parkinson's disease (GBA-PD) face a higher risk of cognitive decline, impacting their quality of life and survival. Ambroxol (ABX), a molecular chaperone that boosts GCase activity, may help slow PD progression.

Objectives: To evaluate the effects of ABX on the progression of cognitive, motor, and non-motor symptoms in GBA1-PD patients.

Methods: In this multicenter, double-blind, randomized, placebo-controlled trial, patients were randomly assigned to ABX 1.2 g/day or placebo. Participants were assessed at baseline (V1) and weeks 12, 26, 38, and 52 (V5). Primary endpoint: changes in the MoCA score and in the frequency of mild cognitive impairment and dementia between V1 and V5. Secondary endpoints include changes in validated scales assessing motor and non-motor symptoms, changes in MRI biomarkers of neurodegeneration and in laboratory measures (GCase activity and CSF neurodegeneration markers). ClinicalTrial.gov: NCT05287503.

Results: We present preliminary findings, including the primary endpoint, from a trial of 65 GBA1-PD patients randomized to receive ABX (n=33) or placebo (n=32). Baseline demographic and neurological assessments showed no significant differences between groups. Nine patients (placebo: 3, ABX: 6) withdrew for reasons unrelated to the IMP, leaving 56 patients who completed the 52-week follow-up. No significant differences were observed in the mean MoCA score change from V1 to V5 between ABX and placebo, even after stratification by mutation severity. Both groups showed a similar progression from normal cognition to MCI and from MCI to dementia. Changes in MDS-UPDRS part II and III scores were also comparable ($p > 0.05$). Notably, pharmacokinetic analysis after an acute levodopa challenge (ABX, n=11; Placebo, n=12) showed a significantly higher maximum plasma levodopa concentration (Cmax) with ABX treatment, unlike placebo.

Conclusions: A 12-month treatment with ABX does not appear to prevent cognitive decline progression in GBA-PD, as indicated by the trial's primary endpoint. Ongoing analyses are evaluating motor and non-motor symptoms, including comprehensive cognitive assessments, alongside laboratory and imaging biomarkers of neurodegeneration. Notably, the significant effect of ABX on levodopa pharmacokinetics suggests a potential indirect clinical benefit through enhanced dopaminergic drive.

C24

Clinical overlap between prion diseases and atypical parkinsonian syndromes and predictive role of clinical features: insights from the Italian Registry of Creutzfeldt-Jakob disease and related disorders

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Prion diseases (PrDs) are fatal neurodegenerative conditions characterized by the accumulation of abnormal prion protein aggregates [1]. Early diagnosis remains challenging due to the significant clinical heterogeneity of the disease [2]. Several case reports suggested that atypical manifestations of PrDs can resemble atypical parkinsonian syndromes (APs) [3,4]. This study aims to identify clinical and demographic features capable of predicting a definitive diagnosis of either PrDs or APs. We retrospectively analysed clinical and pathological data from 531 patients referred to the Italian Registry for Creutzfeldt-Jakob disease and related disorders. These included individuals with clinical presentations resembling APs as well as those initially suspected of having PrDs, but later diagnosed neuropathologically with APs. Multiple logistic regression models were constructed to examine the predictive role of early-onset features and to elucidate associations between symptoms emerging during the disease course and a definitive neuropathological diagnosis of either PrDs or APs. Among the 531 cases, 149 underwent neuropathological evaluation. Of these, 78 patients (52%) had neuropathologically confirmed sporadic or genetic PrDs, while 48 (32%) had a definitive diagnosis of APs, primarily synucleinopathies. A younger age at disease onset (OR = 0.9494; p = 0.0117), together with an onset presentation with cerebellar ataxia (OR = 9.650; p = 0.0030) and visual disturbances (OR = 11.96; p = 0.0314), were associated with PrDs, whereas a slowly progressive dementia course (OR = 0.03857; p = 0.0025) and older age at onset (OR = 0.9065; p = 0.0014) emerged as predictors of APs. During disease progression, myoclonus (OR = 2.350; p = 0.05), cerebellar signs (OR= 10.56; $p < 0.0001$), and visual impairments (OR = 2.894; p = 0.02) showed a stronger association with PrDs than with alternative neuropathologies. Our findings highlight the need to consider PrDs in rapidly progressive APs and to integrate epidemiological information with a careful evaluation of both initial and evolving clinical features.

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C25

B-type natriuretic peptide in Parkinson's disease: a novel biomarker of dysautonomia

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Introduction: The presence of cardiac diseases in Parkinson's disease (PD) patients opens the debate on the identification of early biomarkers of heart damage. N-terminal pro-brain natriuretic peptide (NT-proBNP) may play a role in cardiac autonomic denervation [1].

Objectives: i) To investigate whether there is a relationship between NT-proBNP and measures of cardiovascular autonomic function in PD patients; ii) to elucidate the discrimination power of NT-proBNP levels to identify PD patients with dysautonomia.

Methods: Thirty-one consecutive PD patients were enrolled. NT-proBNP levels were measured and cardiovascular autonomic function tests were performed, including the Head-up Tilt test (HUTT), Valsalva Maneuver (VM), Hand Grip (HG), and Deep Breathing (DB). ROC curve analysis was performed to explore the discriminatory power of NTproBNP levels. The relationship between variables was investigated using correlation analysis. Non-collinear independent variables associated with autonomic parameters were examined using multivariable linear regression models.

Results: We found: i) high levels of NT-proBNP in patients with neurogenic orthostatic hypotension (adj. P=0.001) and pathologically absent overshoot in VM (adj. P=0.001) along with significant associations with 10' ΔSBP and ΔDBP of the HUTT (P=0.011, P=0.027), ΔBP of the VM phase III (P=0.024), and the E/I of the DB (P=0.019); ii) significant correlations with self-reported measures of cardiovascular manifestations; iii) high discriminatory power of NT-proBNP levels in detecting PD patients with dysautonomia (AUC=0.917, P<0.0001).

Conclusions: This is the first study exploring the relationship between NT-proBNP and cardiovascular autonomic function test measures, suggesting its role as a suitable biomarker of dysautonomia in PD patients.

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C26

Longitudinal changes in multitechnique neurophysiological features in Parkinson's disease: unveiling potential predictive and progression markers

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Introduction: Previous cross-sectional studies depicted the pathophysiological basis of early-stage Parkinson's disease (PD) patients, reporting an abnormal cortical excitability and plasticity as well as an altered kinematic performance [1,2]. However, the prognostic relevance of early pathophysiological features of people with PD (PwPD) remains unknown [3].

Objective: In this 4-year longitudinal multitechniquec neurophysiological investigation we aimed to determine the role of pathophysiological abnormalities in shaping disease trajectory in PwPD.

Materials and methods: Fifty-five PwPD participated in the study. PwPD were clinically and neurophysiologically evaluated at early stage and after a 4-year follow-up. The clinical assessment included the administration of standardized clinical scales aimed at evaluating motor and non-motor symptoms. Neurophysiological assessment included: transcranial magnetic stimulation to evaluate motor cortex excitability (input/output curve), intracortical inhibitory and faciliatory machanisms (cortical silent period, short-interval intracortical inhibition and facilitation protocols) and plasticity (intermittent theta burst stimulation protocol); kinematic analysis of finger movements and sensory function testing through somatosensory temporal discrimination threshold.

Results: Clinical assessments showed a progression in motor, non-motor, and cognitive symptoms over the course of the disease. From baseline to follow-up, no significant changes were observed in cortical excitability or plasticity, while a deterioration in kinematic and sensory function was observed in PwPD. Measures of cortical excitability and plasticity at baseline were predictive of the subsequent worsening in motor symptoms. Cortical excitability was also predictive of kinematic performance worsening.

Conclusions: This longitudinal study shows that abnormal motor cortical excitability and plasticity are early and stable pathophysiolohical features in PwPD and can predict motor symptoms progression. Conversely, sensory dysfunction parallels with disease progression. Our findings undercores the potential role of multitechnique neurophysiological assessments as predictive marker of clinical outcome and for monitoring clinical evolution over time in PD.

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C27

Defining the pheno-genotypic spectrum of autosomal recessive PRRT2-related disorder

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Introduction: Heterozygous PRRT2 variants are a well-established cause of miscellaneous paroxysmal disorders, including paroxysmal kinesigenic dyskinesia (PKD), benign familial infantile epilepsy, hemiplegic migraine, and episodic ataxia (EA) [1]. Contrarily, evidence on autosomal recessive PRRT2-related disorder is more limited [2–10].

Objective: To further define the pheno-genotypic spectrum of autosomal recessive PRRT2-related disorder.

Methods: The UCL Queen Square exome dataset and next-generation sequencing repositories of several diagnostic and research laboratories worldwide were screened for homozygous or compound heterozygous PRRT2 variants. Detailed clinical data were collected from referring clinicians. A systematic review of the literature on cases carrying biallelic PRRT2 variants was performed.

Results: We identified eight new cases with biallelic PRRT2 variants from six unrelated families and merged their data with that of 16 from the literature review. Parental consanguinity was reported in 75% of cases, and 75% had a positive family history of PRRT2-related disorder. All patients experienced infantile seizures, with good response to anti-epileptic drugs (response rate: 85%). Paroxysmal movement disorders were observed in 87%, including paroxysmal non-kinesigenic dyskinesia (9/21), PKD (6/21), unspecified paroxysmal dyskinesia (5/21), and EA (8/21), with a mean age of onset of 3.6±3.2 years. Additional neurological features, including attention-deficit-hyperactivity disorder, autistic spectrum disorder, incoordination, hemiplegic migraine, motor tics, gaze-evoked nystagmus, gait ataxia, intellectual disability were present in 42% of patients, and neurodevelopmental delay in 33%. Genotypically, 11 patients were homozygotes for PRRT2 (NM_145239.3) variant c.649dup (p. Arg217ProfsTer8), 3 for c.-65-1G>A (p?), 2 for c.913G>A (p.Gly305Arg), and 2 for c.913G>A (p.Gly305Arg), while patients 6 were compound heterozygotes. Additionally, 5 homozygotes for the variant c.649dup were found in a study screening a cohort of patients with intellectual disability [10].

Conclusions: Our study strengthens the evidence that autosomal recessive PRRT2-related disorder consistently manifests with epilepsy and paroxysmal movement disorders. This condition may also be associated with neurodevelopmental delay and other neurological manifestations.

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C28

PSMF1 variants: a rare cause of early-onset Parkinson's disease

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Introduction: Recently, biallelic Proteasome Inhibitor Subunit 1 (PSMF1) variants have been described in patients with early-onset Parkinson's disease (PD) mainly presenting with atypical aspects [1].

Objectives: To describe prevalence and clinical characteristics of PSMF1 variant carriers in a large cohort of PD patients.

Methods: A total of 1091 DNA samples (collected at the Parkinson Institute of Milan between 2002 and 2023) from early onset PD patients [2] and/or positive family history were analysed with whole-exome sequencing.

Results: Biallelic PSMF1 variants were detected in one patient (estimated prevalence: 0.0009). This woman presented bradykinesia, rest tremor of the right hand and micrography started at the age of 46. She suffered from a depressive syndrome started at the age of 27. Her maternal grandmother was diagnosed with PD at the age of 80. No hyposmia, constipation, or rapid eye movement sleep behaviour disorder were referred. Brain MRI was unremarkable, 123I-FP-CIT single-photon emission computed tomography was compatible with the diagnosis of parkinsonism. Ropinirole improved tremor but induced hallucinations and confusion at higher doses. After a positive acute test with 200mg of levodopa/carbidopa (40% reduction of the UPDRS III score), chronic treatment was started with benefit. Two years later (four years from the first symptoms onset) she developed motor fluctuations (wearing-off, morning akinesia, peak-dose dyskinesia). At neurological examination no atypical signs were present (ocular motility without restriction, normal tendon reflexes). The patient died at the age of 64. Genetic analysis revealed the presence of two PSMF1variants: c.129+2T>C (affecting position +2 of the donor splice site of exon 1) and c.725G>A (p. R242H). Both have already been reported; interestingly, the c.129+2T>C variant have not been associated to PD yet.

Discussion: We confirm that biallelic PSMF1 variants cause a very rare form of early-onset PD, which may also present with a more typical clinical phenotype.

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C29

CSF α-synuclein seed amplification kinetic measures: a possible predictive value for cognitive outcome in Parkinson's disease

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Introduction: Cerebrospinal fluid (CSF) α-synuclein seed amplification assay (αS-SAA) stands out as a promising diagnostic biomarker for Parkinson's disease (PD) [1]. However, its prognostic potential remains underexplored.

Objective: This study seeks to explore the associations between αS-SAA kinetic measures and cognitive outcome in a well-characterized series of PD subjects.

Methods: We conducted a retrospective analysis on a consecutive series of PD patients including cognitively normal subjects (PD-CN, n=40) and PD with mild cognitive impairment (PD-MCI, n=44). A control group of cognitively healthy individuals (HC, n=112) was also included. At baseline, PD patients underwent lumbar puncture for CSF αS-SAA and further CSF biomarkers analysis (Aβ42/40, p-tau-181, t-Tau and NfL, neurogranin, YKL-40 and sTREM-2). Cognitive evaluation was carried out at baseline and after 2 years.

Results: The assay demonstrated 88% sensitivity and specificity in identifying PD vs. OND. In PD-MCI patients, greater cognitive decline (ΔMMSE) over two years correlated with baseline lower time-to-threshold (TTT, r=0.54, p=0.003) and time-to-maximum-slop (TSmax, r=0.53, p=0.004). These associations strengthened after adjusting for CSF total protein content (TTT, r=0.59, p=0.0016; TSmax, r=0.58, p=0.002). When we analyzed αS-SAA measures and other CSF biomarkers in a LASSO model, TTT was the most associated variable with cognitive worsening in PD-MCI, followed by Aβ42/40 and NfL.

Conclusions: Among all the CSF biomarkers considered, αS-SAA kinetics was the most associated measure with cognitive decline in PD-MCI. As previously suggested, a more pronounced seeding activity might reflect higher burden of synucleinopathy in the cortex [2], thus predicting worse cognitive outcome. After accounting for CSF proteins as covariate, the associations between cognitive scores and kinetic measures strengthened. As possible explanation, CSF proteins influence α-synuclein aggregation in SAA, as previously found [3].

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C30

Plasma neuronal and glial biomarkers in Parkinson's disease patients with and without GBA1 mutations: findings from a multicentric study

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Background: Mutations in the glucocerebrosidase gene (GBA1) represent the most significant genetic risk factor for Parkinson's disease (PD). In presence of GBA1 mutations, current evidence suggests a pivotal role of lysosomal dysfunction and glucocerebrosidase (GCase) impaired activity in driving accumulation of alpha-synuclein. [1] Few studies have been done to measure the effect of GBA1 mutations on in vivo plasma biomarkers of neurodegeneration and glial activation.

Objective: Our aim was to investigate the relationship between clinical features and plasma biomarkers in a cohort of PD patients, including both GBA carriers and non-carriers.

Materials and Methods: We consecutively enrolled 122 PD patients from two Italian movement disorder centers (Campus Bio-Medico University of Rome and ASST Spedali Civili of Brescia), including 41 GBA mutation carriers and 81 with the GBA wild type. All participants underwent a detailed neurological examination. The severity of motor symptoms was assessed using Part III of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS III), while the burden of non-motor symptoms was evaluated using the Italian version of the Non-Motor Symptoms Scale (NMSS) and the Montreal Cognitive Assessment (MoCA). GCase enzymatic activity and glucosylsphingosine (Lyso-GBA1) levels were measured via dried blood spot assay in 30 of the GBA-mutated patients and 69 of the GBA-nonmutated group. Additionally, glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), and phosphorylated tau 181 (pTau181) were quantified using the SIMOA assay in a subset of GBA carriers (32/41) and non-carriers (54/81).
Results: No significative differences were found between groups as far as motor features were considered. From a nonmotor prospective, GBA-carriers cohort exhibit a more severe hallucination, mood and cognition symptoms (NMSS, domain 3, p= 0.005; NMSS, domain 4, p= 0.008), despite the global nonmotor symptoms burden being comparable. No significative differences were found between plasma biomarkers of neurodegeneration and glial activation between the two groups. In unadjusted analysis, MOCA showed a negative correlation with NfL and GFAP in both cohorts,

manifesting a stronger correlation in GBA-carriers (GFAP, p=0.001, ρ=- 0.583**; NfL, p=0.002, ρ=- 0.542**) rather than in GBA-wild type (GFAP, p=0.017, ρ=- 0.416*; NfL, p=0.075, ρ=- 0.309).

Discussion: GBA-carriers exhibited overall a more aggressive phenotype in terms of nonmotor symptoms presentation, as far as cognitive, mood and hallucinations symptoms are concerned. NfL, ptau181 and GFAP did not show a significative difference between groups. The presence of GBA mutation did not seem to influence the trend of plasma biomarkers in our PD cohort. However, the presence of a stronger correlation between certain clinical variables and plasma biomarkers in the GBA-PD cohort may suggest a potential influence of the mutation in the neuropathological process. Further studies with higher sample size are required to better understand the contribution of GBA genetic status on in vivo plasmatic biomarkers among PD.

Conclusion: Despite our limited sample, our findings suggest that GBA genetic status did not influence the trend of plasma biomarkers in PD patients.

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C31

Validating the accuracy of clinical diagnosis of Parkinson's disease: a case-control study from UK Brain Bank

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Introduction: Despite advancements in diagnostic criteria, the clinical diagnosis of Parkinson's disease remains suboptimal [1], with post-mortem examination still considered the gold standard [2]. Clinicopathological series have shown that many patients alive-diagnosed as idiopathic Parkinson's disease receive alternative diagnoses post-mortem [3].

Objective: To evaluate the diagnostic accuracy of Parkinson's disease comparing clinical diagnoses during life with post-mortem findings.

Methods: In this retrospective case-control study, patients and healthy subjects who consented to the post-mortem examination at the UK Brain Bank were consecutively enrolled. Medical records were reviewed to classify participants and performance metrics were estimated using neuropathological diagnosis as gold standard. Diagnostic accuracy at early (<3 years from symptom onset) and late (<3 years from death) disease stages was assessed. Clinically misdiagnosed patients were clustered on the presence of copathology at autopsy, assessing corresponding clinical diagnoses during life.

Results. Clinical diagnosis group included 1048 Parkinson's disease patients and 1242 healthy subjects, while pathological diagnosis group comprised 996 Parkinson's disease patients and 1288 without post-mortem abnormalities. For the clinical diagnosis group, Parkinson's disease diagnosis showed 99% sensitivity, 86% specificity, 90.96% accuracy, and AUC of 0.925 (SE±0.006, 95% CI, 0.913-0.937, p<0.001). Early-stage diagnoses achieved 80.7% sensitivity, 97.24% specificity, 96.52% accuracy, and AUC of 0.920 (SE±0.033, 95% CI, 0.855-0.986, p<0.001). Late-stage diagnoses showed 78.4% sensitivity, 98.2% specificity, 97.47% accuracy, and AUC of 0.933 (SE±0.01, 95% CI: 0.915-0.952, p<0.001). Among false positives, dementia with Lewy bodies (19.4%) was the most frequent pathological diagnosis, while Alzheimer's disease (18.5%) was the most common clinical misdiagnosis in false negatives.

Conclusions: Our findings confirm a still significant diagnostic error and emphasize the need for more fine and homogeneous criteria to classify idiopathic Parkinson's patients correctly. These results underscore the need for biomarker integration and refined diagnostic frameworks to differentiate Parkinson's disease from dementias and parkinsonisms.

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C32

Motor, nonmotor and cognitive predictors of early treatment-related motor fluctuations in Parkinson's disease patients

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Introduction: Treatment-related motor fluctuations may emerge within the first few years after levodopa initiation, but may go unrecognized at office visits, particularly in patients with a shorter disease duration.

Objectives: We aimed at investigating motor, nonmotor and cognitive predictors that may be identified at the time of the PD diagnosis and associated with later development of motor fluctuations after 2 years of treatment.

Methods: The study sample was recruited from an ongoing longitudinal project enrolling consecutive drug-naive PD patients. Patients enrolled in this study underwent an extensive motor, nonmotor and cognitive assessments by means of validated scales at the time they were diagnosed with PD. After the baseline assessments, all PD patients were prescribed with dopaminergic treatment and yearly clinically re-assessed. At the 2-year follow-up, 73 patients have developed early signs of wearing-off, defined as having at least 1 h of daily OFF time for at least 4 weeks (PD early-fluctuators, PD-EF), and were automatically matched with 77 patients without motor fluctuations (PD non-fluctuators, PD-NF). Baseline motor, nonmotor and cognitive data were compared between the study groups. A multivariate regression model was used to explore clinical baseline predictors of treatment-related motor fluctuations at 2-year follow-up.

Results: At baseline, PD-EF and PD-NF were similar in terms of age, sex, disease duration as well as motor symptoms severity. Compared to PD-NF, PD-EF were presenting with significantly higher severity of pain, depression, and autonomic dysfunction at baseline. Moreover, significantly worse performances in memory, executive and visuospatial cognitive domains were found at baseline in PD-EF compared to PD-NF.

Conclusions: Our findings demonstrated that specific nonmotor and cognitive features may characterize drug-naïve PD patients more prone to develop early treatment-related fluctuations. Identifying at-risk PD population prior to starting any dopaminergic treatment may help clinical management and foster prevention strategies.

C33

GBA1 gene and the effect of GCase and glucosylsphingosine on Parkinson's disease: insights by the retroGBA study

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Introduction: Mutations in the GBA1 gene, encoding the lysosomal enzyme glucocerebrosidase (GCase), are key genetic risk factors for Parkinson's disease (PD). GCase deficiency, causing Gaucher Disease (GD), leads to the accumulation of glucosylceramide and glucosylsphingosine (GlcSph). This study investigates the impact of GBA1 mutations, GCase activity, and GlcSph levels on PD.

Methods: This retrospective cross-sectional study included idiopathic PD patients screened for GBA1 mutations, GCase activity, and GlcSph levels using dried blood spot tests [1]. GBA1mut/wt-PD (heterozygous mutation carriers) and GBA1wt/wt-PD (non-carriers) were evaluated. Clinical, demographic, and pharmacological data were analyzed using statistical methods, including t-tests, ANOVA, chi-squared tests, and regression models.

Results: The study analyzed 155 GBA1mut/wt-PD and 254 GBA1wt/wt-PD patients. GBA1mut/wt-PD had a shorter time from prodromal symptoms to diagnosis, with more frequent mood-related prodromal symptoms. They exhibited higher Hoehn and Yahr scores and more severe UPDRS I, III, and IV scores, while UPDRS II and total scores were comparable. GBA1mut/wt-PD patients displayed higher akinesia, rigidity, and dyskinesia subscores, along with lower cognitive function, increased depression rates, and more frequent falls. Biochemically, GBA1mut/wt-PD had lower GCase activity, influenced by mutation severity, but similar GlcSph levels across mutation severity. A positive correlation between GlcSph levels and dyskinesia subscores was observed in

GBA1mut/wt-PD, independent of LEDD and partially influenced by disease duration. External validation with 98 PD subjects is ongoing.

Conclusions: GBA1mut/wt-PD patients show distinct clinical and biochemical characteristics, including severe motor symptoms, dyskinesia burden, and cognitive impairment. These findings underscore the role of GCase deficiency and GlcSph in PD, highlighting potential therapeutic targets for managing GBA1mut/wt-PD

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C34

Amplification parameters of the Alpha-Synuclein Seed Amplification Assay on CSF predict the clinical subtype of Parkinson's disease at 10 years follow-up

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Introduction: Alpha-synuclein seed amplification assay on CSF (CSF-αSyn-SAA) identifies Parkinson's disease (PD) subjects with very high accuracy. Several studies are investigating the quantitative and semiquantitative application of the assay with promising results [1,2].

Objective: To assess the association between the amplification parameters of CSF-αSyn-SAA collected at baseline and the clinical evolution of PD at 10 years.

Methods: PPMI dataset was utilized. Sporadic PD subjects were classified as Mild Motor Predominant (MMP), Intermediate (I) and Diffuse Malignant (DM) at baseline (n=323) and 10 years follow-up (n=146), based on previously published motor summary score and three non-motor features (cognitive impairment, rapid eye movement sleep behaviour disorder and dysautonomia) [3]. CSF-αSyn-SAA parameters were collected at baseline, including Fmax (maximum fluorescence), T50 (time to reach 50% of Fmax), TTT (time to threshold), Slope, and AUC (area under the curve).

Results: Baseline times of reaction (T50 and TTT) and AUC respectively decreased and increased from the more benign to the more aggressive 10-years subtype (DM vs MMP: p=0.023, p=0.033, p=0.029). A similar trend without statistical significance was observed when the clinical subtyping was performed at baseline. Shorter T50 and TTT, and larger AUC assessed at baseline were associated with a greater risk of DM subtype versus MMP at 10 years follow-up (OR=2.242, 95%CI=1.239-4.056, p=0.08; OR=1.835, 95%CI=1.036-3.251, p=0.037; OR=0.459, 95%CI=0.256-0.821; p=0.09; amplification parameters expressed as tertiles).

Conclusions: Amplification parameters of CSF-αSyn-SAA collected at baseline predicted the long-term progression of PD. In detail, faster reactions, which may reflect a greater burden of Lewy Body pathology at diagnosis, were associated with a 10-years phenotype of PD severely compromised considering motor, cognitive, sleep and dysautonomic features.

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C35

Cognitive and morphometric features of mild cognitive impairment reversion in early patients with Parkinson's disease

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Introduction: Mild cognitive impairment is a common feature of Parkinson's disease (PD-MCI), even at the earliest disease stages. Growing evidence supports the instability of PD-MCI over time, without a consistent linear evolution to dementia, and in some patients, the potential of reversion to normal cognition. While 20-60% of patients with PD-MCI convert to dementia within 2-5 years, the remaining portion of individuals with PD-MCI have a variable course, such that for some patients, MCI remains clinically stable, while others revert to cognitively normal status (PD-CN).

Objectives: Given the need to better understand the evolution of PD-MCI and causes of MCI reversion, this study aimed to determine the baseline clinical and neuroimaging factors that would predict PD-MCI reversion.

Methods: In our longitudinal study of early drug naïve PD patients, 65 of 134 (48%) patients had PDMCI at baseline. Study participants underwent comprehensive assessments at baseline and 1-year follow-up. Sixteen (24.6%) patients with PD-MCI reverted to normal cognition (Reverters), and 49 (75.4%) had persistent PD-MCI (Non-Reverters) after 1-year follow-up. We performed single- and multiple-variable logistic regression analyses to identify baseline variables predicting reversion of PD-MCI to normal cognition. We also compared brain morphometric measures (cortical thickness and volumes) at baseline between the PD-MCI Reverters and Non-Reverters.

Results: Higher educational level and better performance on measures of attention and memory at baseline predicted the reversion to normal cognition at 1-year follow-up. Reverters had greater cortical thickness in the left inferior temporal gyrus than Non-Reverters.

Conclusions: Our results show PD-MCI with a higher chance of reverting to normal cognition over time have a higher educational level, better frontotemporal-related cognitive function, and increased thickness of the inferior temporal lobe gyrus. These findings may potentially help researchers to select the candidates for clinical trials focusing on the treatment of cognitive impairment in the early stages of PD.

C36

Translational validation of molecular pathways involved in dystonia by DYT1 mouse model and accessible biofluids of affected patients

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Introduction: Dystonia is an hyperkinetic movement disorder characterized by sustained muscle contractions causing abnormal postures. No effective therapies are currently available for dystonia. Synaptic plasticity and alterations of the perineural network represent promising targets that can be explored in animal models and validated in peripheral biofluids of patients.

Objectives: Morphological investigation of synaptic plasticity and perineuronal network in the brain of DYT1 mice and translation to dystonic patients by the analysis of easily accessible biofluids.

Methods: DYT1 and control mice were used for immunohistochemistry (IHC) and immunofluorescence (IF) for synaptic and SNARE complex proteins. Gomori staining, along with IHC and IF for Collagen type I, III and IV were used to investigate changes in the peri-neuronal matrix. 35 cervical dystonia patients and 22 age and sex-matched healthy subject were submitted to ELISA for total and oligomeric a-syn, synaptophysin, CamK2beta, synaptobrevin, TGfbeta and TNFalpha in saliva and serum.

Results: Morphological alterations of synaptic and SNARE complex staining were detected in different brain areas of DYT1 mice, including: striatum, cerebellum and pontine nuclei. A remodelling of the peri-neuronal network was detected, with a different balance between the collagen isoforms. Molecular changes detected in animal models were substantially reproduced in the patient's biofluids, where ELISA analysis showed: increased levels of Tor1A ($p<0.01$) and synaprophysin ($p<0.01$), as well as decreased levels of CamK2beta ($p<0.01$) in the saliva of dystonic patients compared to HS. TGFbeta and TNFalpha were increased in the serum of dystonic patients and positively correlated with the levels of CamK2beta in saliva ($p<0.01$).

Conclusions: Our study provides the first translational analysis of Dyt1 models in relation with dystonic patients and support an altered cross-talk between SNARE complex/synaptic plasticity and peri-neuronal matrix organization in dystonia.

C37

Comparative study between levodopa-carbidopa intestinal gel infusion and deep brain stimulation of the subthalamic nucleus for advanced Parkinson's disease

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Background: Device-assisted therapies (DAT) like Deep Brain Stimulation (DBS) and Levodopa-Carbidopa Intestinal Gel (LCIG) are established treatments for advanced Parkinson's disease (PD). However, evidence comparing their effectiveness on axial symptoms, motor/non-motor symptoms, and the impact of genetic factors remains limited [1-3].

Methods: This observational cohort study included 317 patients (203DBS, 114 LCIG) treated between 2005-2023 at two Italian centers. Assessments were conducted at baseline, 12±3 months, and when available at 5 years±6 months. Motor symptoms were evaluated using UPDRS/MDS-UPDRS Part III, with axial items analysed separately. Motor fluctuations were assessed using UPDRS/MDSUPDRS Part IV. Non-motor symptoms and GBA1 genetic status were also evaluated.

Results: LCIG patients were older at implant (65.7 vs 56.9 years, $p<0.000001$) with greater clinical severity. At 12 months, both groups showed similar motor improvement (UPDRS-III ON, LCIG: -2.76±6.37 vs DBS: -2.50±8.53, p=ns) and reduction in motor fluctuations. LCIG showed greater benefits for falls and hallucinations but less improvement in dyskinesias. At 5 years, both groups demonstrated similar motor deterioration while maintaining benefits for motor fluctuations. DBS showed more pronounced deterioration in gait, posture, and freezing long-term. GBA1 mutations were similarly prevalent (DBS 15.6%, LCIG 18.2%) with comparable long-term outcomes.

Conclusions: Both therapies effectively improve motor symptoms and fluctuations initially, but neither stops disease progression. LCIG shows better long-term control of axial symptoms compared to DBS. The similar presence and outcomes of GBA1 mutations suggest that treatment choice should be based on clinical characteristics rather than genetic factors. Combined treatment might offer better overall outcomes.

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C38

The idiopathic normal oressure hydrocephalus associated with Parkinsonism (NPH-Park) study: rationale, design and preliminary data

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Background: Despite available international guidelines on idiopathic Normal Pressure Hydrocephalus (iNPH), diagnostic uncertainty still persists due to phenotypic variability and overlap with neurodegenerative diseases. Parkinsonism represents an underestimated clinical feature of iNPH, even reported in nearly 70% of cases.

Objectives: The NPH-Park study was developed with the aim to prospectively assess phenomenology, natural history, clinical-instrumental-therapeutic findings in iNPH associated with Parkinsonism (iNPH-P).

Methods: This is an ongoing multicenter observational prospective study. Involved centers share same operative protocol and standardized operating procedures for common data collection. The study involves baseline and follow-up assessments up to 12 months. All subjects with a diagnosis of probable iNPH by Relkin 2005 [1], with parkinsonism fulfilling MDS criteria are enrolled.

Results: By December 2024, 104 patients were enrolled from 12 Italian Centers, completing baseline assessment (women: 28, 27.2%; age: 73.8±5.6 years; age at onset: 71.7±5.8 years). Gait disturbances, isolated or combined to other symptoms, were reported as first sign at disease onset in 76/100 subjects (76%). At the time of the first visit, they were reported as “magnetic gait” in 49/99 subjects (49.5%), as “shuffling gait” in 78/99 subjects (78.8%), as “wide-based gait” in 66/99 subjects (66.7%). Start hesitation was documented on 33/99 subjects (33.3%). Concerning other signs, postural instability was present in 75/100 subjects (75%), sphincter disturbances in 80/99 subjects (80.8%), cognitive disturbances in 50/99 subjects (50.5%). Parkinsonism was reported in 83/99 subjects (83.8%) at the time of first evaluation. Based on available brain MRI data, ventriculomegaly was documented in all subjects, with DESH pattern in 46/68 subjects (67.6%). DaT-SCAN was reported pathological in

13/31 subjects (41.9%). CSF tap-test was performed in 58/78 subjects (74.4%), while external lumbar drainage in 20/78 subjects (25.6%).

Conclusions: Preliminary study findings confirmed the presence of parkinsonism in the context of iNPH, to be characterized by clinical-radiological and progression data.

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C39

MCI-LB brain networks reorganization in relation to specific cognitive domains deficits

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Introduction: Early pre-dementia diagnosis of Lewy Body Dementia (LBD) at the stage of mild cognitive impairment with Lewy bodies (MCI-LB) is difficult to establish due to a variable clinical manifestation and lack of specific imaging findings.

Objectives: Our aim is to study networks disruption and brain compensation in early LBD which might explain the clinical expression in MCI-LB.

Methods: We performed a global analysis of resting state functional MRI (rs-fMRI) data on 38 MCI-LB subjects and 24 healthy controls (HC), and extracted the connectivity matrices of the Cingulo-Opercular Network (CON), Fronto-Parietal Network (FPN), Default Mode Network (DMN), Dorsal Attention Network (DAN), Somato-motor Network (SMN), Visual Network (VN) and Language Network (LN). We compared intra- and inter-network functional connectivity (FC) between the two groups and correlated neuropsychological test results with intra- and inter-network FC of MCI-LB and HC separately.

Results: We found increased FC ($p<0.03$) between the DAN and SMN, the CON and FPN and the FPN and DMN in MCI-LB subjects vs. HC. Decreased FC ($p<0.03$) was found between the SMN and DMN, the DMN and DAN and between the right rostral prefrontal and right anterior insular nodes of the CON in MCI-LB subjects vs. HC. Significant correlation patterns ($p<0.03$) were found among inter-nodal and between-network FC values and cognitive outcomes in the MCI-LB group which were either not present or displayed inversed direction of correlations in the HC. follow-up available after opicapone initiation, revealed a significant improvement in the NMSS global score (T-test, $p = 0.015$), and confirmed the major effects on sleep and pain ($p = 0.026$).

Conclusions: We found a within-network disconnection of the CON, and overall increased inter-network connections as well as aberrant engagement of the networks that are not primarily involved in the performance of specific tasks. Some connectivity patterns revealed inverse direction of

correlations in the MCI-LB and HC groups. These compensatory hyperconnectivity changes do not seem efficient to counteract the cognitive impairment in pre-dementia stages of LBD.

C40

Midbrain organoids of progressive supranuclear palsy: a new experimental model for advancing research and drug discovery

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Background: Developing effective drugs for Progressive supranuclear palsy (PSP) presents challenges due to the absence of robust human models that accurately recapitulate PSP molecular and pathological features. Here, we present a novel induced pluripotent stem cell (iPSC)-derived mosaic midbrain organoid (mMO) obtained from four patients with PSP-Richardson syndrome (PSP-RS), aimed at reproducing key molecular disease features reducing variability across organoids derived from different iPSC donors.

Objective: In this 4-year longitudinal multitechniquec neurophysiological investigation we aimed to determine the role of pathophysiological abnormalities in shaping disease trajectory in PwPD.

Methods: In this study, we generated mosaic midbrain organoids by pooling iPS cells from four patients with probable PSP-RS; the mMOs were monitored over a culture period of 120 days. We performed comprehensive analyses of PSP-derived organoids including immunofluorescence, western blot, real-time PCR and immunochemistry, to investigate the presence of neuronal death and tau deposition (including 4R-tau and several phosphorylated tau isoforms:). For each analysis, PSP-derived organoids were compared with mMO obtained from three healthy control subjects.

Results: The PSP-derived mMO showed a progressive reduction in size compared to HC-derived mMO (up to 50% of the HC-derived organoid size at day 120). Degeneration of dopaminergic neurons was evident, with tyrosine hydroxylasedecrease and neurofilament light chain increase. Western blot and immunofluorescence demonstrated accumulation of all investigated phosphorylated tau isoforms, accumulation of 4R-tau and a dramatic increase in GFAP-positive cells reflecting gliosis with immunoreactive astrocytes in PSP-derived mMO compared to organoids from HC. Immunochemistry showed lesions resembling typical PSP histological alterations (neurofibrillary tangles and tufted-shaped astrocytes) in PSP-derived mMO and not in HC-derived organoids.

Conclusions: We present a robust in-vitro experimental model of PSP, reproducing the key molecular and histologic features of the disease. This result holds significant promise for advancing basic and clinical research in PSP, with significant implications for a better understanding of PSP

pathophysiology, for in-vivo accurate diagnosis and for the development of future disease-modifying therapies to cure this devastating neurodegenerative disease.

C41

Clinical and functional connectivity effects of an anodal transcranial direct current stimulation protocol targeting the primary motor cortex in Parkinson's disease patients

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Introduction: Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique [1]. Applications to Parkinson's disease (PD) are still limited [2], and the biological bases of the potential beneficial effects are largely unclear.

Objective: To estimate the clinical and the EEG-based functional connectivity (FC) effect of an anodal tDCS protocol in PD.

Methods: We performed a sham-controlled, randomized, crossover trial involving 25 PD patients. Anodal tDCS was delivered over the dominant (left) primary motor cortex (M1) at 2.0 mA per 20 min/10 days. The main outcomes were the change in the MDS-UPDRS part III score and EEG-based FC in ON and OFF-medication. High-density EEG (64 channels)-derived brain activity was reconstructed using source analysis, and cortico-cortical FC was evaluated with the weighted phase-lag index (wPLI) across θ, α, β, and low-γ bands [3]. Network-based statistics (NBS) were used to compare FC pre- and post-tDCS, while Wilcoxon signed-rank test compared clinical outcomes.

Results: The anodal tDCS protocol induced a significant reduction in the MDS-UPDRS part III total score (28.12±13.59 vs 24.16±11.30, $p=0.009$) and bradykinesia subscore (13.25±6.62 vs 11.32± 6.60, $p=0.008$) in OFF state. Moreover, a significant increase in α-band FC in both OFF ($p=0.02$) and ON ($p<0.001$) states was observed after treatment, mainly in sensorimotor and temporoparietal regions and mostly in the left hemisphere. Sham stimulation was ineffective.

Conclusions: M1 anodal tDCS engages impaired motor circuits in PD, accounting for clinical and biological effects. Specifically, it improved the OFF state-related motor burden, with a particular reduction in bradykinesia. Moreover, tDCS improved band-specific FC, partially restoring dysfunctional networks in the α-band, which have been found altered in PD patients compared to healthy controls in previous studies [3,4]. These findings confirm the potential of tDCS as a tool for alleviating motor symptoms in PD, but also suggest the central role of the FC modulation in its therapeutic effect.

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C42

L'alterato metabolismo del glutammato come nuova signature sierica della malattia di Parkinson: studio metabolomico 1H-NMR

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Introduction: Using an High-Performance Liquid Chromatography targeted approach, we recently showed increased CSF and serum serine enantiomers levels as putative biomarker of Parkinson's disease (PD) [1,2]. Recent serum metabolomics evidence showed a dysregulation of multiple amino acids pathways in PD patients compared to healthy controls (HC) [3].

Objective: We attempted to identify a metabolomic signature distinctive of PD through an hypothesis-free, untargeted approach.

Methods: We enrolled 69 idiopathic PD patients and 32 age-matched HC. Untargeted metabolomics was carried out using Nuclear Magnetic Resonance (1H-NMR) on serum samples. Partial least-squares discriminant analysis (PLS-DA) and pathway enrichment analysis were used to identify metabolites and biochemical pathways discriminating the two groups.

Results: Serum metabolomics identified two distinct clusters for PD patients and HC (Fig. 1a). Multivariate analyses revealed 11 metabolites independently associated with PD (i.e. with variable importance in projection score>1), including L-glutamate, L-proline, pyruvate and L-serine (Fig. 1b). Univariate analyses showed (i) increased L-glutamate and (ii) reduced L-proline and 2-oxoglutarate levels in PD compared to HC, all showing high predictive power for PD (AUC: 0.99, 0.89 and 0.94, respectively) (Fig. 2a-b). Finally, pathway analysis identified 21 pathways overrepresented in PD at FDR<0.05, almost all involved in amino acids or energy metabolism. Among these, glycine-serine pathway showed the best discriminating value (Fig. 3).

Conclusions: Through unbiased 1H-NMR analyses we identified serum glutamate levels and glycine-serine metabolism dysregulation as distinctive signatures of PD. Our results support the hypothesis that dysregulated amino acids and energy metabolism plays a key role in PD physiopathology and pave the way for future studies evaluating its diagnostic and prognostic value.

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C43

Gait parameters as predictors of DBS outcomes in Parkinson's disease: insights into motor-cognitive interactions

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Introduction: Gait and cognitive performance are closely interconnected, reflecting the relationship between motor control and higher-order cognitive processes [1,2]. In Parkinson's Disease (PD), impairments in these functions lead to reduced quality of life and accelerated disease progression [3]. Moreover, the assessment of gait and cognitive functions are crucial in the decision-making for candidates to Deep Brain Stimulation (DBS) [4].

Objective: To analyze the role of gait parameters as potential predictors for DBS selection outcome and explore the association between gait parameters and cognitive performances.

Methods: We conducted a cross-sectional study on 104 patients undergoing DBS selection at the Movement Disorders Center of Turin. Participants underwent clinical, neuropsychological assessments and gait analysis using wearable sensors during Two-Minute-Walking-Test in ON and OFF medication. Gait parameters and their variations (ONvsOFF states) were tested as predictors of DBS selection outcomes. Boruta identified relevant predictors, then subjects were classified as selected or non-selected using Light-Gradient-Boosting-Machine (LGBM) model. In addition, binary logistic regression analyzed associations between gait parameters and attention, executive frontal functions, reasoning, language, visuospatial abilities, long-term, short-term memory.

Results: The analysis focused on 68 valid patients (ON and OFF gait parameters available): 20 patients formed the final test-set, whereas 48 were used for model-training and validation using 5-fold crossvalidation. Key predictors of DBS selection outcome from Boruta were: ON-Step-Duration-Variability, ON-Stride-Length-Asymmetry, ON-Stride-Length-Variability. LGBM model achieved promising classification performance (validation-accuracy:75.6±14.3%-test-accuracy:75%). Including clinical and neuropsychological data in the model, ON-Step-Duration-Variability-Mean and ON-Stride-Length-Variability-Meanremained significant predictors (test-accuracy:80%-validation-accuracy:84.9±9.3%). Binary logistic regression revealed significant correlation between ON-Step-Duration-Variability and long-term memory (B: -0,927), ON-Stride-Variability and reasoning (B: -0.727) and attention (B:-0,885), Turn-Duration-variation(ONvs.OFF) and visuospatial abilities (B:-10,73).

Conclusions: This study highlights the relevant interplay between gait and cognition in PD, unveiling interesting associations with attention, reasoning, and long-term memory. The integration of kinematic and cognitive data could enhance clinical decision-making, particularly for advanced therapies like DBS.

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C44

Immunometabolic signature and tauopathy markers in blood leukocytes of progressive supranuclear palsy patients

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Introduction: Peripheral immune cells have a central role in the clinical-pathological progression of neurodegenerative diseases and also serve as a reliable frame for translational applications. However, data regarding Progressive Supranuclear Palsy (PSP) are almost scarce.

Objectives: To provide an extensive biological characterization of peripheral immune cells in a selected PSP cohort.

Methods: Seventy-one PSP patients scored on the PSP Rating Scale (PSPRS), and 59 controls were recruited. The blood cell count was collected, and the neutrophil-to-lymphocyte ratio (NLR) was calculated. In a subgroup of n=15 patients and n=15 controls, the peripheral blood mononuclear cells (PBMCs) were extracted and examined by 1) the Seahorse Mito-Stress Test [1], allowing for the mitochondrial bioenergy assessment; 2) the western blot assay of the nuclear factor erythroid 2-related factor (NRF2)/heme oxygenase 1 (HO-1) pathway, total tau (t-tau) and phosphorylated tau (p-tau) proteins. Case-control comparison and correlation analyses were performed.

Results: PSP patients had a NLR higher than controls, with increased circulating neutrophils. The oxygen consumption rate (OCR) was globally increased in all the bioenergy parameters (basal respiration, ATP production, maximal respiration, spare respiratory capacity, non-mitochondrial oxygen consumption) in patients PBMCs and the NRF2/ HO-1 pathway activated. P-tau levels, but not t-tau, were significantly higher in patients PBMCs and inversely correlated with the PSPRS.

Conclusions: In PSP, a systemic inflammatory shift of the peripheral immunity occurs, which may justify a metabolic reprogramming of the blood leukocytes. Consistently, the NRF2/HO-1 pathway, a master regulator of inflammatory and metabolic response [2], was activated in those cells. PBMCs also accumulate tau proteins, especially p-tau, in a way inverse to the disease severity, allowing for the tracking of tauopathy in the peripheral blood of patients. Thus, the immunometabolic targets are relevant to PSP for biomarkers or therapeutic purposes.

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C45

Parkinson's disease associated to RAB32 S71R variant: analysis of 18F-FDG brain PET findings

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Introduction: The RAB32 S71R variant has been recently associated to autosomal dominant form of Parkinson's Disease (RAB32-PD) with reduced penetrance [1]. The RAB GTPases are regulators and substrates of LRRK2 protein [1].

Objective: The aim of this study is to compare brain 18F-FDG-PET findings of RAB32-PD patients with a cohort of non-mutated PD (NM-PD).

Methods: RAB32-PD and NM-PD patients underwent clinical assessment, including MDS-UPDRS scores, H&Y scale and Montreal Cognitive Assessment (MoCA), and 18F-FDG brain PET during the ON medication condition under chronic dopaminergic treatment. All images were normalized to a standard FDG-PET template, then a semi-quantitative analysis was performed on a commercially available fully-automated post-processing software (Cortex ID SUITE, GE Healthcare), which allowed to recognize 26 cortical or subcortical regions of interest. Genetic analysis was previously performed through a next-generation sequencing approach and then validated by Sanger sequencing for RAB32-PD patients.
Results: Eight RAB32-PD patients (males:3/8; age:65.38 years [±8.73]; disease duration:10.50 years [±5.88]; H&Y:2.81 [±1.22]; MDS-UPDRS-III:36.38 [±25.34]; MoCA:24.88 [±5.86]) and 19 consecutive NM-PD patients (males:11/19; age:60.53 years [±8.00]; disease duration:8.68 years [±5.70]; H&Y:2.39 [±.51]; MDS-UPDRS-III:29.95 [±11.14]; MoCA:24.21 [±6.07]) were included. No statistically significant differences in clinical variables and FDG-PET data were found comparing

RAB32-PD and NM-PD cohorts. In five of eight RAB32-PD patients FDG-PET showed reduced cortical or subcortical uptake with a prevalent parietal hypometabolism in 4 of them, similar to previous findings reported in LRRK2-related PD and NM-PD. Finally, PD patients with a higher motor and cognitive burden and a longer disease duration showed a more severe pattern of hypometabolism.

Conclusions: This is the first description of FDG-PET findings in RAB32-PD patients, highlighting a possible similar pattern of hypometabolism to LRRK2- and NM-PD, which is different from that observed in GBA1-PD patients.

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C46

Profiling based on dopaminergic denervation for a biological definition of *de novo* Parkinson's disease in two independent prospective cohorts

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Introduction: Parkinson's disease (PD) is a heterogeneous disorder, and recent insights challenged the view of PD as unitarian disorder.

Objectives: To classify *de novo* PD patients starting from the degree of dopaminergic denervation [D] and motor impairment [M]. We evaluated the agreement between the two classifications, and the ability of the proposed algorithm in subtyping PD patients.

Methods: We included 249 *de novo* PDs from PPMI dataset – disease duration ≤2, H&Y I-II, 123I-FP-CIT-SPECT acquisition and no cognitive impairment. The two-step clustering analysis 123I-FP-CIT-SPECT striatal uptake [D+/D-]. We then performed clustering based on motor assessment scale, and we evaluated the agreement between the two classifications. We compared the emerging subgroups for demographic, clinical, cerebrospinal fluid (CSF) biomarkers, brain morphometry and clinical progression. The mediation effects of biomarkers on the association between subtypes and cognitive deterioration were also assessed. The algorithm was validated on an independent validation cohort (n=84 PD).

Results: Four distinct subtypes emerged: [D+M+]: with greater motor impairment, poorer memory performance, greater Aβ1-42 pathology, and posterior cortical thinning. Fastest motor disability and cognitive decline progression, with severe motor complications at 7.71 years follow-up.

[D-M-]: greater anxiety and GMV reductions in the limbic circuit. [D-M+]: greater rigidity and more rapid rigidity progression, elevated CSF Tau and neurofilament levels, GMV loss in the amygdala and temporal gyrus.

[D+M-]: No evidence of clinical differences, GMV reductions in frontotemporal regions, cerebellum, and thalamus. CSF p-Tau181/α-syn ratio mediated the association between D+ and cognitive decline, while D+M+ and cognitive decline were mediated by Aβ1-42.

The validation cohort confirmed findings regarding clinical features obtained from the PPMI cohort.
Conclusions: This study demonstrated that PD can be categorized into distinct subgroups using information widely available in clinical and research settings. These data offer valuable insights into the underlying co-pathology, disease progression and severity.

C47

CSF levels of tau proteins predict the risk for motor fluctuations in de novo Parkinson's disease patients

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Introduction: Motor fluctuations (MF) are a disabling complication of Parkinson's disease (PD) course. Several factors contribute to MF onset [1], but the role of brain co-pathology, including tauopathy and amyloidopathy [2,3], is still poorly investigated.

Objective: To define the association between CSF-based co-pathology profile and MF development in a longitudinal de novo (DN) PD cohort.

Methods: We conducted a single-center retrospective longitudinal study including 108 DN PD patients assessed by the MDS-UPDRS and MoCA scores, and the measurement of CSF total α-synuclein (α-syn), total and phosphorylated-181 tau (t-tau, p-tau), amyloid-β42 and amyloid-β40 (Aβ42, Aβ40) levels, p-tau/t-tau, Aβ42/Aβ40, and p-tau/Aβ42 ratios. According to the later development of MF (MDS-UPDRS part IV score ≥ 1) over the follow-up period, DN patients were stratified into "fluctuator" (FLUCT) and "no-fluctuator" (NoFLUCT). After a case-control analysis with 107 control subjects, the baseline clinical-biological variables of patients were compared between FLUCT and NoFLUCT, adjusting for main covariates. ROC curve analysis and univariate Cox regression were further run to estimate their predictive value.

Results: The DN PD cohort was followed-up for 5 (±1.45) years and 32 (29.6%) patients developed MF (FLUCT). At baseline, patients had lower CSF α-syn and t-tau levels than controls. FLUCT had higher CSF p-tau levels, p-tau/t-tau and p-tau/Aβ42 ratios than NoFLUCT. The p-tau/t-tau ratio best predicted MF development; above the cutoff value of 0.135, MF were 5 times more likely with a sensitivity of 87.1% and a specificity of 63.5% (AUC=0.81).

Conclusions: DN PD patients with higher CSF p-tau/t-tau ratio have a greater risk of developing MF along the disease course. These CSF-based findings suggest that tau and, to a lesser extent, amyloid-β, co-pathology might be involved in the pathogenic mechanisms leading to MF onset, supporting other lines of evidence that show their contribution to the degeneration of motor circuits in the PD brain.

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C48

Sleep as a biomarker of non motor symptom severity in Parkinson's disease

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Introduction: Sleep disorders are common in Parkinson's disease (PD), often preceding motor symptoms by years [1]. Understanding these disturbances is vital, as they may reflect underlying neurodegeneration and influence disease progression [2,3].

Objectives: This study examines the relationship between sleep macroarchitecture and non-motor symptom severity in early PD.

Methods: Twenty-four early or de novo PD patients underwent clinical evaluations, including the Non-Motor Symptoms Scale (NMSS), Hamilton Anxiety and Depression Rating Scales (HAS, HDS), Apathy Evaluation Scale (AES), Fatigue Severity Scale (FSS), and Beck's Depression Inventory II (BDI II). Polysomnography (PSG) analyzed total sleep time (TST), sleep efficiency (SE), and percentages of N2, N3, and REM sleep. Correlation analyses (Spearman's test) and regression models were used to assess sleep parameters as predictors.

Results: Participants (mean age: 65.5±8.18 years; disease duration: 1.72±1.32 years) exhibited a significant negative correlation between N3% and both NMSS ($p = 0.029$) and HAS ($p = 0.023$). A trend towards significance was observed for HDS ($p = 0.068$). No other significant associations were observed for TST, SE, or REM%. Multilinear regression confirmed N3% as an independent predictor of NMSS ($p = 0.001$) and HAS severity ($p = 0.015$), after adjusting for confounders such as disease duration and fatigue. HDS ($p = 0.053$) and AES ($p = 0.05$) also showed trends towards significance.

Conclusions: Preliminary findings indicate that reduced N3% is associated with a worsening of non-motor symptoms and emotional regulation. These results underscore the critical role of N3 sleep in non-motor manifestations, pointing to its potential as a biomarker for early PD progression. Future studies on sleep microstructure will further validate these findings and explore therapeutic approaches.

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C49

Exploring brain hypometabolism in GBA positive individuals

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Objective: To investigate FDG-PET brain metabolism and its correlation to motor and neuropsychological features in GBA-related PD (GBA-PD) and in non-mutated Parkinson Disease (nonGBA-PD) as well as in GBA non-manifesting PD subjects (GBA-nonPD).

Methods: We analyzed motor, neuropsychological, and FDG-PET data from 45 participants (15 GBA-PD, 18 nonGBA-PD, and 12 GBA-nonPD). Single-subject t-maps were generated using Statistical parametric mapping (SPM) pipeline [1], which compared each participant's FDG-PET to a control dataset. Clinical and neuropsychological data were compared using the Mann-Whitney test. Associations between metabolic patterns and clinical outcomes were examined.

Results: A greater hypometabolism in occipito-parietal and temporal regions was found in GBA-PD than nonGBA-PD. Specifically, 83% of GBA-PD cases demonstrated occipital hypometabolism, whereas 70% of nonGBA-PD cases displayed the Parkinson's disease-related pattern (PDRP) [2]. GBA-nonPD showed common hypometabolism in caudate, occipital cortex and cerebellum. Across the entire PD cohort, striatal hypermetabolism correlated with UPDRS-I, and RBDsq scores.

Conclusions: GBA-PD is associated with unique metabolic patterns, including posterior cortical hypometabolism, supporting the hypothesis of a more malignant phenotype progression towards dementia [3]. Hypometabolism in GBA-nonPD may indicate preclinical neurodegenerative processes. These findings underline the potential of FDG-PET as a biomarker for early disease stages in GBA mutation carriers. Further research with a larger cohort is necessary to validate these initial preliminary results.

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C50

Assessment of Italian neurologists' knowledge and utilization of clinical signs for diagnosing functional movement disorders: insights from an online survey

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Introduction: A positive diagnosis of a functional movement disorder (FMD) is established by identifying specific clinical features indicating internal inconsistency (symptoms that fluctuate over time in both nature and severity and tend to improve with distraction), as well as demonstrating incongruence with recognized neurological conditions [1,2].

Objective: The aim of this study is to investigate, through an online survey, the knowledge of Italian neurologists in using clinical signs and manoeuvres in their clinical practice when FMD is suspected.

Methods: The survey was conducted from January to October 2024 among the members of the Italian Society of Neurology (SIN), Italian Association against Epilepsy (LICE) and Italian Society Parkinson and Movement Disorders (LIMPE-DISMOV). We collected information on clinical experience with positive diagnosis of FMD. Rating ranged from to "rarely" (>5%) to "very frequently" (>75%), with intermediate categories of "occasionally" (5-25%), "sometimes" (25-50%) and "frequently" (50-70%).

Results: Overall, 245 neurologists (mean age: 46.1 + 12.9 years; mean years of practice: 15.1 + 13) completed the survey. Most of the neurologists worked in a general outpatient service (40.4%), while experts in movement disorders and epilepsy were respectively the 35.9% and the 20.8%. As far as clinical signs are concerned, entrainment test in functional tremor patients was performed "very frequently" by 65 respondents (26.6%). Hoover's sign was tested "rarely" and "occasionally" by 49 (20%) and 48 (19.6%) neurologists respectively. Placebo effect with botulinum toxin injection was "rarely" performed by the majority of our sample (n=137, 55.9%).

Conclusions: Our findings indicate that Italian neurologists generally have an adequate knowledge of positive clinical signs for diagnosing FMD. However, despite the well-documented diagnostic importance of some signs, such as Hoover's sign, these are often performed poorly.

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Poster

P01

Lipidic profiles and neuroprotective potential of tDCS in Parkinson's disease: study protocol and preliminary findings

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Background: Parkinson's Disease (PD) is characterized by motor dysfunction, neuroinflammation, and dysregulated energy metabolism. Transcranial direct current stimulation (tDCS) has shown promise in modulating cellular metabolic pathways and promoting neuroprotection in vitro, but its systemic effects in PD remain poorly investigated. This study protocol evaluates the impact of tDCS on cognitive and motor performance, glucose metabolism, lipidic profiles, and biomarkers of neuroinflammation and neuroprotection (e.g., interleukins, BDNF) in people with Parkinson's Disease (PwPD) presenting mild symptoms.

Methods: Eight PwPD (2 females; mean age: 65 years) completed a five-day tDCS protocol. Each session involved 20 minutes of 2 mA stimulation using a bicephalic montage, with anodes placed over the M1 cortices bilaterally and the cathode positioned on the right shoulder. Blood glucose levels were measured at baseline (T0), at the start of the stimulation (T1) end every 10 minute of stimulation (T2, T3) and 10 minutes after the stimulation ended (T4). Sessions on days 1 and 5 were conducted under fasting conditions. Cognitive and motor performance was assessed using the Montreal Cognitive Assessment (MoCA), Simon Task, 10-Meter Walking Test, Berg Balance Scale, Falls Efficacy Scale (FES), and Timed Up and Go (TUG) before (day 1) and after (day 5) the treatment.

Results: Cognitive and motor assessment tests showed no significant changes. During the first session, fasting glucose levels decreased by 2.3% at T2, 3% at T3, and 6.9% at T4 ($p < 0.05$). Lipidomic and biomarker analyses are ongoing and aim to identify specific changes in lipid metabolism and neuroinflammatory pathways.

Conclusions: Preliminary findings from this study protocol suggest that tDCS may modulate glucose metabolism in PwPD, suggesting systemic metabolic effects of tDCS. Ongoing analyses will explore the underlying metabolic and neuroprotective effects of tDCS. Expanding the cohort and conducting longitudinal follow-ups are necessary to confirm these initial observations and clarify the therapeutic potential of tDCS in PD.

P02

Clinimetric properties of the Italian version of the Non-Motor Fluctuation Assessment (NoMoFA) Questionnaire for Parkinson disease

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Introduction: Non-motor symptoms (NMS) in Parkinson's disease (PD) can fluctuate daily, impacting patient quality of life. The Non-Motor Fluctuation Assessment (NoMoFA) Questionnaire, a recently validated tool, quantifies NMS fluctuations during ON- and OFF-medication states [1]. Our study aimed to validate the Italian version of NoMoFA, comparing its results to the original validation and further exploring its clinimetric properties.

Methods: The scale underwent translation, back-translation, and cognitive pretesting, before being administered to a calculated sample of > 200 PD patients. Each patient was assessed using a set of validated measures for assessing PD and cognitive state. We explored NoMoFA's feasibility, acceptability, factorial structure, internal consistency, convergent validity, test-retest reliability (the latter performed on 50 patients after 14 days), and the precision of the scale. We conducted a translation and cross-cultural adaptation of the NoMoFA following published guidelines [2]. Authorization to use and adapt the original NoMoFA for research purposes was obtained from the movement dosrders society (MDS).
Results: 227 PD patients (mean age 65.34, disease duration 9.31 years) were included, with 100% data computability. The scale was free from floor and ceiling effects, and included 7 factors (59.2% of the variance). Cronbach's alpha coefficient was 0.89, indicating strong internal consistency. The intraclass correlation coefficient (ICC) of 0.90 demonstrated satisfactory reproducibility. The NoMoFA total score showed the strongest correlations with MDS-UPDRS Parts I (rS=0.71) and II

(rS=0.60). Significant differences in NoMoFA scores were observed based on disease duration, H&Y score, and LEDD ($p<0.0001$), but not age or sex. The Standard error of measurement (SEM) was 3.40 (for ½ SDpooled = 5.48).

Conclusion: The Italian version of the NoMoFA scale demonstrated strong reliability, validity and precision, making it a robust tool for assessing non-motor fluctuations in PD. Although preliminar evidence is available, future studies should incorporate longitudinal designs to evaluate the scale's ability to detect changes in symptom severity and disease progression [3].

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P03

Optical coherence tomography reveals retinal structural abnormalities in α- synucleinopathies: insights from the Padua-CESNE cohort

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Introduction: The complexity of α-synucleinopathies, namely Parkinson's disease (PD) and multiple system atrophy (MSA), calls for the adoption a multimodal approach integrating biological, morphological, and functional data. Phosphorylated α-synuclein (α-syn) detection in bodily fluids and tissues such as the skin helps provide biological characterization of the disease, but specific and accessible biomarkers are not available yet.

Objective: To define the role of Optical Coherence Tomography (OCT, a minimally invasive retinal imaging technique) patterns as possible biomarkers in the early stages of α- synucleinopathies, also supporting the differential diagnosis.

Methods: Thirty-five (23 PD, 12 MSA), clinically, biologically and genetically characterized patients included in the PADUA-CESNE (Centro Studi per la Neurodegenerazione) cohort underwent OCT. Fourteen PD patients (14/23) and all MSA patients gave consent to execution of skin biopsies to provide biological characterization. All PD and MSA patients underwent OCT, with one MSA patient being eventually excluded for the poor quality of the images. Ten healthy subjects (4 males, mean age 51.3 ± 8.5 yrs) with no evidence of neurological disorders were considered as healthy controls for the hyperreflective intraretinal foci (HRF) counting.

Results: A significant atrophy in the inferior, superior and temporal regions of the Retinal Nerve Fiber Layer (RNFL) and in the inner nuclear layer (INL) were observed in PD compared to controls, differently from MSA. Hyperreflective foci (HRF) counts were elevated across all retinal layers in all patients with PD exhibiting significantly higher numbers, suggesting microglial activation and greater retinal damage.

Conclusions: Further research regarding OCT patterns in PD and MSA may consolidate the role of specific features, such as INL abnormalities and different HRF counts, in supporting the diagnosis and differential diagnosis in α-synucleinopathies. In light of the availability of potentially disease-modifying therapies, studies should focus on newly diagnosed patients, also undergoing thorough clinical, biological and genetic characterization.

P04

Rigidity in Parkinson's disease: the effect of L-dopa and activation maneuver on viscoelastic components

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Introduction: Rigidity is one of the cardinal motor signs in Parkinson's disease (PD) which improves the most following dopaminergic stimulation [1]. Rigidity can be assessed objectively by using instrumental devices able to extract biomechanical components of muscle tone, at rest and during activation maneuver. Recently, by using a robot-assisted wrist extensions device, we demonstrated that the viscous and elastic components of muscle tone were comparable in controls and PD patients ON and OFF state [2,3]. By contrast, previous research based on myotonometric assessment of rigidity in PD was elusive, since the viscous and elastic components were found to change or not in patients OFF and ON state [4].

Objectives: In this study we aimed to assess the contribution of the viscous and elastic components of objective rigidity in PD by using myotonometric device, at rest and during activation maneuver. Also, we investigated the effect of L-Dopa on these biomechanical measures by comparing results in OFF and ON state.

Materials and Methods: Twenty-two early-mid stage PD patients and 16 age- and sex-matched healthy subjects (HS) were enrolled. Patients underwent myotonometry evaluation of the most affected upper limb whereas the dominant limb was assessed in controls. The experimental design consisted of two separate randomized sessions in which several biomechanical measures of muscle tone, including frequency (F), stiffness (S), decrement (D), relaxation time of mechanical stress (R) and creepability (C) were recorded from flexor carpi radialis (FCR), at rest and during activation maneuver. In patients, experimental sessions were repeated OFF and ON state, randomly.

Results: We found that all the biomechianical myotonometric measures of muscle tone, including F, S, D, R and C, were comparable in HS and PD, at rest and during activation maneuver ($p>0.05$). Also, we demonstrated that the biomechianical measures of objective rigidity were comparable in OFF and ON state, at rest and during activation manoeuvre ($p>0.05$).

Discussion: Objective rigidity is not associated to significant changes in viscoelastic components of muscle tone in PD patients. We showed that L-Dopa was not effective on the biomechanical measures of muscle tone as scored by myotonometry. Therefore, we speculate that the present findings would point to the role of neural component in the pathophysiology of objective rigidity in PD patients, as also underscored by our previous study based on robot-assisted wrist extensions. [2,3]

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P05

Sleep as a biomarker of motor symptom severity in Parkinson's disease

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Introduction: Sleep disorders are highly prevalent in Parkinson's disease (PD) often appearing years before the onset of motor symptoms [1]. Understanding and addressing these sleep disorders is crucial, as they may not only reflect underlying neurodegenerative processes, but also contribute to disease progression [2,3].

Objective: To investigate the relationship between sleep macroarchitecture and motor symptoms severity in early PD.

Methods: Twenty-four patients with early or de novo PD underwent clinical evaluation, including the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr (H&Y) stage. Polysomnography (PSG) was performed to analyse total sleep time (TST), sleep efficiency (SE), and percentages of N2, N3, and REM sleep. Correlation analyses (Spearman's tests) and regression models were used to assess sleep parameters as predictors.

Results: Participants (mean age: 65.5±8.18 years; disease duration: 1.72±1.32 years) showed significant positive correlations between N2% and both UPDRS-III scores ($p = 0.023$) and H&Y stage ($p = 0.02$). A negative trend approaching significance was observed between N3% and UPDRS-II scores ($p = 0.059$). However, regression models did not identify N2% as a significant independent predictor of motor symptoms severity ($p > 0.05$) after adjusting for potential confounders (e.g., disease duration and fatigue). No significant correlations were found for other sleep parameters, such as TST, SE, and REM%.

Conclusions: Our preliminary results suggest that an increased N2% may be linked to pathophysiological mechanisms underlying the worsening of motor symptoms in early PD. Although regression models did not confirm N2% as an independent predictor, this parameter warrants further investigation as a potential biomarker for disease progression. Future studies, including the ongoing analysis of sleep microstructure, will provide additional insights to validate these findings and explore therapeutic interventions.

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P06

The CARIPLO Parkinson's disease cohort: phenotypic characterization of patients

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Introduction: Parkinson's disease (PD) is clinically and pathologically a heterogeneous disorder, presenting with a wide spectrum of motor and non-motor features and variable progression. Phenotypic characterization of different subtypes of PD may guide the identification of biomarkers to predict disease progression.

Objective: The aim of this study was to characterize a cohort of non-demented early PD-patients to identify different clinical subtypes to be studied prospectively.

Methods: Patients with a diagnosis of clinically established PD without cognitive decline and an early disease stage were consecutively screened for inclusion. Baseline evaluation included motor and non-motor scales, neuropsychological and autonomic testing, cardiac scintigraphy with 123I- MIBG, and cerebral 18F-FDG-PET. We performed a k-mean clustering analysis based on the following variables: UPDRS III, MoCA and age at onset to identify PD subgroups expressing different clinical severity. We run SPM statistical comparison between each patient's 18F-FDG-PET image and a dataset of healthy control to obtain pattern of brain hypometabolism (t-Map). Experts classified each t-Map as PD-like or posterior-prevalent. Measures of pattern expression (PE) were also obtained.

Results: Fifty-three patients were included in the cohort. Clustering analysis identified two clusters, i.e."mild" and "severe", the last one characterized by a greater motor impairment, a lower global cognitive function and a more advanced age at onset. In addition, the "severe" subgroup showed a significantly greater posterior brain hypometabolism, prevalent in the occipital cortex, a higher autonomic involvement, a lower 123I- MIBG H/M early and delayed ratio and lower scores at cognitive tests assessing visuospatial, attentive and memory domains.

Conclusions: Our results show the identification of a "severe" phenotype at baseline presenting with a posterior-pattern of brain hypometabolism, lower 123I- MIBG H/M ratios and a greater autonomic involvement. Phenotypic characterization of a non-demented PD-cohort sets the base for longitudinal observation and for the identification of biomarkers of disease progression.

P07

Peripheral immunity exhibits sex-specific profiles in Parkinson's disease

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Introduction: Parkinson's disease (PD) differs between the two sexes [1]. The immune system may play a role in the sex-specific aspects of the disease; however, human-based evidence remains scarce [2].

Objectives: Here, we aimed to investigate the relationship between peripheral immune response and the clinical-biological sexual dimorphism of the disease.

Methods: The leukocyte population count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), the neutrophil-to-lymphocyte ratio (NLR), and the monocytes-to-lymphocytes ratio (MLR) were collected and compared in 117 PD patients and 86 controls (CTLs) and then related to blood levels of sex hormones, CSF markers of neurodegeneration (α-synuclein, amyloid-β-42, amyloid-β-40, total tau, and phosphorylated-181-tau), and clinical features in male and female PD patients. Finally, a cluster analysis based on the three main leukocyte populations (neutrophils, lymphocytes, monocytes) was performed in the entire PD cohort.

Results: Male PD patients had lower lymphocyte counts and higher NLR than male CTLs. Females with PD had lower monocyte counts, NLR, and MLR than males with PD. Lymphocyte counts correlated with cognition in male but not female PD patients. Finally, two clusters of the peripheral immune response were found: the "high peripheral inflammation" one, mostly comprising male patients, with worse clinical features and greater central α-synuclein burden, and the "low peripheral inflammation cluster", which mainly comprised female patients, with milder clinical features and a lower central synucleinopathy.

Conclusions: The peripheral immune pattern entails sex-specific clinical-biological profiles in PD. Moreover, systemic inflammation clusters with sex, sexual hormones, motor and cognitive impairment, and central synucleinopathy, supporting the relevance of immunity in the sexual dimorphism of the disease.

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P08

Nonmotor fluctuations in Parkinson's disease: impact on caregiving and quality of life

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Introduction: Parkinson's disease (PD) is characterized by a combination of motor and non-motor symptoms, which can fluctuate over time. The recognition of non-motor fluctuations (NMF) as an important aspect of PD is relatively recent [1], and limited data exists regarding their impact on patients' health-related quality of life (HRQoL) and caregivers' burden.

Objective: To evaluate the impact of NMF on HRQoL of patients and burden of caregivers, and to compare it with the impact of motor complications (MC).

Methods: We collected the "total NMF score" of the NoMoFa, MDS-UPDRS, MMSE, PDQ-39, and Zarit Burden Interview (ZBI). Linear regression analysis assessed total NMF and MDS-UPDRS-IV correlations with PDQ-39 and ZBI. ANCOVA compared ZBI scores between caregivers with no-mild vs. moderate-severe burden (i.e., ZBI score < or > 30), and binary logistic regression analysis estimated odds of moderate-severe caregiver's burden based on NMF. Analyses were adjusted for potential confounders (patient's and caregiver's age, disease duration, MMSE, motor impairment severity).

Results: 108 patients and 95 caregivers were included. Higher NMF scores were associated with worse HRQoL (PDQ-39 single index (SI): Beta=0.276; p=0.005), particularly in ADLs, emotional well-being, cognition, and bodily discomfort domains. MC also correlated with PDQ-39-SI (Beta=0.287; p=0.009), and domains such as mobility, ADLs, communication, and bodily discomfort. Both NMF and MDS-UPDRS-IV scores significantly correlated with ZBI (Beta=0.391 and Beta=0.424, respectively; p<0.001). The strength of correlation with PDQ-39 SI or ZBI did not differ between NMF and MDS-UPDRS-IV (PDQ-39: p=0.294; ZBI: p=0.119). Patients whose caregivers had moderate-severe burden, had two-fold higher NMF scores (p=0.008). Each additional point of NMF score increased the odds of moderate-severe caregiver burden by 1.131 (95%CI=1.027–1.245; p=0.012).

Conclusions: NMF significantly impacts on both patient's HRQoL and caregiver's burden, with effects comparable to, or greater than, MC. These findings underscore the importance of addressing NMF in comprehensive PD management.

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P09

The presence of dyskinesia is associated with a worse gait and balance in Parkinson's disease

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Introduction: Levodopa-induced dyskinesia (LID) affects about 40% of Parkinson's disease (PD) patients after 4–6 years of levodopa treatment, interfering with balance, functional mobility, and increasing fall risk [1,2,3]. While LID's impact on postural sway is well-documented, its effect on gait is less understood [2].

Objective: To assess the impact of LID on postural and gait parameters in the 'OFF' and 'ON' therapeutic condition using APDM Mobility Lab™ wearable motion sensors.

Methods: Advanced PD patients were divided into dyskinetic and non-dyskinetic groups based on anamnestic report and clinical evaluation in the "supra-ON" state, obtained administering 1.5x morning levodopa dose. We assessed gait in OFF (overnight withdrawal of dopaminergic therapy) and ON during a two-minute walk test and Root mean square (RMS) for static balance with a 30-seconds sway test. Propensity score matching (PSM) was used to compare kinematic parameters between two groups matched for age, gender, disease duration, disease severity (MDS-UPDRS III) and the postural instability gait disorder (PIGD) score, using Mann-Whitney or Fisher test. In-group differences from OFF to ON phase were evaluated through Wilcoxon test.

Results: 74 patients (77%) with LID and 22 (23%) without LID were enrolled. After PSM with 22 matched pairs, the dyskinetic patients showed reduced stride length (p=0.006) and gait speed (p=0.007) in the 'OFF' condition, and significantly higher gait variability in the 'ON' condition. RMS sway increased from OFF to ON only in dyskinetic patients.

Conclusion: While confirming higher increase of postural sway in 'ON', dyskinetic patients showed also worse gait performance in the 'OFF' condition compared to matched non-dyskinetic patients. These findings underscore the need for further research into shared mechanisms underlying dyskinesia and gait impairment in advanced PD.

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P10

Parkinson's disease and neuroinflammation: preliminary data on the role of Nfr2 pathway

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Introduction: Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway counteracts cell stress and is involved in Parkinson's Disease (PD) pathogenesis as demonstrated by several preclinical studies.

Objective: To assess the Nrf2 pathway and its downstream enzyme SOD1 in blood samples from PD subjects.

Methods: 75 PD patients at different stages of disease (De Novo, Intermediate, Advanced-PD) and 18 Healthy Controls (HC) were enrolled. Nrf2 and SOD1 levels were measured in peripheral blood mononuclear cells (PBMCs). Plasma levels of pro-inflammatory cytokines (TNF-α, IFN-γ, CX3CL1) and neurofilament light chain (NfL) were dosed. Correlation between biomarkers and MDS-UPDRS-part III, Montreal Cognitive Assessment (MoCA), and Non-Motor Symptoms Scale (NMSS) were explored.

Results: Nrf2 levels were not statistically different between PD subject and HC ($p=0.38$) but tended to be higher in De Novo-PD compared to HC, Intermediate and Advanced-PD. SOD1 expression was significantly lower at the earlier stages of disease ($p=0.03$). Plasma levels of TNF-α, IFN-γ, and CX3CL1 were similar between groups. NfL did not differ between PD and HC ($p=0.14$), but a trend toward higher levels along the disease progression was observed. Motor (MDS-UPDRS-part III) and non-motor (NMSS) impairment were more severe at the advanced stages.

Conclusions: Our preliminary data did not detect significant changes in Nrf2 levels, proinflammatory cytokines. The reduction of SOD1 levels at the initial phases of disease could be interpreted as a failure in protective mechanisms against oxidative stress. Further analysis and a larger sample of subjects are needed to confirm our results.

P11

A computational model of α-synuclein pathology in Parkinson's disease: insights into disease mechanisms and therapeutic strategies.

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Introduction: Quantitative Systems Pharmacology (QSP) models integrate mathematical representations of critical pathophysiological processes underlying diseases, spanning multiple biological scales from signaling pathway dysregulation to organ-level dysfunction [1]. These models are particularly valuable for studying complex disorders and their underlying molecular processes, such as Parkinson's disease (PD) and its interplay with misfolding and aggregation of alpha-synuclein (α-syn). This neuronal protein, involved in synaptic function and neurotransmitter release, and its aggregation represent one of the hallmarks of PD, which currently lacks a cure [2]. By bridging the gap between in-vitro and in-vivo studies, QSP modeling can provide mechanistic insights into the molecular and cellular mechanisms driving PD, facilitating experimental research and supporting the design of therapeutic strategies [3,4].

Objective: This study extends the α-syn aggregation model to include the degradation of this protein and pharmacological interventions, offering insights into Parkinson's disease and aiding drug development [2].

Methods: Implemented through ordinary differential equations, the model was calibrated using preclinical data, including in-vitro, cellular, and animal models, and biomarkers from preclinical and clinical studies. Uncertainty quantification was performed to evaluate the robustness and reliability of the model, accounting for variability in parameters and experimental conditions.

Results: The preliminary results of model simulations for healthy and pathological conditions accurately reproduce dynamics consistent with literature data. Additionally, the model enables the simulation of pharmacological interventions and enabling prediction and validation of hypotheses that may inform experimental, pharmacological, and potentially clinical research.

Conclusions: The developed QSP model provides a robust computational framework for studying α-syn aggregation and degradation in both healthy and PD scenarios. The model consistency with literature data highlights its reliability, while its ability to simulate pharmacological interventions underscores its potential to guide therapeutic strategy development and advance our understanding of neurodegenerative diseases.

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P12

Caregiver burden in Parkinson's disease: a nationwide observational qualitative survey

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Introduction: Caregivers play an important role in Parkinson's disease (PD), especially in the advanced stages when both motor and non-motor symptoms increase. Providing care in the form of physical, social, and emotional support may come at a significant cost to the care partners of PD patients, determining the so-called caregiver burden [1].

Objectives: Aim of this qualitative study is to evaluate the caregiver burden of PD in an Italian sample of caregivers.

Methods: An online anonymous survey was conducted among Italian caregivers funded by "Fondazione LIMPE per il Parkinson ONLUS" and "Confederazione Parkinson Italia". The survey encompassed several dimensions (i.e. caregiving, work, economic and personal health) related to caregivers' activities and patients' characteristics.

Results: The survey was completed by 478 caregivers, 361 were women (75%), and the majority had an age included between 55 and 70 years old (46.4%). The burden of assistance increased from 1-2 days weekly in the first period of the disease to all the weekly days with the progression of the disease. Fifteen percent of caregivers reported not working because of assistance, and among caregivers who were still working, almost 70% reported at least one working day lost monthly due to caregiving activities. Concerning health, most caregivers reported an impact on health due to the assistance, in terms of "excessive tiredness" (74.6%), and "lack of sleep" (60.5%) as the most impacting disturbances. With respect to gender, women caregivers reported that they could not work due to the assistance more than men and complained a higher impact on health than men caregivers.

Conclusions: Caregivers of PD patients experienced and reported the presence of caregiver burden in several domains. Additionally, a gender-related pattern was present suggesting the need of a customized support in order to enhance awareness and minimizing caregiver burden.

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P13

Wearable sensors may detect subtle gait and postural alterations associated with autonomic dysfunction in patients with early Parkinson's disease

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Introduction: Gait and balance disorders are related to risk of falling and significantly affects functional activities of daily life in patients with Parkinson's disease (PD). Previous studies have focused on detection of subtle gait and postural alterations from the early stages of the disease. Autonomic dysfunction is highly associated with falls and gait impairment in patients with advanced PD. Recent studies suggest that earlier development of dysautonomia is associated with more rapid disease progression and shorter survival time.

Objective: To investigate i) gait and postural parameters in early non-demented PD patients using wearable sensors, and ii) to correlate digital parameters with motor and nonmotor symptoms, including autonomic dysfunction.

Methods: Fifteen early PD patients (disease duration <5 years, Hoehn & Yahr ≤2.5) and 15 age and sex-matched healthy controls (HC) were consecutively enrolled. Gait and balance parameters were acquired using six Opal V2R wearable sensors, when performing the Timed up and go, 7 and 10 Meters walking tests in both single and dual task (ST/DT) conditions. Motor and nonmotor symptoms were evaluated using the Unified Parkinson's disease Rating scale part III (UPDRS-III), the Nonmotor Symptoms scale (NMSS) and the Scales for Outcomes in Parkinson's Disease - Autonomic Dysfunction (SCOPA-AUT). Bivariate correlation analysis between motor/nonmotor symptoms and wearable sensors metrics were performed.

Results: Higher SCOPA-AUT scores significantly correlated with worse gait and postural performances as detected by wearable sensors in both ST and DT conditions. Interestingly, no correlations have been found between SCOPA-AUT and UPDRS III, including axial and gait subscores.

Conclusions: Our findings revealed that application of wearable sensors could provide useful information for the characterization of early PD patients, when clinical evidence of gait and postural disturbances may not be detectable. These subtle changes are already associated with autonomic dysfunctions, suggesting a potential role to predict worse clinical outcome.

P14

Trans-anal irrigation in Parkinson's disease patients with chronic constipation: efficacy, safety and impact on gut microbiota

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Introduction: Constipation in Parkinson's Disease (PD) is the main and most disabling non-motor symptom [1]. Laxatives, prebiotics and probiotics are therapeutic options for neurological bowel diseases, and Trans-Anal Irrigation (TAI) is a recognized treatment for poor responders [2].

Objective: The study aimed to i). evaluate the efficacy and safety of TAI in treating PD constipation; ii) to profile the gut microbiota (GM) and assess its changes after TAI and iii) to evaluate changes in motor/non-motor symptoms and dopaminergic medication intake in TAI-treated patients versus conservative-treated patients.

Methods: A cohort of PD patients with constipation (Wexner score ≥6) was enrolled in a prospective, observational, cohort study. All patients had a neurological and proctological assessment at baseline (T0), 6 months (T1) and 12 months (T2). At baseline TAI and faecal sampling for GM profiling were proposed and either TAI or conservative treatment (e.g. laxatives) was prescribed. The TAI group was also asked for faecal samples at T1. Probiotics and prebiotics were forbidden to all patients during the study.

Results: Twenty-six patients were enrolled, 12 accepted TAI (TAI+) and 14 preferred conservative treatment (no-TAI). At baseline, the groups had similar scores on neurological scales and bowel management subjective satisfaction scores. TAI+ had lower Wexner scores than no-TAI ($p=0.001$). At T1 and T2, TAI+ showed statistically improved proctological assessment ($p<0.001$) and unchanged neurological scores except for the PDQ-39 questionnaire at T2 ($p<0.001$). GM was not statistically significantly different between groups at baseline, but TAI+ showed some compositional changes at T1.

Conclusions: TAI is a safe and effective treatment for constipation treatment in PD. Improving intestinal transit not only ameliorates quality of life but it may impact GM balance, laying the foundation for new therapeutic strategies.

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P15

Deconstructing cyberchondria in patients with Parkinson's disease

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Introduction: Cyberchondria involves compulsive online searches of health-related information, which exacerbates distress and interferes with daily life. It involves four key dimensions: compulsion (disruption of daily life), distress (anxiety during searches), excessiveness (repetitive, uncontrolled searches) and reassurance-seeking (persistent doubts despite medical advice).

Objective: This study aims to investigate cyberchondria dimensions among patients with Parkinson's Disease (PD) [1,2].

Methods: A cross-sectional study was conducted with 91 consecutive PD patients from the Campus Bio-Medico of Rome. Participants were assessed using the Cyberchondria Severity Scale (CSS-12), the Symptoms Checklist 90-R (SCL-90-R), and Questionnaire for Impulsive-Compulsive Disorders (QUIP-RS) for PD patients together with other relevant informations (UPDRS III, Hoehn and Yahr, dopaminergic therapy, advanced therapies).

Results: Several correlations intercurred between CSS-12, stratified in tertiles of intensity per domain, and SCL-90-R. It results a significant associations between high levels of CSS compulsion and obsessive-compulsive symptoms (χ^2=11.73; p<0.001), paranoia (χ^2=11.6; p<0.001), somatization (χ^2=10.76; p<0.001), and psychoticism (χ^2=9.35; p=0.010). Similarly CSS distress was strongly correlated with anxiety (χ^2= 11.65; p= <0.001), depression (χ^2= 8.83; p= 0.010), and phobic anxiety (χ^2=13.27; p<0.001). The CSS excessiveness dimension showed weaker but significant associations with obsessive-compulsive symptoms (χ^2=8.5; p=0.010). Lastly, CSS reassurance-seeking was significantly associated with paranoia (χ^2=12.07; p<0.001), phobic anxiety (χ^2=9.42; p=0.010), and obsessive-compulsive symptoms (χ^2=11.55; p<0.001).

Conclusion: Cyberchondria in PD patients is strongly linked to psychological vulnerabilities, including anxiety and obsessive-compulsive tendencies. These findings suggest that compulsive online health searches are associated with psychological issues increasing distress and reducing quality of life. This highlights the need for tailored interventions addressing the interplay of psychological and behavioral factors in this population.

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P16

Progression and prognosis in Parkinson's disease with early onset rapid-eye-movement sleep behaviour disorder

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Introduction: Rapid-eye-movement (REM) sleep behaviour disorder (RBD) is a non-motor symptom of Parkinson's disease (PD). The prevalence of RBD in PD is between 20 to 72% along the disease course and RBD may also predate the motor onset or occur in the first years of the disease.
According to few prospective studies, early onset RBD is associated with a more severe PD phenotypes and shows clinical and prognostic implications.

Objective: Our study aims to prospectively compare clinical and prognostic features of PD patients with (PD-RBD+) and without (PD-RBD-) a videopolysomnograhy (VPSG)-confirmed RBD diagnosis within three years from motor symptoms onset.

Methods: We included 117 PD patients of the prospective "BoProPark" study, consecutively enrolled since 2007 and followed longitudinally yearly through outpatient visits and/or hospital admissions. Evaluation of motor and non-motor symptoms of PD, as well as treatment response and occurrence of milestones of disease progression was performed at enrolment (within 36 months from disease motor onset), after 16 months and during the follow up.

Results: Twenty-two patients/117 patients (19%) received a RBD diagnosis at T0. Compared to PD-RBD- patients, PD-RBD+ were more likely to be males (86.4% vs. 60%, p=0.020) and with an higher age at disease onset (64.8 ± 1.2 vs. 57.5± 1.0, p=0.001). At follow up (mean duration was 7 ±4 years) PD-RBD+ presented more frequently autonomic dysfunction [urinary symptoms (90.9% vs 65.3%, p=0.008), neurogenic orthostatic hypotension (40.9% vs 9.5%, p= 0.001)] and visual hallucination (40.9% vs 16.8%, p= 0.010). PD RBD+ patients also developed more frequently gait disturbance (i.e. freezing of gait) and falls without reaching statistical significance, and a significantly higher death incidence (t-test 0.0028)

Conclusions: Our findings outline a specific disease trajectory in PD patients who received a RBD diagnosis at disease onset, characterized by an higher incidence of non-motor symptoms and a worse prognosis.

P17

Efficacy of remote delivery of occupational therapy for motor and non motor impairment in people with Parkinson's disease

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Introduction: Occupational Therapy (OT) is an effective intervention to rehabilitate and or maintain abilities and skills in People with Parkinson's Disease (PwPD) at any stage of the disease. Remote delivered OT may be effective as face-to-face therapy and easily accessible to a greater number of people, even in places where occupational therapists are not available.

Objective: To evaluate efficacy of OT in telemedicine to improve motor e non motor impairment of PwPD.

Methods: In this observational study, 30 PwPD, (15 men; mean age 75±8,2 years; mean disease duration 10±5,2 years; median Hoehn and Yahr (HY) 3) received remote delivered OT interventions for Activities of Daily Living (ADL) functions disabilities and postural transfers. PwPD were assisted by ParkinsonCare, a multidisciplinary telecare service dedicated to PD. OT interventions, performed by Occupational Therapists (OTh), consisted in videocalls to perform assessment of needs and of environment; caregiver and patients training; tailoring of personalized strategies and follow up. Specific items of part II of MDS-UPDRS (MDS sponsored revision of the Unified Parkinson's Disease Rating Scale, M-EDL) and have been used to rate treatment induced variations.

Results: Mean duration of OT treatment was 2 months, performed with 3-4 interventions for PwPD. All PwPD showed an improvement of the issue targeted by OT intervention: environmental adaptation and routine in 8 patients, micrography in 6 patients, transfers and postural transitions in 3, postural positions in 3, eating in 2, personal care in 1 and walking in 1 patient.

Conclusions: Remote delivered OT is effective in improving disability in ADL functions of PwPD. Videocall interventions, for training and strategies suggestions, have been effective and easily used by patients and caregivers.

P18

Frailty as a prognostic marker in Parkinson's disease: insights from a three-year longitudinal cohort study

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Introduction: Frailty is a state of increased vulnerability to adverse health outcomes due to a decline in reserve and function across multiple physiological system [5,9]. Previous cross-sectional studies have indicated that frailty, assessed using frailty index (FI), is highly prevalent in Parkinson's disease (PD) patients and may influence the clinical manifestations of the disease [1,3,8]. However, its role in modulating PD clinical trajectories remains unexplored.

Objective: To evaluate the impact of frailty on the clinical progression of PD.

Material and methods: A three-years longitudinal study was conducted on a cohort of 150 PD patients at various disease stages. Frailty was quantified using the FI [3,10]. Standardized clinical scales were employed to assess motor (MDS-UPDRS) and non-motor symptoms (NMSS) [2], disease stage (Hoehn and Yahr scale) [4], and cognitive function (MoCA) [7]. Levodopa equivalent daily dose (LEDD) was also evaluated [6]. Statistical analyses included correlation analyses, univariate and multivariate regression models and mixed-effects models to evaluate associations between frailty and clinical outcomes.

Results: Of the 150 patients, 109 completed the follow-up. The FI demonstrated consistent clinometric properties in PD patients, maintaining its association with motor and non-motor features, motor complications, disease stage and LEDDs over time. Univariate and multivariate linear regression models demonstrated that baseline FI was significantly associated with worse follow-up scores on the MDS-UPDRS Part III ($p<0.0001$) MoCA ($p<0.0001$), H&Y ($p<0.0001$) and NMSS ($p<0.0001$). Finally, baseline FI was also associated with a higher risk of wearing-off periods, dyskinesias, and mortality at follow up evaluation.

Conclusion: Frailty, as measured by the FI, may represent a valuable and reliable prognostic marker for clinical outcomes in PD. Incorporating frailty assessment into routine clinical practice may facilitate the early identification of patients at higher risk of deterioration, allowing for more personalized therapeutic strategies.

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P19

Eye movement abnormalities in Parkinson's disease motor subtypes: a video-oculographic study

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Introduction: Eye movement dysfunction has been described in Parkinson's disease (PD) [1], but differences between tremor-dominant (TD) and postural instability/gait difficulty (PIGD) PD motor subtypes remain poorly understood.

Objective: The aim of this study was thus to compare video-oculographic (VOG) features between PD motor subtypes.

Methods: Two hundred and four PD patients and 55 age-matched healthy control subjects (HC) were enrolled in this study. PD patients were stratified into PIGD and TD motor subtype groups [2]. VOG amplitude, peak velocity of upward, downward, and vertical saccades, and square wave jerks (SWJ) number and amplitude were compared across groups. Multivariate linear models also investigated associations between VOG parameters and clinical data on motor severity, gait/balance disturbances, and cognitive function.

Results: The final cohort included 180 PD patients fulfilling criteria for either PIGD (n=121) or TD subtype (n=59) and 55 HC. Both PD subtypes showed reduced upward and downward amplitude compared to HC, with normal peak velocity. By comparing the two subtypes, PIGD patients exhibited significantly decreased upward saccadic amplitude compared to TD patients, with no differences in other VOG parameters. Moreover, the upward saccadic amplitude was associated with motor severity, particularly slowness of gait and bradykinesia/rigidity scores in the PIGD group.

Discussion: This study provides evidence of greater saccadic hypometria in PIGD than in TD patients in upward gaze, contributing to a better understanding of oculomotor impairment in PD. The association of saccadic amplitude with bradykinesia/rigidity severity may suggest a role of underlying dopaminergic deficits in ocular dysfunction in PD patients.

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P20

Effects of gender on non-motor symptoms in Parkinson's disease: a longitudinal study

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Introduction: Parkinson's disease (PD) presents a heterogeneity of non-motor symptoms (NMS) and a growing body of evidence highlights gender-related differences in the prevalence of NMS in PD [1].

Objective: This longitudinal study aims to investigate the trend of NMS in relation to gender within a cohort of PD patients levodopa naive at baseline.

Method: The study included 216 PD patients (139M), starting levodopa treatment after baseline (T0). Clinical scales were administered to assess NMS at T0 and at 2-year follow-up (T1) evaluation. The UPDRS-I assessed non-motor experiences of daily living, the PDQ-39 evaluated quality of life, the AES measured apathy symptoms, and the QUIP-RS assessed impulsive-compulsive behaviors. Cognitive functions, autonomic dysfunction, non-motor symptoms, and depressive symptoms were assessed using the MOCA, SCOPA-AUT, NMSS, and HAM-D, respectively. A two-way repeated measures ANOVA was conducted to analyze the effect of time and gender on the clinical scores at both time points. Specifically, the interaction between time and gender was investigated to assess if the time effect differed by gender.

Results: Significant time-gender interactions were identified. Specifically, we found that men presented a significant worsening at T1 compared to women for gastrointestinal ($p=0.044$) and cardiovascular ($p=0.001$) symptoms, in mood/cognition item of NMSS ($p=0.038$) and in hypersexuality item of QUIP-RS ($p=0.003$). On the other hand, women showed a significant improvement at T1 compared with men in weight item of HAM-D scale ($p=0.027$).

Conclusions: Our results suggest a significant difference between men and women over time in a small spectrum of NMS, in a sample of PD patients starting treatment with levodopa. Gender-oriented research may improve the appropriateness of therapeutic interventions in a distinct way for women and men.

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P21

Handwriting, touchscreen dexterity and bradykinesia measures in Parkinson's disease: a feature selection study

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Introduction: Bradykinesia affects handwriting and smartphone usage in Parkinson's disease patients (pwPD).

Objective: To assess handwriting, hand dexterity, smartphone usage and bradykinesia in pwPD, and at identifying the features that best describe upper-limb alterations in pwPD.

Methods: Forty pwPD and 30 age/sex-matched healthy controls were included. We used standard handwriting/dexterity tests: Manual-Ability-Measure-36, Purdue-Pegboard-Test (PPT) and copy of a text on paper. Spatiotemporal handwriting parameters were assessed using tests on a tablet: copy of text and pre-writing tasks. To obtain objective data on movement speed and amplitude on the smartphone, we developed tests involving the most commonly used gestures (tap, swipe, slide). Bradykinesia during a finger tapping task was evaluated using electromagnetic sensors. Sequential feature selection models were used to identify the parameters best distinguishing pwPD and healthy controls.

Results: PwPD relative to healthy controls showed reduced manual ability and dexterity. They showed reduced movement amplitude and speed in smartphone tests and signs of micrographia during handwriting tests. Moreover, kinematic parameters correlated with both PPT and Movement Disorder Society Unified Parkinson's Disease Rating Scale III. Each feature selection model demonstrated a good accuracy, particularly when including standard handwriting/dexterity tests (R2=0.90), tests on smartphone (R2=0.94) and all the features together (R2=0.97). The best features were self-reported manual abilities, PPT, tap and swipe speed/amplitude on smartphone.

Conclusions: This study showed that technological devices with customized software can provide quantitative measures of handwriting, dexterity and bradykinesia that will be useful to assess PD progression and the effects of interventions in pwPD.

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P22

Cognitive performances are associated with subclinical gait and postural alterations in early cognitively unimpaired patients with early Parkinson's disease

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Introduction: Gait impairment is the most disabling symptom in patients with Parkinson's disease (PD) and is associated with high risk of falls, worse disease progression and shorter survival time. Cognitive impairment has been consistently associated with impaired walking ability, increased risk of falls, and reduced quality of life in PD. Detection of subclinical gait alterations may potentially serve to identify PD patients at risk to develop cognitive impairment from the early stages of the disease.

Objective: To investigate the relationship between cognitive performances and gait and postural parameters using wearable sensors in early cognitively unimpaired PD patients.

Methods: Eleven early PD patients (disease duration <5 years, Hoehn & Yahr <=2.5) and 15 age and sex-matched healthy controls (HC) were consecutively enrolled. Gait and balance parameters were acquired using six Opal V2R wearable sensors, when performing the Timed up and go test, in both single and dual task (ST/DT) conditions. All patients underwent II-level neuropsychological assessment to exclude the presence of any cognitive impairment. Bivariate correlation analysis between clinical and wearable sensors metrics were performed.

Results: Overall, worse gait and postural parameters as detected by wearable sensors in both ST and DT conditions significantly correlated with cognitive tests specifically exploring: (i) visuo-spatial processing; (ii) psychomotor coordination; (iii) executive functions involved in retrieving words from lexical vocabulary and information recalling.

Conclusions: Our findings showed that application of wearable sensors could provide useful information for the characterization of early PD patients, even when gait and postural disturbances are not clinically detectable. These subclinical changes are already associated with cognitive performances in PD patients with normal cognition. Integration of neuropsychological and digital data may help to identify patients more prone to develop clinical overt cognitive impairment over time, that may be targeted for potential novel prevention strategies.

P23

Micrographia in Parkinson's disease: automatic recognition through artificial intelligence

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Introduction: Parkinson's disease (PD) leads to handwriting abnormalities primarily characterised by micrographia [1]. Whether micrographia manifests early in PD, worsens throughout the disease [2], and lastly responds to L-Dopa is still under scientific debate [3].

Objective: This study aims to investigate the onset, progression and L-Dopa responsiveness of micrographia in PD, employing both clinical and artificial intelligence (AI) -based methodologies.

Methods: Fifty-seven PD patients undergoing chronic L-Dopa treatment were enrolled, including 30 patients in the early stages (H&Y≤2) and 27 in the mid-advanced stages (H&Y>2), alongside 25 age- and sex-matched controls. Participants completed two standardized handwriting tasks in an ecological scenario. Handwriting samples were examined through clinically-based (i.e., perceptual) and AI-based (automatic) procedures. Borh consistent (i.e., average stroke size) and progressive micrographia (sequential changes in stroke size) were evaluated. Receiver operating characteristic (ROC) curves were used to evaluate the accuracy of the convolutional neural network in classifying handwriting in PD and controls.

Results: Clinically- and AI-based analysis revealed a general reduction in stroke size in PD supporting the concept of parkinsonian micrographia. Compared with perceptual analysis, AI-based analysis clarified that micrographia manifests early during the disease, progressively worsens and poorly respond to L-Dopa. The AI models achieved high accuracy in distinguishing PD patients from controls (91%), and moderate accuracy in differentiating early from mid-advanced PD (77%). Lastly, the AI model failed in discriminating patients in OFF and ON states.

Conclusions: AI-based handwriting analysis is a valuable tool for detecting and quantifying micrographia in PD.

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P24

Sex hormones and dystonia in early-onset Parkinson's disease: a gender-related relationship

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Introduction: Dystonia frequently occurs in Parkinson's Disease (PD), either as a presenting sign or levodopa-induced motor fluctuation [1], and mostly affects patients with early-onset PD (EOPD) (age at onset <50 years), especially if females [2]. The biological bases underlying this sex dimorphism are unclear, although a contribution of sex hormones could be hypothesized.

Objective: To evaluate gender-specific associations between sex hormones serum levels and motor features, including dystonia, in EOPD patients.

Methods: The study involved 34 EOPD patients, 14 females and 20 males, assessed by the MDS-UPDRS Part II – III – IV, and Hoehn and Yahr scale. Patients were grouped into fluctuating (MDS-UPDRS IV≥1) and non-fluctuating, dystonic (as onset sign or motor fluctuation) and non-dystonic. Serum levels of total testosterone (TT), estradiol (E2), and gonadotropins (FSH and LH) were measured in each participant. Group and correlation analyses adjusted for main covariates were conducted.

Results: Motor scores were similar in females and males, whereas dystonia prevailed in females ($p=0.043$). E2 and TT levels were respectively higher and lower in females than males. Significant associations between hormones and motor features resulted only in females. Specifically, E2 negatively correlated with MDS-UPDRS II-III and was lower in fluctuating than in non-fluctuating ones ($p=0.03$). TT inversely correlated with MDS-UPDRS IV ($p=0.05$) and was lower in dystonic than in non-dystonic ones. TT emerged as a significant dystonia predictor in females ($p=0.022$).

Conclusions: Sex hormone levels may affect motor phenomenology in EOPD, contributing to the peculiar sexual dimorphism. In female patients, the lowering of E2 and TT was associated with greater motor severity, including fluctuations, and higher dystonia prevalence respectively. These findings highlight the fertile female EOPD patients' increased sensitivity to central effects of sex hormones and suggest a potential role for TT levels in the pathophysiology of dystonia, independently from PD.

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P25

Exploring the fatigue phenomenon in individuals with Parkinson's disease

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Introduction: Fatigue is a prevalent and debilitating non-motor symptom in Parkinson's disease (PD), significantly impacting patients' quality of life. Despite its occurrence, fatigue in PD is often underdiagnosed due to its subjective nature and lack of consensus regarding its definition and classification, which hampers the development of effective therapeutic options.

Objective: This study aimed to investigate the prevalence, clinical correlates, and sociodemographic differences of fatigue in a multicenter Italian cohort of 100 PD patients. Correlation analysis focused on fatigue's relationship with disease severity, motor and non-motor symptoms, and sociodemographic factors, aiming to advance understanding and improve clinical management.

Methods: An observational cross-sectional study was carried out in Italy from January to July 2024. One hundred PD patients (Hoehn and Yahr stage ≤4) were assessed using validated tools: Parkinson Fatigue Scale (PFS-16), Fatigue Severity Scale (FSS-9), and Modified Fatigue Impact Scale (MFIS). Clinical variables, including motor and non-motor signs and symptoms (MDS-UPDRS), cognitive status (MoCA), and levodopa dose (LEDD), were analyzed using non-parametric tests and Spearman's correlations. Based on PFS score ≥3.09 the prevalence of fatigue was determined.

Results: Fatigue was present in 36% of patients, more prevalent in women and more severe in those with moderate-advanced disease (H&Y >2). Fatigue correlated strongly with non-motor symptoms (MDS-UPDRS Part I) and moderately with motor complications, but weakly with disease duration, LEDD, and age. Significant intercorrelations among fatigue scales supported their capacity to consistently measure the construct of fatigue.

Conclusions: Fatigue in PD is a multidimensional construct influenced mainly by non-motor symptoms. Gender-specific differences and the association with disease progression underscore the need for tailored assessment and interventions. Comprehensive and integrated management strategies, including non-pharmacological approaches, are essential to address this challenging symptom.

P26

Gender-specific cardiovascular autonomic responses in Parkinson's disease: insights from an observational study

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Introduction: Parkinson's disease (PD) is associated with non-motor symptoms (NMS), including cardiovascular dysautonomia. While gender-specific variations in cardiovascular autonomic responses are documented in healthy individuals [1,2], their presence in PD patients remains unclear.

Objective: This study aimed to investigate gender-related differences in cardiovascular autonomic function using cardiovascular reflex tests and SCOPA-AUT.

Methods: Ninety idiopathic PD patients (52 males, 38 females, aged >50 years) were enrolled, including drug-naïve (dnPD) and pharmacologically treated (PDot) patients. Cardiovascular reflexes were evaluated through head-up tilt test (HUTT), Valsalva maneuver (VM), Deep Breathing, Handgrip test and Cold Face test. SCOPA-AUT was performed. Statistical significance was set at $p < 0.05$.

Results: No significant gender differences were observed in demographics, clinical features, NMS, or risk factors. Cardiovascular tests showed dnPD females had a higher ΔdBP after the Handgrip test compared to PDot females (p=0.03). In dnPD males, higher ΔsBP (p=0.006) and ΔdBP (p=0.024) were observed at the 10th minute of HUTT compared to PDot males, along with a higher OV response (p=0.010) during the VM. No differences were found between dnPD females and dnPD males. Among PDot patients, females exhibited a lower ΔHR during the 3rd and 10th minutes of HUTT (p=0.041) and a higher ΔsBP during the 10th minute of HUTT (p=0.046) compared to males. SCOPA-AUT showed no differences in dnPD patients, however, PDot females reported higher cardiovascular symptom severity compared to males (p = 0.02).

Conclusions: dnPD patients exhibited no significant gender differences, whereas PDot females showed diminished autonomic responses during HUTT and reported more severe cardiovascular symptoms than males [3]. Dopaminergic therapy may influence autonomic responses differently in males and females, highlighting the need for further research on gender-specific effects of treatment.

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P27

Retinal asymmetrical degeneration in Parkinson's disease and REM sleep behavior disorder

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Introduction: According to the Synuclein Origin and Connectome (SOC) model, REM Sleep Behavior Disorder (RBD) patients represent the prodromal phase of "body first" Parkinson's Disease (PD) patients, characterized by a more symmetric disease presentation due to a more symmetric alpha-synuclein spreading. Conversely, "Brain first" PD patients are predicted to have an asymmetrical spreading and clinical presentation, and no prodromal RBD. Thinning of the retinal layers has been described in both RBD and PD patients, however no study has ever assessed the presence of asymmetrical retinal degeneration.

Objectives: To assess the presence of retinal asymmetrical degeneration in PD and RBD patients.

Methods: Early PD "brain first" patients diagnosed according to the MDS-PD diagnostic criteria were recruited, absence of RBD was assessed using the RBDSQ questionnaire (score <6). Isolated RBD patients were diagnosed via videopolysomnography. Macula layer's thickness was evaluated using Spectral-Density Optical Coherence Tomography (SD-OCT). Asymmetry index (AI) was computed for each macular layer.

Results: Thirteen RBD patients and 15 PD "brain first" were recruited. Mean disease duration for PD patients was 25.6±13.5 months, with a mean UPDRS-ME score of 25.5 ±7.3. There was no difference in age, sex, and Moca score between the groups. Concerning macular layers, there was a significant higher AI in the outer plexiform layer (OPL) in PD vs RBD patients (10.7±8.5 vs 4.3±3.2; p=0.02). No differences were found in the other macular layers.

Conclusions: Our findings suggest a more asymmetrical retinal degeneration in "brain first" PD patients and a more symmetrical pattern in prodromal "body first" patients supporting the SOC model.

P28

The role of chaperone clusterin on α-synuclein aggregation in a cell line model of Parkinson's disease

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Background and goals: One of the hallmarks of Parkinson's disease (PD) is the presence in dopaminergic neurons of insoluble proteinaceous aggregates, mainly composed of phosphorylated α-Synuclein (Syn), known as Lewy bodies (LBs). Chaperones are key components of the proteostasis network, and the modulation of their expression is an ongoing research challenge to counteract Syn aggregation process and its detrimental effects. We previously demonstrated in SH-SY5Y cells stably overexpressing Syn (SH-Syn) that the molecular chaperone Clusterin (CLU) is part of the biochemical responses triggered by the cells to manage Syn burden and that CLU down-regulation, in combination with block of proteasome activity, favour the Syn aggregation events. These data paved the way to carry out a loss-of-function study of CLU with the aim to confirm its cytoprotective role in a cell model that recapitulate PD pathology.

Methods: To induce LBs-like inclusions, a time course experiment was performed, treating SH-Syn with Syn Pre-Formed Fibrils (PFFs). Before the experiment, PFFs size and morphology were determined by atomic force microscopy. CLU down-regulation was obtained using siRNA technology. Upon treatment of siRNA-transfected SH-Syn and relative control clone with PFFs, cells viability, phospo-Syn aggregates and their cell-to-cell spreading were evaluated.

Results: We showed that SH-Syn cells take up Syn PFFs in a time dependent manner; we also detected intracellular phosphorylated-Syn aggregates, confirming the formation of LBs-like inclusion. Syn PFFs treatment of SH-Syn with CLU down-regulation resulted in an increase of intracellular phosphorylated-Syn aggregates and their spreading between neighbouring cells, as compared to control clones.

Conclusions: Our results confirm CLU as an important player in counteracting Syn aggregation events in a cell line model that mimic PD pathology. To improve the knowledge about CLU's involvement in the mechanisms underlying PD onset and progression, a gain- and loss-of-function studies of CLU in differentiated dopaminergic-like clones is ongoing.

P29

Addressing palliative care needs in advanced Parkinson's disease: a path to comprehensive patient management

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Introduction: Palliative care is crucial for managing patients with neurodegenerative diseases, including Parkinson's disease and Lewy body dementia. These conditions, with their complex and progressive symptoms, require early and appropriate palliative interventions. However, there is still no standardized approach for integrating palliative care with neurological treatments.

Objectives: This study aims to evaluate palliative care needs of Parkinson's patients, focusing on advanced stages. It assesses both quantitative and qualitative aspects of their care, including physical, psychological, and social needs, while exploring the potential benefits of early palliative care. It also investigates collaboration between neurologists and palliative care specialists to address gaps in managing complex needs.

Materials and methods: This study screened Parkinson's patients for palliative care needs using the SPICT and IDC-PAL ITA scales. Data were collected through clinical assessments and interviews with patients and caregivers, using tools like MDS-UPDRS, Hoehn and Yahr, Beck Depression Inventory, MMSE, PDQ-8, IPOS, and CIRS to assess symptoms, functional status, and psychosocial factors.

Results: Among 124 patients, 27% had palliative care needs, with 36% classified as complex cases requiring consultation with specialized palliative teams. Most were elderly males with longer disease duration, severe motor symptoms, pain, fatigue, sleep disturbances, urinary issues, and dysphagia. Over 50% had moderate-to-severe cognitive impairment, communication difficulties, and nearly all had depressive disorders. CIRS revealed frequent comorbidities, especially age-related conditions. Caregiver support was often insufficient, increasing physical and emotional burden. Additionally, shared decision-making and advance directives were rarely addressed, revealing significant gaps in future care planning.

Conclusions: A considerable proportion of advanced Parkinson's patients require specialized palliative care, particularly due to complex motor and non-motor symptoms. Collaboration between neurologists and palliative care specialists can improve symptom management, reduce hospitalizations, and enhance patient and caregiver support. Shared decision-making and advance care planning should be introduced earlier in the disease trajectory, improving long-term outcomes.

P30

Trace amines and TAAR-1 receptors in the pathophysiology and experimental treatment of parkinsonism

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Monoamines have been implicated in the pathophysiology of CNS disorders. There is growing interest for trace amines, which are present in low amounts in the brain [1,2]. Trace amines activate TAAR-1 receptors, which is widely expressed in the CNS and modulates dopaminergic transmission [3,4]. The study aims at establishing a possible causal link between trace amines, TAAR-1 receptors and the pathophysiology of Parkinson's disease (PD).

In the preclinical study we investigate the effects of TAAR-1 activation in neurodegeneration in the MPTP mouse model of toxicological parkinsonism. C57Black/6J mice are injected with a single dose of MPTP (30 mg/kg) and one week later killed to mimic an acute lesion of the nigrostriatal system. Mice are injected with MPTP and treated with saline or the partial agonist R05263397 (1 mg/kg, i.p.) of TAAR-1 receptors (30 min prior MPTP injection and daily until sacrifice). In order to evaluate and quantitate the effects of pharmacological activation of the TAAR-1 against on MPTP-induced damage of the nigrostriatal system we measure the levels of dopamine and its metabolites in the striatum by HPLC and electrochemical detection. Preliminary data showed increased striatal dopamine levels in mice treated with the TAAR-1 receptor agonist, suggesting that receptor activation may have protective action.

As a clinical counterpart, we perform a genomic analysis of polymorphisms of TAAR1 gene on DNA samples from 730 PD patients and 502 healthy controls. This allows the identification of the polymorphism rs8192620 (A/G) associated with early occurrence and severity of PD. This study involves a collaboration with Prof. Eleonora Aronica (University of Amsterdam) who provide autoptic specimens of subjects with PD. We evaluate the expression of TAAR-1 receptors and its co-expression with dopamine D1 and D2 receptors in 6 striatum samples, by immunohistochemistry, from subjects with PD and 6 samples from healthy control subjects. The analysis showed increased expression of TAAR-1 in the striatum of subjects with PD, and the co-localization between TAAR-1 and D2 receptors.

Results suggest possible involvement of the TAAR1- receptor in the pathophysiology of PD, and its selective agonist as potential neuroprotective drugs in models of parkinsonism.

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P31

Stress and dysbiosis in Parkinson's disease

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Introduction: Animal and clinical studies support the involvement of the gut-brain axis in various central nervous system disorders [1]. The relationship between stress, gut microbiota (GM) and Parkinson's disease (PD) remain underexplored [2]. GM can modulate PD pathogenesis and could provide a new therapeutic target for the prevention and treatment [3]. There is a growing need for practical and affordable tools to identify dysbiosis risk. The Cohen-Sheldon Perceived Stress Scale (PSS) [4] has become one of the most widely used to predict both objective biological markers of stress and increased risk for developing diseases among persons with higher perceived stress levels.

Objective: Our study explorates the relationship between stress and dysbiosis in PD by means of clinical practical screening tools.

Methods: We performed a cross-sectional observational study in 65 PD patients consecutively recruited in the period August-October 2019 at the Azienda Ospedaliera Marche Nord. Patients with a mean age of 64 years and a diagnosis of PD from 2 months to 34 years (average of 7 years) were enrolled. They underwent to the following questionnaires: 1) 10-item PSS, 2) a screening questionnaire to identify risk factors and symptoms suggestive of intestinal dysbiosis.

Results: 57% of the respondents achieved a high level of stress as a result and 22% showed a moderate-high level; 81,5% of the interviewees had provided a response profile compatible with dysbiosis and 17% with probable dysbiosis to the specific questionnaire. Among patients with high levels of stress, there was a significantly higher percentage of dysbiosis (54%), another 15% of patients with dysbiosis was found in the moderate-high level of stress group.

Conclusions: Our study suggests an high level of stress in PD patients and a correlation between perceived stress and dysbiosis, thus intervening on both could be useful to amegliorate PD current treatment.

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P32

Diagnostic and prognostic retinal biomarkers in Parkinson's disease

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Introduction: Parkinson's disease is associated with retinal damage, the clinical and pathogenetic significance of which remains uncertain [1,2,3,5].

Objectives: To identify retinal damage in affected patients as an accessible window for diagnosis and prognosis.

Methods: Forty-seven patients (mean age±SD 63.7±8.7 years) with a diagnosis of PD (mean disease duration±SD 5±3.5 years) were included in the study and underwent routine neurological examinations, as well as ophthalmological screening using Spectral-Domain Optical Coherence Tomography (SD-OCT) analysis. The parameters investigated included the thickness of the macular zone and peripapillary nerve fibers, analyzed by sector and layer in the macula. The obtained values were compared with those of an equal number of healthy subjects matched by age and sex. The data were compared by sector and layer using a t-test, with statistical significance defined as $p < 0.05$. Therapy-related data were analyzed through linear correlation using Pearson's coefficient (r).

Results: A statistically significant difference in the inferior temporal sector of peripapillary fibers was observed in PD patients as compared to healthy controls (p value <0,01). The presence of this difference was confirmed through parametric analysis of specific layers and sectors of the macula [9]. The involvement of the macula was independent of disease duration (r <0.04). Dopaminergic therapy was protective with respect to retinal thickness in patients with a tremor-dominant phenotype [4,7,8].

Conclusions: Retinal damage offers a chance to suggest alternative pathogenetic hypotheses, allow for earlier diagnosis, and provide a simpler, cheaper, and less invasive way to assess prognosis as compared to other techniques.

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P33

Virtual hospital, an empowerment and participatory medicine experience

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Introduction: The care of people with Parkinson's disease (PwP) in the hospital is affected by the limited number of consultations in a year and the lack of a multidisciplinary team. The Virtual Hospital (VH) was developed as an online platform where ParkinZone APS association transferred its activities during COVID-19 pandemic in 2020 and continued since then. Users of the VH are given free online access.

Objective: In this study, we surveyed PwP enrolled in the VH to demonstrate the usefulness of a virtual program for PwP and their carepartners.

Methods: We investigated the preferences, satisfaction, and perceived usefulness of the activities delivered in the VH. The VH includes artistic activities (Theatre, DanceWell), physical exercise (Gymnastics, Feldenkrais, Soft Pilates), scientific dissemination (Question Time), psychoeducation and psychological support (Ti-Sane, Time for me, Learning how to Well-Being). Data on attendance and events were collected through online platform records. Information on participants' experiences was gathered via Google Forms online questionnaire, with multiple-choice and open-ended questions.

Results: From March 2020 to February 2021, the platform recorded a total of 267 events and 8,890 user connections. A total of 85 participants took part in the online survey. Top three most attended activities were: Question Time (QT) (83.53%), Gymnastics (42.35%), and DanceWell (29.41%). Specifically, for QT, most preferred topics were: Psychological Aspects (72.94%), Physiotherapy and Physical Activity (51.76%), Nutrition (49.41%). 85.8% of respondents appreciated the opportunity to receive answers to their questions from a professional, and 72.94% felt included in the discussion. 93% of respondents found participation in VH activities to be useful.

Conclusion: We demonstrated the feasiblity and usefulness of an online program for PwP, which delivers complementary activities and allows education of PwP and their carepartners. The VH represents a concrete example of participatory medicine and patients empowerment, overcoming geographical barriers, isolation and promoting scientific information. The VH could be a feasible and effective tool to ease PD daily management and improve PwP and carepartners' quality life.

P34

Targeting anxiety and depression in Parkinson's disease with tDCS: preliminary findings

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Introduction: Dopaminergic circuit alterations in Parkinson's disease (PD) lead to a range of motor and non-motor symptoms, including neuropsychiatric disturbances that significantly impair quality of life. Anxiety and depression are among the most common, but conventional pharmacological treatments show limited efficacy. Neuromodulation of the dorsolateral prefrontal cortex (DLPFC) using Transcranial Direct Current Stimulation (tDCS) has shown promising results in managing affective symptoms [1,2], although evidence remains limited and heterogeneous.

Objective: This study aims to increase the understanding of the clinical effects of repeated tDCS sessions targeting the DLPFC in managing anxiety and depressive symptoms in PD.

Methods: To date, only three subjects have been involved in this randomized, double-blind, controlled study (age: 71±4.51 years, 2 women). Participants were randomly assigned to an active tDCS group or a sham stimulation group. Both groups received five sessions of intensive stimulation for one week, followed by one maintenance session per week for three weeks. Assessments were conducted at baseline (T0), after the first week (T1), and after the maintenance phase (T4) using a validated scale, including the Parkinson's Anxiety Scale (PAS) [3], State-Trait Anxiety Inventory (STAI Y1-Y2) [4], and Beck Depression Inventory (BDI-II) [5].

Results: Preliminary observational analyses indicate that patients receiving active tDCS showed a 23% improvement in PAS, 11% improvement in STAI Y-1, and a 19% improvement in BDI-II at T1, while the sham patient experienced a 21% worsening in PAS, 68% worsening in STAI Y-2, and a 31% worsening in BDI-II. Additionally, the net percentage change difference between groups appears consistent from T0 to both T1 and T4 for the STAI Y-1 and BDI-II scores.

Conclusions: Preliminary results suggest that modulating activity in the DLPFC may improve affective symptoms in PD. We expect that the consistency of these effects will be validated through ongoing recruitment and statistical analysis.

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P35

Objective evaluation of nocturnal movements in people with Parkinson' disease and association with clinical parameters

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Introduction: Nocturnal hypokinesia is common in people with Parkinson's disease (PwPD) [1]. Wearable devices could help monitoring reduced sleep movements [1], however, only a few studies investigated the association between device-based sleep parameters and clinical assessment in PwPD [2-5].

Objective: To objectively investigate nocturnal movements through wearable devices and the association with clinical measures in PwPD.

Methods: 6 PwPD [females: 2 (33%); age: 68.0±5.1 years; disease duration: 10.0±3.2 years; mHY: 2.5 (2-3)] and 5 age- and sex-matched healthy controls wore a lower-back-mounted inertial sensor (McRoberts MoveMonitor) for 7 days. The percentage time spent in each position while sleeping (left side, right side, prone, supine), the number of small, medium, large, very large and sitting transitions as well as the total number, velocity and duration of transitions were collected and averaged across the 7 days of monitoring. Participants were clinically evaluated by means of MDS Unified Parkinson's disease Rating Scale (MDS-UPDRS), Parkinson's disease sleep scale 2 (PDSS2), Epworth sleepiness scale (ESS), Insomnia severity Index (ISI). Mann-Whitney test was used to compare sleep movements between the two groups. Spearman test was used to assess correlations between clinical and device-based variables in PwPD.

Results: PwPD showed less very large transitions ($p=0.043$) and a tendency toward less small ($p=0.067$), medium (0.067) and total number of transitions during night (0.067). Spearman test showed a positive association between ESS, the time spent supine ($r=0.764$; $p=0.046$) and the velocity of transitions ($r=0.817$; $p=0.025$); between ISI and number of sitting transitions ($r=0.901$; $p=0.006$); a negative association between both MDS-UPDRS total score and disease duration and the number of very large transitions ($r= -0.857$; $p=0.014$ and $r=0.822$; $p=0.023$, respectively) was found.

Conclusions: Our preliminary results confirm that PwPD have reduced bed mobility and suggest that sensor-based sleep movements could provide valuable information on nighttime motor symptoms.

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P36

Differential effect of dopaminergic treatment on bradykinesia features and limb-kinetic apraxia in Parkinson's disease

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Introduction: Bradykinesia is one of the primary motor symptoms in Parkinson's disease (PD) [1]. However, other cognitive-motor disorders, such as limb-kinetic apraxia [2], may contribute to motor dysfunction, influencing the variability in treatment responses [3].

Objective: To investigate the differential effects of dopaminergic therapy on bradykinesia and limb-kinetic apraxia in PD patients using kinematic analysis. Additionally, transcranial magnetic stimulation (TMS) was employed to further elucidate the underlying mechanisms of treatment.

Materials and Methods: Twenty-five patients with PD were assessed in both OFF- and ON-medication states, along with 24 age- and gender-matched healthy controls (HC). Kinematic analysis was performed to evaluate bradykinesia (using a finger-tapping task) and limb-kinetic apraxia (using a 10-second coin rotation task). Corticospinal excitability was examined through TMS, which measured resting motor thresholds, motor-evoked potential input/output curves, short-interval intracortical inhibition, and interhemispheric inhibition.

Results: In the OFF-medication state, PD patients exhibited slower velocity, progressive reduction in amplitude (sequence effect), and decreased regularity in finger-tapping movements compared to HC. Similarly, slower velocity and altered movement regularity were observed in the coin rotation task in PD patients OFF medication compared to HC. Dopaminergic therapy improved finger-tapping velocity but had no significant effect on other finger-tapping parameters or the coin rotation task, highlighting a differential impact on the two motor tasks. Increased M1 excitability was associated, to variable extent, with impaired motor performance, such as slower velocity and/or altered movement regularity, during both the finger-tapping and coin rotation tasks. No such correlations were observed in the ON state. Additionally, no correlations were found between changes in kinematic parameters from the OFF to the ON state and the concurrent changes in TMS parameters.

Conclusion: The differential impact of treatment on bradykinesia and limb-kinetic apraxia in PD may suggest distinct pathophysiological mechanisms possibly involving distributed cortical and subcortical systems with varying sensitivity to dopaminergic therapy.

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P37

Bradykinesia with sequence effect in a trembling patient without evidence of dopaminergic deficit

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Introduction: Patients with clinical features of Parkinson's disease (PD) but normal dopamine transporter imaging are classified as having scans without evidence of dopaminergic deficit (SWEDD). It remains debated whether SWEDD represents a distinct clinical entity or an early form of PD. Key features like bradykinesia with sequence effect, reemergent tremor, and symptom progression are considered exclusive to PD. However, we report a SWEDD case exhibiting these features, expanding the phenotypic spectrum of SWEDD.

Objective: To describe a case of SWEDD that challenges the diagnostic criteria distinguishing it from PD and dystonic tremor.

Methods: We evaluated a 76-year-old man with asymmetric action and rest tremor in the upper limbs, accompanied by other mild parkinsonian and dystonic signs. Neurological assessments, including the Fahn-Tolosa-Marin Tremor Rating Scale for tremor evaluation, sequential DAT SPECT imaging, and kinematic analyses, were conducted over a seven-year follow-up period.

Results: Clinical and kinematic evaluations revealed progressive worsening of upper limb tremor, re-emergent tremor, bradykinesia with sequence effect, and mild dystonic postures. Despite the deterioration of symptoms, DAT SPECT scans remained normal throughout the follow-up period. Tremor showed modest improvement with propranolol and clonazepam.

Conclusions: This case represents the longest documented follow-up of a SWEDD patient in the literature, with the aid of neurophysiological techniques. It highlights the complexity of diagnosing this condition, underscoring the overlapping features with PD and dystonia. Extended follow-up and further investigations are essential to better understand the clinical significance of SWEDD cases.

P38

Short- and long-term effects of apomorphine infusion on motor cortical excitability and plasticity in Parkinson's disease

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Introduction: Abnormally increased excitability and reduced plasticity at the primary motor cortex level play a significant role in the pathophysiology of motor complications in Parkinson's disease (PD). The subcutaneous infusion of apomorphine is an effective treatment in PD patients with motor complications, but no studies have investigated whether apomorphine can modulate abnormal cortical excitability and plasticity in these patients.

Objectives: To investigate the effects of apomorphine on excitability and plasticity in the primary motor cortex of PD patients by conducting a transcranial magnetic stimulation (TMS) study.

Materials and Methods: Twenty-one fluctuator PD patients on levo-dopa participated in the study. Clinical and neurophysiological assessments were performed before and at 1, 12, and 24 weeks after initiating apomorphine treatment. The clinical assessment included standardized scales to score the severity of motor and non-motor symptoms. Neurophysiological assessments were conducted using single, paired, and repetitive TMS paradigms at the primary motor cortex level. To test cortical excitability, we utilized a single-TMS protocol called the input/output curve. Paired-TMS protocols assessed intracortical inhibition and facilitation circuits. Theta burst stimulation, a form of repetitive-TMS, was used to evaluate cortical plasticity. All assessments were performed on treatment.

Results: Subcutaneous infusion of apomorphine induced a significant improvement in the severity of PD motor and non-motor symptoms. Assessments at 12 and 24 weeks post-treatment initiation showed improvements in cortical excitability, as shown by a decreased slope of the input/output curve. Additionally, the 24-week assessment revealed an improvement of altered cortical plasticity, as demonstrated by a significant increase in response to theta burst stimulation.

Conclusion: The subcutaneous infusion of apomorphine elicited a significant enhancement in the altered cortical excitability and plasticity in patients with PD. The continuous post-synaptic stimulation effects induced by apomorphine on motor cortical activity may represent a crucial mechanism underlying the clinical effects of apomorphine.

P39

Cerebellar-cortical tACS enhances cued gait in Parkinson's disease patients unresponsive to auditory cueing strategies

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Introduction: Gait impairments are prevalent in Parkinson's disease (PD). Compensation strategies, like rhythmic auditory cueing (RAC), are evidence-based approaches for gait rehabilitation in PD [1]. While cueing can significantly improve mobility, its effectiveness varies among patients [2]. Posterior parietal cortex (PPC) [3] and the cerebellum (CB) [4] are involved in externally cued movements. Transcranial alternating electrical stimulation in gamma frequency (γtACS) has shown the ability to improve motor performance [5] and restore plasticity in the primary motor cortex (M1) in PD [6].

Objective: The study aims to study the contribution of PPC-M1 and CB-M1 pathways via high-definition γtACS (hd-γtACS) in decreasing gait variability during gait with RAC in PD patients responders and non-responders to cueing strategies.

Methods: Nine RAC responders (Age: 67.6±7.7 years; H&Y: 2.1±0.31) and nine non-responders (Age: 67.6±7.8 years; H&Y: 2.1±0.40) with PD were assessed. RAC responsiveness was assessed in a separate session using inertial sensors during cued and uncued gait, following Tosserams et al.1. Responders showed a 0.5-point reduction in stride time variability compared to uncued gait. Gait variability in cued (RAC) and uncued gait was measured before and after multisite hd-γtACS targeting PPC-M1 and CB-M1 pathways. A control sham session was also performed.

Results: Non-responders to RAC showed reduced gait variability during cued gait after hd-γtACS on CB-M1 ($p = 0.02$, 1.44-point reduction) and PPC-M1 ($p = 0.01$, 0.71-point reduction). Responders showed no significant improvement in either condition.

Conclusions: These findings suggest that hd-γtACS on CB-M1 and PPC-M1 pathways can restore auditory cue responsiveness in patients with no initial improvement during RAC gait, highlighting CB and PPC roles in cued gait and offering insights for non-invasive brain stimulation in gait rehabilitation protocols.

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P40

Morpho-functional correlates of gait disturbances in patients with Parkinson's disease

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Introduction: Gait disturbances still represent a scarcely treatable manifestation complicating Parkinson's disease (PD) course [1]. A deeper understanding of the underlying pathophysiology is needed to advance in this challenge.

Objective: To define the pathological substrate of gait disturbances in PD by integrating MRI-based brainstem morphometry and EEG functional connectivity (FC).

Methods: The study included 75 PD patients scored with main motor and non-motor scales, and 60 healthy controls (HC). For each participant, we collected the Magnetic Resonance Parkinsonism Index (MRPI) [2] and the FC in θ, α, β, and low-γ bands obtained from a 64-channel system EEG analyzed through the weighted phase-lag index (wPLI) [3]. Generalized linear models (GLM) compared MRPI and band-specific FC between PD and HC. Partial Least Squares Path Modeling (PLS-PM) explored reciprocal causal relationships between MRPI, FC, and clinical parameters.

Results: MRPI was higher in PD than HC ($p=0.03$) and directly correlated with MDS-UPDRS-III gait subscores ($r=0.42$, $p<0.001$). In PD patients, α-FC was significantly lower than HC ($t=2.5$, $p=0.04$) and mostly affected prefrontal, sensorimotor, temporal, and limbic regions. α-FC in PD was negatively correlated with both MRPI ($r=-0.26$, $p=0.02$) and MDS-UPDRS-III gait subscores ($r=-0.25$, $p=0.03$). PLS-PM revealed that MRPI had a strong negative direct effect on α-FC (-0.383) and a significant positive total effect on gait (0.441), partially mediated by α-FC (0.097). Additionally, α-FC had a direct negative impact on gait (-0.254).

Conclusions: This study highlights the complex interplay between brainstem morphology, FC, and gait disturbances in PD. Specifically, we noticed that brainstem integrity is critical for gait disorder in PD, as the thinning directly correlates with motor impairment and affects higher level brain circuits accounting for motor behavior. These findings support a multimodal framework for understanding and addressing gait disturbances in PD.

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P41

Subthalamic low beta power and gait in Parkinson's disease during unsupervised remote monitoring

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Objectives: This study investigates the correlation between beta band dynamics and spatiotemporal gait parameters in real-life settings in PD patients with implanted sensing-enabled neurostimulators.

Methods: Ten PD patients with bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) were enrolled. Gait parameters, including step and stride variability, were recorded using an inertial measurement unit (IMU) worn by patients during 10 hours of daily activities. LFP data from the STN were recorded using the Percept™ DBS system. Correlations between normalized STN beta power and gait parameters were analyzed.

Results: A significant correlation was identified between increased right more than left STN low beta power and greater step and stride variability ($p < 0.001$) (n=8). Inverse non-significant relationships were found when high beta was selected as a frequency of interest (n=2). Within-subject analysis revealed stronger correlations in 30% of participants.

Discussion: This study highlights a link between low beta power and gait variability in PD patients, suggesting that heightened beta activity is associated with poorer gait performance. Such a relationship occurred in spite of real life setting, short resolution time span of devices. These findings emphasize the potential of LFPs as biomarkers for gait dysfunction in PD, warranting further investigation.

P42

Attentional functioning in Parkinson's disease with freezing of gait: preliminary data from ERPs

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Introduction: Freezing of gait (FOG) is one of the most disabling symptoms that patients with Parkinson's Disease (PD) may develop. However, the pathophysiology of this disorder is not fully understood. Previous studies hypothesized a deficit in executive attentional control, particularly in inhibitory control, cognitive flexibility, and conflict processing [1].

Objective: The aim of this study is to evaluate the attentional abilities of PD patients with FOG, using event related potentials (ERPs).

Methods: 39 PD patients were assessed using UPDRS-III, H-Y, TUG, NFOG and divided into two groups: FOG-PD (19 patients) and NoFOG-PD (20 patients). All patients underwent ERPs evaluation consisting in two visual motor tasks (Go/NoGo and Novelty-P3) and a battery of neuropsychological tests. Latencies and amplitudes of N1 and P3 and of N2 and P3 components were measured for the novelty task and the GO/NoGo task, respectively. Number of errors and RTs for correct motor responses were measured for the two tasks.

Results: FOG-PD presented 1) significantly lower P3b amplitude (Cz:p=0.05, Pz:p=0.04) in the novelty-P3 task, 2) significantly longer (Cz:p=0.04) NoGo-N2 latency and lower (Cz:p=0.04) Go-P3 amplitude in the Go/NoGo task, 3) significantly longer RTs in both tasks (Novelty-P3:p=0.05; Go/NoGo:p=0.02) than NoFOG-PD.

Conclusions: FOG in PD was associated with difficulty in preparation of functionally appropriate motor responses to the context, as indicated by the reduction of P3-Go amplitude [2], and an impairment in inhibitory control, as indicated by theincrease of N2-NoGo latency. Furthermore, it is associated with difficulty in managing the conflict between new information and expectations derived from a predefined schema, as indicated by the reduction of P3b amplitude in the novelty-P3 task [3]. These cognitive dysfunctions may originate from an alteration in functioning of the fronto-parietal attention network, which receives dysfunctional inputs from the subcortical system (striatum-pallidus-thalamus-tegmental-peduncle pontine nucleus) known to be altered in FOG.

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P43

Psychophysiological assessment in Parkinson's disease subtypes through ERPs

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Introduction: In Parkinson's disease (PD), two main clinical forms can be distinguished: tremor-dominant (TD) and non-tremor dominant (NTD) [1]. The TD form is associated with a more favorable prognosis, a lower risk of cognitive and non-motor disturbances. Conversely, the NTD form is characterized by postural instability and bradykinesia, with a worse prognosis, and early onset of hallucinations, depression, apathy and cognitive deficits. Among the latter, those related to executive functions such as planning, attentional switching, inhibitory control, working memory, and cognitive flexibility are more frequent.

Objective: The aim of this study is to investigate attentional functions in the different clinical forms of PD using evented-related potentials (ERPs).

Methods: 39 PD patients on L-dopa therapy and with a corrected Mini-Mental-State-Examination score >23.8 were assessed using UPDRS-III and H-Y, and were divided into two groups based on the onset form: TD-PD (25 patients) and NTD-PD (14 patients). All patients underwent ERPs evaluation consisting in two visual motor tasks (Go/NoGo and Novelty-P3) and a battery of neuropsychological tests. Latencies and amplitudes of N1 and P3 components were acquired for novelty task; latency and amplitude of N2 and P3 components were measured for Go/NoGo task.

Results: Regarding the Novelty P3 task, no significant differences were observed between groups. In the Go/NoGo task, the N2 amplitude (Cz: $p=0.01$) and the P3 amplitude for the NoGo stimulus (Cz: $p=0.04$) were significantly lower in NTD-PD compared to TD-PD.

Conclusions: NTD-PD form was associated with a more pronounced executive attentional deficit, particularly in inhibitory control and conflict management, than the TD-PD form, as indicated by the reduction of N2-NoGo and P3-NoGo amplitudes [2].
We hypothesize that NTD-PD presents with this executive attentional deficit due to a more severe involvement of the fronto-parietal attentional network [3], within the framework of a pathological disruption in the fronto-striato-subthalamic-pallidal circuitry.

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P44

Beta-band suppression after contralateral STN activation: refining the concept of unilateral motor control in Parkinson's disease

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Introduction: In humans, the control of voluntary movement is mainly lateralized. However, several studies suggest that both the contralateral and ipsilateral basal-ganglia systems are implicated during unilateral movement. Moreover, bilateral improvement of motor signs has been reported in patients with Parkinson's disease (PD) with unilateral lesion or Deep Brain Stimulation (DBS) of the Subthalamic nucleus (STN) [1]. The possibility of in-vivo recordings of brain activities, allowed by the recently commercialized implantable pulse generator (Percept, Medtronic, Dublin, IR), offers new possibilities in understanding how STNs influence each other.

Objectives: To examine how the activation of the more affected STN influences LFP in the contralateral, never activated nucleus in advanced-PD patients undergoing DBS.

Methods: STN-LFPs were recorded one month after bilateral STN-DBS implantation, from 13 consecutive PD-patients. Clinical assessments and LFP-recordings from both sides were performed in the morning, after overnight withdrawal of PD-medications. Worst-side-STN (W-STN)-stimulation was then activated at therapeutic intensity (2.5 mA), recording from the contralateral, less-affected-STN (B-STN). Power spectra were normalized as previously described [2]. The most represented beta band in the B-STN was compared in two study conditions: W-STN OFF and W-STN ON. Clinical evaluations were performed in the same experimental conditions using MDS-UPDRS lateralized motor scale.

Results: PD-patients (7F; age 63±6 years; disease-duration 13±4 years; MDS-UPDRS OFF motor score: 53±17) most represented beta-band in the B-STN was at 18±5 Hz (range 11-23). A significant modification of normalized beta-power was detected in the B-STN in the W-STN OFF versus ON condition (3.6±0.8 vs 3.2±0.6 respectively, p=0.02), with clinical improvement mirroring neurophysiological modifications in the less affected side (MDS-UPDRS lateralized motor score: 16.5±5 vs 13.9±5.6, in W-STN OFF vs ON condition, respectively; p=0.01).

Conclusions: Unilateral activation of STN-DBS in the most affected hemisphere is able to suppress beta-signal and contemporary to alleviate parkinsonism in the contralateral, less affected side.

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P45

Clinical neurophysiology of functional hemifacial spasm preceding contralateral peripheral facial palsy

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Introduction: The hemifacial spasm (HFS) is characterized by paroxysmal unilateral facial contractions. Different causes are recognized including psychogenic forms. Functional neurological disorders (FND) have already been reported in some neurological disease, also preceding the diagnosis of Parkinson's disease, multiple sclerosis and contralateral peripheral facial palsy (PFP) [1,2].

Objective: To describe the clinical neurophysiology of a functional HFS preceding the diagnosis of contralateral PFP.

Case report: A 59-year-old woman came to our attention for the acute onset of right hemifacial involuntary contractions since three hours. She complained paresthesias and jerks of the right facial muscles mildly spreading to the ipsilateral shoulder. In the past medical history she had a transitory ischemic attack fifteen years before, but she did not take any medication, and untreated anxious disorder. The CT-brain scan was negative. Since she presented frequent facial jerks, we performed an EEG that had been normal. Because of intermittent symptoms, and slowly progressive improvement without medication, we scheduled a visit after three days. The absence of the "other Babinski sign", the inconsistency and incongruence of the phenomena leaded to the suspicion of a psychogenic form. At the follow-up she presented early signs of contralateral PFP. The neurophysiological evaluation disclosed a blink reflex (BR) consistent with the left PFP, while the BR recovery cycle on the right side was normal. The polysynaptic component of the BR (R2) on the right side was enhanced for afferent inputs from the paralyzed side compared to the healthy side, as already described in the early phase of PFP [3,4].

Conclusions: Functional HFS may precede the diagnosis of contralateral PFP. Clinical neurophysiology can help clinicians to disclose subtle PFP and to support the diagnosis of FND. In our case the sensitization of the polysynaptic pathway of the BR could have played a role in inducing an abnormal facial motor behavior [5].

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P46

Basal ganglia oscillations dynamics during continuous emotional stimulation in Parkinson's disease

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Introduction: The intrinsic response to emotions plays an important role in Parkinson's disease (PD), shaping not only the non-motor, but also the motor profile of the patient [1]. Emotional stimuli are typically characterized by valence (positive or negative) and arousal (relative strength of the emotion) [2]. While many studies elaborated on the neurophysiological processing of emotions at the cortical level [3], the role of the basal ganglia is not well understood [4].

Objective: To investigate the impact of prolonged exposure of different emotional stimuli on basal ganglia oscillatory activity in patients with PD.

Methods: PD patients chronically implanted with a sensing-enabled Deep Brain Stimulation (DBS) system in the Subthalamic nucleus (STN) were enrolled. Patients on their usual dopaminergic medication underwent multiple iterations of 2-minutes video-based emotional stimulation using a validated videoclip dataset eliciting emotions with different valence and arousal content, as well as a white-noise control condition. Local field potentials (LFP) were recorded in parallel using the BrainSense streaming mode. Spectral data ranging from the theta (4-7 Hz) to the high gamma band (60-90 Hz) were analyzed in the context of the various emotional stimuli.

Results: STN alpha band (8-12 Hz) activity was clearly modulated by the emotional arousal level, with high-arousal stimuli reducing the alpha power compared to low-arousal stimuli. This effect was evident both for positive and negative valence stimuli as well as in both hemispheres with a stronger effect when LFPs were recorded in a broad bipolar montage. Importantly, low (13-20 Hz) and high beta band (21-30 Hz) activity were largely unaffected by the different emotional stimuli.

Conclusions: Our findings expand on the important role of alpha oscillations in emotion processing at the subcortical level in PD5 and highlight its modulation by different emotional arousal-levels. Importantly, our results are suggestive that the accuracy of beta-driven adaptive DBS might not be affected by various emotional stimuli in PD.

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P47

Dysregulated EEG theta activity suggests impaired synaptic build-up in levodopa-induced dyskinesia in Parkinson's disease

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Introduction: Slow-wave activity (SWA) during slow-wave sleep (SWS) facilitates synaptic downscaling, crucial for brain plasticity. SWA, typically occurring early in the night, serves as a primary electrophysiological marker for the homeostatic process. Conversely, theta activity during wakefulness indicates synaptic potentiation, with SWA decreasing during sleep and theta increasing during wakefulness.

Objectives: Levodopa-induced dyskinesia (LID) in Parkinson's disease (PD) has been linked to impaired sleep-mediated synaptic downscaling. However, it is unclear whether this dysfunction stems from impaired SWA-mediated downscaling or reduced synaptic build-up. This study focuses on analyzing theta activity during wakefulness to investigate the build-up process in resting state.

Methods: Three PD groups – *de novo* (n = 7), advanced (n = 7), dyskinetic (n = 9) – were compared with healthy volunteers (n = 7). Participants underwent physical and neurological exams and wore inertial sensors to monitor their sleep-wake cycles for one week. EEG recordings were obtained during resting state (eyes closed) in the morning and after 9 hours in the evening. Theta activity (4-8 Hz) was analyzed, and statistical comparisons included Mann-Whitney U tests with Bonferroni correction (adjusted $p < 0.0083$) for inter-group changes, and one-sided Wilcoxon signed-rank tests for intra-group diurnal changes.

Preliminary Results: Dyskinetic patients displayed significantly altered theta activity compared to all other groups during morning and evening recordings ($p <$ adjusted-p). Healthy, *de novo*, and advanced PD groups showed higher evening theta activity, while dyskinetic patients exhibited no significant diurnal changes. Notably, a higher percentage of dyskinetic patients lacked significant evening theta increases ($p < 0.05$).

Conclusions: Dysregulated theta activity in dyskinetic patients suggests impaired synaptic build-up. Larger studies analyzing regional theta activity and connectivity are needed to confirm these findings and explore therapeutic targets for LID.

P48

Intermittent Theta Burst Stimulation improves motor and non-motor symptoms in Parkinson's disease

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Introduction: Parkinson disease (PD) is a complex neurodegenerative disorder characterized by degeneration of dopaminergic system leading to motor and non-motor symptoms. Growing evidence suggests that Repetitive Transcranial Magnetic Stimulation (rTMS) enhances neuroplasticity [1,2] and thereby may ameliorate symptoms in PD [3,4]. Intermittent Theta Burst stimulation (iTBS) is an excitatory protocol of rTMS which has shown benefits in animal model of PD.

Objective: The aim of this study was to investigate the effects of iTBS on motor and non-motor symptoms and on cortical excitability in PD.

Methods: 40 patients with PD were recruited in a single-blind sham-controlled study (PNRR Project MAD 2022 12375804). Patients on medications were randomized in two groups: real iTBS and control (sham) iTBS. Every patient received 10 sessions of bilateral motor cortex (M1) iTBS for 5 consecutive days for 2 consecutive weeks. All participants were assessed at baseline (t0), after intervention (t1) and after 3 months (t2) with Movement disorder society Unified Parkinson disease rating scale (MDS-UPDRS), Nonmotor Symptoms Scale (NMSS), Montreal Cognitive Assessment (MOCA), Time Up and Go (TUG) and cortical excitability measures.

Results: Real group had a significant reduction in MDS-UPDRS-III ($p < 0.001$) after sessions of iTBS (t1) which was maintained at t2 ($p=0.008$). At t1 there was also a benefit in MDS-UPRDS I and II score (respectively $p < 0.001$ and $p=0.004$) which was lost at t2. NMSS was significantly reduced at t1 ($p=0.017$) and TUG time was significantly shorter at t1 in treated patients ($p=0.009$). In the sham group no differences were found in any of clinical scores. Finally, iTBS improved also cortical excitability in the real group ($p=0.023$).

Conclusions: iTBS of bilateral motor cortex is a potential tool to restore synaptic plasticity and improve motor and non-motor symptoms in PD.

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P49

Levodopa effects in SWEDD: clinical and kinematic insights from a case report

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Introduction: A subset of patients with clinical features suggestive of Parkinson's disease (PD) have normal dopaminergic imaging, a condition referred to as scan without evidence of dopaminergic deficit (SWEDD). It is still unclear whether SWEDD represents an early form of PD or a distinct clinical entity. The diagnostic uncertainty presents a significant challenge, especially when determining whether to initiate dopaminergic treatment.

Objective: To thoroughly assess the effects of dopaminergic therapy in a patient with SWEDD, using both clinical scales and objective kinematic analysis.

Methods: We evaluated a 73-year-old man with minimal bradykinetic-rigid syndrome, asymmetric rest tremor, and re-emergent tremor predominantly on the right side. He had a recent negative DAT scan and was referred to our clinic while undergoing dopaminergic treatment initiated at another center. The patient was assessed using standardized clinical scales, including MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Additionally, we conducted kinematic analysis of finger tapping and tremor in both the "ON" (with medication) and "OFF" (after discontinuation of levodopa) states.

Results: Clinical assessments showed minimal differences between the ON and OFF states (FTM-TRS: 33 vs 34; MDS-UPDRS: 25 vs 26). Kinematic analysis revealed a worsening of the re-emergent tremor in the OFF state (0.177 vs 0.285 $GRMS^2$), while rest, kinetic, and head tremor remained unchanged. Finger tapping velocity, in both the ON and OFF states, was within the normal range on both sides. However, we observed a lower velocity on the right side compared to the left, regardless of dopaminergic treatment (ON: 1215 vs 1358 degrees/sec, OFF: 1012 vs 1152 degrees/sec). Additionally, in the OFF state, patients exhibited slower finger tapping and a greater sequence effect compared to the ON state [velocity: 1082 vs 1287 degrees/sec; sequence effect: -0.16 vs -0.43 (degrees/sec)/n mov)]. The data suggest a subtle but measurable impact of levodopa withdrawal on motor performance and re-emergent tremor amplitude in SWEDD.

Conclusions: This case underscores the value of clinical and neurophysiological assessments in evaluating treatment response in SWEDD patients. The observed changes in movement parameters indicate a mild effect of levodopa on motor symptoms, despite the evidence of dopaminergic deficits on imaging. Apart from therapeutic implications, these findings also have potential pathophysiological significance.

P50

Arm swing kinematics in Parkinson's disease: clinical insights

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Introduction & objectives: Parkinson's disease (PD) commonly manifests with arm swing reduction during gait. So far, few researchers examined the evolution of abnormal arm swing across different disease stages [1]. Furthermore, the topographic distribution of this phenomenon according to arm joints and its correlations with cardinal motor symptoms of PD is still to be investigated [2,3]. In this research, we firstly investigate kinematic changes of arm swing reduction across different stages of PD. Moreover, we describe the topographic distribution of arm swing reduction in PD according to arm joints. Lastly, we evaluate correlations between arm swing experimental features and MDS-UPDRS clinical scores.

Materials and methods: Forty PD patients and twenty age-matched healthy subjects (HS) were recruited. Patients were divided into two cohorts: 20 early PD patients with no previous exposure to L-dopa (PDdrug naive) and 20 mid-advanced PD patients under chronic dopaminergic treatment (PDL-dopa). We performed a sensor-based analysis of arm swing during gait, extracting features from distinct topographic areas (shoulder vs elbow). Time and frequency domain analysis was performed, followed by statistical analysis for clinical-behavioral correlations.

Results: In the sub-group analysis, arm swing features were significantly different between HS and PDdrug naive, as well as between HS and PDL-dopa. When comparing PDdrug naïve and PDL-dopa, no significant difference was detected. Both shoulder and elbow kinematic features were significantly different between PD patients and HS. Experimental parameters correlated with clinical scores for rigidity and bradykinesia.

Discussion and Conclusions: Arm swing is decreased in PD and it can be accurately detected by a network of wearable sensors. Arm swing reduction is a distinct feature of early PD but does not progress alongside the disease history. Both shoulder and elbow impairment equally contribute to this phenomenon. Lastly, arm swing kinematics significantly correlate with standardized clinical scores for rigidity and bradykinesia.

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P51

Boosting the LTP-like plasticity effect of intermittent theta-burst stimulation using gamma transcranial alternating current stimulation improves bradykinesia in Parkinson's disease

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Introduction: Gamma-band (γ) oscillations in cortico-basal circuits are reduced in Parkinson's disease (PD), and the plasticity of the primary motor cortex (M1) is impaired [1–3]. Enhancing γ oscillations through transcranial alternating current stimulation (tACS) has shown potential to restore M1 plasticity alterations in PD [1–3]. It remains unclear, however, whether the effects also translates to motor improvements.

Objective: This study aimed to determine whether γ-tACS applied to M1 improves long-term potentiation (LTP)-like plasticity and alleviates bradykinesia, a hallmark motor symptom of PD, assessed using kinematic techniques.

Methods: 18 PD patients (OFF medication) and 15 healthy controls (HCs) were recruited. Participants underwent two randomized sessions: intermittent theta burst stimulation (iTBS) combined with γ-tACS (iTBS-γ tACS) and iTBS combined with sham-tACS (iTBS-sham tACS). We assessed M1 activity, including corticospinal and intracortical excitability, with transcranial magnetic stimulation (TMS) at baseline (T0) and 5 (T1), 15 (T2), and 30 (T3) minutes post-stimulation. Also, bradykinesia was assessed through kinematic analysis of finger-tapping before and after stimulation [4].

Results: At baseline, PD patients showed reduced M1 intracortical inhibition (SICI) compared to HCs, alongside impaired motor performance during finger-tapping, i.e., reduced velocity and amplitude, altered rhythm, and sequence effect. iTBS alone failed to evoke M1 plasticity in PD patients, whereas iTBS-γ tACS elicited significant plasticity improvements, demonstrated by increased MEP amplitudes post-stimulation. Kinematic results indicated improvements in movement velocity and amplitude following iTBS-γ tACS in PD patients, whereas no changes were observed with iTBS-sham tACS or in HCs.

Conclusions: This study demonstrates the potential of γ-tACS to restore M1 plasticity and improve voluntary motor execution in PD patients. These findings offer further insights into the mechanistic role of impaired γ oscillations and their contribution to altered motor control and reduced M1 plasticity in PD. The present results may also contribute to the development of novel non-invasive brain stimulation strategies.

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P52

Role of β-band functional connectivity for α-synuclein propagation in early-stage Parkinson's disease: insights from the analysis of brain network properties

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Introduction: Parkinson's disease (PD) is characterized by the pathological aggregation of α-synuclein, which spreads through the brain in a prion-like manner [1]. PD patients present band-specific functional connectivity (FC) alterations since the early stage [2]. Intrinsic graph properties are also critical for network efficiency. Among these, the scale-free organization, characterized by a few highly connected hubs and many sparsely connected nodes, is crucial in maintaining network robustness and optimizing communication [3].

Objective: To investigate the relationship between CSF α-synuclein levels and EEG-based network properties, aiming to clarify their role in PD pathophysiology.

*Methods: 2*0 early-stage PD patients and 30 healthy controls (HC) were included in the study. CSF α-synuclein levels were assessed in PD. 64-channel EEG recordings were used to compute FC across θ-α-β-low-γ bands. The sigma coefficient (σ), which describes the degree distribution following a power law, was used to assess the scale-free network topology [4]. Moreover, hub regions were identified using betweenness centrality.

Results: PD patients showed a higher σ coefficient than HC ($p<0.001$) in β-band, indicating a more scale-free organization. No significant differences were found in the other bands. Moreover, we observed a negative correlation ($r=-0.56$, $p=0.025$) between σ coefficient and CSF α-synuclein levels in our PD cohort in β-band. The analysis also revealed a significant negative correlation between CSF α-synuclein levels and β-band betweenness centrality in specific regions, particularly parahippocampal and entorhinal cortex.

Conclusions: These findings indicated that α-synuclein accumulation in PD may be influenced by β-band cortical network properties. Brain β networks characterized by a few highly connected hub nodes and many secondary, sparsely connected nodes could lead to greater accumulation of α-synuclein in the brain [5]. The parahippocampal and entorhinal cortices, regions affected early in PD, may act as critical hubs facilitating the propagation of α-synuclein, highlighting the importance of network topology in disease progression.

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P53

The language of gait: interpreting emotional states through gait features

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Introduction: The complex interplay between gait alterations and emotions in Parkinson's disease (PD) requires further investigation.

Objective: To investigate whether the observation of emotional gait conditions can modulate spatio-temporal gait parameters and gait-related functional brain correlates in healthy subjects (HC) and PD patients by evoking those emotions.

Methods: We first administered a questionnaire containing videos of an actress walking with different gait patterns according to specific emotions (e.g. happiness, sadness, fear/anxiety and neutral) in order to select the videos with the mostly recognized emotional gait patterns in a cohort of 110 HC. Then, we administered the selected videos to 19 HC and 21 PD, which were asked to imitate the emotional gait patterns observed in the videos and to report the intensity and valence of the evoked emotions. The spatio-temporal gait parameters were monitored using six inertial sensors. All subjects observed the same videos during a functional MRI (fMRI) task in order to obtain neural correlates of emotional gait observation.

Results: In both HC and PD, happiness promoted an improvement in gait kinematics (e.g., increased stride length, turn velocity, upper limb and trunk movement amplitude) and an enhanced recruitment of the sensorimotor network during the fMRI task in PD. Sadness and anxiety were associated with a worsening of spatiotemporal gait parameters and to an extensive reduction of fMRI activity of sensorimotor areas, mirror neuron system and cerebellum.

Conclusions: This study suggests that positive and negative emotions specifically influence gait kinematics and fMRI activity of the sensorimotor system.

P54

Italian translation, cultural adaptation, and validation of the fear of falling scale in people with Parkinson's disease

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Background: Fear of falling (FoF) is a significant concern among individuals with Parkinson's disease (PD), contributing to increased fall risk, diminished quality of life, and social isolation [1]. Despite its clinical importance, no validated instrument specifically tailored to assess FoF in this population exists in Italian. This study aimed to translate, culturally adapt, and validate the Fear of Falling Scale (FFS) [2] for Italian individuals with PD, providing a robust tool for evaluating FoF.

Methods: The study adhered to the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) guidelines for translation and cultural adaptation [3]. The FFS was translated into Italian and validated through rigorous psychometric testing. Internal consistency was assessed using Cronbach's alpha, and test-retest reliability was evaluated with the Intraclass Correlation Coefficient (ICC). Construct validity were examined through correlations with gold standards.

Results: A total of 84 adults with PD (mean age = 70.5±9.1 years) participated in the study. The Italian FFS demonstrated excellent internal consistency (Cronbach's alpha = 0.94 for subscale 1; 0.92 for subscale 2) and high test-retest reliability (ICC = 0.93 and 0.92). Construct validity was confirmed through significant correlations with measures of quality of life, balance, and cognitive function. Cross-cultural validity analysis revealed a significant association with disease duration, highlighting the progression-related nature of FoF.

Conclusions: The Italian FFS is a reliable, valid, and culturally appropriate instrument specifically designed to assess FoF in individuals with PD, considering the unique motor challenges of this population.

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P55

Establishment of a semi-residential center for Parkinson's disease patients within the Fondazione Roma Village

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Introduction: Emerging evidence showed that exercise, complementary therapies, and training of patients and caregivers can improve quality of life. Fondazione Roma expanded its commitment to neurodegenerative diseases by establishing a Semi-Residential Center for patients sufferig of parkinsonism within the Fondazione Roma Village.

Objective: This study aimed to evaluate the implementation and outcomes of an innovative, complementary care service for Parkinson's patients, focusing on physical therapies and a holistic approach to disease management [1,2].

Methods: Tai-Chi, Tango therapy, physical activities and Joga were identified as the key component in PD. The program was developed in collaboration with specialized associations and incorporated a multidisciplinary team including psychologists, social workers, and therapists. A reference team from IRCCS S. Raffaele, provided expert guidance. The center opened in May 2024, offering services to 15 patients per day, divided into two groups according to disease severity.

Results: By the end of 2024, 21 patients had been enrolled, with a service utilization rate of 67%. Activities included Tai-Chi, Tango therapy, and individual cognitive training. Patients reported significant improvements in mood, anxiety, apathy, socialization, and overall well-being. Positive motor effects, such as improved posture and balance, were also noted. Family caregivers reported reduced emotional and caregiving burden.

Conclusions: The Semi-Residential Center for Parkinson's patients successfully integrated complementary therapies with conventional care, leading to improvements in both physical and psychological health for patients and their families. Future objectives include expanding patient numbers and enhancing activities based on patient needs.

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P56

The role of high-intensity exercise in enhancing cognitive and functional outcomes in people with Parkinson's disease

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Introduction: Parkinson's disease (PD) is a neurodegenerative disorder characterized by both motor and non-motor symptoms. Several studies suggest that physical activity can provide therapeutic benefits for motor symptoms, improving gait-related parameters [1], as well as for non-motor symptoms. Cognitive impairment is one of the predominant non-motor symptoms in PD patients, and evidence support that physical activity may promote the preservation and enhancement of cognitive functions in these individuals [2] and improve mood disorders [3].

Objective: The aim of this study is to evaluate whether a high-intensity neurorehabilitation treatment can improve both motor and non-motor symptoms in early-stage PD patients.

Methods: Forty patients diagnosed with PD were enrolled and randomized into two groups: 20 in a sedentary group and 20 in an active group. The intervention involved vigorous-intensity treadmill exercise (70-85% of maximum heart rate) three sessions per week, 45 minutes each, over 3 months. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), depressive symptoms with the Beck Depression Inventory (BDI-II), motor performance with the MDS-Unified Parkinson's Disease Rating Scale section III (MDS-UPDRS-III), and functional mobility with the Timed Up and Go Test (TUG). Project-Code: PNRR-MAD-2022-12375804.

Results: At follow-up (T1), the intervention group showed significant improvements in cognitive performance ($p<0.05$), depressive symptoms ($p<0.05$), and TUG test performance ($p<0.05$). Conversely, the control group showed significant worsening in depressive symptoms ($p<0.05$) and TUG performance ($p<0.05$). No significant changes in MDS-UPDRS-III scores were observed.

Conclusions: The findings indicate that vigorous-intensity physical activity effectively improves non-motor symptoms of PD, as evidenced by enhanced cognitive performance and reduced depressive symptoms. Furthermore, the observed improvement in functional mobility suggests a reduced risk of falls. Although motor scores in MDS-UPDRS remained stable, the improvement in TUG highlights the protocol's potential to improve axial signs. Overall, these results support the efficacy of high-intensity exercise as a non-pharmacological treatment for PD.

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P57

Combined physiotherapy and occupational therapy in people with Parkinson's disease: a pilot study

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Introduction: People with Parkinson's (PwPD) frequently engage in physiotherapy (PT) and occupational therapy (OT) to ameliorate motor symptoms and improve functional independence [1-3]. However, studies investigating the effect of PT and OT combined are lacking.

Objective: To investigate the effect of combined PT and OT in PwPD.

Methods: Nine PwPD [females: 1 (11%); age: 70.4±6.9 years; disease duration: 10.3±5.6 years; LEDD: 821±295 mg; mHY: 2.5 (2-3)] underwent a 6-week rehabilitation program consisting of one weekly 90-min home-based session (45 minutes PT and 45 minutes OT) with an occupational therapist and a physiotherapist for a total of 6 sessions. The last 3 sessions could be performed remotely through a video conference platform, depending on individual conditions and progress, to promote empowerment and self-management. PT intervention was focused on gait, balance and functional mobility whereas OT was focused on s self-care, fine motor skills, coordination and planning. Participants were evaluated at baseline (T0) and after the intervention (T1) by means of MDS Unified Parkinson's disease Rating Scale (MDS-UPDRS) parts III, the Canadian Occupational Performance Masure (COPM), the Short Physical Performance Battery (SPPB) and Parkinson's Disease Questionnaire 8 (PDQ8). Patient Global Impression of Change (PGIC) and three 7-point Likert scales were used to assess subjective improvement, satisfaction, reengagement willingness and perceived treatment usefulness. Wilcoxon test was used to compare clinical scores between T1 and T0.

Results: No patient reported adverse events during treatment. A significant improvement in SPPB ($p=0.007$, median difference: 2), COPM performance ($p=0.009$) and COPM satisfaction ($p=0.009$) was found at T1 compared to T0. No significant difference was found for the other examined variables. Eight out of 9 (89%) participants reported improvement at PGCI and were satisfied with the treatment.

Conclusions: Our preliminary results suggest that the combined treatment of PT and OT could be effective and safe in treating PwPD.

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P58

Beyond walking: how gait context and demands shape arousal and valence evoked by observation in Parkinson's disease

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Introduction: Gait disturbance is a hallmark of Parkinson's disease (PD) that can manifest as continuous (e.g., reduced gait speed) as well as episodic (e.g., freezing of gait). Challenging walking conditions might influence emotional reactions [1] and in turn worsen gait disorders [2].
Walking environments can affect emotions, with nature potentially reducing stress and enhancing positive feelings and attention compared to built environments (i.e., urban or indoor scenarios) [3].
Emotional dimensions like arousal and valence, which are linked to task performance, can be studied through observation of figures or actions [4]. PD patients usually show impaired emotional responses regarding arousal, valence, and emotion recognition compared to healthy subjects (HS) [5]

Objective: To determine how observing gait with different task demands and context affects arousal and valence in PD.

Methods: Fifty PD participants and 50 age-matched HS completed a questionnaire evaluating arousal (i.e., activation) and valence (i.e., pleasantness) of gait observation. This consisted of 36 videos showing a person walking in a built environment or nature, under low (e.g., usual walking), moderate (e.g., balance), and high (e.g., balance in a high bridge) demands.

Results: Valence ratings were similar between groups, while arousal was consistently higher in PD patients compared to HS across all task demand levels (low, moderate, and high). When comparing context, PD patients showed higher arousal in both natural and built environments.

Conclusions: Our findings on arousal might reflect the extent of motor and cognitive activation in PD patients, with an emotional component (i.e., valence) comparable to that of HS. The increased arousal of PD might reflect their awareness about their motor deficits, even in relatively simple gait conditions, such as usual walking in a built environment. This study will enhance our understanding of gait-related difficulties in PD, in relation to context and complexity.

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P59

Role of intensive aerobic exercise in Parkinson's disease: clinical and biochemical preliminary results from the multicentric PD 2.0 study

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Introduction: Exercise improves motor and non-motor functions in Parkinson's disease (PD) [1], however biochemical mechanisms underlying remain unclear.

Objective: To investigate clinical and biochemical modifications following intensive aerobic exercise in a cohort of Parkinson's Disease subjects.

Methods: We enrolled 41 PD patients (H&Y: 1–3, age: 40–80 years). Each subject underwent clinical (UPDRS I–IV, MMSE, MoCA, NMSS, TUG) and biochemical assessments (small endovescicles (sEVs) quantification, ILs, BDNF and alpha-synuclein dosage) at baseline. Afterward, a subgroup of subjects was selected for the longitudinal section of the study and randomly assigned to either PD-sport group (n=11) or PD-sedentary group (n=10). The PD-sport group underwent 3 months of high-intensity treadmill training. PD-sedentary group acted as a control group. Dopaminergic therapy was kept stable for both groups. Serial evaluation were performed at 3 (T1), 6 (T2), and 9 months (T3).

Results: At baseline sEVs blood levels correlated with UPDRS III ($r = -0.37$, $p = 0.017$), MOCA ($r = 0.4$, $p = 0.0087$), and age ($r = -0.31$, $p = 0.045$). After 3 months, PD-sport group showed a significant motor improvement (UPDRS III: 27.64±9.44 vs. 25.09±9.06, $p = 0.032$), compared to PD-sedentary group. sEVs levels were similar between baseline and T1 in both groups. A negative strong correlation of ΔsEVs levels with both disease duration ($r = -0.78$, $p = 0.0043$) and ΔUPDRS III ($r = -0.73$, $p = 0.01$) was observed in PD-sport group.

Conclusions: Intensive training reduced short-term motor impairment progression, supporting the positive effect of exercise on PD-related motor symptoms. Biochemical analysis of sEVs showed a correlation with motor and non-motor parameters in overall cohort, with higher sEVs levels in younger and less severe patients. Physical exercise did not modify sEVs levels, however, after training, a major improvement in motor impairment was accompanied by slight increase in sEVs levels. In the next months, further analysis of vesicle load and characterization will follow to deepen understanding.

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P60

Correlations between the development of axial postural abnormalities and genetically determined Parkinson's disease

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Introduction: Axial postural abnormalities (PA), namely camptocormia, antecollis and Pisa syndrome, can complicate Parkinson's disease (PD) progression, with typical onset in advanced stages and consequent quality of life impairment. Age and motor severity have been found as established predictors of PA impairment, but the role of genetics remains underexplored.

Objective: To evaluate the influence of main genetic variants in GBA, LRRK2 and SNCA on PA development in PD patients over a four-year follow-up.

Methods: We analysed 429 patients from Parkinson's Progression Markers Initiative (PPMI), including GBA, LRRK2, or SNCA pathogenic variants carriers (127 patients). PA were assessed using MDS-UPDRS III item 3.13 and compared between genetic subgroups. Risk factors for PA development were analysed with Cox-regression, adjusting for age and motor severity.

Results: General PA prevalence was 11.2% at baseline, increased to 32% at 4 years. PA incidence over four years was 23% overall, with the highest results in SNCA (30%) and GBA (29%) mutations carriers and the lowest in LRRK2-PD (17%) and idiopathic-PD (24%). No significant differences in PA prevalence were found across genetic groups ($p = 0.680$ at baseline, $p = 0.362$ at 4 years), and genetic status was not a significant predictor for PA development ($p = 0.742$), in contrast with age at baseline and MDS-UPDRS scores.

Conclusions: Although no significant genetic differences were found, trends suggest that GBA and SNCA mutations may be associated with greater levels of PA. The higher incidence of PA in SNCA-PD despite younger age, and the lower in LRRK2-PD despite older age, warrant further studies in larger datasets to explore the role of genetics in the development of these PD-related complications.

P61

Effects of a daily intensive multidisciplinary outpatient rehabilitation program on neurotrophic factors quantified in serum neural-derived extracellular vesicles (NDEVs) in individuals with Parkinson's disease: A Randomized Clinical Trial

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Introduction: Parkinson's Disease (PD) is a chronic neurodegenerative disorder characterized by motor and nonmotor symptoms. Rehabilitation, particularly aerobic exercise, enhances neuroplasticity by promoting synaptogenesis and neurogenesis through neurotrophic factors like Brain-Derived Neurotrophic Factor (BDNF), Glial cell line-Derived Neurotrophic Factor (GDNF), and Cerebral Dopamine Neurotrophic Factor (CDNF). Specifically, BDNF, produced by neurons and somatic cells, is upregulated in response to physical activity [1]. Measuring neurotrophic factors within neuronal-derived extracellular vesicles (NDEVs), which transport intracellular proteins and nucleotides, provides a more accurate reflection of neuronal responses to an intensive rehabilitation program.

Objectives: This study aimed to evaluate the effects of an intensive multidisciplinary rehabilitation program on serum NDEVs-associated neurotrophic factors.

Methods: Serum samples were collected from 70 individuals with PD (29 females, 41 males), with 36 subjects participating in a daily multidisciplinary intensive outpatient rehabilitation program (experimental group) and 34 performing home-based stretching exercises (control group). Samples were obtained at T0 (enrollment), T1 (end of rehabilitation), and T2 (3 months post-rehabilitation). NDEVs were isolated using an immunoaffinity method with L1CAM antibody, then lysed to measure BDNF, GDNF, CDNF, and TrKB concentrations by ELISA. Statistical significance ($p<0.05$) was determined using repeated measures analysis of variance.

Results: The experimental group exhibited a statistically significant increase in NDEVs-associated BDNF concentrations at T2 compared to T0, a change not observed in the control group. No significant differences were identified between the groups for other neurotrophic factors (GDNF, CDNF, or TrKB) across the study period.

Conclusions: Intensive, multidisciplinary outpatient rehabilitation significantly increased BDNF concentrations in NDEVs compared to home-based exercise. The observed increase in NDEVs-associated BDNF at three-month post-rehabilitation emphasizes the potential role of structured aerobic exercise in enhancing neuroplasticity in individuals with PD. The sustained increase in NDEVs-associated BDNF underscores the importance of incorporating such interventions into PD management strategies.

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P62

Intensive multidisciplinary, aerobic, motor and cognitive rehabilitation does not alter oligomeric α-synuclein and SNARE complex proteins in extracellular vesicles of neural origin in Parkinson's disease

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Introduction: Parkinson's Disease (PD) is characterized by the accumulation of misfolded α-Synuclein (α-Syn) protein, which disrupts synaptic function through interactions with SNARE proteins and other synaptic components. Neural-derived extracellular vesicles (NDEVs), isolated from blood, have emerged as promising biomarkers for diagnosing and monitoring neurodegenerative diseases [1]. Elevated α-Syn levels in NDEVs from PD patients have been previously reported [2]. Measuring α-Syn and SNARE complex proteins in NDEVs may provide insights into neuronal responses to intensive aerobic rehabilitation and its effects on neuropathological mechanisms, complementing functional improvements.

Objectives: This study aimed to evaluate the effects of an intensive multidisciplinary rehabilitation program on serum NDEVs-associated α-Syn and SNARE complex proteins.

Methods: Serum samples were collected from 70 PD patients (29 females, 41 males). Among these, 36 patients participated in a daily, intensive, outpatient, comprehensive multidisciplinary rehabilitation program (EXP-Group) and 34 performed home-based stretching exercises (CTRL-Group). Samples were obtained at T0 (enrollment), T1 (after 6 weeks of treatment), and T2 (at 3-month follow-up). NDEVs were isolated using an immunoaffinity method with L1CAM antibodies, lysed, and analyzed for oligomeric α-Syn and SNARE complex protein (SNAP25, VAMP2, and STX1A) concentrations via ELISA. Statistical significance ($p<0.05$) was assessed using repeated measures analysis of variance.

Results: Oligomeric α-Syn and SNARE complex protein levels (SNAP25, VAMP2, and STX1A) in NDEVs remained unchanged following intensive rehabilitative treatment. No significant differences were observed between the experimental and control groups.

Conclusions: The findings indicate that an intensive multidisciplinary rehabilitation program does not significantly alter oligomeric α-Syn or SNARE complex protein levels in serum NDEVs. While aerobic and motor-cognitive rehabilitation may provide functional benefits, these interventions do not appear to directly affect the molecular biomarkers of synaptic dysfunction and the neurotoxic oligomers of α-Syn measured in this study. Future research should investigate the long-term molecular effects of rehabilitation in PD, including studies involving larger cohorts.

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P63

Intensive rehabilitation reduces neurofilament light chain and modulates myokines in Parkinson's disease: preliminary results from a randomized clinical trial

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Background: Non-pharmacological interventions are often employed as part of integrated therapeutic approaches for managing Parkinson's disease (PD). The clinical benefits of exercise may be mediated through various mechanisms, including the synthesis of exercise-responsive myokines.
Biomarkers such as neurofilament light chain protein (NfL), a marker of neuronal damage, along with irisin, interleukin-6 (IL-6), and soluble interleukin-6 receptor (sIL-6R), myokines associated with physical activity, may offer valuable insights into the effectiveness of rehabilitation interventions.

Objectives: This study aimed to assess whether plasma concentrations of NfL and myokines, including irisin, IL-6, and sIL-6R, could serve as indicators of the long-term effects of a daily, intensive, multidisciplinary rehabilitation program in PD patients.

Methods: Blood samples were collected from 40 individuals with PD who were randomly assigned to either an intensive outpatient motor-cognitive and aerobic exercise program (experimental group, N=20) or a home-based stretching exercise regimen (control group, N=20). Samples were obtained at three time points: T0 (baseline), T1 (end of the rehabilitation program), and T2 (three months post-rehabilitation follow-up). Motor performance was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III. Plasma levels of NfL (measured via SIMOA), irisin, IL-6, sIL-6R, and gp120 (measured via ELISA immunoassay) were analyzed at T0, T1, and T2.

Results: The experimental group demonstrated a statistically significant reduction in NfL plasma concentrations compared to the control group. Additionally, IL-6R and irisin concentrations were significantly elevated at T1. Notably, changes in NfL levels showed a negative correlation with improvements in UPDRS scores.

Conclusions: These findings suggest that a daily, intensive, multidisciplinary rehabilitation program leads to a significant reduction in plasma NfL levels, indicating potential neuroprotective effects. Moreover, increases in IL-6R and irisin concentrations underscore their possible roles in mediating the benefits of exercise. These results support the utility of these biomarkers for monitoring the long-term effects of rehabilitation in PD.

P64

Impact of multidisciplinary rehabilitation on cognitive and behavioral symptoms in Parkinson's disease: preliminary results of a randomized clinical trial (RCT)

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Introduction: Parkinson's Disease (PD) is a neurodegenerative disorder characterized by motor and non-motor symptoms. Although a beneficial effect of multidisciplinary intensive training programs on People with Parkinson's Disease (PwPD) has been documented [1,2], results in literature about the entire spectrum of "non-motor symptoms" are not consistent [3].

Objective: The main objective of this project was to assess the broad effect on cognitive and behavioral symptomsof an RCT about multidisciplinary intensive treatment in an Experimental Group (EXP-Group) compared to a Control Group (CTRL-Group).

Methods: 73 randomly allocated PwPD (35CTRL/38EXP; 31F/42M; Age: 69.5±6.4; mH&Y: 1.5-3) underwent multidimensional assessment at baseline (T0), after 6 weeks of treatment (T1), and at a 3-month follow-up (T2). The EXP-Group participated in a daily-intensive-outpatient-multidisciplinary rehabilitation program, while the CTRL-Group followed a home-based self-treatment program (muscle-stretching/active mobilization exercises). In addition to measuring motor impairment, a complete neuropsychological assessment was carried out for all participants, at each timepoint.

Results: About cognitive domains, enhancements in frontal lobe functioning (assessed by the Frontal Assessment Battery -FAB-), were observed in T1 in both groups; however, only the EXP-Group maintained these improvements at T2. Concerning psycho-emotional aspects, a significant reduction in depressive symptoms, as measured by the Beck Depression Inventory (BDI), was observed exclusively in the EXP-Group at T1, with marked improvements that tended to be sustained at T2.

Conclusions: These results underlined the efficacy of a multidisciplinary rehabilitation program in improving both depressive symptoms and frontal lobe functioning compared to a home-based self-treatment program. The EXP-Group exhibited significant reductions in depressive symptoms by the end of treatment, with improvements showing a tendency to persist at follow-up. Additionally, while both groups showed enhancements in frontal lobe functioning during the intervention, only the EXP-Group sustained these cognitive benefits at the follow-up.

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P65

Parkinson's disease and Parkinsonism Family Center: a psychoeducational program for patients, families and caregivers

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Introduction: Parkinson's disease (PD) is characterized by motor and non-motor symptoms that significantly impact the quality of life of patients and their families [1]. Effective PD management requires addressing both motor and the associated non-motor challenges [2]. Patients and caregivers often face uncertainty and difficulty in adapting to the disease's chronic nature. Consequently, comprehensive informational support - including disease education, self-management strategies, and guidance on healthcare systems and available services - is crucial.

Objective: To address the need for comprehensive PD management, encompassing therapeutic, rehabilitative, psychosocial, and caregiving aspects, the Parkinson's Disease and Parkinsonism Family Center was established within the Parkinson Institute at ASST Pini-CTO, Milan, promoted by Pezzoli Foundation and ATS Milano.

Methods: This one-year pilot project aims to bridge diagnostic and treatment centers with local healthcare, administrative, and social services while providing psychoeducational interventions. These interventions include informational support, group and individual psychoeducational sessions, and peer support groups for patients, families, and caregivers. Users complete two ad hoc-designed questionnaires: one gathering expectation and another measuring satisfaction with the services received.

Results: A preliminary analysis of the data after 5 months showed that 86 users participated in the program: 35 patients and 51 caregivers (12-93 years, mean = 62.3); 34 individuals completed the intervention (12 informational sessions, 22 psychoeducational sessions). All the satisfaction questionnaires completed by patients and caregivers who attended psychoeducational sessions indicated a high satisfaction rate (mean = 4.55/5), highlighting improvements in disease knowledge, quality of life, psychological well-being, management of daily activities, interpersonal relationships, and awareness of local services.

Conclusions: We argue that psychoeducational interventions demonstrate potential for improving the well-being of both PD patients and their caregivers by enhancing coping strategies, psychological adaptation, and social support. These programs could contribute to a better quality of life and alleviate the psychological burden associated with the disease.

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P66

Upper limb rehabilitation using virtual reality vs a real-setting training in people with Parkinson's disease: a clinical and fmri study

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Introduction: Bradykinesia is a cardinal sign of Parkinson's disease (PD) and can impact upper-limb functions. People with PD (pwPD) often complain difficulties in repetitive hand movements, handwriting and use of smartphone.

Objective: To assess the efficacy of physiotherapy on upper-limb motor function and brain activity in patients with PD (pwPD) comparing virtual-reality and real-setting training.

Methods: Forty pwPD and 30 age-/sex-matched healthy controls (HC) were included. We obtained kinematic data on touchscreen gestures and handwriting through customized tests on tablet/smartphone. Subjects performed a fMRI hand-tapping task. PwPD were randomized into two groups performing 8-week rehabilitation program stimulating speed/amplitude of handwriting and tap/swipe/slide movements in a real-setting (RS-training-group) or using technological devices/virtual-reality (VR-training-group).

Results: Relative to HC, pwPD showed reduced manual dexterity and movement speed/amplitude, and reduced fMRI activity of motor-related brain areas. After rehabilitation, VR-training-group showed greater improvement in manual dexterity. Both patient groups showed improved speed/amplitude during handwriting; however, VR-training-group showed greater improvement in handwriting on tablet. Both patient groups improved in tap/swipe tasks on smartphone, particularly RS-training-group. Both patient groups showed reduced sequence effect on amplitude during finger-tapping task, with RS-training-group showing greater improvement. After training, RS-training-group showed increased activity of sensorimotor areas and reduced activity of extra-motor areas; VR-training-group showed increased activity of thalamus and parietal areas and reduced activity of caudate and temporal areas.

Conclusions: Physiotherapy can promote improvements in upper-limb function and brain functional reorganization in pwPD. Real-setting or virtual-reality trainings have some specific effects that might help tailoring the therapeutic approach, but one cannot be considered superior. Imaging results could be interpreted as a pattern of recovery in RS-training-group and of mixed compensatory/recovery mechanisms in VR-training-group.

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P67

Effects of an intensive multidisciplinary outpatient rehabilitation program versus a home-based self-treatment program in Parkinson's disease: preliminary results on patients' quality of life and functional abilities, and caregivers' burden

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Introduction: Parkinson's Disease (PD) is a progressive neurodegenerative disease that progressively affects motor function; as the disease progresses, there are repercussions on both the patient's perceived Quality of Life (QoL) and the caregiver's burden. While rehabilitation strategies are recognized as essential in managing PD motor symptoms [1,2], current literature provides limited evidence regarding the effectiveness of multidisciplinary rehabilitation programs in addressing these issues comprehensively [3].

Objective: The main objective was to assess the broad effect of multidisciplinary intensive treatment in an Experimental group (EXP-group) of People with PD (PwPD) compared to a Control group (CTRL-group) on motor impairment, functional activities, QoL, and caregivers' burden.

Methods: 73 randomly allocated PwPD (35CTRL/38EXP; 31F/42M; Age:69.5±6.4; mH&Y: 1.5-3) underwent multidimensional assessment at baseline (T0), after 6 weeks of treatment (T1), and at a 3-month follow-up (T2). EXP-Group participated in a daily, intensive, outpatient, multidisciplinary rehabilitation program, while CTRL-Group followed a home-based self-treatment program (stretching/active mobilization). For all participants, at each timepoint the following data were collected: MDS-UPDRS-III (motor impairment), PDQ-39 (QoL), CBI (caregiver's burden), and FAQ (functional activities).

Results: At T1, both groups improved PDQ-39 scores compared to T0, indicating enhanced QoL. In contrast, ΔT1-T0 in FAQ scores revealed a decline in CTRL-Group, whereas EXP-Group remained stable. Furthermore, a significant time effect was observed for CBI scores in both groups at T2.

Conclusions: This study highlights the benefits of intensive multidisciplinary rehabilitation in improving QoL, and preserving functional abilities in PwPD, as evidenced by the stability of these abilities across timepoints in the EXP-Group and the progressive decline observed in the CTRL-Group. The engagement in the program seemed to stabilize caregivers' burden since CBI's scores remained stable only for EXP-Group during the treatment while increasing at T2. These findings

emphasize the value of structured rehabilitation programs and the need for additional support for caregivers.

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P68

Spatial perception and gait adaptation deficits in Parkinson's disease: a study on programmed and exceeding-the-motor-program steps

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Introduction: Parkinson's disease (PD) is characterized by cognitive symptoms such as cognitive rigidity, executive disfunctions and visuospatial deficits [1]. These cognitive impairments affect patients' ability to estimate distances and spatial relationships [2], impairing movement control and gait stability [3].

Objective: To evaluate the characteristics of gait during the execution of programmed steps and steps exceeding-the-program in a walking task.

Methods: Patients with PD (PwPD) underwent assessments of balance (BBS) and gait and functional mobility (10MWT, TUG, FOGQ), and were asked to hypothesize the number of steps required to make a 5-meter walk and then to walk 5 meters being video-recorded. Gait kinematic parameters (number, speed, frequency, length, time, time of double support of programmed and exceeding semi-steps) were calculated through software Kinovea®. Primary outcome was Δsemi-steps (i.e., difference between the number of programmed and exceeding semi-steps). Paired t-test was used to assess differences in gait kinematic parameters between programmed and exceeding semi-steps in underestimating patients, while Pearson's r was calculated to assess correlation between Δsemi-steps with gait kinematic parameters and clinical assessments in whole sample (for all, significance was set at $p<0.05$).

Results: 8 PwPD (mean ± SD: age, 67.62 ± 8.34; PD duration, 5.8 ± 4.73; 1F) minimally compromised (mean ± SD: BBS, 43.63 ± 13; TUG, 18.32 ± 15.31) were recruited. Paired t-test revealed a significant difference only in frequency between programmed and exceeding (mean age ± SD: 1.57 ± 0.30 and 1.68 ± 0.31, respectively) semi-steps [t (3) =8752, p=0.003]. A positive and moderate (r=0.509, p<.001), negative and strong (r=-0.878, p=0.004), and positive and moderate (r=0.562, p<.001) correlation was found between Δsemi-steps and TUG, BBS and disease duration, respectively.

Conclusions: PwPD presents deficits in planning and adapting gait performances, with unplanned gait characteristics resembling festination and freezing of gait. Motor rehabilitation should focus on spatial perception and motor programming deficits.

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P69

Real-world gait training for persons with Parkinson's disease: a long-term tele-rehabilitation program

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Introduction: People with Parkinson's disease (PD) suffer from gait and balance impairments that significantly affect their independence and well-being [1,2]. Rehabilitation programs that use real-time feedback of spatiotemporal gait parameters have shown promising results in improving gait performance in people with PD [3,4], however, retention and long-term effects have not been well-established.

Objective: This study aims to assess the feasibility and the effectiveness of a long-term gait training program using a digital wearable system (Gait Tutor, GT - mHealth Technologies) that provides real-time audio biofeedback to correct or reinforce gait behaviour.

Methods: Twenty people with PD agreed to perform home-based gait training in their ON medication state for 30 minutes, 3 times/week for 9 months using GT. The GT system is a medical device consisting of three inertial wearable sensors and an Android-based smartphone with a dedicated app for real-time data processing. The system provides real-time audio feedback on selected gait and posture parameters based on the observed patterns and clinicians can remotely monitor the results of the gait workouts. We evaluated adherence, usability, and, preliminarily, efficacy.
Results: Seventeen participants (85%) completed the study. No adverse events occurred while using the system. Adherence to training was higher for persons with an intermediate disease stage (80.5%) compared to those with a more advanced disease stage (46.2%). All participants reported extremely positive scores on the questionnaire about ease of use and effectiveness (4.37±0.42). People with an

intermediate disease stage showed an improvement trend in both clinical and digital mobility outcomes, with a significant reduction in dual-task Timed Up and Go duration (p=0.01). Overall, the mean MDS-UPDRS motor score was stable.

Conclusions: For the first time, the present study shows the feasibility of long-term, real-world gait training for persons with PD, providing preliminary evidence that personalized, technology-driven rehabilitation strategies can be sustained over extended periods.

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P70

Reduced cardiorespiratory fitness in Parkinson's disease

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Background: Parkinson's disease (PD) may contribute to reduced cardiorespiratory fitness [1,2]. VO_2 max, a key indicator of cardiovascular health [3], is often diminished in PD due to disease-related factors and their impact on the body.

Methods: This study compared VO_2 max levels between 39 individuals with PD (Hoehn and Yahr stages I–III) and 33 healthy controls, matched for age, sex, comorbidities, and physical activity. VO_2 max was measured using a maximal exercise test on a cycle ergometer. Statistical analyses, including t-tests and MANOVA, were employed to identify differences between groups. In the PD group, relationships between VO_2 max, disease severity (UPDRS scores), sickness years and physical activity level (IPAQ) were examined.

Results: VO_2 max/kg/min was significantly lower in PD patients (22.7±4.6 mL/kg/min) than in controls (26.8±6.8 mL/kg/min), a 12% reduction ($p = 0.004$). This difference was consistent across sexes and age groups. Lower VO_2 max correlated with higher disease severity and longer duration but was not associated with physical activity levels, highlighting the direct impact of PD pathology on cardiorespiratory function.

Conclusion: These findings underscore the importance of addressing cardiorespiratory fitness in PD through targeted interventions. Such strategies could mitigate disease-related declines in fitness, improving overall health outcomes for this population.

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P71

Efficacy of remote occupational therapy delivery for people with Parkinson's disease dementia and related behavioral symptoms and their caregivers

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Introduction: Occupational Therapy (OT)is an effective intervention to rehabilitate and or maintain abilities and skills in people with Parkinson's Disease (PwPD) at any stage of the disease. Remote delivered OT may be effective as face-to-face therapy and easily accessible to a greater number of people, even in places where occupational therapists (OTh) are not available. PwPD with dementia often show disabling behavioral symptoms that require high levels of care, provided, in most cases, by family or informal caregivers (CG).

Objective: To evaluate the impact of a structured occupational teleassistance intervention aimed at the dyad of a person with Dementia-Parkinson's disease and a caregiver in the home context.

Methods: The program, developed involving geriatricians, psychologists, neurologists, nurses and PTh, includes a multidimensional clinical assessment and the drafting of a telecare plan. The OTh, as care manager, supported by the multidisciplinary team, interfaces with the patient and/or CG through a telemedicine platform that incorporates a series of clinical assessment tools.23 PwPD with dementia(assisted by ParkinsonCare, a multidisciplinary telecare service dedicated to PD)18M/5F; mean age 79.35 years, mean disease duration 11,13 years; modified Hoehn Yahr (HY) median 4, and 19 CG 2 M/15F; mean age 66,47 years were enrolled in this observational study. Basal evaluations showed a Barthel Index 56,82/100, IADL 1,50/8, NPI 17,18/144, DKAS 7,63/10, NPI STRESS 6,26/60, Zarit 38,19/88. The dyads received OT treatments in telemedicine with application of the principles of the COTID program. The intervention included two assessment accesses and an average of 4-5 treatment accesses and 1 follow up. Each access, carried out via videocall, is aimed at understanding and managing the BPSD by the CG.

Results: 11/23 PwPD and 10/19 CG were reevaluated after 8,7 months of treatment. PD IB: T0 62,27-T1 51,36;IADL:T0 0,82-T1 0,82;NPI:T0 17,82-T1 8,55.CG DKAS(8/10CG):T0 7,25-T1 9,25;ZARIT:T0 39,30-T1:30,90;NPI STRESS:T0 8,90-T1 5,20. All enrolled PwPD showed a reduction in NPI scores; CGs showed a reduction in burden and stress related to BPSD.

Conclusions: Remote delivered OT is effective in improving better managing of BPSD by caregivers. Videocall interventions, for training and strategies suggestions, have been effective and easily used by patients and caregivers.

P72

Functional evaluation and exercise training for people living with cerebellar ataxia: the ATAEXER trial

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Introduction: Cerebellar ataxias cause poor motor coordination, with a progressive deterioration of gait and balance control. No satisfying disease-specific treatments exists, and rehabilitation programmes are necessary.

Objective: To provide a hybrid, supervised and home-based multicomponent training intervention model for people living with cerebellar ataxia with a focus on coordination and rhythm auditory stimulation, recording changes in clinical, functional and patient-related outcomes.

Methods: Patients with mild neurodegenerative cerebellar ataxia able to walk independently, and some healthy and age-matched subjects were enrolled. Patients were assigned to an eight-week phase of usual care as control period (t0–t1) followed by an eight-week intervention phase (t1–t2). The primary outcome was the change in the walking efficiency at the preferred walking speed, secondary outcomes were the ataxia severity, muscular endurance and strength, balance control and walking ability.

Results: 7 individuals with mild cerebellar ataxia (spinocerebellar ataxia type 1=3, fragile X-associated tremor/ataxia syndrome=1, idiopathic cerebellar ataxia=3) and 9 healthy subjects completed the study. Discriminability between ataxic and healthy subjects was a characteristic of almost all measured parameters, and the whole panel of outcome category improved with the exercise programme. The walking efficiency improved significantly only after the intervention phase (0.202 at t0, 0.206 at t1 and 0.183 mL·(kg·m)-1 at t2). Walking ability during a stress-walk at fast speed and corresponding spatio-temporal parameters, as well as muscular endurance appeared most strongly associated with measures of clinical and self-reported ataxia severity (Rho=0.77 to 0.86), while static balance control and muscular strength appeared less correlated.

Conclusions: Specific, hybrid exercise training programme should be considered as a standard clinical intervention in patients with degenerative cerebellar ataxias. A set of evaluations has been recommended with focus on (i) discriminability between healthy and cerebellar ataxic individuals, (ii) association with ataxia severity and (iii) responsiveness to an exercise training programme of wearable technologies in objectively evaluating different therapeutic approaches to optimize treatment in advanced PD.

P73

Evaluating the usability of XRFog: a mixed reality platform for the treatment of freezing of gait in Parkinson's disease

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Introduction: Virtual Reality (VR) and Mixed Reality (MR) applications are effective for the treatment of Freezing of Gait (FoG) in patients with Parkinson's disease (PD) [1,2]. The computational capacity of recent VR technologies has increased significantly, with the introduction of new devices implementing both VR and MR, such as Oculus Quest 3. In this context, we developed XRFog, a digital platform for Oculus Quest 3 to support patients with PD to overcome FoG. The XRFog application offers structured exercises to stimulate mobility, improve coordination and foster body awareness in space based on traditional training (obstacle avoidance and door crossing) [3].

Objective: The aim is to carry out a usability study and test the platform in a real environment in order to evaluate the usability of XRFog by the users involved and thus improve the application.

Methods: Fourteen participants (N= 10 with PD, N=4 without PD; 6 men; age: 62.77±11.78 years) tested XRFog with the Oculus headset. Usability and tolerability were assessed using the System Usability Scale (SUS) [4] and the Virtual Reality Sickness Questionnaire (VRSQ) [5].

Results: The results of the SUS questionnaire showed a high level of usability and acceptability perceived by participants (M=82.14, SD=13.7). No significant problems related to motion sickness were reported in the VRSQV scale, demonstrating the tolerability of the platform during MR training (M= 5.95, SD=7.30).

Conclusions: XRFog represents an innovative approach that integrates MR into traditional physical therapy for movement disorders. By combining advanced technology with clinical expertise, there is the potential to reduce FoG episodes, improve patient safety and improve rehabilitation outcomes. The results will inform further improvements to the system and support its introduction into clinical practice.

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P74

Efficacy of Dance Well as a complementary treatment for Parkinson' s disease: our experience at Casa Parkinson

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Background: Physical activity based on dance is emerging as a complementary therapeutic approach to a range of Parkinson's disease (PD) symptoms, with evidences in promoting neuroprotection. Dance Well (DW) is a dance project with a multi-rehabilitative approach, which includes aerobic exercise, motor imagery, cueing techniques, proprioceptive and sensori-motor training.

Methods: We enrolled 76 PD outpatients attending Casa Parkinson, a shared project with a partnership between USL Toscana Centro and Fresco Foundation. Patients attended DW twice/week for 12 months. We assessed effects on motor performance using MDS-UPDRS part III, non motor symptoms with NMSS and aspects of well-being with PDQ-39 before (T0), and after 6 (T1) and 12 months (T2). LEDD was calculated at each visit. Data were analysed with SPSS ANOVA repeated measures.

Results: At T0, patients showed a mean age of PD onset of 66.1±1.2 years, mean LEDD 620.2±87 mg, mean MDS-UPDRS 15.2±2.1, mean NMSS 47.4±2.3, mean PDQ-39 43. Four patients were lost at follow up. At T1 and T2 we found no significant association between time and MDS-UPDRS part III, NMSS and LEDD while we found a significant association with time and PDQ-39 ($P = 0.03$).

Conclusion: Our results evidenced a significant improvement of PDQ-39 in patients treated with DW, while motor and non motor symptoms, as well as LEDD, remained stable over one year. DW is a useful complementary treatment, able to improve the quality of life and to maintain symptoms stable, as well the amount of medical therapy.

P75

Benefits of archery in PD patients: preliminary results

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Background: Parkinson's disease (PD) affects functional mobility, balance, and gait, compromising many activities of daily living. Many physical activities have already been proposed for motor and cognitive improvement in PD. However only few experiences exist about benefits of archery's activity on PD [1]. We conduce a preliminary observational study to evaluate the effects of continuous archery activity on patients diagnosed with PD.

Methods: Fifteen PD patients (14 males, 1 female, average age 66.0 years) participated in non-competitive archery for an average of 9.5 months, with a minimum of 3 months and an average disease duration of 8.7 years. To evaluate the benefits of the activity, pts were submitted to a self assessment questionnaire based on validated motor and cognitive scores [2]. Benefits were expressed by a score from 1 (low benefit) to 5 (excellent benefit). Informed consent was obtained from all the patients.

Results: The average score across 12 questions was 3.10/5, indicating significant perceived benefits. Motor improvements included movement coordination (3.35/5) and reduction in movement rigidity (2.95/5). Cognitive benefits were notably in concentration (3.50/5), socialization (4.10/5), and mood improvement (3.90/5). The overall quality of life score was 3.10/5 [3].

Conclusions: The study shows promising preliminary results, with notable cognitive and social benefits. Despite inherent biases, such as sex and age heterogeneity and varying activity duration, archery appears to be a beneficial activity for PD patients, particularly in enhancing cognitive functions and social interactions.

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P76

Therapeutic exercise for balance rehabilitation in Parkinson's disease: a systematic review with dose-response analysis

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Introduction: Balance disorders are very common and disabling symptoms in people with Parkinson's disease (PwPD) [1]. However, they are difficult to treat [2]. Solid evidences suggest that physiotherapy (PT) is an effective treatment for these symptoms [2,3], although it is not clear the most effective type and dosage of treatment [4,5].

Objective: To evaluate the benefits of PT treatments for mobility and balance in PwPD, and to define a dose-response relationship.

Methods: The literature search was conducted in PubMed/MEDLINE, Embase and Web of Science in March, 2024. Guidelines were followed for screening process [6] and methodological assessment [7]. We considered only RCTs or crossover studies assessing the effects of PT interventions [8–10] on balance in PwPD. We conducted random effects meta-analysis to assess the effects of PT on PwPD balance and meta-regression to identify dose-response predictors.

Results: From 4195 studies, 29 RCTs were included in systematic review. Only 16 studies had low overall methodological risk (55.1%). Most studies (17, 58.6%) had an active control group and provided a specific balance training (13, 44.8%) or multiple exercises (4, 13.8%). Great heterogeneity was found for duration (3 to 24 weeks), frequency (mostly 2 times a week), intensity (30 to 60 minutes) and dose (6 to 60 hours) of treatments. Specific balance training (n=662) and multiple exercises (n=136) showed a moderate pooled effect size (SMD=0.64; IC 95% 0.35-0.93 and SMD=0.60; IC 95% 0.09-1.10, respectively).
Age showed non-linear relationship with PT effect size, indicating larger effects in younger and older adults. In studies with active control group, balance improvements correlated positively with UPDRS III at baseline ($\beta = 0.0317$, $p = 0.0442$) and negatively with LEDD ($\beta = -0.0014$ $p = 0.0145$).

Conclusions: PT treatment with specific balance interventions and multiple exercises improves balance in PwPD. However, no specific intervention dose can be established due to the high heterogeneity.

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P77

Plasma NfL, GFAP and extracellular vesicles profile predicts cognitive impairment in Parkinson's disease

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Introduction: The mechanisms underlying cognitive decline in PD remain largely unclear.

Objective: We investigated the relative contribution of a selected panel of biomarkers of neurodegeneration and variants in the GBA and APOE genes in driving cognitive dysfunction in PD.

Methods: We enrolled 222 PD patients in a multicentric, cross-sectional study. The cohort was stratified in (i) 103 PD with cognitive impairment (PD-CI), including 82 with mild cognitive impairment (PD-MCI) and 21 with dementia (PDD); (ii) 119 PD with normal cognition (PD-NC). GBA sequencing was available in 216 patients (184 wild-type, 32 positive). APOE4 genotype was available in 217 patients (48 carrying ≥1 APOE4 allele; 169 negative). Plasma levels of neurofilament light chain (NfL), tau, p-tau181, Aβ1-40, Aβ1-42, α-synuclein, glial fibrillar acidic protein (GFAP), and extracellular vesicles (EVs concentration and mean size) were analyzed using SIMOA and Nanoparticle Tracking Analysis.

Results: Compared to PD-NC, PD-CI showed higher plasma levels of NfL, ptau181 and GFAP (FWER-corrected $p<0.05$). Binary Logistic Regression adjusted for age, sex, disease duration, APOE4 and GBA genotypes showed higher NfL ($p=0.009$) and GFAP ($p=0.028$) levels associated with PD-CI. Stratifying the cohort in three groups (PD-NC, PD-MCI and PDD), age-adjusted-ANCOVA showed higher Aβ1-40, Aβ1-42, NfL, p-Tau, t-Tau in PDD than PD-NC. PD-MCI showed higher NfL, p-Tau and EVs mean size compared to PD-NC. A multinomial logistics regression model adjusted for demographics and genetic variables showed higher EVs mean size ($p=0.023$) and NfL concentration ($p=0.037$) associated to PD-NC and PDD group, respectively. There were no differences in plasma biomarker profiles between GBA-PD and nonGBA-PD.

Conclusions: We identified plasma NfL, GFAP and EVs mean size as independent predictors of cognitive dysfunction in PD, independently from GBA and APOE status. The longitudinal follow-up of this well-characterized cohort holds promises in identifying novel biomarkers able to identify clusters of PD patients with distinct cognitive trajectories.

P78

Plasma neurofilament light chain and orthostatic hypotension in isolated REM Sleep Behavior Disorder: insights into α-synucleinopathies trajectories

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Introduction: Rapid-Eye-Movement (REM) sleep behavior disorder (RBD) is a recognized prodromal marker of α-synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Isolated RBD (iRBD) provides a unique population for studying early biomarkers of neurodegeneration. Among these, neurofilament light chain protein (NfL), a neuron-specific axonal marker, shows promise for tracking disease progression.

Objective: This study aims to assess plasma NfL levels in iRBD and their utility in detecting early neurodegenerative changes.

Methods: A total of 178 participants aged-matched [PD: 54 (M:39, F:15); iRBD: 54 (M:47, F:7); MSA: 16 (M:9, F:7); HC: 54 (M:34, F:20)] were enrolled and underwent comprehensive clinical evaluations at the Mondino Foundation and Univeristy Hospital of Pisa. Plasma NfL levels were measured at the Mondino Foundation using the Ella platform.

Results: Plasma NfL levels were elevated in PD and MSA groups compared to HC (PDvs.HC p=0,0045; MSAvs.HC p<0.0001). Notably, iRBD patients also exhibited significantly higher plasma NfL levels compared to HC (p = 0.0173) and lower levels compared to MSA (p = 0.0094). No significant difference was observed between PD and iRBD (p = 0.7561). Among iRBD patients, those with OH exhibited significantly higher plasma NfL levels (p=0.0385). In contrast, no significant differences were observed based on the presence of hyposmia, constipation, or cognitive impairment. Additionally, plasma NfL levels showed no correlation with MDS-UPDRS-III within the iRBD population.

Conclusions: Elevated plasma-NfL levels in iRBD reflect early axonal damage, aligning with the presence of ongoing neurodegeneration. The association between OH and higher NfL levels suggests a potential association with MSA, where autonomic dysfunction is a defining feature. This observation warrants further longitudinal studies to validate our hypothesis. Plasma NfL holds promise as a biomarker for CNS damage, offering valuable insights into the progression and differentiation of α-synucleinopathies when integrated with clinical data.

P79

Inflammation and REM Sleep Behaviour Disorder: candidate premotor biomarkers for Parkinson's disease

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Introduction: Rapid eye movement (REM) sleep behaviour disorder (RBD) is a parasomnia characterized by the loss of muscle atonia and the presence of abnormal behaviours during REM sleep. RBD is a α-synucleinopathy, and up to 66% of individuals will eventually develop Parkinson's disease (PD), Lewy body dementia, or multiple system atrophy [3,5]. Therefore, RBD patients represent an ideal cohort for studying the prodromal phase of parkinsonian disorders. In particular, inflammation is emerging as a critical factor in the pathogenesis of PD [1,2,4] and may also play a role in non-motor disturbances such as RBD.

Objective: Here, we present preliminary data from a study examining the inflammatory profile in a cohort of patients with idiopathic RBD and PD patients exhibiting RBD symptoms (PD-RBD), compared to healthy controls (HC). The study aims to identify novel immunological biomarkers, providing insights into the complex relationship between RBD and PD, with the ultimate goal of enabling earlier disease intervention and improving clinical outcomes.

Methods: A total of 70 participants (25 PD, 25 iRBD and 20 HC) were included in the study. Plasma and serum samples were collected, and inflammatory cytokines were analysed using a custom-designed panel with ELLA™ technology. Statistics was performed using non-parametric tests.

Results: Significant differences in inflammation levels were observed among the three groups, as well as between individual categories. Controls, iRBD and PD-RBD had significant differences in the distribution of IL-1b ($p=0.013$), IL-12 p70 ($p=0.003$) and IL-4 ($p=0.004$), Neurofilaments ($p=0.048$); Differences between iRBD and PD-RBD were specifically noted in IL-6 ($p = 0.036$) and neurofilament content ($p = 0.022$).

Conclusions: These findings suggest that inflammatory factors may play a role in the pathogenesis of these conditions, and are more prominent in the iRBD cohort. They may represent prodromal PD markers and potential therapeutic targets for the early or premotor phase of the disease.

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P80

Blood derived extracellular vesicles as predictors of rehabilitation recovery in Parkinson's disease

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Introduction: Extracellular Vesicles (EVs) and EV-like particles are known mediators of the trafficking of pathologic proteins associated to Parkinson's disease (PD) progression as well as of products of the oxidative damage that characterizes the disease.

Objectives: In the effort to understand the complex interplay among biomarkers, rehabilitation, and neurodegeneration, the primary aim of this study was to identify markers of neuroplasticity and brain remodelling potentially associated with the beneficial effects of an intensive motor rehabilitation program, by detecting changes in EVs isolated from the bloodstream of pwPD.

Methods: EV-like particles were isolated from the serum of 30 subjects with PD before and after an intensive rehabilitation program using a treadmill, with or without augmented virtual reality [1]. Raman spectroscopy was used to verify modifications in the biochemistry of circulating particles and proved that an intensive motor rehabilitation program can affect the molecular composition of EV-like particles in the blood of people with PD (pwPD).

Results: Analysis performed before and after 8 weeks of intensive rehabilitation demonstrated significant changes in the biomolecules associated to EV-like particles, in particular in the antioxidant content. The presence of carotenoids associated to circulating particles was proved to be informative for the profiling of pwPD at admission and prognostic of the rehabilitation recovery in a treatment-specific manner.

Conclusions: Our data support the hypothesis that EVs and EV-like particles have a dual role in PD, both in the neurodegenerative processes and in the response to rehabilitation. Besides, the Raman fingerprint and the spectral signature of carotenoids can represent measurable biomarkers of rehabilitation.

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P81

Brainstem raphe hyperechogenicity in GBA-associated Parkinson's disease: a potential indicator of non-motor symptoms

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Introduction: Parkinson's disease (PD) associated with glucocerebrosidase (GBA) mutations (PD-GBA+) often exhibits distinct clinical features compared to sporadic PD. Transcranial sonography (TCS) has proven useful in exploring these differences by assessing substantia nigra (SN) hyperechogenicity, third ventricle diameter (TVD), and brainstem raphe (BR) echogenicity. Of particular interest is the median raphe, a key structure implicated in serotonergic regulation. Changes in its echogenicity may signal underlying neurochemical alterations, including inflammation, microglial activation, or oxidative stress [1], processes that are frequently observed in PD-GBA+. These features could contribute to the distinct neuropsychiatric and autonomic symptoms [2] often reported in this subgroup of patients.

Objective: To investigate whether TCS parameters differ significantly between PD-GBA+ and PD without GBA mutations (PD-GBA-) patients and explore their potential implications for disease characterization and prognosis.

Methods: TCS was conducted on 7 PD-GBA+ patients and a comparative group of 18 PD-GBA- patients. Clinical data, including sex distribution, age of onset and disease duration, were examined to ensure group comparability. Echogenicity of the SN, TVD and BR echogenicity were assessed.

Results: Despite the small sample size, the groups were comparable. Female representation was 42.8% in PD-GBA+ and 27.7% in PD-GBA-. Mean age of onset was similar (53.8 years in PD-GBA+ vs. 53.6 years in PD-GBA-), with longer disease duration in PD-GBA+ (7.7 vs. 5.3 years). No significant differences were found in SN hyperechogenicity (left SN: 0.34 cm^2 vs. 0.24 cm^2; right SN: both 0.23 cm^2) or TVD (4.5 mm vs. 4 mm). However, BR hyperechogenicity was more frequent in PD-GBA+ (28.5% vs. 3.7%).

Conclusions: The increased prevalence of BR hyperechogenicity in PD-GBA+ may reflect neuroinflammatory or microglial processes linked to oxidative stress and neuroinflammation, hallmark features of PD-GBA. This finding suggests BR hyperechogenicity could be a marker for neuropsychiatric and autonomic dysfunctions, supporting its potential as a prognostic tool for non-motor symptoms. Further studies are needed to confirm these observations in larger cohorts and elucidate their clinical relevance for early disease characterization and management strategies.

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P82

Biocollection effort in Parkinson's disease, parkinsonism and neurodegenerative disorders: the PADUA-CESNE cohort

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Introduction: Recently, many studies have shown the potential role of fluid and tissue-based biomarkers in Parkinson's disease (PD) and neurodegenerative disorders [1-3]; further work is needed to integrate them with other clinical and instrumental data, and translating them into clinical practice.

Objective: Describe PADUA-CESNE biocollection program aimed at studying disease mechanisms and aiding in diagnosis and prognosis definition and therapy selection.

Methods: Patients referred to our center undergo a standardized assessment including neurological examination to confirm the clinical diagnosis of PD, parkinsonism or other related diseases and to classify them according to clinical features. The biocollection program includes clinical data (motor and non-motor scales, extensive neuropsychological assessment), genetic testing (NGS Illumina NextSeq550, custom gene panel targeting >150 movement disorders and dementia related genes; CNV, MLPA) to define genetic diagnosis and select patients for specific target therapy trials, skin/tissue biopsy (immunohistochemistry for detection of phosphorylated alpha-synuclein - pSyn SER129, alpha-synuclein oligomers – Clone 5G4, phosphorylated Tau protein – pTau Clone AT8, inflammatory markers, and RT-QuIC assay), to define disease pathology at a biological level, and fluid biomarkers collection (SIMOA test for serum GFAP, NFL and pTau181; chemiluminescence test for plasma pTau217 and CSF 1-42/1-40 beta-amyloid, pTau181 and total Tau; RT-QuIC assay for synuclein in serum, CSF and plasma) to monitor disease progression and prognosis [4-9]. Finally, instrumental data encompass structural and functional neuroimaging (MRI, fMRI, ^{123}I-FP-CIT SPECT, PET) and neurophysiology evaluation (HD-EEG recordings) to measure cortical connectivity.

Results: 204 serum samples, 165 plasma samples, 66 skin biopsies (22 fibroblast cultures, 22 RT-QuIC samples), 203 MRIs, 135 EEG, 400 DNA samples were collected so far from patients and healthy controls.
Conclusions: Biocollection effort is a fundamental approach to study PD and neurodegenerative disorders, obtaining cohorts with integrated multimodal data and comprehensive biomarker profiles for each patient, to improve diagnosis and personalized medicine and define prognostic features.

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P83

Genetic findings through exome sequencing in dystonia patients

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Introduction: Dystonia is a hyperkinetic movement disorder characterized by abnormal repetitive movement and/or postures [1]. Dystonia can be related to several causes. Recent studies with whole exome sequencing (WES) have shown a diagnostic yield of 20%, with higher rates in young onset, generalized and combined/complex dystonia, suggesting genetic testing only in selected patients [2].

Objectives: Evaluating diagnostic yield of genetic testing in an Italian dystonia cohort.

Methods: 100 dystonic patients (45% males, mean age at evaluation 46±19 years) were studied by means of WES, neurological examination (dystonia classification according to 2013 consensus), disease history collection and brain MRI.
Results: Childhood-onset dystonia was documented in 31% of the cohort, adult-onset in 51%; mean age at onset was 24.6±19 years, with 25% of subjects with first symptoms over age 40. Family history was positive in 53%. Dystonia distribution was focal in 19% of the cohort, segmental in 17%, multifocal in 26%, generalized in 38%. In 52% of subjects, dystonia was isolated, in 19% combined,

in 29% complex (mainly associated with intellectual disability). Myoclonus was the most frequently associated movement disorder, followed by parkinsonism. A genetic diagnosis was reached in 26% of cases, the most frequent genes being KMT2B (4 cases), VPS16 (3), GNAL (2), GCH1 (2). Diagnostic yield was higher in childhood onset (35%), generalized dystonia (39%) and complex phenotypes (41%), although a genetic cause was found also in 15% of isolated dystonia, 21% of focal dystonia and in 20% of adult-onset dystonia (8% adult-onset isolated focal dystonia). Unlike family history, brain MRI (iron deposition, basal ganglia alterations, cortical or cerebellar atrophy, leukopathy) provided significant diagnostic clues in 38% of patients with a positive genetic diagnosis.

Conclusions: WES is a powerful tool for genetic diagnosis in dystonia, with better results in complex phenotypes, young patients and suggestive alterations at brain MRI.

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P84

A novel RAB39b mutation in a family with juvenile and late-onset Parkinson's disease

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Introduction: Parkinson's disease (PD) is a neurodegenerative disorder in which genetics can play a major role, especially when in the form of pathogenic variants that are per se responsible for PD in a Mendelian fashion. Among them, the gene RAB39B on Xq28 has been described as a rare cause of early-onset PD, associated with intellectual disability and seizures (Waisman's syndrome [1,2]. Affected patients are usually males, whereas females tend to manifest a more classical parkinsonian syndrome.

Objective: To clinically and genetically describe the case of two familial members affected by PD, one of them displaying an atypical and complex clinical manifestation.

Methods: We describe a 45-year-old Caucasian male with a parkinsonian syndrome comprising a developmental delay with intellectual disability, generalised tonic-clonic seizures since the age of 2 and a parkinsonian syndrome since he was 37. Proband firstly showed good response to L-dopa therapy, but early therapy-related complications presented within three years, leading to DBS implantation. Stimulation efficacy lasted for 7 years without significant motor fluctuations. In parallel his mother presented a typical parkinsonian syndrome at the age of 75 with good response to L-dopa. Therefore, Next Generation Sequencing (NGS) genetic analysis was performed on both patients and other family members, revealing a pathogenic variant c.463C>T in RAB39B gene in the two affected members while proband's healthy brother tested negative.

Conclusions: We described a de novo heterozygous mutation in the RAB39B gene that has not yet been observed, expanding the number of described mutations in individuals with young onset PD with X-linked scheme of transmission [3] and contributing to the limited number of case reports and genetic studies in female affected subjects. The report also contributes to the description of the response of rare genetic PD patients to advanced therapies. This will help to tailor therapeutic approaches to this specific subpopulation.

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P85

Assessment of glymphatic system dysfunction in idiopathic and GBA-associated Parkinson's disease using diffusion tensor imaging-along the perivascular space (DTI-ALPS)

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Introduction: The glymphatic system is a clearance pathway for misfolded proteins such as alpha-synuclein from the brain. Its dysfunction has been suggested to play a role in the pathophysiology of Parkinson's disease (PD) [1]. Nevertheless, its impact in GBA-associated PD has not been explored yet.

Objective: To evaluate glymphatic system function using Diffusion Tensor Imaging-Along the Perivascular Space (DTI-ALPS) [2] in PD patients with (GBA-PD) and without (PD non-carriers) GBA1 gene mutations and in clinically-defined PD subgroups compared to age and sex-matched healthy controls (HC). Associations between DTI-ALPS index and clinical features were also evaluated.

Methods: Clinical and radiological data of GBA-PD (n=20), PD non-carriers (n=20) and HC (n=17) were retrospectively reviewed and DTI-ALPS index was calculated for each hemisphere. PD were further categorized according to motor phenotype and disease stage. Group comparisons were performed with non-parametric tests and adjusted with Benjamini-Hochberg method. Correlation analyses were performed between DTI-ALPS index and symptoms of motor and cognitive impairment.

Results: PD patients overall, GBA-PD, PD with postural instability gait disorder phenotype, and those with H&Y stage ≥2 showed reduced DTI-ALPS index compared to HC. In PD non-carriers, DTI-ALPS index of the hemisphere ipsilateral to the side of symptoms onset (ipsilateral DTI-ALPS) was negatively correlated with age at onset, age at evaluation, and MDS-UPDRS total score, and positively correlated with motor improvement after levodopa challenge (delta% OFF-ON MDS-UPDRS-III). GBA-PD with impaired visual memory and frontal lobe functions showed reduced ipsilateral and left hemisphere DTI-ALPS, respectively, compared to cognitively unimpaired subjects. The associations between DTI-ALPS indices and delta% OFF-ON MDS-UPDRS-III, visual memory and frontal lobe functions remained significant adjusting for age, sex and GBA1 mutation status.
Conclusion: Our data support the hypothesis that the glymphatic system is impaired in PD, with a different profile of motor and cognitive impairment between PD non-carriers and GBA-PD.

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P86

Accurate detection of clinically relevant GBA variants in Parkinson's disease using enhanced PCR and nanopore sequencing

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Introduction: Mutations in the GBA gene are associated with Gaucher disease when biallelic and are significant risk factors for Parkinson's disease when heterozygous. Accurate GBA analysis is challenging due to the presence of the highly homologous GBAP pseudogene. This study evaluates a recently developed long-read sequencing method for comprehensive GBA variant detection.

Objective: To assess the accuracy and reliability of a novel approach combining PCR enrichment, nanopore sequencing, and a machine learning model in detecting clinically relevant GBA pathogenic or likely pathogenic variants associated with Parkinson's disease.

Methods: Genomic DNA from 14 individuals diagnosed with Parkinson's disease was obtained from the CSS-Mendel Laboratory of Medical Genetics, Rome, Italy. Participants had previously undergone targeted next-generation sequencing (NGS) panel analysis, multiplex ligation-dependent probe amplification (MLPA), or GBA sequencing using long-range PCR and Sanger sequencing. Six participants carried heterozygous GBA missense variants classified as likely pathogenic/pathogenic. One participant was a compound heterozygote for a likely pathogenic variant and a variant of uncertain significance (VUS). Another participant was heterozygous for a VUS, and six participants were wild type for GBA. Long-read sequencing was performed using Oxford Nanopore Technologies (ONT) MinION flow cells on a ONT GridION device. Results were compared with those obtained by orthogonal methods (MLPA, long-range PCR/Sanger sequencing, and/or targeted NGS analyses).

Results: The PCR/nanopore assay demonstrated 100% concordance with orthogonal methods for detecting single nucleotide variants (SNVs) in GBA. The assay accurately genotyped all known GBA missense variants and identified wild-type GBA cases. Zygosity was correctly determined, including confirmation of compound heterozygosity in one case.

Conclusions: The PCR/nanopore sequencing assay reliably detects pathogenic and likely pathogenic GBA variants, as well as GBA-related Parkinson's disease risk factors, even within the challenging genomic context posed by its pseudogene. The Oxford Nanopore MinION facilitates accurate identification of missense variants and provides additional capabilities for phasing analysis. Its streamlined, single-platform workflow makes it a highly efficient research tool for comprehensive GBA variant analysis.

P87

A MAPT – related familial case of Parkinson's disease

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Introduction: Mutations in the MAPT gene encoding for tau-protein are mostly associated with neurodegenerative disorders marked by abnormally aggregated tau-protein.

Objective: We describe an Italian family carrying the MAPT p.Asn296del mutation, reporting phenotype, genetics and functional neuroimaging.

Methods: Proband was a 70-year-old man presenting with lateralized rest tremor and gait disturbances, responsive to Levo-dopa. MRI was unremarkable, whereas DAT-SPECT revealed reduced uptake in both striata (mostly right-sided), with prevalent involvement of the putamen. A diagnosis of idiopathic PD was made. One year after symptoms onset, episodic freezing of gate developed. The patient's mother showed bilateral hand tremor since 75 years of age; two siblings of hers had been diagnosed as PD. We performed a targeted next generation sequencing panel, covering PD-related and dementia-related genes. Genetic analysis for genes causing familial forms of PD were negative.

Results: A heterozygous in-frame deletion of three nucleotides (NM_005910.6: c.887_889del) in the exon 9 of MAPT gene, resulting in the deletion of the highly conserved asparagine N296 (p.Asn296del), was identified and classified as pathogenic according to the ACMG criteria. The proband's sister carried the same mutation. Analysis of MAPT gene transcription to understand how/whether the reported mutation affects exon 10 expression is ongoing.

Conclusions: The delN296 mutation lies in the sequence corresponding to the second tubulin-binding repeat of tau-protein, affecting one highly conserved asparagine residue. DelN296 changes are known to affect microtubules assembly and increase the in-vitro aggregation of recombinant tau-protein [1]. The homozygous delN296 mutation have been linked to severe dementia and early onset progressive supranuclear palsy [2]. Heterozygous individuals have an incompletely penetrant mutation and might display a phenotype resembling idiopathic PD with a late AAO, as in our cases. Indeed, in PD patients both α-synuclein and NFTs aggregations have been found [3]. Clinical monitoring of this family will provide further information.

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P88

A de novo SCN2A variant in a patient with adult-onset dystonia-parkinsonism and nigro-striatal denervation

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Introduction: Pathogenic variants in the Sodium Voltage-Gated Channel Alpha Subunit 2 (SCN2A) gene are traditionally linked to epilepsy and neurodevelopmental disorders [1]. Late-onset movement disorders associated with SCN2A mutations have not been previously described. This report presents a novel case of adult-onset dystonia-parkinsonism in a patient carrying a likely pathogenic de novo SCN2A variant.

Case Description: A 51-year-old male presented with slow, unsteady gait, frequent falls, and involuntary patterned movements of the trunk and upper limbs. He exhibited mild intellectual disability from childhood and experienced three tonic-clonic seizures, the last occurring around age 35. Neurological evaluation revealed axial and upper limb rigidity, bradykinesia, dystonic movements, and gait disturbances. Episodes of paroxysmal severe dystonia affecting all four limbs were observed, without epileptiform EEG abnormalities. Brain MRI was unremarkable. Ioflupane [123I] SPECT imaging documented moderate and mild reduced tracer uptake in the left caudate nucleus and anterior putamen, respectively. Exome sequencing identified a novel de novo missense SCN2A variant (c.973C>G, p.His325Asp), classified as likely pathogenic based on ACMG criteria (PS2, PM2, PP2).

Conclusions: This case expands the phenotypic spectrum of SCN2A-related disorders to include adult-onset dystonia-parkinsonism. We speculate that the missense variant p.His325Asp is associated with a gain of function mechanism leading to developmental-epileptic phenotype and movement disorders. Nigrostriatal pathway denervation observed in this case aligns with parkinsonism features such as bradykinesia, rigidity, and gait disturbances. The additional presence of paroxysmal dystonic episodes and minimal response to levodopa suggests alternative mechanisms linked to the SCN2A mutation. These findings underscore the importance of integrating SCN2A testing into genetic panels for movement disorders, especially in patients with a history of epilepsy or developmental delay. Further studies are necessary to elucidate the relationship between SCN2A function, the nigrostriatal system, and movement disorders.

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P89

Genetic influences on Parkinson's disease clinical manifestations: the role of number and function of different variants

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Introduction: Genetic risk factors for Parkinson's Disease (PD) range from rare, high-risk genetic mutations to highly prevalent variants with a much less defined pathogenicity. How all these variants influence clinical characteristics is currently quite unexplored.

Objective: We studied the link between genetic characteristics and clinical phenotypes of a selected population of PD patients, particularly assessing the genetic impact of more-than-one mutations in single subjects.

Methods: We collected clinical and genetic data of 143 PD patients with age at onset (AAO) ≤ 60 years or with positive familial history for parkinsonism (FH+). We investigated if the distribution of clinical characteristics differed significantly between subjects with negative test (GT-) and positive test patients categorised according to the main function(s) of each mutated gene(s). Finally, we evaluated the correlation between 12.5th percentiles and number of one-mutation and more-than-one-mutations carriers per percentile.

Results: We found no significant differences between positive and GT- patients when comparing AAO ($p = 0.872$), FH+ ($p = 0.764$) and each symptom. When considering patients divided in functional classes, we discovered in "lysosomal" class patients a higher prevalence of orthostatic hypotension ($p = 0.038$) and, in "protein synthesis" class, a higher AAO ($p = 0.012$) than in GT- subjects. We also detected a significant correlation between 12.5th percentiles' mean AAO and number of more-than-one-mutations carriers per percentile ($R = -0.796$; $p = 0.018$).

Conclusions: Based on our data, AAO and FH+ seem not related to a higher probability of obtaining a positive genetic test. We saw in "lysosomal" class mutations a higher presence of orthostatic hypotension and in "protein synthesis" subjects a higher AAO than in GT- subjects. We also observed an inverse association between AAO and chance of obtaining more than one mutation in positive genetic test results, possibly reflecting an additive role in favouring PD onset.

P90

Spatio-temporal characteristics in glucocerebrosidase mutation carriers and idiopathic patients with Parkinson's disease: comparison between groups

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Introduction: Mutations in the glucocerebrosidase gene (GBA) are the most common genetic risk factor for Parkinson's disease (PD) [1]. GBA-PD is associated with earlier onset, faster progression, and a higher non-motor burden, particularly psychiatric disorders (especially psychosis).

Objective: To compare spatiotemporal characteristics across medication states in GBA-PD and Non-Mutated (NM)-PD patients using quantitative motion analysis.

Methods: A consecutive cohort of GBA-PD patients has been paired with a cohort of consecutive NM-PD patients. Clinical assessment included the MDS-UPDRS motor subscore (part-III) and the Montreal Cognitive Assessment (MoCA). Accelerometric data were collected using an inertial sensor (G-WALK, BTS Bioengineering®) during three trials of instrumented Timed Up and Go (iTUG) and WALK (iWALK) in three conditions: off-medication (MedOFF), on-medication (MedON), and MedON with a cognitive task (DUAL TASK). Mann-Whitney and Wilcoxon tests were used for statistical analyses, with significance set at 5%. Patients included in the study are part of the FIN-RER study.

Results: Thirty-one GBA-PD (male:19; age:62 years; MDS-UPDRS III OFF: 39; MDS-UPDRS III ON: 33; MoCA: 23) and 31 NM-PD (male:19; age:62 years; MDS-UPDRS III OFF: 32; MDS-UPDRS III ON: 21; MoCA:25) patients were included. Most patients were able to perform the test in all conditions. No differences were found in spatiotemporal variables between GBA-PD and NM-PD, considering all conditions examined. A significant reduction in the normalised parameters was found in the MedON condition compared with the MedOFF ($p < 0.001$) and DUAL TASK ($p <$

0.001). On average, the effect of the DUAL TASK condition led to indices similar to those in the MedOFF condition.

Conclusions: No differences were found in spatiotemporal characteristics between GBA-PD and NM-PD. The average results recorded in MedON and MedOFF align with the literature [2]. Results during DUAL TASK suggest using attentional strategies in a tailored rehabilitation program, as indicated in the EU physiotherapy guidelines for PD [3]. Rehabilitation is strongly recommended for patients whose performance in DUAL TASK matches MedOFF levels. Dual-task walking deficits in PD, influenced by motor and cognitive impairments, can be mitigated with interventions like external cues, cognitive strategies, and dual-task gait training.

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P91

POLG-related progressive external ophthalmoplegia and dementia: a case report

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Introduction: Polymerase Gamma gene (POLG) mutations are one of the most important causes of mitochondrial impairment leading to systemic disease. Such gene is responsible for replication and proofreading activity of mitochondrial DNA, and its dysfunction leads to mitochondrial DNA depletions and deletions, thus affecting high energy-dependent tissues, especially nervous system and muscles. According to the specific variant, different and varied phenotypes may manifest as a consequence of POLG mutation [1].

Objective: here we report a case of a 49 years-old patient with subtle onset of memory deficit at the age of 46, slowly progressing up to severe and generalized cognitive impairment in two years; slowing of ocular movements, starting from first degree nystagmus to complete paralysis, accompanied cognitive deterioration, together with development of gait instability and aphasia.

Methods: We characterised the clinical picture of the patient through different approaches. He underwent a Magnetic Resonance of brain documenting generalized atrophy particularly evident on temporal lobes, and posterior periventricular gliosis. A Photon Emission Tomography with 18FDG revealed moderate hypometabolism of parietal and lateral temporal areas, mild hypometabolism in bilateral precuneus with left predominance and dorso-lateral left prefrontal area. Cerebrospinal fluid neurodegeneration biomarker analysis resulted normal; antibodies associated to paraneoplastic and autoimmune syndromes were not detected. RT-QuIC for prion protein did not confirm the diagnosis of prion disease. A Next Generation Sequencing genetic test was then performed with evidence of mutation c.3140G>A in POLG gene, which have been previously described in literature in a single case of PEO [2].

Conclusions: POLG mutations can be responsible of different neurological syndromes, sometimes combining cognitive and motor impairment in an elusive clinical picture. Detecting the molecular origin of such complex diseases may represent a fundamental diagnostic tool and could serve as the ideal target for tailored therapies.

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P92

GALC variants in adult patients with neurodegenerative diseases: results from LysoLate study

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Introduction: The GALC gene encodes galactoctosylceramidase (GALC), an enzyme that degrades sphingolipids. The alteration of GALC activity causes defects in myelination and in neuronal metabolism and accumulation of neurotoxins. Homozygous mutations in the GALC gene are associated with Krabbe disease, while heterozygous variants are linked to the development of neurodegenerative diseases.

Objective: The aim of the LysoLate study is to investigate the presence of late onset lysosomal storage diseases (LSDs) in adult patients with neurodegenerative diseases and multi-organ involvement. Moreover, we wanted to deeper the genotype-phenotype correlation. This research project is funded by Tuscany Region.

Methods: A cohort of 49 patients was selected at Parkinson Unit. Gene analysis with Next Generation Sequencing (NGS) panel including more than 64 genes involved in LSDs was conducted. For patients who tested positive for GALC variants, the enzymatic activity was screened by in vitro GALC enzyme tests.

Results: In 5 patients (10,2%) the NGS analysis identified GALC gene variants: 4 patients were heterozygous for the disease-associated c.550C>T polymorphism leading to p.(Arg184Cys), while 1 patient was heterozygous for c.956A>G variant leading to p. Tyr319Cys. At the enzyme tests a reduction of GALC activity (<18 nmoli/mg/h) was found in 3 patients. In this group, 4 patients were diagnosed with parkinsonism, while 1 patient presented movement disorders such as myoclonus, postural and telekinetic tremor and mild bradykinesia. Other neurological conditions were recurrent: neuropathy, cognitive decline, vascular leukoencephalopathy and psychiatric disorders. Moreover 1 patient presented childhood learning deficit. Abou+t multisystem involvement, recurrent clinical features have been immunological pathologies, cancer history and cardiac diseases.

Conclusions: We found in our cohort a high carrier status of Krabbe disease's gene variants indicating a possible involvement of systems linked to LSDs in the pathogenesis of neurological syndromes associated to systemic medical conditions and suggest assessing in-depth analyses of genes causing LSDs.

P93

Instrumental evaluation of the acute effect of medium-chain triglycerides oil oral intake on paroxysmal exercise-induced dyskinesia in GLUT1 deficiency syndrome: a case report

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Introduction: GLUT1 deficiency syndrome is a rare genetic metabolic disorder characterized by impaired glucose transport in the central nervous system, leading to energy failure. Clinically, it presents with a broad range of neurological manifestations, including paroxysmal exercise-induced dyskinesia (PED) [1,2]. While pharmacological treatments often show limited efficacy, ketogenic diet and medium-chain triglycerides (MCTs) appear to be effective in controlling seizures [3,4], although their efficacy in movement disorders remains under investigation [2].

Case presentation: A 29-year-old with GLUT1 deficiency syndrome diagnosed at the age of 18 underwent periodic instrumental gait analysis at our LAM-Motion Analysis Laboratory. The disease started in the childhood with atypical absence seizures, paroxysmal eye–head movements and mild learning disorders followed by paroxysmal episodes of foot-dystonia, occasionally spreading to the upper limbs, with twisting foot block and dystonic postures of the toes, lasting several minutes or hours. Triggers include exercise, fasting, emotional stress, fever, and menstruation. Management with 3:1 ketogenic diet and MCTs led to absence seizure disappearance and reduction of dystonic attacks. During the last gait assessment, a dystonic episode occurred and was resolved after MCTs oil oral intake (10 ml). Instrumental gait analysis performed before and after MCTs intake showed that joint kinematic was normal in both conditions, while the Instrumented Timed Up and Go and IWALK tests showed a relevant increase in spontaneous walking speed few minutes after MCTs assumption. The delay in plantiflexors activation, resulting in increased ankle dorsiflexion and hip and knee flexion, was amplified during gait with MCTs, where walking speed is higher.

Conclusion: In our case, MCTs intake was effective in the acute management of PED as confirmed by the instrumental gait analysis [5]. In the literature, data on the efficacy of MCTs are largely limited to epilepsy and specific neurodegenerative diseases [6]. Future research should investigate its use in GLUT1DS-associated paroxysmal movement disorders.

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P94

Interplay of GBA mutations and sex on determining depressive symptoms in Parkinson's disease

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Introduction: Depression affects 35% of Parkinson's disease (PD) patients and is closely linked to both motor and non-motor symptoms, making it one of the most significant predictors of reduced quality of life [1]. Neuropsychiatric symptoms are common in PD carriers of GBA mutations (GBA-PD) [2] although the impact of other clinical features and sex in predicting their severity remains unclear.

Objectives: To study the association between GBA mutations and depressive symptoms and their interaction with sex and other clinical factors in shaping depression outcomes.

Methods: This is a multicenter study involving 4 Italian centers. A cross-sectional analysis was conducted in 78 GBA-PD and 156 nonGBA-PD patients matched in a 1:2 ratio based on age, disease duration and MoCA scores. BDI-II scores were compared between PD groups and stratified by sex. A multivariate regression model was performed to identify predictors of depressive symptoms. Moreover, a longitudinal analysis on 57 GBA-PD and 83 nonGBA-PD patients with BDI-II scores available at 3-year follow-up was performed using a linear mixed-effects model.

Results: GBA-PD had worse BDI-II scores, with 3-times higher odds of clinically significant depression (BDI≥14) compared to nonGBA-PD. Assessing sex/genotype combined effect, depressive symptoms were significantly less prevalent in nonGBA-PD males compared to all other groups. In GBA-PD, only RBDSQ predicted depressive symptoms, whereas sex, UPDRS-IV, and MoCA emerged as predictors in nonGBA-PD. Longitudinally, GBA-PD patients showed faster progression of depressive symptoms than nonGBA-PD and these were more severe in those with clinically RBD at baseline, regardless of sex. Contrarily, sex had an impact on BDI-II scores overtime in nonGBA-PD, with females showing significantly higher scores than males.

Conclusions: GBA mutations are associated with a distinct pattern of depressive symptoms in PD, characterized by a stronger link with RBD and a faster progression of severity over time, regardless of sex differences.

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P95

The influence of age of onset in determining Parkinson's disease phenotype among GBA and non-GBA carriers

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Introduction: Mutations in the GBA1 gene are identified in 10%-15% of Parkinson's Disease (PD) patients [1,2], with carriers (PD-GBA+) showing faster symptom progression [1,3–5]. Although the influence of age at onset on the clinical course is well documented in idiopathic PD [6–8], its impact on the PD-GBA+ population remains overlooked.

Objective: To investigate whether age at PD onset influences the risk of cognitive decline in PD-GBA+ patients and compare motor and non-motor symptoms between PD-GBA+ and PD-GBA-, stratified by age of onset.

Methods: PD patients tested for GBA1 were recruited from four Italian centers. Patients were categorized as early-onset PD (<50 years), intermediate-onset PD (50–60 years), and late-onset PD (>60 years). Demographic-clinical data and scores of MDS-UPDRS, MoCA (for cognition), SCOPA-AUT (for dysautonomia), and BDI (for depression) were compared across age groups in PD-GBA+ vs PD-GBA- cohorts using ANOVA. ANCOVA assessed effects of age of onset, GBA status, and their interaction, controlling for disease duration. External validation on cognition was conducted using the same model on data obtained from the PPMI cohort.

Results: 316 PD patients were included: 80 PD-GBA+ and 236 PD-GBA-. Mean disease duration at the time of assessment was 7.34±4.32 years. Among PD-GBA+ patients, late-onset correlated with worse cognitive ($p=0.045$) and axial scores ($p=0.037$), while early-onset had more severe motor complications ($p=0.007$) and dysautonomia scores ($p=0.012$). Age of onset, but not GBA genotype, significantly affected MoCA scores ($F=6.635$; $p< 0.001$). GBA genotype independently affected MDS-UPDRS parts I and II ($F=8.334$; $p<0.001$ and $F=9.527$; $p=0.019$) and BDI scores ($F=3.601$, $p=0.002$), with consistently worse outcomes in PD-GBA+ patients. PPMI data confirmed that age at onset but not GBA genotype, significantly correlated with MoCA scores ($F=13.579$, $p<0,001$).

Conclusions: Cognitive decline in PD is primarily determined by age of onset, rather than GBA genotype. These findings underscore the importance of considering age of onset in clinical decision-making.

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P96

GBA mutations, glucocerebrosidase activity and glucosylsphingosine levels in a large cohort of patients with Parkinson's disease and atypical parkinsonisms

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Background: Mutations in the lysosomal glucocerebrosidase (GBA) gene represent the most common genetic risk factor for Parkinson's Disease (PD) [1], however its role in Atypical Parkinsonisms (AP), namely Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP) and Corticobasal Syndrome (CBS), is still unclear. Glucosylsphingosine (Lyso-Gb1), a deacylated form of glucosylceramide, is degraded by the ß-glucocerebrosidase enzyme (Gcase). Lyso-Gb1 was proved to be a highly sensitive and specific biomarker for diagnosis and monitoring of patients with Gaucher's Disease (GD) [2]. Aim of our study was to screen for GBA mutations, Gcase activity and Lyso-Gb1 levels a large cohort of PD and AP patients.

Methods: We studied 400 unrelated consecutive patients with clinical diagnosis of primary parkinsonism (PD=355; MSA=16; PSP=18; CBD=11). The entire cohort was screened with dried blood spot tests assessing GCase activity. Lyso-Gb1 dosages, and genetic sequencing for GBA-mutations were carried on 62% and 55% of PD and AP-cohort respectively. Difference in clinic-demographic characteristics between PD vs AP were further analyzed.

Results: Overall the prevalence of GBA mutations was lower in AP-cohort than in PD patients. However, in AP group, while MSA and PSP subjects did not display any mutation, two subjected in the CBS subgroup (2/11) carried a GBA mutation. As expected, forty PD-subjects displayed mutations in GBA-gene (40/220 sequenced-PD,18%). G-case activity was significantly different between groups, with parkinsonian patients showing a reduced enzymatic activity (4±1.5 vs 4.8±1.9 for PD and AP, respectively; p=0.002). A trend toward higher Lyso-GB1 levels in the PD-group was also noticed.

Conclusions: GBA dysfunction is probably relevant not only for synucleinopathies [3], and a role in CBS could be hypothesized. Furthermore, the reduced G-Case activity and the increase in Lyso-Gb1 observed in PD patients deserves further investigation, as it could represent a reliable biomarker of PD, also supporting the differential diagnosis from AP.

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P97

Early-onset Parkinson's disease associated with heterozygous PINK1 mutation: a case report

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Introduction: Early-onset Parkinson's disease (EOPD) is usually genetic in origin and may be due to homozygous mutations in the PINK1 gene. The role of heterozygous PINK1 mutations as a risk factor for EOPD remains controversial [1, 2].

Objectives: This case explores the influence of multiple factors on EOPD development in a patient with a heterozygous PINK1 mutation.

Materials and methods: A 62-year-old male presented with an 8-years history of parkinsonism. He had been diagnosed with epilepsy at age 12 and treated with valproate for 40 years. The patient's clinical presentation began with postural tremor, followed by the onset of rest tremor, mild rigidity and bradykinesia, with a progressive worsening. Urinary and cognitive disturbances, along with postural instability also emerged. Neuroimaging and genetic testing were performed.

Results: Brain magnetic resonance imaging (MRI) showed left globus pallidus fibro-calcific deposits and cortical atrophy. Dopamine transporter (DAT) imaging revealed bilateral presynaptic nigrostriatal dopaminergic system impairment, with a right-side predominance. Levodopa resulted in motor improvement and early dyskinesia. Genetic testing using a next generation sequence (NGS) panel for movement disorders identified a likely pathogenic heterozygous PINK1 variant (p.G409V). Additionally, we detected variants of uncertain clinical significance in CACNA1H (p.P1260L) and EIF4G1 (p.S988G) genes. Multiplex Ligation-dependent Probe Amplification (MLPA), chromosomal microarray and cDNA sequencing did not identify compound heterozygousity, supporting the heterozygous status of the PINK1 variant.

Conclusions: This case illustrates EOPD in a 62-year-old patient with a heterozygous PINK1 mutation, chronic valproic acid use, and an EIF4G1 variant. While the role of heterozygous PINK1 pathogenic variants in EOPD is debated, the combination of EIF4G1 variant-induced mitochondrial stress susceptibility [3] and mitochondrial stress from long-term valproate use [4] may amplify the effects of PINK1 variant. This suggests a multifactorial model for disease pathogenesis.

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P98

A novel pathogenic MAPT variant causes levodopa-responsive parkinsonism: insights into clinical, imaging, and skin biopsy features

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Introduction: Several neurological syndromes have been associated with MAPT gene variants, mostly characterized by cognitive, behavioral, and motor dysfunction. In patients with sporadic tauopathies, the α-synuclein signal is lower compared to patients with Parkinson's disease (PD) and other synucleinopathies [1].

Objective: We herein describe a family carrying a novel pathogenic variant in the MAPT gene.

Methods: Patients underwent neurological/neuropsychological evaluations, imaging, skin biopsy, and genetic analyses. Volar forearm skin biopsies containing the sweat gland were analyzed to evaluate α-synuclein oligomers and quantified as Proximity Ligation Assay (PLA) score [2]. Biopsies from six patients with sporadic PD (sPD) and six healthy controls (HC), matched for age, sex, and disease duration, were also analyzed.

Results: The index case is a 60-year-old man from Sri Lanka referring to our clinic for a 5-year history of parkinsonism and the recent emergence of motor fluctuations. The neurological examination showed asymmetric parkinsonism with no oculomotor abnormalities. The levodopa challenge test resulted in a 25.71% improvement in the UPDRS-III. Brain MRI showed hypointensity in the basal ganglia. The dopamine transporter scintigraphy imaging scintigraphy was remarkable for severe nigrostriatal denervation. The neuropsychological and behavioral evaluation showed executive function deficits, preserved global cognition, and moderate anxiety/depression. His family history was positive; therefore, one sister (age 55) and one brother (age 58) performed the same evaluations. Both patients benefited from dopaminergic therapy and similar executive dysfunctions were observed. The NGS panel, screening for major PD genes, revealed the heterozygous c.2249A>T variant in MAPT in affected family members. Skin biopsy analysis showed similar PLA scores in MAPT-mutated patients versus sPD patients (P=0.61), but significantly higher scores than HC (P=0.02).

Conclusions: This case report emphasizes the clinical heterogeneity of MAPT mutations and the role of α-synuclein pathology in genetic forms of tauopathies.

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P99

WDR45-dependent impairment of cell cycle with upregulation of the ferrous iron transporter DMT1 and concomitant increase of ferrous iron in fibroblasts from NBIA/BPAN patients

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Introduction: Mutations in WDR45 gene, coding for a beta-propeller protein, have been found in patients affected by Neurodegeneration with Brain Iron Accumulation type 5 (NBIA5 or BPAN), a rare X-linked dominant movement disorder with Non-Transferrin Bound Iron (NTBI) accumulation in the basal ganglia as common hallmark between NBIA classes [1]. The essential equilibrium of the cellular iron homeostasis with tight control of intracellular iron level and transport due to the possible damaging role in the Haber Weiss/Fenton autocatalytic reactions is highlighted, with involvement of DMT1, in NBIA/BPAN. Also, premature senescence with reduced proliferation dependent from impaired autophagy is already reported [2]. We thus investigated whether this phenotype was associated with impaired autophagy in NBIA/BPAN.

Objective: WDR45 has a role in autophagy, while the impairment of iron metabolism and cell cycle in the different NBIA/BPAN has not been currently clarified.

Methods: DMT1 and TfR protein expression, ferrous iron evaluation by Turnbull's staining, growth curve analysis of primary fibroblasts of NBIA/BPAN patients, with or without transfection of the master autophagy regulator, TFEB.

Results: We initially found the up-regulation of the ferrous iron transporter (-)IRE/Divalent Metal Transporter1 (DMT1) and down-regulation of Transferrin receptor with iron overload in the fibroblasts of two BPAN affected patients with splicing mutations 235+1G>A (BPAN1) and 517_519DVal 173 (BPAN2) [3]. Conversely, Transferrin Receptor was down-regulated in BPAN fibroblasts, while Turnbull's staining revealed the increase of intracellular ferrous iron, after starvation. A new picture is thus highlighted for the WDR45-dependent impairment of autophagy in relationship to cell cycle impairment in BPAN fibroblasts [4].

Conclusions: Further investigation will clarify the relationship between iron, autophagy and cell cycle regulation in NBIA/BPAN.

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P100

Glucocerebrosidase screening of Parkinson's disease patients unveils Gaucher disease in carriers of E326K and T369M GBA1 variants

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Introductions: The prevalence of GBA1 variants in Parkinson's disease patients is 5-20%, with a consistent observation of carriers of two variants [1], one of which is classified as risk or benign due to their association with Parkinson's but not with Gaucher disease - the most frequent lysosomal storage disorder (LSD).

Objectives: We aimed to characterize the clinical and molecular aspects of PD patients harboring biallelic GBA1 variants and low GCase activity.

Methods: A retrospective longitudinal case series was conducted. Gaucher disease cases were identified through glucocerebrosidase dosage screening. A Parkinson's disease cohort screening for Gaucher disease was performed using dried blood spot tests. Parkinson's and Gaucher disease clinical features, GBA1 mutations, glucocerebrosidase activity and glucosylsphingosine levels were assessed.

Results: Six newly diagnosed Parkinson's patients with features of Gaucher disease signs were included. Parkinson's disease patients with biallelic GBA1 mutations and reduced glucocerebrosidase activity exhibited skeletal, visceral, and hematological signs of Gaucher disease. Four out of six patients harbored the E326K or the T369M GBA1 variants in combination with a GD causing mutation 2 patients harbored other LSD variants (i.e. CLN6).

Conclusions: GBA1 variants classified as benign for Gaucher Disease (E326K, T369M) are highly represented in patients with Parkinson's disease, and may cause Gaucher Disease in subjects carrying an additional GBA1 mutation with or without other LSD variants.

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P101

Genetic background and phenotype characterization of Parkinson's disease in an italian cohort

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Introduction: Since the impending development of "gene-targeted" disease-modifying treatments [1], the identification of patients with monogenic Parkinson's disease (PD) is crucial, and clear decision-making criteria for performing genetic testing are needed.

Objective: The objective of this study is to define the genetic profile and corresponding phenotypes in an Italian cohort of PD patients (PwPD).

Methods: PwPD with PD family history (≥1 affected relative), early-onset (≤55 years [2]), and/or atypical phenotype underwent genetic testing using an NGS panel, complemented by MLPA when needed. Patients underwent comprehensive neurological examination and clinical-demographical data were collected. Genetic results were interpreted based on ACMG/AMP criteria [3]; reports with ≥1 variant were categorized as positive (with a definitive genetic diagnosis), inconclusive (with uncertain interpretation), and non-diagnostic (with genotype-phenotype mismatch or incompatibility in segregation analysis). Clinical features across groups were identified and compared statistically.

Results: A total of 132/275 (48%) PD patients' genetic reports identified ≥1 variant (for a total of 188 variants). Monogenic PD (MPD) was diagnosed in 49 patients (17.8%), with 30 (10.9%) carriers of deleterious variants in GBA1, 9 (3.3%) in PRKN, 5 (1.8%) in LRRK2. 43 reports (15.6%) remained of uncertain interpretation. MPD patients demonstrated a higher prevalence of hyposmia [p=0.025], urogenital disorders [p=0.029], and impulse control disorders related to dopaminergic therapy [p=0.012] compared to those with Non-Mutated-PD (NMPD). Compared to NMPD, GBA1-PD showed a higher prevalence of neuropsychiatric [p=0.022] and urogenital disorders [p=0.020]. Conversely, dystonia was more frequent in LRRK2-PD patients [p=0.036] than in NMPD. No significant differences in motor onset age were observed between GBA1-PD or LRRK2-PD and NMPD.

Conclusions: In our cohort, MPD accounted for 17.8% of cases, with GBA1 being the most frequently implicated gene. Phenotype may guide clinical suspicion toward specific forms of MPD, even when motor onset occurs within the typical age range for idiopathic PD.

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P102

A rare case of Parkinson's disease with SPTBN1 gene mutation and levodopa-induced segmental spinal myoclonus

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Background: A 68-year-old male with right-sided tremor-dominant Parkinson's disease (PD) and a mutation in the SPTBN1 gene c.6118C>G (p.Leu2040Val, NM_003128, esone 30) came to our outpatient clinic presenting stereotypical movements in his right lower limb. The disturbances began two years after starting levodopa therapy at a dose of levodopa/benserazide 200/50 mg t.i.d. and resolved when the medication was withheld. The movements were characterized by brief, sudden, shock-like jerks, predominantly affecting the right tibialis anterior and peroneus longus muscles. The phenomenon occurred both at rest and during activity, and was unaffected by external stimuli.

Objective: To define and characterize the movement disorder, exploring its relationship with levodopa therapy and the underlying genetic mutation.

Methods: A jerk-locked back averaging study was conducted using BrainVision Analyzer (version 2.1.0.327; Brain Products GmbH) during levodopa therapy and four days after levodopa wash-out. The muscles recorded included the peroneus longus, tibialis anterior, rectus femoris, external abdominal oblique, biceps brachii, trapezius, and orbicularis oris.

Results: Baseline recordings revealed involuntary, predominantly arrhythmic muscular bursts affecting the right tibialis anterior and peroneus longus muscles. The mean burst duration was 487 ms (range: 219–756 ms). No electrical activity on the EEG was observed to correlate with these muscular bursts. After levodopa wash-out, no identifiable muscular bursts were recorded. Both SSEP and brain-spine MRI were normal.

Conclusions: We report a rare case of levodopa-induced spinal segmental myoclonus involving the L5 myotome. While dyskinesias are a well-known side effect of levodopa therapy, levodopa-induced myoclonus is rare and has been described in only a few studies. Most cases describe cortical myoclonus, and to our knowledge, segmental spinal myoclonus has not been previously documented [1-2]. The underlying mechanism of levodopa-induced myoclonus is not yet fully understood, with most studies focusing on cortical myoclonus [3]. Our case may suggest a potential genetic contribution to the development of this phenomenon.

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P103

Sex differences in spinocerebellar ataxia type 1: clinical presentation and progression

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Background: Spinocerebellar ataxia type 1 (SCA1) is characterised by both motor and cognitive symptoms, but sex-specific differences in disease presentation and progression remain poorly understood. This study aimed to investigate the role of sex as a variable in clinical-demographic features and motor and cognitive outcomes in SCA1 patients.

Methods: We conducted a monocentric, longitudinal observational cohort study at the University Hospital of Ferrara between 2021-2024. Consecutively genetically confirmed SCA1 patients were evaluated at baseline and after 24±3 months. Assessments included comprehensive neuropsychological testing and auditory event-related potentials (aERPs). Motor function was evaluated using the Scale for Assessment and Rating of Ataxia (SARA).

Results: Sixteen SCA1 patients (9 males, seven females) were enrolled at baseline, with 10 patients (5 males, five females) completing follow-up at 24±3 months. At baseline, while most cognitive functions were preserved in both sexes, male patients showed significantly worse performance in emotion attribution tasks than females (42.8±8.5 vs 53.1±5.7, p=0.029). At follow-up, males demonstrated more pronounced cognitive decline, showing deficits in verbal fluency, visual memory recall, and emotion attribution, while females maintained normal ranges across all tests. Although both sexes showed a slight worsening in cognitive performances over time, the differences were not statistically significant. Motor impairment was more severe in males at follow-up, though not significantly (SARA: 18.8±6.8 vs 14.0±6.5, p=ns). Analysis of aERPs revealed no differences between sexes at follow-up.

Conclusion: This study suggests that sex may influence cognitive outcomes in SCA1, with male patients showing greater vulnerability to cognitive decline, particularly in emotional processing, verbal fluency, and visual memory domains aERPs did not show similar progression. These findings highlight both the importance of considering sex-specific approaches in the clinical management of SCA1 patients and the higher values of neuropsycologhical assessment compared to neurophysiological approach to reach these slight changes over time.

P104

From brain MRI to genetic examination: a case report of TUBB3 variant

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Introduction: A 57 year-old male was referred to our movement disorder clinic for mild gait ataxia and slowness of movements, with a progressive worsening over the last few years. His medical history included mild-to-moderate intellectual disability since childhood, delayed developmental milestones and ophthalmological impairment with mild strabismus, attributed to fetal distress from dystocic labor. He was also in psychiatric care for oppositional defiant disorder and under pharmacological treatment for hypothyroidism and hypercholesterolemia.

Methods: Neurologic examination revealed intellectual disability with ideomotor apraxia, bilateral pendular nystagmus in all gaze directions, minimal hypokinesia at finger tapping, bradykinetic gait with reduced pendular synkinesis, mild camptocormia, postural instability during tandem gait. FMR1 expansions and CGH array results were negative, while the results of brain MRI scans were further in-depth discussed with neuroradiologists.

Objective: Discussion with neuroradiologists, considering the clinics and brain MRI showing dysmorphic basal ganglia with caudate atrophy, asymmetric dilatation of lateral ventricles, hypogenesis of the corpus callosum, diffuse atrophy (more prominently in the brainstem and cerebellum), lead to a suspected genetic tubulinopathy. Genetic testing with Next Generation Sequencing (NGS) was performed to confirm the diagnosis.

Results: The analysis detected an uncertain significance variant (VUS) in heterozygosity at c.1057G>A in the TUBB3 gene. Although previously unreported, silico analyses suggested a pathogenic role for this variant. The TUBB3 gene is linked to complex cortical dysplasia syndrome, an autosomal dominant inherited condition, characterized by onset in early childhood, a progressively worsening course, intellectual disability, nystagmus, cortical dysgenesis with micropolygyria, hypoplasia of the corpus callosum, and dysmorphisms affecting the basal ganglia [1,2,3].

Conclusions: Collaborative efforts among neurologists and neuroradiologists enabled the identification of a long-neglected genetic diagnosis. This case underscores the importance of interdisciplinary cooperation and meticulous clinical examination together with careful MRI analysis in recognizing rare conditions, ensuring appropriate diagnosis and management.

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P105

Isolated generalized chorea in a patient with small-expanded allele spinocerebellar ataxia 17

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Introduction: Spinocerebellar ataxia type 17 (SCA17) is an autosomal dominant cerebellar ataxia caused by a polyglutamine-encoding CAG/CAA repeat expansion within the TATA box-binding protein (TBP) gene [1]. It is characterized by a markedly heterogeneous phenomenology and complex genotype–phenotype relationships. This includes decreased penetrance forms where the clinical presentation ranges from pure cerebellar ataxia to a Parkinson's disease-like phenotype [2].

Objective: We report the case of a patient carrying 41 CAG/CAA repeats in the TBP gene, presenting with isolated chorea and depressive symptoms, in order to contribute to the understanding of the phenotype heterogeneity associated with small-expanded alleles of SCA17. To date, in fact, only a few SCA17 patients with 41 CAG/CCG repeats have been reported.

Methods: We describe the clinical, neuropsychological, and neuroimaging findings of a 73-year-old patient who presented with depressive syndrome and a 10-year history of generalized hyperkinetic movements. The patient's family history was unremarkable. Neurological examination revealed choreic movements affecting the upper and lower limbs, the face and the trunk with no additional neurological signs. Blood sample analysis, brain imaging, and neuropsychological evaluation revealed normal results. Genetic analysis identified, in the TBP gene, the 41-CAG pathological allele with reduced penetrance.

Results: Our case of depressive symptoms and generalized chorea, without additional neurological features, in a patient carrying 41 CAG/CAA repeats, supports the recently proposed new clusters of repeat expansion sizes for SCA17 [1].

Conclusion: The present case report provides further insight into the small-expanded allele SCA17 associated phenotype.

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P106

A twisting diagnosis: a new case of VPS16-hyperkinetic spectrum and literature summary

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Introduction: Autosomal dominant mutations in the VPS16 gene are gaining major interest in the pathogenesis of early onset dystonia. Clinical phenotype is usually characterized by a focal onset isolated dystonia with subsequent generalization. Oromandibular and cervical presentations are described as most common sites of onset for VPS16 dystonia patients.
Many patients have been reported with combined dystonia, where myoclonus presented as the most frequent associated movement disorder. Few patients with chorea are described [1,2].

Case presentation: We present a 70 years-old patient with generalized dystonia and choreo-athetosis. Dystonia first involved the left leg at the age of 17, then spread to the upper limbs, trunk, oromandibular district and larynx. Since age 30, choreo-athetosis and marked depression were associated symptoms. In literature, 59 other patients with VPS16 dystonia are described. Writer's cramp emerges as the most frequent phenotype at onset (18/59; 30,5%), followed by cervical dystonia (14/59; 23,7%), oromandibular dystonia (7/59; 11,8%) and dysphonia (5/59; 8,5%). Meanwhile, only few cases with lower limbs onset are reported. Speech and laryngeal involvement are reported during disease course (26/59), which frequently evolves leading to segmental or generalized dystonia. Few patients experienced complex dystonia, mainly in association with myoclonus. Chorea and athetosis are described in VPS16-related phenotype, only rarely.

Conclusion: Even if cervical and oromandibular dystonia were identified as specific symptoms of VPS16 dystonia, our literature review and our patient description exemplify the variability of the disease, with limb onset and other hyperkinetic movement disorders which prompts a possible diagnosis of VPS16 dystonia.

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P107

A presentation of PDGFRB-related parkinsonism without cranial CT calcifications

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Introduction: Mutations in PDGFRB are linked to Primary Familial Brain Calcification (PFBC), a neurodegenerative disorder marked by basal ganglia calcifications [1]. Tadic et al. provided a systematic review of neuroimaging in PFBC with known gene mutations, showing calcifications on cranial computed tomography (CT) in all cases [2].

Objective: We present a 46-year-old man with young onset parkinsonism and likely pathogenic PDGFRB variants, but without CT-detected calcifications.

Methods: Symptoms began at age 39 with asymmetric resting tremor and bradykinesia, minimally responsive to dopaminergic treatment. He had also developed anxiety and gambling issues prior to dopaminergic therapy, with a family history of hearing loss (father) and late-onset Parkinson's disease (paternal grandfather).

Results: Magnetic resonance imaging was normal. Genetic testing (Next Generation Sequencing) revealed a Variant of Uncertain Significance (VUS) in PDGFRB (c.2325C>G, shared with the father); a second PDGFRB VUS (c.763G>A) and a LRRK2 VUS (c.7337G>A), both shared with the mother. Neither the patient nor his parents exhibited calcifications on cranial CT.
PDGFRB variants follow an autosomal dominant inheritance pattern with variable expressivity. The VUS PDGFRB: c.2325C>G, present in father and likely in the affected paternal grandfather, is a null variant in a gene where loss of function is a known disease mechanism, suggesting its pathogenicity. However, parkinsonism associated with PDGFRB mutations in the absence of cranial CT calcifications has never been described before [2].

Conclusions: This case could highlight a novel presentation of PDGFRB mutation-linked parkinsonism without CT calcifications, expanding the phenotypic spectrum of PDGFRB-associated disorders. Further studies are needed to clarify the pathogenicity of these variants and their clinical manifestations.

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P108

Psychometric properties and clinical correlates of the Neuropsychiatric Inventory (NPI) in progressive supranuclear palsy: data from the PSP-NET

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Background: Progressive Supranuclear Palsy (PSP) is a neurodegenerative disorder with motor, cognitive, and behavioural symptoms. However, there is a lack of specific instruments to evaluate behavioural disturbances [1].

Objective: We aim to evaluate the psychometric properties of the Neuropsychiatric Inventory (NPI) in PSP patients and explore clinical correlates of behavioural symptoms.

Methods: A cohort of 268 PSP patients, predominantly with Richardson Syndrome (80.6%), was recruited from multiple Italian Centers under the PSP-NET project supported by the Fondazione LIMPE. PSP was diagnosed using the Movement Disorder Society (MDS) criteria. Neuropsychiatric symptoms were assessed using the NPI, measuring both the frequency x severity (FxS) and caregiver distress. Reliability was tested using Cronbach's alpha, internal validity through item-total correlations, and construct validity with convergent and divergent measures, including the Frontal Behaviour Inventory (FBI), EuroQoL-5D, and Visual Analogue Scale (VAS). Clinical correlations between NPI scores and motor, cognitive, and affective symptoms were examined using Pearson's correlation and t-tests. Multiple linear regression identified predictors of caregiver distress.

Results: The NPI demonstrated strong reliability (Cronbach's alpha: FxS = 0.855, distress = 0.955) and internal validity (item-total correlations: FxS $r = 0.368$, distress $r = 0.476$, $p < 0.001$). Construct validity was confirmed by correlations between NPI FxS and the FBI ($r = 0.445$, $p < 0.001$), and EuroQoL-5D Index ($r = 0.340$, $p < 0.001$). NPI scores correlated with motor, cognitive, and affective measures. Finally, regression analysis identified NPI FxS as the strongest predictor of caregiver distress ($B = 0.778$, R^2 adjusted = 0.593, $p < 0.001$).

Conclusion: The NPI is a reliable and valid tool for evaluating neuropsychiatric symptoms in PSP, particularly in Richardson Syndrome, which represents the predominant clinical phenotype. These results highlight its value in both clinical and research contexts for addressing patient needs and alleviating caregiver burden.

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P109

Gender differences in progressive supranuclear palsy

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Introduction: Progressive Supranuclear Palsy (PSP) is a rare, rapidly progressive 4- R tauopathy characterized by ocular dysfunction, postural instability, akinesia and cognitive alterations [1]. A spoonful of studies focused on gender differences in PSP [2].

Objective: The aim of this study is to investigate gender differences in the PSPNET dataset.

Methods: Five hundred sixty-three (563) PSP patients (249 females and 314 males) diagnosed according to the Movement Disorder Society (MDS) criteria were included.
All underwent clinical, motor and cognitive evaluations at inclusion (T0) and a subgroup was re-evaluated at six and twelve months follow up (T1, T2). Data were collected from several centres throughout Italy within the PSP-NET supported by the Fondazione LIMPE.
Gender differences were evaluated with t test for continuous variables and $\chi 2$ test for categorial one.

Results: As for demographic characteristics, no significance differences were showed.
As for motor features, there were significant differences in the PSP Rating Scale (PSP-RS) total score both at T0 (p=0.016) and T1 (p=0.01). Women showed higher PSP rating scale (PSP-rs) total score than men at both baseline and follow up (p=0.016 and p=0.01, respectively). Such gender discrepancy was confirmed also for the following PSP-rs subscores: History, Limb and Gait. As for cognition, women showed lower Montreal Cognitive Assessment (MOCA) attention subdomain scores than men in at T0 (p=0.002). As for quality of life, women showed worse scores at T for PSP-Quality of life (PSP-QoL) total score (p=0.002) and its sub-domains (physical p=0.007, mental p=0.003). As for behavioural features, women showed worse scores for the Hospital Anxiety and Depression Scale (HADS) total score (p=0.003) and anxiety sub-domain (p=0.001) at T0 and T1. Accordingly, a greater percentage of women was treated with antidepressants women 18.1% vs men 15.9%, p=0.286).

Conclusions: PSP-NET data suggest that women with PSP have a worse phenotype of the disease in terms of motor, cognitive, behavioural features significantly impacting quality of life.

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P110

Moving beyond the hospital: in-depth characterization of daily life mobility in patients with atypical parkinsonian disorders

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Background: Multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) are atypical parkinsonian disorders (APD) which share rapid progression and early loss of mobility. Due to the rarity of these diseases, knowledge of gait in APD patients is limited, with no studies evaluating daily life mobility.

Objectives: To fill this gap, this manuscript comprehensively characterizes a large cohort of patients with MSA, PSP, and Parkinson's disease (PD) through clinical assessments, patient-reported outcomes (PROMs), and sensor-derived gait data.

Methods: Patients on stable medication without relevant comorbidities were included and underwent two outpatient visits for motor and cognitive assessments. An instrumented gait analysis (IGA), collecting gait data by shoe-mounted sensors, was performed during the second visit. Between visits, patients wore the same wearables during the day for one week conducting a physical activity monitoring (PAM) of their daily lives. Clinical, IGA and PAM parameters were compared across the three groups.

Results: Out of 106 patients recruited, 84 were included in the analysis (23 MSA, 20 PSP, and 41 PD). While APD patients showed a shorter disease duration than patients with PD, participants with MSA and PSP featured more severe motor impairment, as reflected by higher MDS-UPDRS III scores. They presented reduced gait velocity during IGA, with higher variability and asymmetry in most sensor parameters. In daily life, apart from a lower step count per day, APD participants showed

also less activity, lower intensity, and simpler mobility patterns. Disease-specific characteristics, differentiating MSA and PSP, were observed in both sensor and clinical parameters.

Conclusion: This work presents a comprehensive characterization of gait and mobility in patients with APD, assessed concurrently through clinical evaluations, PROMs, supervised IGA, and unsupervised PAM. The findings provide new opportunities for researchers and clinicians to gain deeper insights and a better understanding of atypical parkinsonism.

P111

A short Progressive Supranuclear Palsy Quality of Life Scale (PSP-ShoQoL): data from the PSP-NET

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Introduction: Jensen and colleagues proposed a condensed version of the Progressive Supranuclear Palsy quality of life scale (PSP-ShoQoL) as a reliable and practical tool to evaluate quality of life in PSP patients. With 12-month follow up data on a subgroup of 94 patients, the authors showed the PSP ShoQoL presented fair sensitivity to change and test-retest reliability [1].

Objectives: We present data on the PSP-ShoQoL on an independent PSP cohort, the PSP-NET supported by Fondazione LIMPE [2-3].

Methods: Four-hundred and thirteen (413) PSP patients, performed the PSP-ShoQoL, the PSP rating scale (PSP-rs), the Montreal Cognitive Assessment battery (MoCA) and the Hospital Anxiety and Depression Scale (HADS).

Results: We found a fair internal consistency for both the total score (Cronbach's alpha: 0.87) and subscores of the PSP-ShoQoL (Physical: 0.89; Mental: 0.80). It significantly correlated with the original PSP-QoL ($r=0.945$, $p<0.001$), the PSP-rs ($r=0.646$, $p<0.001$), the MoCA (-0.340, $p<0.001$) and the HADS ($r=0.602$, $p<0.001$). With 6-month follow up data available for 80 patients, we found a significant increase of both PSP-ShoQoL total score ($t=5.24$, $p<0.001$) and Physical ($t=5.45$, $p<0.001$) and Mental (-2.78, $p<0.05$) subscores. Test retest reliability was good both for PSP-ShoQoL total score (ICC= 0.78, $p<0.001$), as well as for its subscales (Physical ICC=0.80, $p<0.00$; Mental ICC= 0.68, $p<0.001$). Finally, by analyzing the Area Under the Curve (AUC), we identified a value of 34.5 as a discriminating cut off for a significant impairment of quality of patients' life measured by the PSP-ShoQoL within the PSP-NET (sensitivity: 0.97; specificity: 0.15; UC: 0.93).

Conclusions: Our results largely replicate those by Jensen et al [1]. Furthermore, we propose a cut off of 34.5 as a discriminating value for a significant impairment of quality of patients' life measured by the PSP ShoQoL.

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P112

The influence of neuropsychiatric and stress-related disorders on tremor variability in patients with essential tremor

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Introduction: Essential tremor (ET), one of the most common movement disorders, is characterized by a high clinical variability [1–4]. Several factors contribute to this variability, including non-motor symptoms such as neuropsychiatric comorbidities, which are more prevalent in ET than in general population [2,3]. Neuropsychiatric disorders, in turn, contribute to increasing stress and stress-related disorders, as well as the disease-associated social burden.

Objectives: To examine the influence of neuropsychiatric and stress-related disorders on tremor variability in patients with ET.

Methods: Thirty-five ET patients (age range: 23-83 years) underwent thorough clinical evaluation [2-4]. Also, participants were assessed through clinical scales to specifically evaluate neuropsychiatric disturbances, stress, resilience and stress-related disorders. We analyzed data using non-parametric tests. Spearman correlation coefficient served to assess possible relationships between demographic and clinical data.

Results: We observed a considerable prevalence of neuropsychiatric disorders, i.e., mood and personality disorders, in patients (37%). Compared to normative data, we also found a higher-than-normal level of perceived stress (Perceived Stress Scale scores: 15.6±6.1). Eight patients (22.9%) reported insomnia. Notably, ET patients with insomnia had higher tremor scores compared to those without insomnia ($P<0.001$). Accordingly, we observed a positive correlation between insomnia and tremor severity (p ranging from 0.01 to <0.001). No other correlations were identified between neuropsychiatric scores, perceived stress levels and tremor severity (p-values>0.05).

Conclusions: In ET, a high prevalence of neuropsychiatric disorders and elevated stress levels were observed, both of which significantly contribute to a reduced quality of life. The relationship identified between insomnia and tremor severity provides valuable pathophysiological insights, potentially pointing to shared mechanisms involving the locus coeruleus [5]. Future studies should further explore the pathophysiological roles of noradrenergic systems and the locus coeruleus in ET.

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P113

A smart tool for non expert clinicians for the dissemination of the MDS criteria for progressive supranuclear palsy

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Introduction: Progressive supranuclear palsy is a rare, rapidly progressive, neurodegenerative 4R-tauopathy, characterized by ocular motor dysfunction, postural instability, akinesia and cognitive dysfunction. While PSP Richardson's syndrome is the most common clinical phenotype, other distinct variants of the disease have been described, each featured by a specific predominant symptom. Definite diagnosis of PSP relies on neuropathological criteria. Based on the identification of four core clinical domains, the MDS-PSP criteria provide different degree of diagnostic certainty and allow the attribution of the clinical phenotype. The Multiple Allocations eXstinction (MAX) rules were conceived to establish a precise hierarchy among the phenotypes and to guide the clinician in reaching the correct diagnosis.

Objective:, Our objective was to provide a clear and straightforward framework for non-expert clinicians for the application of the MDS-PSP criteria. Such tool may be of support for the dissemination strategy of the MDS-PSP criteria and pivotal to increase awareness of this disease in the broader medical community.

Methods: All pictures and videos were extracted from the archive of the PSP outpatient clinic of the Center for Neurodegenerative Diseases at the University of Salerno, Italy. Each recording was evaluated by two movement disorder experts (MP, RE). MDS diagnostic criteria and MAX rules were used for the smartsheet creation.

Results: We propose a practical tool, including a video-guided slide-set and a smartsheet, to increase confidence in non-expert clinicians towards suspicion and diagnosis of PSP. The video-guided slide set may serve as a teaching resource for both general neurologists and practitioners, while the smartsheet may represent a valid support in attributing the degree of diagnostic certainty and phenotype based on the identified clinical features.

Conclusion: Application of our tool may improve early recognition of patients in primary and secondary care and determine a prompt referral to third level movement disorders centers for consideration in clinical trials testing disease-modifying treatments.

P114

Safety and efficacy of dual-target MRgFUS thalamotomy for dystonic tremor: preliminary observations in three patients

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Introduction: MR-guided focused ultrasound (MRgFUS) is a minimally invasive technique that uses high-intensity ultrasound to create submillimetric lesions in deep brain structures under real-time imaging. While thalamotomy targeting the ventral intermediate nucleus (VIM) has proven effective for essential tremor [1,2], its efficacy in dystonic tremor remains unclear [3]. Emerging evidence suggests that anterior targets may improve outcomes [3,4]. Based on the distinct neural networks involved, we explored targeting both the VIM and the ventralis oralis complex (VO), two key relays in the cerebello-thalamic and basal ganglia circuits.

Aim: To evaluate the safety and feasibility of dual-target MRgFUS (VIM and VO) in patients with dystonic tremor.

Methods: Initial targeting of the VIM followed standard coordinates routinely applied at our center. Due to partial tremor control, additional targeting was performed at the VO using stereotactic coordinates from the Schaltenbrand Atlas. Safety assessments included acute and delayed adverse effects, while efficacy was evaluated using tremor-specific (CRST) and functional (QUEST) scales at baseline, 1 month, and 6 months.

Results: Three patients (two women, one man; mean age 72 years) underwent dual-target MRgFUS without severe or permanent adverse events. One patient experienced transient dysarthria and mild ataxia, which resolved within one month. Variability in individual outcomes was observed. At six months, CRST (parts A+B) scores for the treated-hand showed a 52–74% reduction in tremor severity, while functional improvements were noted in CRST Part C (50–82%) and QUEST scores (45-80%).
Conclusion: Preliminary findings suggest that dual-target MRgFUS is a feasible and safe option for dystonic tremor. While efficacy is promising, the small sample size and variability emphasize the need for further research to confirm its therapeutic role.

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P115

Prospective multi-center evaluation of the MDS 'suggestive of PSP' diagnostic criteria

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Background: The recent MDS-progressive supranuclear palsy (PSP) diagnostic criteria conceptualized three clinical diagnostic certainty levels: "suggestive of PSP" for sensitive early diagnosis based on subtle clinical signs, "possible PSP" balancing sensitivity and specificity, and "probable PSP" highly specific for PSP pathology.

Objective: To prospectively validate the criteria against long-term clinical follow-up and characterize the diagnostic certainty increase over time.

Methods: Patients with "possible PSP" or "suggestive of PSP" diagnosis and clinical follow-up were recruited in two German multicentre longitudinal observational studies (ProPSP; DescribePSP). The cumulative percentage of patients longitudinally increasing diagnostic certainty was assessed over up to 2.5-years of follow-up. The sample size per arm required to detect 30% attenuated rate in diagnostic certainty increase in trials was estimated over multiple time intervals.

Results: Of 254 patients with available longitudinal data, 61 patients had low diagnostic certainty at baseline (48 suggestive of PSP; 13 possible PSP) and multiple clinical visits (median:3, range:2-4). The cumulative percentage of patients increasing diagnostic certainty progressed with follow-up duration (30.4% at 6 months, 51.7% at 1 year, 80.4% at 2.5 years). The sample size required to detect 30% reduction of diagnostic certainty increase rate within one year was 163, slightly smaller than that required using the PSP-rating-scale.
Conclusions: Most suggestive of PSP patients increased diagnostic certainty upon longitudinal follow-up, providing the first prospective multicentre validation of MDS-PSP diagnostic criteria. Our data support the design of trials tailored for these early-stage patients and suggest the PSP-rating-scale and the diagnostic certainty increase rate as potential endpoint measures.

P116

Motor and non-motor predictors for prescription of symptomatic pharmacological therapy in patients with progressive supranuclear palsy

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Introduction: Progressive Supranuclear Palsy (PSP) is an atypical parkinsonism and no effective pharmacological therapies are available to slow or prevent the progression of disease. Currently, therapeutic strategy involves symptomatic medications to improve quality of life [1].

Objective: Aim of this study is to identify motor and non-motor predictors of pharmacological treatment prescribed in a large cohort of PSP patients enrolled nationwide within Italian network PSP-NET.

Methods: 563 patients were enrolled. Disease severity was assessed using the PSP rating scale (PSPrs), cognitive impairment with the Montreal Cognitive Assessment (MoCA),behavioral disturbances with the Neuropsychiatric Inventory (NPI),mood disorders with the Hospital Anxiety and Depression Scale (HADS),quality of life with the PSPQoL. Pharmacological therapies were categorized in dopaminergic therapy, cholinesterase inhibitors and memantine, antipsychotics, antidepressants. Parametric and non-parametric tests were used to analyze differences between groups and logistic regression models to identify predictive variables for specific pharmacological treatments.

Results: Dopaminergic therapy is associated with greater disease severity ($p<0.001$), worse mood disorders ($p=0.005$), and poorer quality of life ($p=0.042$). Antidepressant therapy is primarily prescribed in women ($p<0.001$) and in patients with worse mood disorders ($p=0.022$). Dementia treatment is prescribed in patient with worse cognitive performance ($p<0.001$). Antipsychotic therapy is associated to younger age ($p=0.008$) and lower frequency of behavioural disturbances ($p<0.001$). Amantadine is associated with more severe behavioral disturbances ($p=0.038$). The identified predictors of dopaminergic therapy were older age, greater disease severity and worse affective symptoms. The identified predictors of antidepressant therapy were female gender and longer disease duration. The identified predictor of dementia treatment was worse cognitive impairment.

Conclusion: The most common therapy prescribed in PSP is dopaminergic medication. Motor and non-motor predictors for the prescription of symptomatic therapy have been identified. Antipsychotics appear to be effective in behavioral symptoms. Amantadine appears to have no effect on axial symptoms but results in worse cognitive-behavioral performance.

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P117

Sex differences in essential tremor

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Introduction: Essential tremor (ET) is one of the most common movement disorders, with a worldwide prevalence of approximately 0.9% in the general population. Sex differences in ET have been poorly explored, despite the importance of reporting disaggregated data [1].

Objective: To explore sex differences about epidemiology, age of onset, motor and non motor symptoms and prognostic factors in subjects who received a diagnosis of ET.

Methods: A review of the published evidence was performed using Pubmed with the following search terms: ["sex" OR"gender" AND "essential tremor"]. Only original articles were considered and the reference lists of the selected articles were checked for additional research not identified through the electronic search.

Results: The electronic search retrieved 392 items, of which 153 were excluded because were not focused on ET (11), did not report sex differences (115) or did not represent original research (27). Most of the studies did not report any differences in terms of prevalence/incidence of ET. However, a recent study reported a significant association between female sex and ET+, although this was not confirmed by others. Female sex was associated with an increased risk of tremor spread to the body midline (e.g., head and/or voice). Additionally, women with ET have been reported to manifest with more social anxiety and embarassement than men. Finally, one study evidenced that females with ET were less likely than males to receive advanced treatments such as Deep Brain Stimulation.

Conclusions: There are some clinical aspects of Essential Tremor in which sex differences exist. This can lay the foundation for investigating the biological mechanisms underlying this difference, for correct counseling and for achieving a tailored therapy for patients. Moreover, there seems to be a sex-related divide in terms of access to treatment that needs to be mitigated.

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P118

The management of iatrogenic parkinsonism due to neuroleptics in intellectual disability

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Introduction: The use of neuroleptics is widespread in intellectual disability; these are long-term therapies which often generate side effects [1]. The reduction/suspension of antipsychotic pharmacotherapies in people with intellectual disability improves the iatrogenic effects on movement but frequently generates increased behavioural deterioration [2]. The use of integrated interventions represents an opportunity to improve quality of life in patients with intellectual disabilities [3].

Objective: The aim of a pilot study, conductedon patients with intellectual disability, was to ascertain the effect of an integrated intervention protocol involving, in addition to drug treatment, physiotherapy, occupational therapy and behaviourist psycho-educational interventions on: a) the dosage of neuroleptics, b) iatrogenic parkinsonism c) the behavioural aspect.

Method: A sample of 20 patients suffering from intellectual disability, admitted to an extensive managed by the Alteya social cooperative, under treatment with olanzapine for more than 15 years, suffering iatrogenic parkinsonism, was selected. The UPDRS III was used to estimate motor disturbances and a diary of dysfunctional behaviour episodes to assess patients. The 12-month evaluation was carried out at time 0 (exclusively pharmacological treatment) and time 1 (integrated treatment). The average daily dosages of antipsychotics taken by the sample, the average number of behavioural episodes presented by the subjects over the course of a week and the sample's average scores on the UPDRS III were calculated.

Result: Comparison of the mean scores for the two types of intervention indicate that with the integrated intervention it was possible to reduce the mean daily dosage of olanzapine by 2.5 mg without incurring an increase in behavioural episodes (T0 27; T1 24). The mean score of the sample at UPDRS III went from 33 (T0) to 31 (T1).

Conclusions: What emerged from this smallscale study indicates the feasibility of a subsequent study to be conducted on a larger sample.

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P119

Neuropalliative care in atypical parkinsonism, a novel approach of care

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Introduction: Neurological diseases cause physical, psychosocial and existential suffering since the diagnosis. Recent studies suggest that Palliative Care (PC) improve patient's and caregiver's outcome in several neurological disorders. [1] In 2024 the Italian Society of Palliative Care and Neurological Society collaborated to identify the triggers for referral neurodegenerative diseases to specialized palliative care. For parkinsonisms the task force considered only the Parkinson Disease (PD) but Multiple System Atrophy (MSA) or Progressive Supranuclear Palsy (PSP) have different peculiarities and progression from PD, so its could be considered separately.

Objective: Considering the work of task force in PD and the lack of evidence in atypical ones, we decided to evaluate outpatients and caregiver needs for home-based neuropalliative care.

Methods: In 2024 we considered the patients with atypical parkinsonism, selected by referring neurologists, in outpatient setting with neurological, palliative and social needs evaluation. After evaluation for each patient, we've proposed different specifical service: neuropalliative home care, non-specialized home based care, outpatients setting. According to PC we discuss with all patients the Advance Care Planning (ACP) to reduce the hospitalizations and support end of life care.

Results: We evaluated in outpatient setting 18 patients with atypical parkinsonism, 4 with MSA and 14 with PSP; 7 female and 11 males. Nine of them were referred to neurological PC (3 MSA and 6 PSP), the mean of age of symptoms was 60,8 ± 8,4 years, the age at time of clinical evaluation was 76,4 ± 6,4 years.

Conclusions: We want to demonstrate that early specialized PC are essential to patient with extrapyramidal disorders, particularly in atypical parkinsonism, which need a neuropalliative team for complex care to reduce inappropriate hospitalizations and improve Quality of life. Furthermore, PC approach contemplates the ACP that permit to personalize treatments.

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P120

Somatosensory temporal discrimination threshold (STDT): a key marker for differentiating tremor syndromes

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Introduction: Tremor is the most common and highly disabling movement disorder. Differentiating tremor syndromes, including essential tremor (ET), dystonic tremor (DT), and task-specific tremor (TST), is clinically challenging due to overlapping features and incomplete understanding of their underlying mechanisms [1] Somatosensory temporal discrimination threshold (STDT) has emerged as a potentially valuable neurophysiological diagnostic marker for dystonia, as it reflects altered sensory-motor processing [2].

Objective: This study aimed to evaluate the diagnostic utility of STDT in distinguishing ET, DT, and TST.

Methods: A total of 24 patients were recruited and allocated into ET, DT, or TST groups. Each participant underwent comprehensive clinical examinations and neurophysiological testing, with STDT assessed using standardized protocols. Statistical comparisons were performed to identify significant differences across the three groups.

Results: STDT proved to be a distinguishing marker, with markedly higher thresholds in TST (183.33 ± 49.80 ms) and DT (169.63 ± 51.46 ms) compared to ET (104.81 ± 36.86 ms). These findings suggest that DT and TST exhibit greater deficits in sensory processing, aligning with their distinct neurophysiological patterns.

Conclusions: Our data underscore the potential of STDT as a robust tool for differentiating tremor syndromes. Moreover an elevated STDT observed in task-specific tremor (TST) discriminates a dystonic component of this type of tremor, not present in essential tremor (ET). Future investigations should include larger cohorts and expand neurophysiological protocols to validate these preliminary findings. Integrating STDT into routine clinical evaluations may enhance diagnostic precision, with more targeted therapeutic interventions for patients with tremor disorders.

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P121

An "atypical" case of levodopa-responsive parkinsonism related to SPG7 gene variant

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Introduction: SPG7 mutation cohorts show mostly AR pure spastic paraplegias phenotypes with only a small proportion exhibiting complex forms of disease, combining spasticity with ataxia and parkinsonism [1,2]. A dominant/heterozygous mode of inheritance has also been reported among PD patients [1].

Objective: We describe the case of a 63-years old man presenting with a form of levo-dopa responsive asymmetrical parkinsonism, associated with atypical oculomotor signs, carrying a SPG7 gene mutation.

Methods: Patient's symptoms started at 59 with bradykinesia and rigidity of the left limbs, and tremor of the left arm. He reported mood disorders (depression and loss of initiative) and subjective memory deficits.
The patient displayed bilateral eyelid ptosis present since birth, also described in other family members, mild saccadization of horizontal gaze movements and upward gaze paresis.
Patient's family history included maternal uncle affected by Late Onset Alzheimer's Disease.
Patient underwent: cerebral 3T MRI with a previous left thalamic hematoma and symmetric cortical atrophy; [123I] ioflupane SPECT imaging showed bilateral symmetric hypometabolism in putamen; neuropsychological tests and cerebral F- FDG PET scan were normal.
Levodopa/Benserazide was prescribed starting from a daily dosage of 100 mg tid with good response but with early appearance of motor complications (ballistic-athetosic involuntary movements of the right upper limb), so it was reduced to 150 mg daily which were better tolerated.
A comprehensive genetic analysis of this case was performed using a targeted next generation sequencing (NGS) panel covering PD and other movement disorders-related genes. MLPA for PD genes and GBA was also performed.

Results: We identified in heterozygous state the c.1529C>T variant (p.Ala510Val), in exon 11 of SPG7 gene (NM_003119.2) classified as probably pathogenetic according ACMG criteria.

Conclusion: SPG7 is expressed in the cerebellum and brainstem and its mutations impair mtDNA maintenance [3]. SPG7 c.1529C>T was the only variant identified on the patient and it was frequently observed among PD patients in genetic databases, suggesting SPG7 could be a novel candidate gene/risk factor for PD [4].

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P122

Mitochondrial dysfunction in a patient displaying symptoms of atypical parkinsonism and α-synuclein pathology at skin biopsy

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Introduction: Genetic mutations in the mitochondrial genome may manifest with a variety of clinical phenotypes, including features consistent with central and peripheral nervous system involvement. This complexity often leads to a diagnostic delay, with mitochondrial diseases being frequently overlooked.

Case presentation: We report the case of a 48-years-old man showing non-investigated intellectual disability, who developed parkinsonism at age 44 with rigidity in the lower limbs, walking difficulties, general slowness and dysautonomic symptoms (hyperhidrosis, fatigue, bowel abnormalities). DAT Scan showed reduced tracer uptake in the striatum, and the patient was started on levodopa, with partial motor benefit but worsening of autonomic dysfunction and evidence of orthostatic hypotension. Hypoactive tendon reflexes were observed, with neurophysiological studies consistent with an axonal neuropathy in the lower limbs. Due to impaired visual acuity (previously attributed to glaucoma), the patient underwent visual evoked potentials, showing right optic nerve neuropathy. Cardiac scintigraphy disclosed abnormal MIBG metabolism. Skin biopsy was also performed, showing a low burden of phosphorylated α-synuclein (p-syn).
In light of the complex clinical features, the patient and his parents underwent whole-exome sequencing and mitochondrial DNA sequencing, showing a mutation in the mitochondrial MT-ATP6 gene with 98% heteroplasmy (89937T>G).

Conclusions: Parkinsonism with dysautonomic features and p-syn deposition on skin biopsy can be the presenting feature of rare mitochondrial diseases; the association with peripheral neuropathy, visual symptoms, fatigue and undiagnosed mild intellectual disability should suggest a mitochondrial genome alteration.

P123

Seven-year follow-up of clinical and neurophysiological features in essential tremor

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Introduction: Essential Tremor (ET) is a slowly progressive condition, as observed in a limited number of previous longitudinal studies [1,2].

Objective: To comprehensively and prospectively follow-up a sample of ET patients to identify key trends in disease progression over a period of approximately 7 years.

Methods: We assessed 21 ET patients (11 males) diagnosed with ET/ET-plus at three follow-up points (T0, T1, T2) over a span of 80 months. Evaluations included clinical scales (Fahn-Tolosa-Marin Tremor Rating Scale - FTMTRS, MDS-UPDRS Part III, MMSE) and kinematic movement analysis of postural and resting tremor amplitude, as well as finger-tapping velocity. Statistical analyses included repeated-measures ANOVA and Spearman correlation analysis.

Results: FTMTRS and UPDRS III scores significantly increased over time from T0 to both T1 and T2, reflecting worsening tremor severity (both $p<0.001$), with 80.95% of subjects showing an increase in tremor scores. Subjects with higher FTMTRS scores at baseline exhibited worse cognitive scores (Rho=-0.65, p=0.002). MMSE scores remained stable, but the number of ET patients with scores of 25 or lower increased from one (4.76%) to four (19.05%). Kinematic analysis showed variability in data related to tremor (postural, kinetic, and action tremor) and finger-tapping velocity over time. The data, however, demonstrate that progression can highly vary in ET, with some patients deteriorating rapidly in the first few years after diagnosis, while others experience slower, more gradual progression in the early stages, followed by more pronounced decline in the later stages of the disease.

Conclusions: This is the first prospective longitudinal study to include neurophysiological data, based on the largest follow-up to date. Overall, the study results indicate that ET patients are highly heterogeneous in the progression of their condition over time. Further investigation is needed to deepen our understanding of clinical and/or neurophysiological predictors of ET progression over time.

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P124

Genetic landscape of primary dystonic syndromes: insights from next-generation sequencing in a cohort of 65 patients

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Introduction: Dystonia represents the manifestation of several pathogenetic entities and can occur isolated or combined [1]. TOR1A (DYT1) variants were first recognized as the hereditary cause of primary dystonia. However, the recent optimization of gene sequencing procedures allowed to identify many other genes involved in the pathogenesis of dystonic syndromes [2].

Objective: Our aim is to analyze the prevalence of genetic variants associated with dystonic syndromes in a group of selected patients and define their clinical phenotype.

Methods: We studied 65 patients with primary dystonic syndrome, analyzing their Next-Generation Sequencing (NGS) dystonia panel to identify mutations and assess their association with compatible clinical phenotypes.

Results: NGS panels of 26 of these patients (40%) were negative. In 39 patients (60%) variants were detected. A total of 62 variants were reported, among which 13 were classified as pathogenetic/likely pathogenetic, and 49 as variants of unknown significance (VUS). Six patients received a genetic diagnosis (ATM, PRRT2, TH, GNAL, GLB1 and SGCE). Four patients presented VUS in ANO3, CIZ1, TOR1A, ATP7B and had clinical signs and a segregation of the variants compatible with the related clinical phenotype. The remaining twenty-nine patients had inconclusive results.

Conclusions: In our series, a definitive genetic diagnosis was achieved in 9% of patients, with a probable diagnosis in 6%. Although the diagnostic yield was low, it enabled the identification of genetic syndromes with atypical phenotypes, emphasizing the importance of genetic counseling. The most common findings were Variants of Uncertain Significance (VUS), presenting challenges in interpretation and family counseling. The accessibility of NGS panels enhances diagnostic precision, benefiting patients through improved treatment and counseling. However, it is crucial to provide appropriate pre-test counseling, preparing patients for the possibility of inconclusive results.

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P125

Gait and balance impairment in cervical dystonia: the role of tremor, pain, and botulinum toxin

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Introduction: Cervical dystonia (CD) is often associated with gait and balance impairments, which increase disease burden [1-5]. A potential beneficial effect of Botulinum Neurotoxin (BoNT) treatment on these symptoms has been postulated; however, the role of clinical factors influencing gait and balance impairment in CD, such as head tremor (HT) and pain, remain poorly understood.

Methods: Objective gait and balance quantitative parameters were collected using wearable inertial sensors in CD patients before and one month after BoNT injections, together with assessments of dystonia severity, pain and quality of life using validated clinical scales. Healthy controls (HC) underwent the same analysis for comparison. Multivariate linear regression analyses were used to evaluate the association between gait and balance characteristics at baseline and clinical outcomes. The role of HT as a potential influencing factor was also investigated.

Results: 21 CD patients were enrolled, including 9 patients with HT (CD-HT+). CD patients showed significantly reduced gait speed (p=0.013) and stride length (p=0.008) compared to HC. Stride length variability was the strongest predictor of subjective gait complaints (R=0.396, p=0.035), while pain severity was the strongest predictive factor of stride length variability (R=0.391, p=0.038). After one month of BoNT treatment, significant improvements in gait asymmetry were observed. CD-HT+ patients exhibited greater postural sway (p=0.028), and prolonged double support time (p=0.034) compared to HC, with improvements in postural sway following BoNT treatment (p=0.011). After correcting for confounders, HT was confirmed as an independent predictor of sway variability in the entire cohort of CD patients (r=0.338, p=0.030).

Conclusions: While confirming the presence of slight gait abnormalities in CD patients, this study demonstrated that: 1) stride length variability is a potential predictor of clinical impairment in CD, correlating with subjective gait complaints and pain severity; and 2) HT significantly contributes to gait and balance impairment in CD.

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P126

40-year evolution of blepharospasm, orofacial dystonia, and hemifacial spasm: a study of botulinum toxin-treated patients

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Introduction: Blepharospasm (BS), Orofacial dystonia (OFD), and Hemifacial spasm (HFS) are chronic, progressive facial disorders significantly affecting quality of life [1-3]. Despite differing pathophysiology, all respond effectively to botulinum neurotoxin (BoNT) [3,4]. This study evaluates differences in disease progression through quantitative changes in BoNT treatment during a very long-term observation period.

Methods: Data from 183 patients (BS=60; OFD=13; HFS=110) undergoing periodic BoNT treatment were retrospectively analyzed. Comparisons were made across groups regarding demographic and clinical data, proportion of treatment sessions with stable/increasing/decreasing dosage, number of injection sites, toxin type changes, mean BoNT dosage over decades and adverse events. A linear mixed-effects model including disease, time, clinical and demographic data, was used to compare mean annual doses among groups.

Results: No significant differences were found in sex, age, and age at disease onset between BS, OFD, and HFS. Analyzing data from 5925 BoNT treatment sessions, we observed significant increase in the mean BoNT dose over decades for all groups. BS patients had the highest proportion of stable BoNT treatment (70.6%, $p<0.001$), significantly differing from HFS patients ($p=0.001$). OFD showed the highest discontinuation rate (64.3%, $p=0.015$). Time, disease, and treatment duration were all factors significantly influencing BoNT dosage changes ($p<0.001$). Adverse events occurred in 30.6% of patients, with ptosis being the most common.

Conclusions: Our study highlights long-term differences among BS, OFD, and HFS in the trajectory of BoNT treatment, emphasizing the influence of both time and underlying condition on dosage variability needed for effective symptom control. The observed variability suggests that adjusting protocols based on disease duration or treatment phase may enhance BoNT efficacy. Moreover, our findings suggest that disease severity of these conditions continues to increase over decades, very long-term BoNT treatment causes habituation, or both. These insights support a more informed and individualized therapeutic approach for managing each condition.

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P127

AOPEP, a potential novel link between myoclonus and dystonia: a case report and literature review

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Introduction: Hyperkinetic movement disorders can manifest alone or as part of complex phenotypes. Myoclonus classically presents as a brief non-rhythmic jerk movement. Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal postures or movements. The combination of myoclonus and dystonia could represent a diagnostic challenge for movement disorders expert recognizing either genetic or acquired etiologies.

Objective: To describe a case of juvenile onset generalized myoclonus associated with upper limb dystonia associated with a heterozygous pathogenic variant in AOPEP.

Methods: An 18-year-old male has been followed at our outpatients clinic for a six-years history of rapid and brief movement involving the head, upper and lower limbs. Neurological examination revealed generalized myoclonus associated with distonic features of upper limb.

Results: Family and physiological history were unremarkable. Laboratory findings were normal. Brain MRI revealed left middle-inferior frontal polymicrogyria, partial empty sella, and a pseudonodular thickening of the pituitary stalk of uncertain significance (e.g., hamartoma). Whole-exome sequencing identified a heterozygous c.703C>T variant in AOPEP. To our knowledge, this is the first reported case of generalized myoclonus with very mild dystonic features associated with a monoallelic AOPEP variant.

Conclusions: AOPEP encodes aminopeptidase O, a zinc-binding metalloprotease involved in protein turnover, neuroprotection, and synaptic plasticity. Pathogenic variants in AOPEP, particularly in biallelic form, have been associated with progressive limb dystonia [1]. However, no cases have been reported with monoallelic variants. [2]. In this case the prominent motor features (myoclonus rather than dystonia) may suggest a partial retention of enzymatic function. Further studies are needed to clarify the link between AOPEP and epilepsy or monoallelic dystonia.

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P128

Evaluation of botulinum neurotoxin treatment in a cohort of patients with dystonic head tremor: quantitative analysis with gyroscope

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Background: Dystonic head tremor (DHT) [1] is a key feature of cervical dystonia (CD), presenting in about half of the patients and typically manifesting as a no-no or yes-yes tremor. [2] Botulinum Neurotoxin (BoNT-A) treatment is a first-line therapy for CD, but DHT can negatively impact treatment response. Gyroscopes are used to assess tremor quantitatively and to evaluate effects on tremor characteristics. [3]

Methods: We evaluated patients with DHT attending the botulinum toxin clinic (IRCCS Fondazione Don Gnocchi) from January to July 2024. Clinical and instrumented evaluations were performed before and after US and EMG guided BoNT-A at T0 and T1 (4-6 weeks post-treatment). TWSTRS, Tsui scale, Tremor Rating Scale (TRS) Head score, CDQ-24, HADS, subjective disability (VAS-disability, PGIC) assessed clinical impact. Gyroscope recordings, focused on muscles targeting, were obtained during different tasks: rest with eyes closed/opened, seated with outstretched arms, standing with eyes closed/opened. Data collected included: frequency, power spectral density (PSD), mean rotation (MR), maximum burst rotation (MBR), standard deviation and interquartile range of the inter-cycle variation of frequency (ICVFstd, ICVFiqr). Statistical analysis was made using Wilcoxon signed-rank test.

Results: Seventeen of nineteen patients with DHT recruited, completed the assessment. Significant improvements were observed in TWSTRS, Tsui scale, TRS, CDQ-24, and VAS disability ($p<0.05$). Gyroscope data showed significant reductions in tremor PSD and MR during rest seated tasks ($p<0.05$), and in tremor MBR during all tasks ($p<0,05$). Treatment was well tolerated, with neither cervical weakness nor dysphagia.

Conclusion: Despite the limited sample size, our pilot study demonstrates that BoNT-A is an effective and safe treatment for DHT when assessed at maximum pharmacological effect. BoNT-A modifies the clinical severity and the quantitative indices of DHT, with the effect being more pronounced in the seated than in the standing position. Inertial sensors provide quantitative insight into the phenotypic features of DHT and aid in muscle selection. Further studies are needed to assess long-term effects.

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P129

Assessing the role of theta rhythm activity in cervical dystonia

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Introduction: Cervical Dystonia (CD) features involuntary neck muscle contractions, it remains unclear what distinguishes these from voluntary ones. [1] Preliminary evidence suggests theta oscillations dominate dystonic contractions, indicating a central drive shown by increased theta Intermuscular coherence (IMC) [2].

Objectives: To demonstrate increased theta activity in clinically affected muscles in CD patients, explore its origin via IMC and cortico-muscular coherence (CMC), and its modulation by sensory trick (ST).

Materials and Methods: We studied 15 CD patients with effective ST (ST+), 17 without (ST-), and 14 healthy controls (HCs). EEG and surface EMG from bilateral sternocleidomastoid (SCM) and biceps were recorded during rest and ST/mimicked ST. Theta EMG power, theta IMC, and theta CMC were analyzed. Mixed ANOVA evaluated factor group and site effects while Granger causality (GC) analysis inferred connectivity directionality.

Results: Theta SCM power was higher in both CD groups vs. HCs; no differences were observed for theta biceps power. Theta IMC between SCMs was significantly higher in ST+ than HCs. GC analysis showed theta band connectivity predominantly from SCM to cortex. ST produced no significant changes in theta power, significant increase in IMC only in ST+, and a decreased in ST-.

Discussion: In CD, increased theta activity is present only in affected segment and reflects a central drive to dystonic muscles as shown by the increased theta IMC. CMC and GC results showed theta synchronization is not cortically driven. The observed increase in theta IMC with ST, i.e. when dystonia improves, suggest theta oscillations may reflect a compensatory activity trying to rebalance SCMs activity rather than a pathophysiological drive.

Conclusion: Theta oscillations in dystonic muscles may reflect compensatory activity of a subcortical structure trying to correct head position. The ST may rebalance descending inputs to this putative subcortical structures allowing active head position correction.

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P130

Vibro-tactile stimulation of the neck induces head righting in people with cervical dystonia

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Introduction: Cervical dystonia (CD) is characterized by involuntary neck muscle spasms that lead abnormal head movements or postures. It is associated with somatosensory (tactile and proprioceptive) dysfunction.

Objectives: To investigated whether vibro-tactile stimulation (VTS) of the cervical muscles constitutes a non-invasive form of neuromodulation of the somatosensory system that can provide temporary symptom relief for people with CD.

Methods: In a multi-centre study, 67 CD patients (44 female) received VTS to sternocleidomastoid and/or trapezius muscles for up to 45 minutes under 9 different stimulation conditions. Retention was assessed 1, 5, and 20 minutes past VTS. Head angles and neck muscle EMG were recorded. The primary outcome measure was a head angle index (HAI), a composite measure reflecting the head deviation across the three axes of the head.

Results: After identifying the most effective VTS condition for each participant, analysis showed that 85% (57/67) of participants experienced an improvement in HAI of at least 10% during the application of VTS. HAI improved by 50% or higher in 26/67 of participants. For those responding to VTS, the effects tended to decay within 20 minutes. For the different CD phenotypes several stimulation sites could induce similarly large relative improvements in head posture.

Conclusions: The study provides first systematic evidence that cervical VTS can induce fast-acting improvements in abnormal head posture in patients with CD. It demonstrates that a stimulation of somatosensory afferent networks modulates the innervation of dystonic muscles. It highlights the potential of cervical VTS as an adjuvant, non-invasive neuromodulation treatment in CD.

P131

Understanding cognitive features of cervical dystonia: application of the cerebellar cognitive affective syndrome scale (CCAS-S)

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Introduction: Cervical Dystonia (CD) is now recognized to encompass a constellation of non-motor symptoms, including sensory, cognitive, and psychiatric manifestations, which significantly affect patients' quality of life. Cerebellar dysfunction may affect cognitive and affective processing in CD, mirroring cognitive and affective patterns observed in Cerebellar Cognitive and Affective Syndrome (CCAS).

Objectives: To investigate impairments in cerebellar-dependent cognitive and affective domains in CD patients using the Cerebellar Cognitive and Affective Syndrome scale (CCAS-S), and to analyze the potential relationship between cognitive deficits and clinical features of CD.

Methods: The CCAS-S was administered to twenty CD patients and twenty healthy controls (HC) matched for age, gender, level of education, and MMSE score. For CD patients, disease severity and disability were evaluated using the Toronto Western Spasmodic Torticollis Rating Scales (TWSTRS), while tremor was assessed through the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (FTM).

Results: CD exhibited a significantly lower total CCAS score and a higher number of failed tests compared to HC, with marked deficits in specific sub-items such as fluency, delayed verbal recall, similarities, and affective domain. The total number of failed tests revealed high predictive ability (AUC = 0.90), with no significant correlations between disease duration, clinical outcomes, and CCAS performance.

Conclusions: The CCAS scale is a sensitive screening tool in differentiating cognitive performance in CD and HC, showing a critical cerebellar involvement in the cognitive and affective symptoms of dystonia.

P132

Longitudinal assessment of blepharospasm severity in patients with long disease duration

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Introduction: Blepharospasm (BSP) represents one of the most common idiopathic adult-onset dystonia [1,2]. A few longitudinal observations indicated progression and worsening of BSP severity within 16 years of onset [3]. Information is lacking about the trend of BSP severity in the later stages of the disease.

Objective: To shed more light on this issue that may have prognostic relevance, we used a standardized video protocol to longitudinally evaluate a cohort of 18 patients with idiopathic BSP over time.

Methods: The study comprised 15 women and 3 men that underwent a standardized video protocol at two time points: 14 ± 9 years after BSP onset and 11 ± 2 years later. BSP severity was rated by the Blepharospasm Severity Rating Scale (BSRS). Two independent observers reviewed 36 videos in a pseudo-randomized order, yielding satisfactory agreement.

Results: Mean total severity score was 7.6±3.9 years at baseline, 6.4±2.5 at the last examination ($p = 0.14$). The last video examination showed a stable BSRS score in 14/18 patients, while the score of 4 patients decreased by two points or more, due to disappearance (n.3) or reduction (n.1) of prolonged spasms with complete rim closure. Over the long term, the BoNT dosage increased in those who improved, but remained stable in the other patients. On follow-up examination, dystonia spread to the lower face or neck in two new patients. No significant correlations emerged between disease duration and BSP severity. The presence of sensory trick significantly correlated with disease duration but not with BSP severity.

Conclusions: This study provides novel information on the long-term prognosis in patients with idiopathic BSP, showing that severity of BSP may not worsen in the later stages of the disease.

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P133

Phenotypic comparison between combined dystonia-parkinsonism and idiopathic adult-onset dystonia

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Introduction: Opicapone is a long-acting, third generation selective catechol-o-methyl transferase (COMT) inhibitor, which is indicated as an adjunctive treatment to levodopa in people with Parkinson’s disease (PwPD) and motor fluctuations. Non-motor effects have been poorly evaluated, although BIPARK-II study showed some positive signal on non-motor symptoms (NMS) in PwPD [1,2].

Objectives: To assess the long-term effects on NMS in PwPD after opicapone adjunctive treatment.

Methods: Retrospective analysis of data collected before and after opicapone initiation, among patients followed in our Movement Disorders Center from September 2023 to December 2024. Data

included the MDS-NMS rating scale [3], UPDRS-III, H&Y stages, demographics information and LEDD.

Results: 28 PwPD and motor fluctuations, who were initiated on opicapone, were identified. 2 patients dropped out for intolerance to the treatment. Data of 26 patients at baseline and after 6 months were collected. 24 (86%) of them presented NMS at baseline. NMSS global score did not show statistically significant changes (Wilcoxon-test, $p = 0.059$), but a tendency to that. The analysis of each item of the NMSS disclosed a statistically significant improvement in sleep ($p = 0.026$) and pain ($p = 0.026$). According to a multivariate linear regression analysis, those improvements were stronger in female than male ($p = 0.014$), and in subjects with lower baseline UPDRS-III score ($p = 0.008$). A subgroup analysis, including only the 22 subjects who presented with NMS at baseline and had a 6-month follow-up available after opicapone initiation, revealed a significant improvement in the NMSS global score (T-test, $p = 0.015$), and confirmed the major effects on sleep and pain ($p = 0.026$).

Conclusions: NMS in PwPD and motor fluctuations can improve with opicapone adjunctive treatment, and its effect is significant for sleep and pain. These improvements may be stronger in female and in subjects with lower UPDRS-III score.

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P134

Subclinical cerebellar dysfunction in idiopathic dystonia: insights from gait analysis and neurocognitive assessment

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Introduction: Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions that result in abnormal movements and/or postures [1]. Adult-onset idiopathic dystonia (AOID) is the most common form of dystonia and it is construed to be a network disorder involving the sensorimotor cortex, the basal ganglia and the cerebellum [2].

Objective: Our study aims to identify subclinical signs of cerebellar dysfunction from both motor and cognitive perspectives, further exploring the gait pattern of patients with AOID who do not exhibit overt gait abnormalities.

Methods: We evaluated 25 patients (11 males and 14 females) with a mean age of 61.2 years. Each patient underwent a clinical assessment using validated scales for dystonia [the Fahn-Marsden Dystonia Scale (FMDS]) and its Total Movement and Disability subscores], for ataxia (Scale for the Assessment and Rating of Ataxia, SARA), and for cerebellar cognitive functions (Cerebellar Cognitive Affective Scale, CCAS) [3]. All patients also underwent a gait analysis using the BTS Gait system according to the Davis protocol, with an assessment of spatiotemporal gait parameters. Gait analysis data were compared with those of a group of healthy controls (HC).

Results: All patients had abnormal CCAS scores, especially in the items assessing executive functions. Significant differences in spatiotemporal gait parameters, including reduced gait speed, shorter step length and a decreased single support phase, were observed compared to HC. Of note, an increased step width was also observed in patients that negatively correlated with CCAS items related to executive dysfunction.

Conclusions: Our study identified subclinical features of cognitive and motor cerebellar dysfunction, supporting the role in the pathophysiology of dystonia. Moreover, our findings confirm a close relationship between cognitive functions and gait performances.

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P135

Focal head tremor can preceed cervical dystonia: evidence from a case with ZNF142-associated neurodevelopmental disorder

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Introduction: Biallelic variants of ZNF142 have been associated to a syndromic neurodevelopmental disorder with impaired speech and hyperkinetic movements.

Objective: We report on a patient with a homozygous single-nucleotide deletion including ZNF142, who has developed a focal head tremor subsequently progressing to an overt cervical dystonia.

Methods: This patient is 25 years old. Motor developmental milestones were delayed (sitting age: 10 months; walking age: 18 months), first word was at 3 years-old. He has a moderate intellectual disability (Total-IQ 36) and moderate-to-severe behavioral problems with social disorder, and occasional aggressive behaviors. He has never been exposed to dopamine-blocking agents. He was noted to have tremor of the head that was particularly evident during episode of stress (QRcode1).

Results: At the first examination, he did not have any sign of overt dystonia; a slight tremor of the neck in the primary position was observed soon after he got angry (QRcode1). Slight irregular "no-no" type head tremor in the primary position which abolished when the patient turns his head fully to the right. No range-of-motion restriction on either side when he turn his head. After one year during which he was managed with botulinum toxin injections (ABO-BoNT; 100 UI SC bilaterally), he developed an abnormal posture characterized by a lateral shift of the head to the right on the frontal plane and a mild tilt of the head to the left. His head tremor was worse when turning the head to the left (QRcode2). The pattern of injections was therefore changed (ABO-BoNT; 200 UI left LS; 50 UI right SC), which was beneficial.

Conclusions: This case supports 1) the concept that a focal head tremor, especially in the presence of some phenomenological features, might anticipate the development of cervical dystonia, and 2) the close relationship between dystonia and neurodevelopmental disorders.

P136

Psychosocial and body image alterations associated with focal dystonia

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Introduction: Focal dystonia is a movement disorder characterized by involuntary muscle contractions resulting in abnormal postures and repetitive movements [1]. These symptoms are often pronounced and can cause significant physical disfigurement, body image concerns, an increased risk of mental health problems, such as depression and anxiety, and impairments in quality of life (QoL) [2].

Objective: The aim of this study was to examine the psychosocial correlates of various forms of focal dystonia, including cervical dystonia, blepharospasm, and hemispasm, focusing on the relationships between altered body image, the prevalence of anxiety and depression, and QoL.

Methods: This study included 32 patients with focal dystonia and 18 patients with hyperhidrosis as controls. Participants completed standardized tests including the Beck Depression Inventory-II (BDI-II) for depression, the State-Trait Anxiety Inventory-Y2 (STAI-Y2) for anxiety, the Body Uneasiness Test (BUT) for body image perception, and the 36-item Short Form Health Survey (SF-36) for QoL.

Results: Post-hoc comparisons revealed significant differences in both BUT and SF-36 scores between groups. Cervical dystonia patients had higher depersonalization symptoms than hyperhidrosis patients (BUT-D: 0.5±0.7 vs. 0.1±0.1; $\rho = 0.027$). Cervical patients also reported lower SF-36 Physical Role scores (55.6±44.7) compared to hemispasm (65.4±43.9), blepharospasm (87.5±31.7), and hyperhidrosis (95.8±17.7) ($\rho < .001$). Hemispasm patients scored lower on SF-36 Emotional Role (63.9±39.6) than other groups (blepharospasm: 90 ± 31.6; cervical dystonia: 70.2±39; hyperhidrosis: 85.2±34.8, $\rho < .001$). Depression (BDI-II: 6±6.1 vs. 3.9±4.3) and anxiety (STAI-Y2: 34.4±11 vs. 35.8±10.5) were prevalent but did not differ significantly between groups.

Conclusions: Focal dystonia, particularly cervical dystonia, appears to profoundly affect body image perception and QoL, exacerbating psychological distress. Integrating targeted psychological support and stigma reduction strategies is critical to improve outcomes for these patients.

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P137

Connectomics in DYT1 mouse models: unveiling pathophysiology and therapeutic potential in dystonia

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*Introduction: D*ystonia is a movement disorder with a complex pathogenesis involving functional and structural alterations in neural circuits regulating voluntary movement and motor control. This network encompasses anatomical structures within the basal ganglia circuit, cerebellar pathways, brainstem nuclei, and cerebral cortex.

Objectives: To develop a connectomics-based approach and apply it to a DYT1 mouse model carrying a GAG deletion in the TOR1A gene encoding torsin A, mirroring young-onset generalized dystonia in DYT1 cases.

Methods: The proposed method involves staining implicated regions in the dystonic network with neurotransmitter-specific antibodies (anti-ChAT for acetylcholine, anti-TH for dopamine and norepinephrine, anti-glutamate, and anti-GABA). Histological images were acquired in Z-stacks using confocal microscopy to construct a significant brain volume. Machine learning models (via Ilastik) and data analysis software (Vaa3D, Gephi) were used to reconstruct neural networks, elucidating neurotransmitter-specific pathways and impulse directionality through 3D maps and network graphs.

Results: Connectomics analysis starting from histology identified how individual structures in the dystonic network function and interact under physiological and pathological conditions. Profound cholinergic system alterations were observed, including changes in cerebellar connectivity and output to the ponto-mesencephalic tegmentum. The pedunculopontine nucleus emerged as a key player, highlighting the importance of reverberating circuits in the substantia nigra and red nucleus in symptom pathogenesis.

Conclusions: Confocal microscopy-based neural connection analysis offers an efficient and rapid approach for understanding movement disorder pathophysiology. Connectomics is invaluable for elucidating the underlying mechanisms of dystonia and holds promise for guiding therapeutic strategies, including pharmaceutical interventions and neuromodulation techniques.

P138

GPi-DBS in SERAC1-Mutation Related Dystonia: case report

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Introduction: SERAC1 mutation is a rare cause of dystonia and parkinsonism with a range of manifestations of variable severity. We here report the clinical effects of bilateral GPi DBS in a patient with a mild form of SERAC1 mutation refractory to drug treatment.

Case Presentation: We evaluated a 56-year-old woman with severe cranio-cervical dystonia, asymmetrical bradykinesia, postural and resting upper limbs tremor. 3 years later orobuccal and cervical dystonia occurred. After a long period of stability, tremor, dysarthria and dysphagia worsened in the last two years, leading to anarthria and malnutrition with necessity of PEG placement. Family history was negative for neurological diseases, brain MRI, DAT Scan and metabolic workout were negative. Cognitive assessment resulted normal.
She had no benefit from Levodopa (1000 mg/d), BZD, and anticholinergic drugs. Botulinum toxin was able to partially reduce cervical pain and orobuccal involuntary movements.
Whole-exome sequencing identified a homozygous rare missense mutation in the SERAC1 gene: c.1231 C>T (p.Arg411Cys). This variant is classified as a VUS but is predicted to be pathogenic by most in silico prediction tools (ACMG-PP3).
In September 2024 the patient underwent bilateral deep brain stimulation (DBS) of the globus pallidus internus (GPi), resulting in a marked improvement in dysarthria, tremor and bradikinesia

Discussion: SERAC1 mutations are associated with a broad spectrum of clinical presentations, ranging from severe spastic paraparesis with developmental delay to adult-onset dystonia-parkinsonism. In our knowledge only one other case has been treated with DBS [1].
Outcomes of GPi DBS in craniocervical dystonia are variable and few data in patients with mitochondiopathies are available. Our case suggests that it should also be considered in adult-onset phenotypes with long disease duration.
In cases of dystonia-parkinsonism the presence of SERAC1 mutations could predict a good response to GPi DBS that should therefore considered a valuable therapeutic option.

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P139

The impact of sex and glucocerebrosidase activity on cognitive function in GBA-related Parkinson's disease

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Introduction: Mutations in the glucocerebrosidase gene (GBA1) constitute the most significant risk factors for Parkinson's disease (PD) and contribute to accelerated cognitive decline.

Objectives: To elucidate the clinical and biochemical profiles of GBA1 individuals and investigate the molecular interactions between glucocerebrosidase (GCase) and alpha-synuclein (a-syn) in relation to clinical manifestations and sex at different disease stages.

Methods: Motor and non-motor signs of PD were collected using the following scales: UPDRS-I-IV, MOCA, SCOPAUT, UPSIT, RBDSQ, BDI, and HADS-A. Disease duration cut off was set at 10 years from onset. GCase activity and monomeric and aggregated α-syn levels were measured in peripheral blood mononuclear cells (PBMCs).

Results: This cohort included 140 participants (57 GBA-PD, 83 nonGBA-PD). The two groups had similar clinical features except for a younger disease onset and higher BDI scores in GBA-PD subjects. Neuropsychiatric symptoms were milder in nonGBA-PD males, while nonGBA-PD females were similar to GBA-PD males and females. GCase activity was lower in GBA-PD compared to both HC and nonGBA-PD subjects. A positive correlation between GCase activity and MOCA scores was found only in the GBA-PD group with cognitive impairment (MOCA < 26) and disease duration $\leq$ 10 years. This effect was driven by female patients and remained significant after adjusting for multiple demographic variables.

Conclusions: GBA status was associated with worse neuropsychiatric symptoms. Gcase variability correlates with MOCA scores only in cognitively impaired patients, suggesting its relevance in the presence of cognitive decline. The significant Gcase-MOCA correlation in females indicates a sex-specific interaction in cognitive decline mechanisms in GBA-PD. Longitudinal studies should explore if enhancing GCase activity could support cognitive health in GBA-PD.

P140

Cognitive function and dopaminergic therapy impact on non-motor fluctuations in Parkinson's disease: insights from the NoMoFA scale

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Objectives: Non-motor fluctuations (NMF) are a significant burden in Parkinson's disease (PD) [1], and the Non-Motor Fluctuation Assessment (NoMoFA) is a validated tool that assesses their severity and impact [2]. This study aims to assess the correlation of main demographic and clinical features with NMF in a cohort of PD patients with motor fluctuations.

Methods: A total of 227 PD patients were included. NMF were assessed using the NoMoFA scale, analyzed as total scores and subscores (ON+OFF, ON, OFF, No Difference). Demographic and clinical variables included: age, disease duration, total LEDD, Levo Dopa LEDD (LD LEDD), Hoehn and Yahr (H&Y) staging, and MDS-UPDRS I-IV scores. Cognitive impairment was assessed using the Montreal Cognitive Assessment (MoCA).
Univariate and multivariate linear regression were performed on the full sample (n=227) to identify factors associated with NoMoFA Total and subscores. Independent variables were selected based on their significant association in the univariate linear regression analysis. A separate analysis was performed on the subset of patients with MoCA scores (n=170) to assess the association between cognitive performance and NoMoFA Total, subscores, and subdomains (cognitive, mood, sensory, autonomic, and "others").

Results: For NoMoFA total the multivariate model was significant, explaining 46.1% of the variance ($p<0.001$) with MDS-UPDRS I (ßstd:0.497; $p<0.001$) and LEDD LD (ßstd:0.192p=0.008) as the strongest correlates. For ON+OFF, the model explained 29.8% of the variance ($p<0.001$), with LEDD LD (ßstd:0.194p=0.019) as the strongest predictor. For No Difference subscore, the model explained 34,3% ($p<0.001$), with significant contribution of total LEDD (ßstd:-0.225; p=0.016), MDS-UPDRS part I (ßstd:0.573; $p<0.001$) and III (ßstd:0.181; p=0.01). Influence of LEDD LD was found also in the NoMoFA ON (ßstd:0.232; p=0.013) while NoMoFA OFF showed influence only by MDS-UPDRS I (ßstd:0.174;p=0.045). In the subset with MoCA, the analysis showed a trend towards significance for the influence of cognitive impairment on NoMoFA total (ßstd:-0.122;p=0.115) and No Difference (ßstd:-0.141;p=0.086). Furthermore, MoCA was significantly associated with specific NoMoFA subdomains, particularly cognitive (ßstd:-0.403;$p<0.001$), mood (ßstd:-0.216;p=0.005), and autonomic (ßstd:-0.373;$p<0.001$) domains.

Discussion and conclusion: Dopaminergic therapy significantly influences NMF, particularly during ON states, while motor fluctuations seem not directly related to NMF. The association of cognitive performance with multiple NoMoFA subdomains underscores the need for targeted cognitive and therapeutic interventions in PD.

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P141

First-level screening tools for detecting cognitive deficits in patients with Parkinson's disease: a comparison between MMP and MMSE

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Introduction: Parkinson's disease (PD) is a neurodegenerative disorder that cause cognitive impairment in 25-30% of patients [1]. The MMSE is a reliable scale for brief screening of Alzheimer's type cognitive deficits, but it is less accurate to identify cognitive impairments in PD [2]. The Mini-Mental Parkinson (MMP) was specifically designed to cover cognitive areas more frequently affected in PD patients [3].

Objective: To demonstrate higher accuracy of MMP compared to MMSE in detecting early cognitive impairment in PD patients.

Methods: Twenty-five patients (age 66.48±6.9) underwent a neuropsychological assessment targeting executive functions (Stroop Test/TMT B-A), attention (SDMT/TMT A), visuo-spatial (ROCF) and verbal (RAVLT) long-term memory, in addition to the MMSE and MMP. We identified PD patients with MCI based on the impairment of at least two tests per domain [4]. We analysed through ROC curves the discriminative ability of MMSE and MMP in identifying MCI. We also conducted Pearson's correlation analysis to assess the relationship between these screening tools and neuropsychological tests per domain.

Results: MMP showed a higher ability to identify MCI in PD (cut-off:26.55; sensitivity:0.92; specificity:0.70; accuracy:0.80; AUC:0.84) compared to MMSE (cut-off:25.95; sensitivity:0.50; specificity:0.85; accuracy:0.68; AUC:0.67). Furthermore, MMP exhibited a lower ceiling effect (4%) compared to MMSE (24%). Both MMP and MMSE negatively correlated with TMT A ($r=-0.51$, $p=0.009$; $r=-0.55$, $p=0.004$), TMT B-A($r=-0.58$, $p=0.003$; $r=-0.66$, $p<0.001$) and positively with SDMT($r=0.57$, $p=0.003$; $r=0.62$, $p=0.001$), while only MMP positively correlated with ROCF-Copy($r=0.44$, $p=0.03$), ROCF-I($r=0.41$, $p=0.04$), ROCF-D ($r=0.45$, $p=0.03$), RAVLT-I($r=0.42$, $p=0.4$), RAVLT-D($r=0.50$,$p=0.01$).

Conclusions: These findings highlighted the accuracy of the MMP in identifying MCI-PD patients, showing its potential as a first-level screening tool helping clinicians to identify those in need of specialized neuropsychological examination. The strong correlation between the MMP and comprehensive tests of visuospatial planning and visual/verbal declarative memory suggests it provides a reliable estimate of cognitive abilities when detailed assessment is unavailable.

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P142

Subjective cognitive complaints in patients with Parkinson's disease: a single-center study of a large sample of patients

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Introduction: Subjective cognitive complaints (SCCs) are common in patients with Parkinson's disease (PD) and may predict neurocognitive decline [1,2]. However, little is known about the clinical, demographic, and neuropsychological correlations of SCCs in PD patients, and cross-sectional studies on this topic often involve small groups of patients [3].

Objective: This study aimed to evaluate the cross-sectional association between SCCs and demographic, clinical, affective, and neuropsychological factors in a large cohort of PD patients, and to investigate whether SCCs can predict cognitive impairment associated with PD.

Methods: A comprehensive neuropsychological battery was used to assess global cognitive status, executive-attentional abilities, memory, language, visuospatial skills, behavioral profile, and general functioning (MMSE, MoCA, FAB, Raven's Matrices, Trail Making Test, Stroop test, Digit Span, Corsi Span, RAVLT, verbal fluencies, Boston naming test, Token Test, Benton Visual Retention Test, CDT, Rey-Osterrieth test, BDI, NPI). Data were analyzed using independent samples t-tests, and multivariable regression analyses were conducted to assess the impact of SCCs on neuropsychological test scores, adjusting for potential confounders.

Results: A total of 779 PD patients (mean age 65.3±9.0 years, disease duration 9.0±6.4 years, mean MMSEc 27.9±1.5) were included. Of these, 454 patients were in the SCC+ group, and 325 in the SCC- group. Patients with SCCs had significantly lower scores in executive function, memory, and attention compared to those without SCCs ($p<0.05$ all). Regression analyses showed significant associations between SCCs and cognitive test performance (Raven's Matrices, RAVLT, CDT, TMT), as well as with depression and neuropsychiatric scores (BDI, NPI).

Conclusions: These findings highlight the need for a comprehensive assessment of cognitive, emotional, and behavioral symptoms in PD patients, particularly those with SCCs. Early identification and targeted interventions may be crucial in improving patients' quality of life and addressing cognitive and neuropsychiatric disturbances.

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P143

Social Cognition impairments in Huntington's disease progression

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Introduction: Huntington's disease (HD) patients often show social cognitive impairments, particularly in understanding others' mental states, defined as Theory of Mind (ToM) [1].
Objective: We explored whether early (stage I) and mid (stage II) HD patients differ in cognitive and affective ToM abilities, specifically regarding both first-order (simple) and second-order (complex) representations.

Methods: A total of 12 Shoulson's stage [2] I HD patients (TFC 11-13), 12 stage II HD patients (TFC 7-10), and 24 healthy controls (HC) completed the Yoni task [3], which assesses cognitive and affective ToM at different complexity levels while limiting interference from language and executive functions. Control items assessed general task comprehension.

Results: Stage I patients exhibited deficits in cognitive ToM items at both complexity level of inference (first- and second-order), but no significant impairments on simpler (first-order) affective tasks. In contrast, stage II patients demonstrated pervasive ToM impairments across both cognitive and affective components and at both complexity levels, with more severe difficulties in the cognitive domain. Performance on control items was significantly lower only for stage II patients compared to HC, confirming general task understanding difficulties in advanced stages.

Conclusions: Social cognitive deficits in HD emerge early in the cognitive ToM domain, while both cognitive and affective ToM are progressively impaired in the mid stage. These findings emphasize the importance of ToM assessments as potential clinical markers of disease progression and for designing rehabilitation programs tailored to strengthen interpersonal relationships in HD patients.

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P144

Cognitive impairments in Parkinson's disease: development of a battery and new methods for visualizing cut-offs

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Introduction: The assessment of cognitive impairments (CI) in Parkinson's disease (PD) represents a key challenge in the clinical management of this condition [2]. However, to date there is a lack of neuropsychological batteries specifically developed and validated for this purpose. In addition, the arbitrariness of the cut-offs used to define "cognitive deficits" as scores below the 5the percentile of the healthy population, might influence the interpretation of tests scores.

Objective: To develop and validate a comprehensive neuropsychological battery of tests specific for the assessment of CI in PD and introduce new methods for the visualization of test scores.

Methods: When calculating the normative standards, the influence of key demographic variables was introduced using an automated regression model selection method [1]. Cut-offs were calculated using the method of Crawford and Garthwaite [3], which distinguishes between sample and population. Exploratory analyses (e.g., PCA) were also conducted to investigate additional characteristics of the battery. Conceptual alternatives and graphical representations (via a web application) for visualizing results relative to the cut-offs are also presented.

Results: The findings indicate that different tests are variably influenced by demographic variables, predominantly showing non-linear effects. The exploratory PCA analysis revealed that approximately 44% of the variance in the scores across the various tests is attributable to a single component.

Conclusions: The study demonstrated that, by employing a robust methodological approach during data collection and focusing on alternative statistical methods for norms calculation, it is possible to overcome some of the limitations present in traditional normative data. These tools can then be employed to support the development and validation of neuropsychological batteries specific for the assessment of CI in PD.

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P145

How subjective age relates with neurodegenerative diseases: an exploratory analysis among patients with Parkinson's disease

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Background: Parkinson Disease (PD) is the second most common neurodegenerative disease in the elderly. Beyond its physical effects, PD affects cognitive and emotional well-being, leading to distress, loss of control, and lower quality of life (QOL). In healthy older adults, subjective age, i.e., felt age (FA) or the discrepancy between the age people feel they are and their actual chronological age, was found be associated with cognitive functioning and QOL. This perception is often linked to a sense of mastery which might be influenced by the presence of a chronic illness such as PD. While research has explored how FA relates with physical and psychological functioning in the elderly general population, few studies have examined how chronic conditions like PD influence this construct.

Objectives: This study aimed to explore how clinical, cognitive, psychological and behavioral characteristics of PD patients are linked to the FA construct (mental-age, physical-age).

Methods: A total of 25 PD patients (15 males, mean age: 68,94, SD: 12,66) with normal cognition were included. They underwent a comprehensive clinical and neuropsychological examination reported their overall, mental and physical felt age and completed a questionnaire assessing QoL. Regression analyses were conducted to explore the associations between FA and various clinical and non-clinical variables.

Results: The overall FA was positively associated with activities of daily living ($p<0.05$). Interestingly, mental FA was negatively associated with trait anxiety (STAI-Y2, $p<0.05$) and perceived cognitive changes (PD-CFRS, $p<0.05$). Physical FA was then linearly associated with overall QOL (WHOQOL, $p<0.005$).

Conclusion: These preliminary results indicate that perception of subjective age plays a role in PD. However, FA associations with functional, clinical cognitive domains and QOL seems to depend on some of its specific facets (mental or physical). Further analyses in a larger sample are needed to investigate the role of PD motor/non-motor symptoms on FA.

P146

The role of cognitive reserve in coping with subjective cognitive complaints: an exploratory study on people with Parkinson's disease

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Introduction: Depression, anxiety, and apathy are often associated with subjective cognitive complaints (SCC) in people with Parkinson's disease (PwPD) without cognitive impairment [1]. Cognitive reserve (CR) enhances the emotional resilience allowing to better cope with stress and emotional challenges [2].

Objective: CR has been studied in relation to cognitive decline in PWPD. We aimed at exploring the relationship between CR and mood/anxiety in cognitively intact PwPD with and without SCC.

Methods: This cross-sectional study involved 133 PwPD (M=84; mean age 60.3±6.8yrs; disease duration 8.9±5.5yrs), with normal cognitive function (PD-MCI level II criteria). We evaluated CR using Hindle's proxis [3]; SCC through the PD-Cognitive Functional Rating Scale (PD-CFRS [4]). Quality of life by the PDQ-8 [5]; mood, anxiety, and apathy were assessed by BDI II, Parkinson anxiety scale (PAS), STAI scales, and Apathy Scale.
After verifying the normality of the distributions, t-test was used to effectively compare groups based on the presence of SCC (PD-CFRS=0 vs PD-CFRS≥1). Correlation analyses was used to evaluate the relationship between CR and pertinent behavioural characteristics; moderation analysis assessed the extent to which CR influences the symptoms and quality of life.
Results: The two groups were comparable for demographical and clinical characteristics; the group with SCC had significantly ($p<0.05$) higher scores in PDQ8, Apathy, STAI, PAS and BDI-II scales. In this group, CR was significantly correlated with PAS (avoidance behaviour) and BDI-II and moderation analyses indicated that CR (late life proxy, concerning social relationship) influences how anxiety is perceived in relation to scores on PDQ8.

Conclusions: In agreement with literature, we found that PwPD and SCC are more depressed and anxious compared those without SCC. Furthermore, we found a relationship between depressive symptoms, anxiety and CR. We therefore hypothesize that PwPD with SCC may rely on cognitive reserve to better cope with anxiety and depression.

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P147

Cognitive impairment and neuropsychiatric symptoms in GBA-related Parkinson's Disease: a systematic review and meta-analysis

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Introduction: GBA mutations, classified according to severity, are the main genetic risk factor for Parkinson's Disease (PD). GBA-PD is typically an early-onset disorder with fast-progressing and severe motor impairment and early cognitive and psychiatric involvement. Many studies focused on the correlation between GBA-PD and neuropsychological disturbances and new investigations are still ongoing.

Objective: To assess the presence and severity of cognitive and neuropsychiatric symptoms in GBA-PD compared to idiopathic-PD and explore the role of mutation severity.

Methods: Three databases (PubMed/MEDLINE, Web of Science, EMBASE) were analysed up to November 2024. We included all article types (cohort and case-control studies, case-series, case-reports) published in English, where cognitive and neuropsychiatric symptoms were assessed with validated scales and compared between GBA-PD and idiopathic-PD. Risk of bias was evaluated with the Newcastle-Ottawa-Scale (NOS). Quantitative data were analysed with Review Manager according to a random effect statistical model. Neuropsychological investigation included global cognition, attention-working memory, executive function, memory and visuospatial abilities. Neuropsychiatric domains included depression, anxiety, apathy and impulse control disorders.

Results: A subgroup of 78 studies (65 cross-sectional/cohort, 10 longitudinal, 3 case-reports/series) was included in the systematic review, and 23 in the meta-analysis. GBA-PD patients showed worst performances in selective/divided attention ($p=0.01$), visuoperceptual, visuoconstructional and visuospatial skills ($p=0.02$-0.0001), and short-term and long-term memory ($p=0.02$), while verbal working memory and executive function were borderline for significance ($p=0.05$). GBA risk variants were associated with greater cognitive impairment than mild mutations ($p=0.002$). The other comparisons were not significant. NOS yielded good methodological quality of the included studies (6.8 ± 1.0).

Conclusions: GBA-PD patients showed worse cognition in selective/divided attention, visual skills and memory. More studies are needed to investigate the role of mutation severity. These data may help understanding and treating GBA-PD.

P148

Optimal cut-off scores for the Mini Mental State Examination and Montreal Cognitive Assessment to detect MCI and dementia in multiple system atrophy

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Introduction: Mild cognitive impairment (MCI) and dementia are reported in up to 44% and 7% of patients with Multiple system atrophy (MSA), respectively [1,2]. So far, no study has explored the sensitivity and discriminative power of Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA) to detect MCI and dementia in MSA [3].

Objective: We aimed to identify the optimal cut-off scores of MMSE and MOCA in order to distinguish MSA patients with MCI and dementia from patients with normal cognition (NC). The fluency item of MOCA was also assessed separately for the same purpose.

Methods: Sixty-two MSA patients underwent a comprehensive II level neuropsychological evaluation, in order to diagnose dementia, MCI or NC according to DSM-5. ROC analyses were used to establish the optimal cut-off scores for MMSE, MOCA and fluency item of MOCA for MCI and dementia, respectively.

Results: According to the II level neuropsychological evaluation, 4.8% of MSA patients were demented and 53,2% had MCI.The optimalcut-offs for MMSE to identify dementia (AUC=0.915) and MCI (AUC = 0.698) were 20.5 and 26.5, respectively. The optimal cut-offs for MOCA to detect dementia (AUC=0.919) and MCI (AUC=0.702) were 14.0 and 19.5, respectively. ROC analysis suggested that both tests were more accurate to identify MCI than dementia. The optimal cutoff for MOCA fluency item to identify MCI was 8.5 words (AUC=0.717).

Conclusions: Our findings support MMSE and MOCA as easy and accurate instruments to detect MCI and dementia in MSA. MOCA fluency item is also a reliable tool to detect MCI in the same population.

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P149

Neuropsychological profile in GBA-Parkinson's disease patients

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Introduction: Mutations in the GBA1 gene is the commonest genetic risk factor for Parkinson's disease (PD) and are associated with a more aggressive disease progression [1]. However, a deep cognitive phenotyping in GBA-PD patients remain poorly explored.

Objectives: Here we assessed neuropsychological and motor and other non-motor characteristics in GBA-PD PD patients and compared them to a group of mutation negative PD (nonGBA-PD).

Methods: A total of 47 PD patients were included (18 GBA-PD and 29 nonGBA-PD). All participants underwent a comprehensive clinical and neuropsychological battery. Clinical and neuropsychological data comparisons between GBA-PD and non-GBA-PD groups were performed using the Mann-Whitney U-test for continuous variables and chi-square test for dichotomous variables.

Results: The two PD groups were similar for all clinical parameters except for age, age at onset, disease duration and motor fluctuations that were worse in the GBA-PD group. GBA-PD exhibited poorer performance on visuospatial (Rey–Osterrieth Complex Figure Test, copy task), visuoperceptive (Gollin Incomplete Figures Test), executive functions tasks (Trail Making Test) and visual memory (Rey–Osterrieth Complex Figure Test, delayed recall) compared to nonGBA-PD patients. These results became even more evident when variables were adjusted for demographic confounding factors (age at onset, sex and disease duration). Moreover, GBA-PD subjects carrying severe mutations had worse scores in visuospatial, visual memory and executive functions tasks compared to nonGBA-PD.

Conclusions: Our results confirmed that GBA mutations are associated with a more severe cognitive profile. Visuospatial and visuoperceptive impairments, which may serve as clinical predictors of dementia [2], emerged as the key cognitive domains distinguishing GBA-PD from non-GBA-PD. Further studies with larger longitudinal cohorts are needed to validate these preliminary findings and clarify if these parameters may have the potential to predict disease outcome, since the prodromal phases.

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P150

The NeuroMaP project: assessing the concordance between telematic and in-person PD-CRS in Parkinson's disease

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Introduction: Parkinson's disease (PD) is a progressive neurodegenerative disorder with motor and non-motor symptoms, including cognitive impairments that may lead to dementia [1]. Mild cognitive impairment (PD-MCI) is common in non-demented PD patients and predicts dementia (PDD), affecting up to 80% of patients [2,3,4].
Diagnosis relies on comprehensive neuropsychological assessments or screening tools [5]. The Parkinson Disease Cognitive Rating Scale (PD-CRS), developed specifically within the context of Parkinson's Disease, is a screening tool, sensitive to executive and attentional deficits that offers detailed subtests and scores [5,6]. Recently (2022), a parallel version of the PD-CRS has been developed (Parkinson Disease Cognitve Rating Scale/ Alternative Form, PDCRS/ AF) [7]. This version has been standardized and validated on the Italian population. The Covid-19 pandemic highlighted the importance of telematic neuropsychological assessments to improve access, enable early diagnosis, and support longitudinal monitoring of cognitive deficits [8, 9, 10, 11, 12].

Objective: To assess the concordance of results between an online version of the PD-CRS, administered via video call using a specifically designed format, and the traditional in-person administration of the same tool on the same patient.

Methods: Thirty patients whit PD were recruited during follow-up visits. Each patient was administered both the PD-CRS and the PD-CRS/AF in telematic and in-person format. The order of administration and the version of scale were determinate in advance using a randomization list created with Sealed Enveloped.

Results: No statistically significance differences were observed between telematic and in-person administration in PD-CRS total score ($p = 0.872$).

Conclusions: The telematic administration of PD-CRS appears to be consistent whit its in-person administration. However, a larger sample size is necessary. Remote administration of PD-CRS could potentially reach a broader population by addressing motor o logistical difficulties associated with traveling to patient's reference center. This approach could facilitate better monitoring of cognitive function in individuals with PD, enabling earlier detection of degenerative trajectories.

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P151

Mental body representation alterations in patients with Parkinson's disease

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Introduction: Mental body representation (MBR) is a complex system including structural, spatial, lexical and semantic body attributes. It is typically divided into action-oriented (aBR) and non-action-oriented (NaBR) body representation. Little is known about MBR in PD and the relationship between MBR and the specific motor subtype of PD (tremor-dominant (TD) versus postural instability/gait difficulty (PIGD) [1].

Objective: The present study aimed at exploring MBR in PD patient, also considering the specific motor subtype of PD.

Methods: 25 PD patients and 24 healthy controls (HCs) were enrolled. They underwent a neuropsychological battery to assess global cognitive functioning, MBR, the occurrence of depressive, anxious and apathetic symptoms, along with impulsive-compulsive disorders.

Results: Mann-Whitney U test highlighted that PD patients and HCs significantly differed in emotional apathy ($p<0.001$) and MBR tasks ($p=0.003$), with PD patients showing higher apathy scores and lower performance on the aBR task. PIGD and TD PD patients did not differ in tasks assessing MBR. Moreover, correlation analyses showed significant correlations between NaBR and Hoehn and Yahr stage ($p=0.019$), between MoCA total score and aBR task ($p=0.028$) and between PD-CRS total score and both aBR ($p=0.001$) and NaBR tasks ($p=0.012$). Finally, regression analysis showed that MoCA scores significantly predicted aBR scores ($p=0.034$), while PD-CRS total score significantly predicted both aBR ($p=0.007$) and NaBR ($p=0.003$) scores.

Conclusions: The present study showed a significant impairment of MBR in PD patients, with no difference between PIGD and TD PD; this evidence, suggesting a characteristic difficulty of PD patients to mentally self-represent body attributes, is not fully in line with the recent literature, which highlighted a MBR deficit in PD limited to its most explicit component [1]. Moreover, MBR ability seems to worsen according to disease progression and global cognitive status.

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P152

Flexibility of action verbs processing in Parkinson's disease

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Introduction: The processing of action verbs partially relies on the motor system, aligning with theories of embodied cognition [1]. Whether the involvement of the motor system during semantic processing is automatic or not, it is still an open question [2]. Parkinson's disease (PD) offers a valuable model for investigating how motor and cognitive systems interact in action semantic processing.

Objective: This study aims to investigate action language processing abilities in PD compared to healthy controls (HCs). By focusing on implicit versus explicit task demands, the study evaluates how semantic processing differs in PD according to context demands and whether these differences align with a flexible embodied cognition approach.

Methods: Participants included 31 PD outpatients and 31 age-matched healthy controls. Two tasks were designed to evaluate semantic processing: an explicit task (semantic judgement task, SJ) and an implicit task (letter detection task, LD). Performance was measured through reaction times (RTs) and accuracy scores (Acc) during the processing of action and abstract verbs. All participants also underwent a comprehensive neuropsychological evaluation.

Results: PD patients were slower and less accurate than HCs only during the explicit SJ task but not the LD task. Moreover, action verbs were processed slowly and less accurately. Slower RTs in the SJ task were predicted by language and executive functioning (i.e., semantic fluency) and disease progression (i.e., H&Y stages) for both action and abstract verbs. As for the LD task, slower RTs were predicted by executive functioning (i.e., the Stroop task) for action verbs and attention (i.e., Trail Making Test Part B) for abstract verbs.

Conclusions: The findings suggest a context-dependent involvement of the motor system in action language processing, supporting a flexible embodied approach to conceptual semantic processing.

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P153

Psychological characterization of FND patients: a pilot study

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Background: Functional Neurological Disorders (FNDs) are an ever-growing field. Advances in terminology, mechanisms, and a multidisciplinary approach have improved understanding of this conditions, but further exploration of the psychological profile of FND patients is essential for personalized care.

Objectives: Our study aims to assess the psychological and behavioural characteristics of the patients, their quality of life, coping strategies, and avoidance symptoms, and establish if these characteristics could help develop patient-tailored therapeutic approaches.

Methods: The study, conducted via an online survey, involved 19 female participants (11 with FNDs and 8 healthy controls) aged 20 to 60. Data on socio-demographics, psycho-socio-emotional variables, and quality of life were collected. Participants were assessed using psychometric tools: SF-12 (Short Form Health Survey) [1] for quality of life, COPE-NVI (Coping Orientation to Problems Experienced – New Italian Version) [4], for coping strategies, and the Life Event Impact Scale for post-traumatic stress [5]. Statistical differences were analyzed using a one-tailed t-test, Cohen's d, and Welch's formula to account for sample size variations.

Results: Our results suggest that participants with FND show greater life event intrusion compared to the control group (mean score of 25.27±7.87 vs 16.62±9.76), with non-significant trends towards higher scores in the other dimensions of the scale (avoidance and hyperarousal). A significant difference was found between the groups regarding quality of life, which was more compromised in both physical (mean score of 37.83 ± 12.78 vs 49.61±7.78) and mental (mean score of 37.86±9.61 vs 45.96±8.53) components for participants with FND.

Conclusions: Treatment of FNDs must a holistic one, focusing on approaches that comprise both Neurology and Psichiatry. In fact, an integrated mind-body approach, utilizing therapies like Cognitive Therapy [2], EMDR [3], and Schema Therapy, has shown success in reducing symptoms and facilitating the processing and rewriting of past traumas, when present.

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P154

Are patients with Parkinson's disease impaired in the recognition of emotion's authenticity?

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Background: In recognising emotions expressed by others, one can make use of both embodied cognition and mechanisms that do not necessarily require activation of the limbic system, such as evoking from memory the meaning of morphological features of the observed face [1]. Instead, we believe that the recognition of the authenticity of an emotional expression is primarily based on embodied cognition, for which the mirror system would play a significant role [3].

Objective: The aim of the study is to assess the ability of parkinsonian patients to recognise the authenticity of displayed emotions.

Methods: We submitted 20 parkinsonian patients and 20 healthy control subjects to the Emotional Authenticity Recognition test, a novel test using dynamic stimuli to evaluate the ability to recognise emotions and their authenticity [2].

Results: Analysis of variance of the test scores shows that Parkinsonian patients perform worse than controls when they had to recognise the authenticity of emotions, although they are able to identify them. Our results confirm a deficit in the recognition of the authenticity of emotions in patients with Parkinson's disease.

Conclusion: We believe that the impaired ability shown by parkinsonian patients in our study could be attributable to the disruption of extrapiramidal limbic circuit between ventral striatum and orbitomesial-prefrontal cortex.

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P155

Unveiling the functional neural network of freezing of gait in Parkinson's disease: a coordinate-based network study

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Background: Freezing of gait (FoG) is a debilitating symptom in Parkinson's disease (PD), yet its pathophysiological mechanisms remain poorly understood. Several studies have investigated the FoG neuroimaging correlates, with heterogeneous results.

Objectives: This study investigated in a large PD cohort whether the disparate neuroimaging findings may converge to a common brain network.

Methods: T1-weighted MRI scans of 500 PD patients (90 with FoG [PD-FoG] and 410 without FoG [PD-nFoG]) were acquired from the Parkinson's Progression Markers Initiative. A voxel-based morphometry (VBM) analysis was conducted to identify clusters of decreased gray matter (GM) in PD-FoG patients. Subsequently, VBM coordinates of significant clusters were used as seed regions to generate connectivity network maps using a large functional normative connectome, and these maps were overlapped to identify regions connected with most VBM clusters.

Results: PD-FoG patients showed GM atrophy in cerebellar lobes, hippocampus, putamen, insula, inferior temporal gyrus and lateral orbitofrontal gyrus compared with PD-nFoG patients. Network analysis revealed that these regions localized within a specific brain network focused on midbrain, substantia nigra, subthalamic nucleus, globus pallidus, inferior putamen and dorsal medial cerebellum. These findings were confirmed by using coordinates from previous VBM studies for the network analysis, validating our results.

Conclusions: This study reveals a brain network underlying freezing of gait in Parkinson's disease, reducing the heterogeneity of previous neuroimaging evidence on FoG. These results may represent a significant step forward in the understanding of FoG and may be relevant for optimized targeted neuro-modulatory treatments to reduce FoG in PD patients.

P156

Molecular connectivity and gray matter alterations in GBA-Associated Parkinson's disease

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Introduction: Parkinson's disease with GBA mutations is characterized by a faster disease progression, more severe symptomatology and reduced survival than sporadic PD (sPD). Furthermore, GBA-PD is more frequently associated with prodromal PD risk factors, such as REM sleep behavior disorder (RBD) and dysautonomia. However, not much is yet known regarding the anatomical and functional bases of the observed clinical differences.

Objectives: Here, we aimed at investigating the degeneration of dopaminergic pathway in sPD and GBA-PD, both locally and through molecular connectivity approach. Moreover, we were interested in examining the presence of extra-dopaminergic pathology by means of assessment of brain volume and cortical thickness.

Methods: We included, from the Parkinson's Progression Markers Initiative (PPMI) database, 86 PD patients (sPD/GBA-PD: 43/43) – disease duration <2, H&Y I-II and no cognitive impairment- and 86 control subjects (HC) for comparison, who underwent 123I-FP-CIT SPECT and structural MRI. We assessed between-group differences in the: i) local dopaminergic activity; ii) dopaminergic pathway connectivity; iii) voxel-based morphometry and cortical thickness. Significant threshold was set at $p<0.01$.

Results: GBA-PD exhibited younger age at onset and greater RBD scores. We found comparable striatal degeneration in sPD and GBA-PD. When compared to HC, molecular connectivity analysis showed greater loss of connectivity in sPD (16% hypo-connectivity between striatal and limbic and motor nodes) than GBA-PD (4% hypo-connectivity between striatal and motor nodes). Whereas only the GBA-PD group showed significant brain atrophy and cortical thinning than HC, affecting occipito-temporal cortex. The direct comparison with sPD showed that GBA-PD exhibited decreased gray matter volume in bilateral lingual gyrus, left superior temporal gyrus and hippocampus.

Conclusions: Our results suggest a more severe vulnerability of extra-dopaminergic pathway affecting GBA-PD, in regions belonging to the cholinergic neurotransmitter system [1], which have been already associated with higher susceptibility to hallucinations and cognitive decline in PD [2].

P157

Brain parenchyma sonography findings in Parkinson's disease patients with tremor dominant subtype compared to those with akinetic rigid dominant subtype

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Introduction: Parkinson's disease (PD) may present different motor subtypes depending on the predominant symptoms (tremor or rigidity/bradykinesia). Brain Parenchyma Sonography (BPS) is used to evaluate the hyperechogenicity of Substantia Nigra (SN), found in more than 90% of PD patients [1]. BPS has been recommended as a tool for the early and differential diagnosis of PD [2]. Correlations among PD different subtypes and BPS findings were not clearly studied.

Objective: The aim of this study is to describe the BPS finding in akinetic-rigid (PD-AR) and tremor-dominant (PD-T) Parkinson's subtypes and to elucidate whether PD motor subtypes show a different pattern of BPS.

Methods: The study included 52 patients with sporadic PD according to the Postuma criteria, with akinetic-rigid (n = 16) or tremor-dominant (n = 36) subtype (24 women, 28 men). Baseline parameters including age of onset, motor subtype and disease duration, were assessed. Patient's characteristics and BPS results were analyzed and compared for the subgroups tremor-dominant versus akinetic-rigid.

Results: BPS revealed hyperechogenicity of SN in 12 PD-AR patients and in 29 PD-T's; in 11 patients (4 PD-AR's and 7 PD-T) BPS were normal. Disease duration ranging from 0 to 40 years, with a mean of 5±4,47 in PD-AR's and 6,38±7,9 in PD-T patients ($p>0.05$). Mean age of onset was 57,5±10,11 in PD-AR's and 63,13±12,41 in PD-T's ($p>0.05$). The mean hyperechogenicity of SN (cm (2)) was slightly lower in PD-AR's (0,20± 0,15 at the right and 0,22±0,13 at the left) than in PD-T's (0,24±0,20 at the right, 0,27±0,16 at the left) without significant difference between the two groups ($p>0.05$).

Conclusions: It is known that PD-T patients showed a slower disease progression compared to those with the PD-AR subtype [3]; furthemore several neuroimaging methods (including diffusion imaging and positron emission tomography) distinguish specific PD motor subtypes well [4]. In our study we found no correlations between BPS findings and PD motor subtypes.

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P158

Ultra-high field MRI imaging to detect iron deposition in genetic Parkinson's disease

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Introduction: Iron deposition in the substantia nigra is a pathological hallmark in Parkinson's disease (PD) and can be assessed in vivo with quantitative susceptibility mapping MRI. The abnormal radiological appearance of Nigrosome 1 (N1) is associated with sporadic degenerative Parkinsonisms and cases of premotor PD.

Objective: To investigate the radiological appearance of N1 and analyze its iron content in sporadic PD, genetic PD, carriers of genetic PD mutations (LRRK2 and GBA) and HC.

Methods: All participants underwent 7T-brain MRI and susceptibility values were obtained from 3D-Gradient-Recalled Multi-Echo sequences. The qualitative assessment of radiological normality/abnormality of N1 and the quantification of N1 susceptibility was performed for each participant.

Results: We enrolled 21 sporadic PD, 21 genetic PD (8 LRRK2 and 13 GBA), 7 LRRK2 and 2 GBA asymptomatic carriers, 13 HC.
Abnormal N1 was found in 90% of genetic PD (100% of GBA PD and 75% of LRRK2 PD) and 95% of sporadic PD patients. In asymptomatic mutation carriers, N1 was abnormal in 25% of LRRK2 carriers but not in the GBA carriers.
The quantification of N1 susceptibility revealed significantly higher values in genetic and sporadic PD than in both HC and mutation carriers ($p<0,005$ for all comparisons). Grouping patients and carriers based on the affected gene, N1 susceptibility was significantly higher in PD patients with GBA mutation than in PD-LRRK2 ($p<0.05$), and higher in GBA than in LRRK2 carriers, even though without statistical significance.
N1 susceptibility values measured in each subgroup of PD patients were higher in patients with mutation in GBA, followed by sporadic PD patients and, by PD patients with mutation in LRRK2 .

Conclusion: Different genetic mutations might be due to different pathological mechanisms of nigrostriatal damage: the low N1 magnetic susceptibility values found in LRRK2 cases might be due to the possibility of low/absent αsynuclein load in these patients.

P159

Investigating the impact of white matter hyperintensities on longitudinal progression in progressive supranuclear palsy

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Introduction: Progressive Supranuclear Palsy (PSP) is a rare neurodegenerative disease characterized by motor dysfunction, postural instability, vertical gaze palsy, and cognitive impairment. White matter hyperintensities (WMHs), traditionally linked to cerebral small vessel disease, represent a common finding in PSP.

Objective: This study aimed to evaluate the prognostic significance of WMHs in PSP, focusing on their role in motor and cognitive progression of disease.

Methods: This is a longitudinal perspective study enrolling 60 PSP patients who underwent 3 Tesla Magnetic Resonance Imaging (MRI) at baseline and then were followed for 47.20±25.88 (mean ± standard deviation) months with extensive motor (PSP rating scale, PSP-rs) and cognitive (MoCA) evaluations. Based on the computation of the ARWMC score, patients were divided into two groups: ARWMC = 0 (without WMHs) and ARWMC > 0 (with WMHs). Disease milestones (e.g., unintelligible speech, wheelchair dependency, PEG placement) and death were also recorded over the follow up. Longitudinal changes in PSP-rs and MoCA scores were evaluated using a linear mixed model. Kaplan-Meier and Cox regression analyses assessed the association between WMHs and time to disease milestones or death.

Results: Linear mixed models showed no significant impact of WMHs on PSP-rs or MoCA scores over the follow up. WMHs were not associated with an increased risk of disease milestones (e.g., unintelligible speech, wheelchair dependency, PEG placement) or death.

Conclusions: WMHs do not appear to influence the clinical trajectory of PSP, suggesting a limited role in motor or cognitive progression of the disease.

P160

Extending the radiological phenotype of SCA27B: the Hot Cross Bun Sign

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Introduction: Spinocerebellar ataxia (SCA27B) is a newly identified form of late-onset cerebellar ataxia (LOCA) caused by dominantly inherited GAA repeat expansion (RE) in FGF14 [1]. The clinical presentation of SCA27B is growing rapidly and dysautonomia and hypokinetic clinical features are frequently described. Earlier reports [3,4,5,6,7] and a more recent review describe a quite homogenous neuroradiological picture in SCA27B [8] characterized by slight cerebellar atrophy, combined with several degrees of supratentorial atrophy, and frequent impairment of the superior cerebellar peduncles [2].

Objective: To describe the spectrum of MRI features in Italian SCA27B patients.

Methods: We re-analyzed clinical and MRI features in SCA27B patients described in our previous multicenter study [3].

Results: In 13/16 patients we observed vermian and hemispheric cerebellar atrophies. One patient showed vermian atrophy without involvement of the hemispheres after 5-years of disease progression. Cortical cerebral atrophy was present in 11 patients. We detected the Hot Cross Bun (HCB) Sign in 2 patients. Patient 1, a 71-year-old man with a 5-year disease history and a RE of 266 GAA, exhibited mild ataxia and vertigo episodes. His brain MRI also showed cortical and cerebellar atrophies. Patient 2, a 64-year-old woman with a 14-year disease duration and a RE of 280 GAA, showed severe ataxia, hypokinetic symptoms, and features of sleep behavior disorder. Her MRI also revealed cerebellar and cerebral atrophies along with middle cerebellar peduncle atrophy. Dysautonomia and urinary features were not recorded in the two patients.

Conclusions: The HCB sign is a hallmark feature of MSA-C typically observed in advanced stages of the disease; however, it can also present in other conditions such as SCA2, making the differentiation challenging. Our findings suggest precise monitoring of MRI patterns in SCA27B that often overlaps with other movement disorder conditions. Whether HCB sign occurs early in a subset of patients requires further studies.

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P161

Symmetric striatal degeneration in dementia with Lewy bodies: a comparison with Parkinson's disease subtypes

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Introduction: A new model of Lewy body disease pathogenesis, the α-Synuclein Origin site and Connectome (SOC) model, has been proposed for both Parkinson's disease (PD) and dementia with Lewy bodies (DLB). This model suggests two subtypes based on the initial α-synuclein pathology: a "brain-first" subtype, where pathology begins unilaterally (e.g., in the olfactory bulb or amygdala), and a "body-first" subtype, where it originates in the peripheral nervous system and ascends bilaterally [1]. DLB is more likely to present with a "body-first" phenotype, characterized by early cardiac sympathetic and parasympathetic colon denervation, prodromal REM sleep behavior disorder (RBD), and symmetric striatal degeneration on dopamine transporter (DAT) SPECT imaging.

Objective: To compare the symmetry of striatal dopaminergic degeneration in patients with probable DLB and PD, categorized into "brain-first" and "body-first" subtypes.

Materials and Methods: This retrospective study, conducted at Pisa University Hospital (2017–2021), included patients diagnosed with probable DLB and clinically established PD, all of whom underwent DAT-SPECT imaging at diagnosis. PD patients were classified as "brain-first" or "body-first" based on the presence of polysomnographically confirmed RBD. Dopaminergic degeneration was quantified using DaTQUANT software.

Results: The study included 36 DLB patients, 33 with "body-first" PD, and 36 with "brain-first" PD. DLB patients were older and had lower MMSE scores compared to PD patients. DLB showed more symmetric dopaminergic degeneration in the caudate and striatum compared to both PD subtypes. No significant differences in putamen degeneration or dopamine transporter availability were observed between "body-first" PD and "brain-first" PD.

Conclusions: The pattern of striatal DAT uptake in DLB patients, characterized by greater symmetry and a diffuse rostrocaudal gradient, aligns with features of the "body-first" subtype proposed in the SOC model [2]. However, this pattern remains distinct from that observed in PD patients, including those with "body-first" PD, suggesting unique nigrostriatal degeneration dynamics in DLB.

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P162

DTI tractography changes of olfactory tract in early stage Parkinson's disease

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Introduction: Olfactory impairment is a key clinical feature of the prodromal phase of Parkinson's disease (PD) [1]. The pathophysiology of olfactory dysfunction in PD is recognized as a complex phenomenon and poorly understood [2]. Magnetic resonance imaging techniques, including diffusion tensor imaging, reliably allow to investigate for any axonal damage in the olfactory tract. Neurodegenerative changes of the olfactory tract in PD have been previously highlighted by diffusion tensor imaging fiber tracking analysis (DTI-FTA) [3].

Objective: The purpose of this paper was to investigate for DTI-FTA changes in the peripheral olfactory system of early-stage PD patients, aiming to identify potential markers of early phase of disease.

Methods: All patients were assessed using the Italian Olfactory Identification Test (IOIT), the MDS-UPDRS III and the H&Y scale. Diffusion imaging was conducted using a 3T MR scanner. The estimates of the overall tract volume (TV), fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were registered for each subject.

Results: 26 early-PD patients and 20 controls were recruited. No statistically significant differences in age and gender were observed between the two groups. DTI-FTA of the olfactory tract showed significant MD increase and TV decrease for PD group compared with controls. MD and age, only in the PD group, were significant for multiple correlations.

Conclusion: DTI-FTA could identify microstructural changes in the olfactory tract even during the early phases of PD.

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P163

Handwriting difficulties in Parkinson's disease: technological assessment and resting-state fMRI correlates

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Introduction: Handwriting is a complex activity requiring cognitive and motor abilities, often impaired in people with Parkinson's Disease (pwPD). Proper handwriting assessment is essential to develop and evaluate the effect of rehabilitation protocols.

Objective: To assess handwriting alterations in pwPD compared to healthy controls (HC) and to identify the functional neural correlates of handwriting changes through using resting-state fMRI functional connectivity (RS-FC) analysis.

Methods: Forty pwPD and 30 age- and sex-matched HC underwent handwriting and hand dexterity assessments, neuropsychological evaluation, and RS-fMRI. A tablet-based handwriting assessment included four tasks: the Systematic Screening for Handwriting Difficulties-SOS test (copying a text), the funnel test (coloring a shape), the closed loop task (drawing specific symbols), and the repetitive cursive loop task (writing repeated symbols). SOS test was executed also on paper. RS-fMRI analysis used MELODIC to identify RS-FC differences, and correlations with clinical variables significantly differing between groups were assessed.

Results: Compared to HC, pwPD showed smaller word size, slower drawing speed, and poorer performance in the handwriting tasks on tablet. SOS test on paper confirmed slower writing speed, smaller size, and lower writing quality in pwPD. RS-FC analysis revealed decreased connectivity in the basal ganglia, cerebellum, ventral default mode, and visual networks, alongside increased RS-FC in the salience and executive control networks. Correlations showed that smaller writing amplitude and poorer handwriting quality were associated with altered RS-FC in motor and cognitive networks.

Conclusions: PwPD exhibited handwriting impairments that were correlated to RS-FC changes in motor and cognitive networks, highlighting the neurological basis of handwriting difficulties in pwPD.

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P164

Analysis of gait with wearable inertial sensors in progressive supranuclear palsy and idiopathic normal pressure hydrocephalus

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Introduction: Gait disorders are prominent symptoms of progressive supranuclear palsy (PSP). PSP gait is typically wide-based, slow, with short steps and poor trunk control. Similar gait disturbances are observed in idiopathic normal pressure hydrocephalus (iNPH), raising questions about differential diagnosis and management.
Few studies have analyzed gait kinematic to support early diagnosis of PSP [1], differentiate it from similar disorders such as Parkinson's disease and iNPH [2], and track its clinical progression.

Objective: This study aims to perform a quantitative gait analysis in patients with clinical diagnosis of PSP and iNPH to identify common and distinctive gait features between the two conditions.

Methods: Demographic and clinical characteristics, cognitive function (Montreal Cognitive Assessment – MoCA), gait and balance assessment (Tinetti Performance Oriented Mobility Assessment – POMA and Gait Status Scale – GSS), temporal and spatial gait parameters (Timed Up and Go test – TUG and 18m walking test – 18mW test) with wearable inertial sensors were collected for PSP patients and age- and sex-matched iNPH patients.

Results: This study revealed significant overlap in gait patterns between PSP and iNPH making it difficult to identify a distinctive motor signature.

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P165

L-Dopa/Carbidopa intestinal gel in advanced Parkinson's disease: long-term monitoring through wearable sensors

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Introduction: While the intrajejunal infusion of L-Dopa/Carbidopa intestinal gel (LCIG) is clinically approved and widely used, its impact on patients' daily functioning through instrumental measures remains underinvestigated [1,2].

Objective: This cross-sectional study evaluates the added value of wearable sensor data in assessing real-world behavioural outcomes of continuous LCIG infusion versus oral L-Dopa in advanced PD, alongside patient-reported measures.

Methods: Thirteen patients on continuous LCIG infusion and 25 matched patients on oral L-Dopa were assessed using standardized scales and sensor-based measures. A validated wearable sensor monitored gait for at least 5 days, estimating daily ON/OFF time, physical inactivity, dyskinesias, and freezing of gait (FOG), while stride fluidity was measured to evaluate gait performance and potential correlations with clinical outcomes.

Results: The sensor-based monitoring lasted for a median duration of 7 days (range: 5-9). Patients treated with LCIG showed lower OFF time ($p=0.009$) as well as higher physical activity ($p=0.003$) than those under oral L-Dopa. Conversely, total ON time, dyskinesia, and FOG were comparable among the two subgroups ($p>0.05$). Finally, stride fluidity inversely correlated with patients' motor deterioration (MDS-UPDRS III: $r=-0.48$, $p=0.027$) and quality of life (PDQ-39: $r=-0.42$, $p=0.016$).

Conclusions: Long-term gait monitoring with wearable sensors is a feasible method for objectively assessing motor performance in advanced PD. Our evaluation highlighted the positive impact of LCIG on reducing total OFF time and increasing overall physical activity in advanced PD patients. Although no significant changes were detected in ON time, dyskinesia, or FOG, this may be due to specific population features or inherent technological limitations. Nevertheless, the notable correlations observed between gait performance and clinical outcomes emphasize the opportunity to monitor PD patients on LCIG therapy through wearables. Accordingly, our findings support the use of wearable technologies in objectively evaluating different therapeutic approaches to optimize treatment in advanced PD.

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P166

Assessing postural instability in Parkinson's disease by instrumented pull test

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Introduction: Postural Instability (PI) is one of the most debilitating feature of late-stage Parkinson's Disease (PD), frequently associated with disease complications such as falls and fractures. This cardinal motor sign has been poorly investigated quantitatively, also to define possible instrumental biomarkers.

Objectives: Primary outcomes of the study were to quantify postural instability in a cohort of PD patients and to reliable discriminate stable from unstable PD subjects.

Methods: We enrolled N=32 patients diagnosed with "clinically definite" PD. Two groups were identified according to the score of the "postural instability" MDS-UPDRS item: 18 PD with Postural Stability (PD-PS) (score 0 to 1) and 14 PD with PI (PD-PI) (score equal or above 2). Each patient performed the "instrumented pull test" five times both in OFF and in ON state, wearing a passive marker on the sternum. Marker positions were recorded by an integrated optokinetic system. Then, an index called "Total Time" (TT) was estimated for all patients, indicating time expressed in seconds (s) occurring from the onset of postural change until full recovery. Healthy Controls (HC) data were used as reference.

Results: Considering the mean TT values for each group, statistically significant differences were found when comparing HC to PD-PS and PD-PI. Moreover, TT values of PD-PS were different from PD-PI. Statistically significant differences were also found when comparing mean TT values evaluated for each trial among "stable trials" vs "unstable trials" as well as when comparing TT values before and after levodopa administration in each group. Based on single trials, a TT threshold equal to 3.64 s was estimated to discriminate between stable and unstable trials, with an accuracy of 83.2%.

Conclusions: TT index may represent a reliable biomarker of PI in PD, resulting modified by levodopa. Study results highlight dopaminergic mechanisms underlying PI in PD.

P167

Home monitoring with wearable sensors supports the superiority of new adaptive deep brain stimulation strategies: preliminary data on three patients with Parkinson's disease

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Introduction: Adaptive deep brain stimulation (aDBS) for Parkinson's disease (PD) promises to improve DBS treatment through real-time adaptation of stimulation delivery according to the patient's needs. Due to the characteristic of aDBS to vary over time, its programming may particularly benefit from prolonged evaluations in a daily-life context.

Objectives: To describe the value of home monitoring in defining the assessment of the benefit of aDBS treatment.

Methods: We recruited three patients (males, age: 59-66y, disease duration: 9-16y, days from surgery: 42-62) with PD who received subthalamic DBS and directional leads. Patients were treated with cDBS and aDBS for two weeks in each condition, in randomized order, and with unchanged drug therapy. In aDBS mode, our device applies a linear algorithm that changes the stimulation current every minute based on the average local field potential (LFP) amplitude calculated in a patient-specific beta frequency range [1,2]. The patients were assessed in the clinic with multiple scales (MDS-UPDRS, MDS-UDysRs, FOG-Q, etc.) and for three days at home with the Hauser diary and a wearable device.

Results: All patients preferred aDBS over cDBS for a better improvement in motor fluctuations and gait. Despite overall comparable evaluations in the clinic, real-world monitoring showed for all patients an increase in good-on-time (on time without troublesome dyskinesia) by an average of 2 hours per day. STN-LFP were recorded successfully and correlated with the patient's daily activities.

Conclusions: Home monitoring with inertial sensors can help in documenting the additional benefit of new stimulation paradigms such as aDBS.

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P168

Observational study to evaluate therapeutic compliance and side effects in patients with Parkinson's disease using electronic diaries

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Introduction: Motor fluctuations significantly impact quality of life and management of Parkinson's disease. Traditional paper diaries are hindered by poor adherence and recall bias, limiting their reliability [1]. Electronic diaries (e-Diaries) overcome these limitations capturing motor states and therapy-induced complications, providing a comprehensive and user-friendly alternative for therapeutic management [2].

Objective: To evaluate compliance, motor performance, and side effects of monoamine oxidase-inhibitors in fluctuating patients using e-Diaries.

Methods: This observational, longitudinal, monocentric study enrolled 120 fluctuating patients treated with safinamide (50/100mg) or rasagiline (1mg). Over nine months, patients used e-Diaries to record daily motor performance, therapeutic adherence, and side effects. Clinical data were collected over three visits, including neurological examinations, diary analysis, therapy-related side effects and dropout rates.

Results: The cohort included 56.6% males and the mean age was 69.6 years. Average Levodopa Equivalent Daily Dose was 780mg, with mean Hoehn&Yahr scale of 2.3 and disease duration of 6.7 years. Safinamide was prescribed to 50.8% of participants (32.5% on 50 mg, 18.3% on 100 mg), while 49.1% received Rasagiline 1mg. Therapeutic compliance was 82.5% for Safinamide and 88% for Rasagiline. Patients on Safinamide spent 73% of time in ON, 13% in OFF, and 14% in dyskinesias, while patients on Rasagiline reported 77% ON, 13% OFF, and 10% dyskinesias. Adverse events occurred in 28.2% and 50% with respectively Safinamide 50mg and 100mg, and 23.8% with Rasagiline 1mg, with dyskinesias as the most common (12.8% Safinamide 50mg, 45.4% Safinamide 100mg, 18.6% Rasagiline). Dropouts were 12.8% for Safinamide 50mg due to dyskinesias, somnolence, hypertension, headache, and incontinence (20% each), 9% for Safinamide 100mg, 8.5% for Rasagiline, with the latter two exclusively dyskinesias-related (100%).

Conclusions: This study highlights the utility of e-Diaries in monitoring motor fluctuations and therapeutic adherence in Parkinson's disease, holding potential to enhance clinical decision-making while emphasizing the need for personalized treatment adjustments.

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P169

Music therapy plus physiotherapy for Parkinson's disease related tremor: a pilot randomized trials with digital outcome assessment

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Background and purpose: Tremor and impairment of manual dexterity are very common symptoms in patients with Parkinson's disease (PD) with limited response to pharmacological treatments. A combination of physiotherapy and music-based intervention may improve Parkinson's symptoms, but no randomized trials have evaluated their efficacy yet.

Methods: The randomized study included 42 PD patients with tremor categorized into four groups: an experimental group receiving selected music and physiotherapy (SMG), a group receiving randomized music and physiotherapy (RMG), a group receiving only physiotherapy (PG) and a control group (CG). Each participant underwent a comprehensive clinical and functional protocol; a digital assessment of tremor in different condition was used a secondary outcome measure.

Results: Repeated measures revealed a higher improvement in SMG patients compared to PG and CG, with better results in MHT parameters during tremor tasks and quality of life (QUEST). SMG patients also had reduced tremor severity (TETRAS), faster performance on the Nine-Hole Pegboard Test, and lower UPDRS-III tremor scores. Mid-term data (60 days) indicated continuous improvement in tremor symptoms for SMG, highlighting the potential durability of the treatment outcomes. MHT parameters showed a strong correlation with clinical scales (all $r>0.5$ and all $p<0.01$).

Conclusions: The pilot study demonstrated for the first time the beneficial effect physiotherapy and music-based treatment alone for the management of parkinsonian tremor, with higher effect size when combined. Further larger studies are needed to explore the feasibility and applicability of such non-pharmacological interventions in real-life setting.

P170

Implementation of a digital telerehabilitation protocol for the improvement of motor and non-motor outcomes and quality of life in patients with functional motor disorders: a two-arm randomised controlled clinical feasibility study

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Introduction: Functional motor disorders (FMD) are neurological conditions characterized by involuntary movements that cannot be traced to organic causes and impair patients' quality of life [3]. Recent technological advances, such as wearable objective measurement devices (TOMs), offer new opportunities to support home symptom management and remote monitoring, opening promising perspectives for improved rehabilitation treatments [4].

Objectives: The main aim of this study is to assess the feasibility of the procedures required for the main study, which aims to compare the efficacy of a digital telerehabilitation program integrated with wearable devices on motor symptoms in FMD patients [1,2]. A secondary objective is to examine the effects of such a program on non-motor symptoms (fatigue, pain, depression, and anxiety), self-perception of clinical change, and health-related quality of life [1,2].

Materials and methods: Patients with FMD in this single-blind randomized controlled trial were recruited at the Azienda Ospedaliera Universitaria Integrata of Verona and randomly assigned to a control or experimental group (EG), which used wearables. All participants followed an intensive 5-day individualized rehabilitation program of 2 hours/day and a personalized self-management plan. Clinical evaluations were carried out before the start of the rehabilitation program, at the end, and after 12 weeks. The feasibility of the intervention was assessed through the recruitment rate and the acceptability of the intervention. The Simplified Functional Movement Disorders Rating Scale (S-FMDRS) was used for motor symptoms, while fatigue was measured with the Multidimensional Fatigue Inventory Scale (MFI-20). Pain, depression, and anxiety were assessed with the Brief Pain Inventory (BPI), the Beck Depression Inventory (BDI-II), and the Beck Anxiety Inventory (BAI), respectively. Perception of clinical change was measured with the Clinical Global Impression (CGI), while TOM sensors were used to monitor physical activity, metabolic consumption, and sleep in an ecological environment.

Results: In this study, 62 patients were assessed for eligibility during the seven-month observation period from May 2024 to December 2024. Of these, 30 patients (48,4 %) met the inclusion criteria (summarized in the previous section). Of these eligible patients, 23 were recruited into the study, with a recruitment rate among eligible patients of 76,67%. These results represent a good percentage, considering the small sample available. The recruitment rate was 76,66%, showing good adherence to the study. The results confirm the feasibility and accessibility of this tool. In the experimental group, the protocol showed an improvement in both non-motor and motor symptoms. An improvement in quality of life and non-motor symptoms was observed.
Conclusions: This pilot study demonstrates the feasibility of wearable in rehabilitation for patients with FMD. Their integration into care pathways could be an innovative approach to improve patients' quality of life and enable more effective symptom management. Preliminary results will have to be confirmed once the sample size envisaged by the study has been reached.

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P171

RAPIDO (teleRehabilitation for pAtient with ParkInson's Disease at any mOment): system acceptability and clinical outcome

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Introduction: Parkinson's disease (PD) is a chronic neurodegenerative condition that leads to progressive disability in daily activities (ADL) and social participation limitations. Rehabilitation reduces disability progression, but access to specialized care is challenging. Continuous remote monitoring and telerehabilitation are viable options for long-term care, but few studies explored their effects [1,2].

Objective: To evaluate the acceptability and feasibility of an integrated system of telerehabilitation and telemonitoring in people with PD (pwPD) at any stage (RAPIDO) and test its impact on motor and non-motor function, quality of life, and caregiver burden.

Methods: One hundred pwPD were enrolled in a prospective multicenter interventional study of a continuous monitoring via a smartwatch (24 hours a day, at least 5 days a week) combined with home-based training (3 times weekly, 45 minutes per session) for 3 consecutive months, connecting via a tablet to a web application. Health status was assessed at the beginning and end of training (12 weeks).

Results: Adherence to the system was 75.6% (68.4% of participants achieved ≥70% adherence). Usability scores (SUS) were significantly higher than expected, with 72% patients scoring ≥68/100. Multivariate analysis revealed that higher MoCA scores ($p=0.049$) and greater perceived effort ($p=0.036$) were associated with better usability. 90% subjects maintained or improved independence in ADL (MDS-UPDRS II), while older age ($p=0.049$) and lower perceived competence ($p=0.012$) was associated with functional decline. MDS-UPDRS III score was either stable or improved in 83% patients, with lower BMI ($p=0.02$) and overall mobility ($p=0.032$) being significantly associated with a worsened score. Finally, Perceived health significantly improved ($p<0.001$). No serious adverse events were reported.

Conclusions: The RAPIDO system, based on widely available, low-cost consumer devices, proved to be usable and safe in a monitored home environment.

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P172

Kinematic gait pattern associated with freezing of gait in Parkinson's disease

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Introduction: Freezing of Gait (FOG) is a disabling symptom in Parkinson's disease (PD) and can significantly impact quality of life [1]. To date, most studies focused on spatio-temporal variables associated with FOG, whereas only few researches analyzed kinematic findings, namely relationships between body segments in terms of joint angles during gait cycle [2].

Objectives: We aim to characterize kinematic gait pattern associated with FOG in PD.

Methods: 52 PD patients - 20 with Freezing of Gait (PD-FOG) and 32 without (PD-noFOG) - were evaluated through MDS-UPDRS, Hoehn and Yahr scale (H&Y) and gait analysis. Kinematic variables were extracted, and univariate statistical analysis (t-test for independent samples or Mann-Whitney U-test, as appropriate) was conducted to compare groups. Significance was set at $p < 0.05$. Furthermore, kinematic variables have been used as input for various Machine Learning (ML) algorithms to classify patients as PD-FOGvsPD-noFOG.

Results: Comparing demographic and clinical variables, PD-FOG patients exhibited worse scores across all sections of MDS-UPDRS, other than Part III, whereas there were no significant differences in disease duration, H&Y stage and Levodopa equivalent daily dose. Regarding kinematic parameters, PD-FOG as compared to PD-noFOG showed reduced pelvic tilt, and knee flex-extension, increased hip extension on the sagittal plane, whereas they displayed increased trunk obliquity on the frontal plane and reduced knees range of motion on the transversal plane. As regards ML algorithms, tree-based ML classifiers obtained more than 80.0% accuracy in distinguishing between PD with and without FOG.

Conclusions: Our study demonstrates PD-FOG vs PD-noFOG exhibit distinct kinematic parameters, indicating different postural configurations during gait. Specifically, FOG patients vs noFOG show a tendency toward increased extension in the sagittal plane and increased axial curvature in the coronal plane. This distinctive postural profile appears to be sufficiently characteristic to enable ML algorithms to distinguish PD-FOG from PD-noFOG.

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P173

Effects of opicapone in Parkinson's disease: a multicenter, longitudinal retrospective 'Real-World' study to identify patient characteristics for sustained treatment benefit

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Introduction: Opicapone (OPC) is a third-generation COMT inhibitor proven effective and safe for managing motor fluctuations in Parkinson's disease (PD) patients, including those with both long-standing fluctuations and earlier ones. However, real-world data are limited but essential for identifying suitable candidates for sustained OPC therapy.

Objectives: To evaluate long-term outcomes of OPC therapy and identify predictors for safe and prolonged use of the drug.

Methods: We set up a real-world, longitudinal, multicenter, retrospective study. Demographics, medical history, motor subtype, severity, neuropsychiatric issues, and therapy were collected from medical charts at OPC initiation (T0) and last follow-up (T1). The discontinuation rate was calculated, and its main causes were recorded. We compared clinical features between OPC continuers (PDcont) and discontinuers (PDdisc) at T0 and T1, identifying predictors for drug discontinuation and defining the long-term outcome for the successful add-on. The analysis was run explicitly for sex.

Results: One hundred and seventy-eight patients (35% female), 64.1±9.2 years old were enrolled. PDcont (85%) continued OPC up to T1 for a total of 30.2 ± 19.64 months, while PDdisc (15%, 13.4% female) discontinued within 8.9±11.30 months from introduction due to causes related to disabling dyskinesia (100% female), hypotension (33.3% females), gastrointestinal disorders (50% females) or psychiatric disturbances (14.3% female). At T0, PDcont were younger than PDdisc, with no differences in motor severity, neuropsychiatric comorbidities, or therapies. At T1, H&Y stage and night-time akinesia differed significantly, while LEDD and motor/neuropsychiatric complications were similar. Discontinuation causes varied by sex, but clinical outcomes did not.

Conclusions: Safety and long-term OPC tolerability were higher in younger patients with milder motor severity. When continued for a three-year period, OPC treatment was associated with a lesser degree of motor impairment and reduced night-time akinesia. The clinical response did not differ between males and females, although side effects had some sex-specificity.

P174

REONPARK-IT: Real-life, observational study on opicapone in patients with Parkinson's disease and early motor fluctuations in Italy

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Background: The efficacy and safety of opicapone in patients with motor fluctuations were demonstrated in the clinical trials BIPARK I and II. Several post-hoc analyses of BIPARK's trials suggested an enhanced efficacy and safety of opicapone in patients who are earlier versus later in their disease course and L-dopa treatment pathway [1,2]. More recently, the trial ADOPTION showed the efficacy of opicapone as an alternative to an additional 100 mg dose of L-dopa to treat early wearing-off in patients with PD [3]. However, there are no data on the usage of opicapone in early wearing-off in the real-life.

Objective: The REONPARK-IT aims to evaluate the effectiveness and safety of opicapone in PD patients with less than 2 years of motor fluctuations in a real-world setting at centers for Parkinson's disease located in Italy.

Methods: This multicentre, prospective cohort study involves approximately 200 idiopathic PD patients experiencing motor fluctuations for less than two years, who have been on levodopa/DDCI for at least one year. It aims to measure long-term effectiveness using the Patient Global Impression of Change (PGI-C) at intervals up to 24 months. Secondary outcomes include changes in Clinical Global Impression of Change (CGI-C), Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Non-motor Symptoms Scale (NMSS), among other metrics. Safety, treatment persistence, and adjustments in PD therapy will also be monitored. Routine clinical visits will facilitate data collection, maintaining standard medical practices.

Results: The study will include 20 centers across Italy, with the first patient expected in June 2025 and the last patient-out by December 2026.

Conclusions: REONPARK-IT will help to understand the role of opicapone in treating early motor fluctuators in Italian clinical practice.

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P175

Treatment stability comparison among different ADD-ON therapies in fluctuating Parkinson's disease patients

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Introduction: Motor fluctuations are a major challenge in advanced Parkinson's disease (PD) [1], often managed using add-on therapies such as catechol-O-methyl transferase (COMT) or monoamine oxidase-B (MAO-B) inhibitors [2]. However, real-life comparisons between these therapies are limited [1,2]. This study investigates the efficacy and tolerability of selegiline (SL), rasagiline (RS), safinamide (SF), and opicapone (OP) in fluctuating PD patients, focusing on treatment stability and demographic influences.

Methods: This retrospective longitudinal study included 160 fluctuating PD patients treated at two Italian tertiary centers (2012–2023). Inclusion criteria required motor fluctuations (WOQ-19 ≥2) and at least 12 months of follow-up. Patients were grouped by add-on therapy (SL, RS, SF, OP). The primary outcome was the stability of antiparkinsonian therapy, defined as months without significant modifications in treatment or adverse events (AEs). Demographic and clinical factors were analyzed using Cox regression.

Results: The OP group had the longest disease duration (9.8±4.6 years, p=0.003) and the highest baseline LEDD (p=0.022). Stability did not differ significantly between groups (p=0.167). However, females exhibited higher therapy modification rates (p=0.013). AEs occurred in 15% of patients, predominantly dyskinesia (6.9%) and hallucinations (5%). OP was more frequently prescribed to younger patients (64.3±7 years).

Conclusions: No single add-on therapy demonstrated superior stability, highlighting comparable efficacy across options. Sex significantly influenced therapy adjustments, with females requiring more frequent modifications. These findings underscore the importance of personalized treatment strategies in fluctuating PD management.

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P176

Safinamide might modulate dopamine-induced oxidative stress in neuronal cells

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Introduction: Dopamine (DA) is critical in Parkinson's disease (PD) pathophysiology; however, there is evidence that it may promote the production of reactive oxygen species (ROS) with a detrimental effect on neuronal cells. Although numerous in vitro and in vivo studies suggest that MAO-B inhibitors (iMAO) might have neuroprotective properties by decreasing DA catabolism, data for newer agents like safinamide remain inconsistent.

Objective: To examine the impact of safinamide on DA-induced oxidative stress in cultured SH-SY5Y neuroblastoma-derived cells, using NRF2 expression as a readout.

Methods: SH-SY5Y were pretreated for 1h with 30μM safinamide (Zambon), 30μM tranylcypromine (Sigma-Aldrich, PHR3427) and 300μM n-acetylcysteine (NAC, Sigma-Aldrich, A9165-5G) and then treated for 8h with 200μM DA (Sigma-Aldrich, H8502). Cell viability was assessed by using different concentrations of safinamide (ranging from 1nM to 390μM), through a colorimetric method (MTS Assay). Half-maximal inhibitory concentration (IC50) calculation was estimated with non-linear regression on normalized Absorbance values. Westen blot analysis was used to determine NRF2 protein levels using an anti-NRF2 antibody (Cell Signaling, 12721). Densitometric analysis was performed using ImageJ, and values were analyzed by two-way ANOVA.

Results: Cell viability was decreased at safinamide >390 μM. IC50 for viability was 35.5 mM. DA-treated cells exhibited a significant increase in NRF2 expression compared to DA-untreated cells. Both safinamide- and NAC-pretreated cells exhibited a statistically significant reduction in DA-induced NRF2 expression. In contrast, tranylcypromine-pretreated cells showed no statistically significant changes in NRF2 expression.

Conclusions: In neuronal cells, DA can trigger the overexpression of NRF2, a transcription factor activated by oxidative stress. However, pre-treatment with safinamide or NAC effectively reduced the DA-induced NRF2 overexpression, whereas another iMAO (tranylcypromine) was ineffective. The comparable effect of safinamide and NAC, a well-known antioxidant agent, highlights the potential of safinamide in mitigating DA-induced oxidative stress in neuronal cells. Additional confirmatory studies are now required.

P177

Comparative study on the efficacy of cholinesterase inhibitors in patients with Parkinson's disease dementia, Lewy Body disease, and Alzheimer's disease

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Introduction: Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are progressive neurodegenerative disorders with overlapping clinical and neuropathological features. While cortical involvement is the primary contributor to dementia in these conditions, degeneration of subcortical structures, particularly the cholinergic nuclei of the basal forebrain, plays a crucial role in cognitive impairment. [1,2] Therefore, acetylcholinesterase inhibitors (AchEIs) are commonly used for symptomatic treatment in both conditions, but long-term efficacy compared to Alzheimer's disease (AD) remains unclear.

Objective: To compare the efficacy of AchEIs in patients with PDD, DLB, and AD over three years of continuous therapy, focusing on differences in cognitive progression.

Materials and Methods: This retrospective study included 100 patients (30 with PDD, 30 with DLB, and 40 with AD) who were followed at the Unit of Neurology, University of Pisa Hospital, between 2016 and 2020. All participants had confirmed diagnoses and underwent annual cognitive assessments using the Mini-Mental State Examination (MMSE) [3]. They received continuous therapy with AchEIs (rivastigmine or donepezil) for three years. The percentage change in MMSE score from baseline to the third year was used as an objective measure of the response to therapy.

Results: Cognitive decline progressed more slowly in PDD patients compared to those with AD, with DLB patients exhibiting an intermediate trajectory. Neither the type of AchEI nor the daily dosage significantly influenced thesedifferences. However, the diagnostic group ($p = 0.031$) and age at dementia onset ($p = 0.010$) were identified as key determinants of cognitive outcomes, with slower decline observed in PDD patients and those with later-onset dementia.

Conclusions: Our study demonstrated that neither the type nor the dosage of AchEI influenced cognitive performance over three years in PDD, DLB, and AD patients. Interestingly, PDD patients showed less cognitive decline than AD patients, and those with older dementia onset exhibited slower cognitive decline, regardless of dementia type.

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P178

Hyper-acute parkinsonism-hyperpirexia syndrome (PHS) after dopaminergic therapy withdrawal: a case report

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Introduction: Parkinsonism-hyperpirexia syndrome (PHS) is a rare but life-threatening condition that can occur in patients with Parkinson's disease (PD) following abrupt discontinuation of dopaminergic therapy. It is characterized by symptoms resembling neuroleptic malignant syndrome, including rigidity, hyperthermia and autonomic dysregulation.
We report a case of PHS occurring in a patient before deep brain stimulation (DBS) leads implantation.

Case Description: A 59-year-old male with advanced PD was scheduled for DBS implantation to address medication-refractory motor fluctuations and dyskinesias. All dopaminergic therapy was stopped 12 hours before surgery (amantadine, safinamide, pramipexole and opicapone had already been stopped before hospital admission). Upon arrival in the operating room, the patient developed severe rigidity with axial and segmental hypertonia, hyperthermia (up to 38.2°C), tachycardia, hypertension (up to 200/120 mmHg), without loss of consciousness or cognitive involvement. PHS was promptly identified, immediate administration of subcutaneous apomorphine (3+2 mg) and melevodopa/carbidopa via NGT (125/12,5 mg, 3+2 tablets) resulted in rapid resolution of symptoms. The patient was stabilized and successfully underwent DBS implantation several days later under general anesthesia, without stopping dopaminergic drugs.

Discussion: This case underscores the risk of PHS in perioperative settings. In centers that use neurophysiological and clinical monitoring during DBS surgery, dopaminergic agents must be stopped before surgery and this may pone patients at risk to develop PHS, albeit it is a rare eventuality (1 on about 150 patients at our center). Prompt recognition, rapid reinstatement of dopaminergic therapy, and careful perioperative planning are essential to prevent and manage this complication.

Conclusion: PHS in the setting of DBS surgery is a rare but critical condition that demands heightened vigilance during preoperative and perioperative care in PD patients. Multidisciplinary coordination with surgeons and anesthesiologists is critical for minimizing risks and ensuring successful surgical outcomes in DBS candidates.

P179

Botulinum toxin injection in patients with Parkinson's disease and axial postural abnormalities: multi-channel EMG study and outcome analysis

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Introduction: Axial postural abnormalities (APAs) are common complications of Parkinson's disease (PD) and Parkinsonisms [1]. The pathophysiology of APAs is complex and may involve either central (basal ganglia dysfunction, cognitive deficits) and peripheral (myopathic and soft tissue changes) mechanisms [2-4]. Firstly, our aim was to study APAs with a multi-channel polygraphy to reveal any muscular hyper-activity that may be dystonic and contribute to lateral or anterior trunk flexion (LTF and ATF respectively), or be compensatory and counteract the abnormal posture; secondly, to evaluate the efficacy of botulinum toxin (BTX) therapy injected in dystonic hyperactive muscles.

Methods: We studied 52 out-patients with LTF and ATF: among them, 20 patients (mean age 74, SD +/-6,5 years) were selected on the basis of the polygraphic pattern and injected with abobotulinum toxin; BTX was injected in paraspinal muscles (iliocostalis thoracis and lumborum) ipsilateral to bending or anterior abdominal wall (external abdominal oblique, rectus abdominis), according to the type of APAs (LTF or ATF); doses varied between 240 and 480 U, depending on the type of muscles and muscular hyperactivity.

Results: At one month follow-up, no significant reduction in the APAs angle was recorded; conversely, a significant pain reduction was reported after BTX injection (mean NRS pre-BTX: 6,35, NRS post-BTX: 4,85 p=0,010). Moreover, 10 patients declared a reduction of pain according to the clinical global improvement (CGI-pain) scale, 8 patients declared no change, 1 patient reported more pain and 1 patient was already pain-free before BTX injection.
9 patients declared a subjective improvement in posture and motility measured with CGI- posture, 10 were unchanged, while only 1 reported a worsening of his APAs

Conclusions: A multi-channel polygraphy is mandatory in the evaluation of patients with PD and APAs who may benefit from BTX therapy. BTX reduces pain and may improve motility in these patients.

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P180

Gender-differences in efficacy and tolerability of opicapone in add on of levodopa. A real-world observational study

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Background: Opicapone is a peripheral catechol-O-methyltransferase inhibitor, approved in add on to levodopa (LD) in Parkinson's disease (PD) patients with motor fluctuations [1].

Objective: To evaluate gender-differences in efficacy and tolerability of opicapone in add on to LD treatment.

Methods: PD patients with motor fluctuations who started opicapone in add on to LD and who were followed up for at least 6 months were enrolled in the study.

Results: Seventy-seven PD patients (51 men; 66.2%) with a mean age at onset of 57.3±9.4 years and a disease duration of 11.0±4.2 years were enrolled. Baseline characteristics were not significantly different between sexes. At follow-up a significant reduction of the total daily OFF time was observed. Overall 41.6% reported some adverse events (AEs) and incidence of AEs was significantly higher among women (65.4% among women and 29.4% among men; p-value 0.002). At multivariate analysis, adjusting by LEDD, female sex was significantly associated with the presence of AEs with an OR of 4.42 (p-value 0.004); 27.3% patients discontinued opicapone due to AEs and women had significantly higher odds of discontinuation (OR 3.00; p-value 0.04).

Conclusion: Opicapone is highly effective for the treatment of motor fluctuations. Women experienced significantly higher AEs resulting in a higher frequency of drug discontinuation. The higher frequency of AEs, including dyskinesias, may be explained by higher levodopa bioavailability among women. To avoid an early discontinuation due to the presence of AEs in women with motor fluctuations, LD dosage should be reduced before the introduction of opicapone. Our study provides novel insights regarding gender-differences in PD treatment, suggesting a personalized management for women with PD, according to the principle of precision medicine.

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P181

Opicapone improves end-of-dose neuropsychiatric fluctuations in patients with Parkinson's disease

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Introduction: Non-motor fluctuations (NMF) represent one of the main complications that patients with Parkinson's disease (PD) may experience during long-term levodopa treatment [1]. Opicapone (OPC), a COMT inhibitor indicated for end-of-dose motor fluctuations (MF), has not yet been extensively investigated for the management of NMF [2,3].

Objective: We aim to evaluate the efficacy of OPC on end-of-dose neuropsychiatric fluctuations, the most frequent and severe NMF.

Methods: We assessed 15 PD patients (8 males/7 females; mean age ± SD: 69.5±7.1 years; disease duration: 7.2±1.7 years) with endof- dose MF and NMF, confirmed by 19-item Wearing-Off Questionnaire (WOQ-19). For each patient, we identify the first end-of-dose deterioration period through MDS-UPDRS-III administered every 30 minutes over two consecutive days. On the third day, a comprehensive clinical and neuropsychological battery was administered during this designated period. Subsequently, OPC was prescribed. After 6 months, patients were re-evaluated using the same baseline assessments during the same end-of-dose period.

Results: At 6-month follow-up, PD patients showed a significant improvement in the following tests: WOQ-19 ($p<0.001$), total MDSUPDRS and each of its four parts ($p<0.001$), NMSS scores ($p<0.001$), neuropsychological tests assessing executive functions/attention (Weigl's, $p<0.001$; FAS fluency, $p<0.001$; STROOP, $p=0.003$) and mood related symptoms (BDI-II, HAM-A; both $p<0.001$). In contrast, there were no significant differences in the scores of Visual Search ($p=0.033$), RAVLT-I ($p=0.225$), and RAVLT-D ($p=0.136$).

Conclusion: OPC improved end-of-dose fluctuations in anxiety, depression, and executive functions/attention, where dopamine plays a critical role, while less dopamine-dependent domains, such as memory and visuospatial abilities, showed no significant changes.

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P182

Transcranial direct current stimulation and dual-task activity in Parkinson disease. A pilot study

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Introduction: Parkinson's Disease (PD) is a neurodegenerative disorder primarily marked by motor symptoms, but cognitive decline can also occur as the disease progresses. Several studies demonstrated the efficacy of Dual-Task (DT) training on improving gait, balance and cognition in PD [1,2,3]. Recent studies suggest that transcranial direct current electrical stimulation (tDCS), a low-cost, non-invasive brain stimulation, could be an effective intervention for PD.

Objective: By associating DT treatment and tDCS, we aimed to investigate the efficacy of a rehabilitation treatment that combines tDCS and DT in patients with PD.

Methods: In our on-going project, we are evaluating clinical effects of this combined therapeutic approach through a quadruple-blind Randomized Controlled Trial (RCT). Until now, we have enrolled 14 patients (3 dropped-out) randomized into 2 groups, who performed DT associated with tDCS real or tDCS sham, over 12 rehabilitation sessions. Each participant was assessed at the baseline (T0) and after 6-week treatment (T1) for disease severity (Unified Parkinson's Disease Rating Scale-UPDRS-III) and performed Instrumented Time Up and Go (iTUG) single and DT conditions (iTUG alone, iTUG motor, iTUG cognitive).

Results: UPDRS and iTUG motor 180° turn duration showed an improvement trend. At baseline, both groups (tDCS real vs tDCS sham; mean (SD)) were not comparable for UPDRS (43.66 (31.92) vs. (30 (12.28)) but for iTUG motor180° (2.74 (0.68) vs. (2.49 (0.88)) were similar. At the end of the treatment, UPDRS scores improved in tDCS real more than tDCS sham (32.16 (12.52) vs. 31.6 (17.85) and also iTUG motor180° (2.45 (0.46) vs. 2.86 (0.86)) scores more than tDCS sham.

Conclusions: When compared with tDCS sham, tDCS real appears to offer benefits to patients with PD. Future analysis should confirm these data and a larger sample size is warranted to draw further conclusions about our approach.

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P183

Effects of opicapone on non-motor symptoms in people with Parkinson's disease: a real-life retrospective study

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Introduction: Opicapone is a long-acting, third generation selective catechol-o-methyl transferase (COMT) inhibitor, which is indicated as an adjunctive treatment to levodopa in people with Parkinson's disease (PwPD) and motor fluctuations. Non-motor effects have been poorly evaluated, although BIPARK-II study showed some positive signal on non-motor symptoms (NMS) in PwPD [1,2].

Objectives: To assess the long-term effects on NMS in PwPD after opicapone adjunctive treatment.

Methods: Retrospective analysis of data collected before and after opicapone initiation, among patients followed in our Movement Disorders Center from September 2023 to December 2024. Data included the MDS-NMS rating scale [3], UPDRS-III, H&Y stages, demographics information and LEDD.

Results: 28 PwPD and motor fluctuations, who were initiated on opicapone, were identified 2 patients dropped out for intolerance to the treatment. Data of 26 patients at baseline and after 6 months were collected. 24 (86%) of them presented NMS at baseline. NMSS global score did not show statistically significant changes (Wilcoxon-test, $p = 0.059$), but a tendency to that. The analysis of each item of the NMSS disclosed a statistically significant improvement in sleep ($p = 0.026$) and pain ($p = 0.026$). According to a multivariate linear regression analysis, those improvements were stronger in female than male ($p = 0.014$), and in subjects with lower baseline UPDRS-III score ($p = 0.008$). A subgroup analysis, including only the 22 subjects who presented with NMS at baseline and had a 6-month follow-up available after opicapone initiation, revealed a significant improvement in the NMSS global score (T-test, $p = 0.015$), and confirmed the major effects on sleep and pain ($p = 0.026$).

Conclusions: NMS in PwPD and motor fluctuations can improve with opicapone adjunctive treatment, and its effect is significant for sleep and pain. These improvements may be stronger in female and in subjects with lower UPDRS-III score.

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P184

Real-world evaluation of opicapone in italian patients with Parkinson's disease: insights into safety, tolerability, and withdrawn prediction

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Background: Opicapone, a third-generation catechol-O-methyl-transferase inhibitor, is currently used to manage motor fluctuations in Parkinson's disease [1]. While clinical trials have demonstrated its efficacy and safety, data on the use of opicapone in daily clinical practice are limited and particularly lacking for an Italian population [2,3]. Objectives: This study aimed to assess the real-world tolerability and safety of opicapone in managing motor fluctuations related to Parkinson's disease.

Methods: A total of 91 patients with Parkinson's disease were enrolled and monitored over a 2-year period following the introduction of opicapone. Baseline clinical and demographic data, including disease duration, stage, phenotype, and axial/non-motor symptoms, were collected. Reasons for discontinuing treatment and adverse events arising after starting opicapone were also recorded.

Results: Adverse events were reported by 20 patients (22%), and 17 patients (18%) discontinued the therapy. Adverse events were less frequent in patients at earlier stages of the disease or earlier phases of l-Dopa treatment. Predictors of therapy discontinuation included a motor fluctuation duration of ≥12 months and a Hoehn and Yahr score of ≥2.5.

Conclusions: The tolerability and safety of opicapone in real-world use were improved when the therapy was started earlier in the disease course and during the initial stages of L-dopa treatment. The most significant clinical predictors of opicapone discontinuation due to treatment-related side effects were the disease stage, as indicated by the Hoehn and Yahr, and the length of motor fluctuations.

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P185

The role of MAO-B inhibitors in fatigue in Parkinson's disease

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Introduction: Fatigue is a prevalent and debilitating non-motor symptom (NMS) in Parkinson's disease (PD), significantly impacting patients' quality of life [1]. MAO-B inhibitors are effective therapy for motor symptoms and fluctuations, displaying a possible role in some NMS. We sought to examine the existing literature on the potential role of MAO-B inhibitors in managing PD-related fatigue.

Methods: We searched PubMed for English-language articles published between January 1978 and August 2024 using keywords such as "selegiline", "rasagiline", "safinamide", "MAO-B", "fatigue", and "Parkinson's disease". We included clinical trials, observational studies, and preclinical studies.

Results: While the precise role of MAO-B inhibitors in fatigue management is not fully understood, research suggests they may have a positive impact on this symptom. Studies have shown that rasagiline may be associated with less progression of fatigue in patients with early PD. In contrast, others have reported significantly improved fatigue in patients treated with rasagiline compared to placebo. With its unique dual action as both an MAO-B inhibitor and a modulator of glutamate release [2], Safinamide offers additional potential for treating fatigue. Its ability to reduce glutamate release is particularly noteworthy given the role of glutamate overactivity in PD-related fatigue. Studies have shown that safinamide treatment can significantly reduce fatigue levels in PD patients, suggesting that its anti glutamatergic action may contribute to its efficacy in managing this symptom.

Discussion: Fatigue in PD is a complex symptom with multiple contributing factors, including neuroinflammation, alterations in the hypothalamic-pituitary-adrenal axis, and neurotransmitter dysregulation [3,4]. In conclusion, while the existing evidence suggests that MAO-B inhibitors may offer a supportive strategy in managing fatigue, their exact role and optimal utilization remain to be determined.

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P186

Safety and tolerability of opicapone in Parkinson's disease: from early-stage (EPSILON study) to late-stage (BIPARK studies)

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Introduction: Opicapone (OPC) is a once-daily catechol-O-methyl transferase inhibitor used as an adjunctive therapy to levodopa for the treatment of end-of-dose motor fluctuations in patients with Parkinson's disease (PD). OPC has been shown to be generally well tolerated and effective in reducing OFF-time in the two large pivotal clinical trials BIPARK-I and BIPARK-II [1,2]. OPC has a more favorable tolerability profile when used earlier in PD patients with motor fluctuations [3]. The EPSILON study evaluated the efficacy and safety of OPC 50 mg as an add-on to levodopa therapy in early PD patients without signs of motor complication [4].

Objective: To compare the safety and tolerability of OPC 50 mg as an adjunctive therapy to stable L-DOPA/DDCI therapy in patients with early-stage (included in ESPILON) and late-stage PD (included in the BIPARK studies).

Methods: In both BIPARK studies, a total of 522 patients received either OPC (n=265) or placebo (n=257). The EPSILON study included 355 patients (OPC, n=177; placebo, n=178).

Results: Overall, the incidence of any treatment emergent adverse event (TEAE) was greater in the combined BIPARK studies (OPC, 64.2% vs placebo, 57.2%) than in EPSILON (OPC, 47.5% vs placebo, 47.2%). Similarly, the incidence of dyskinesia was higher in the OPC than in the placebo arm in the BIPARK studies (20.4% vs 6.2%, respectively) but lower in EPSILON (1.1% vs 3.9%, respectively). Discontinuations due to TEAEs were more frequently reported with OPC than placebo in the BIPARK studies (8.7% vs 7.0%), but less frequently in EPSILON (1.1% vs 3.9%). No fatal case related to OPC was reported in the three studies.

Conclusions: The safety and tolerability comparison between the BIPARK studies and EPSILON confirms the favorable tolerability profile of OPC 50 mg in PD patients. Furthermore, OPC demonstrated a similar safety profile to placebo in PD patients without motor complications.

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P187

Exploring Art Therapy in Parkinson's disease: insights from a pilot study

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Introduction: Art Therapy (AT) has emerged as a promising multimodal rehabilitation strategy for Parkinson's disease (PD), with recent studies suggesting its potential to improve visuospatial abilities and cognitive performance [1]. By engaging cognitive, sensory, and motor pathways, AT promotes neuroplasticity and self-expression [1]. Neuroimaging studies have provided functional and anatomical evidence supporting AT's efficacy in PD [2,3], suggesting its potential as an integrated strategy to address persistent challenges in both motor and non-motor domains.

Objectives: This pilot study evaluates the effect of AT on visual perception in PD patients, hypothesizing that improved visuospatial and executive functions could contribute to better motor outcomes. Although specific movement analyses were not included, the study demonstrated the feasibility of integrating AT into a clinical setting.

Methods: A total of 21 participants (15 PD patients, 6 age-matched controls) underwent neuropsychological assessments before and after a 13-week AT intervention. The intervention consisted of weekly 90-minute sessions involving diverse visual art forms. Cognitive performance was assessed using the Montreal Cognitive Assessment (MoCA), Trail Making Test (TMT), Rey-Osterrieth Complex Figure Test, and other validated tools. Quality of life was evaluated using PDQ-39, PHQ-9, and GAD-7 scales.

Results: PD patients demonstrated significant cognitive improvements post-AT, particularly in the MoCA ($p \leq 0.002$), Rey-Osterrieth Copy ($p \leq 0.009$), Rey-Osterrieth Recall ($p \leq 0.038$), and TMTB ($p \leq 0.05$). No significant changes were observed in clinical or quality-of-life measures.

Conclusions: This study highlights AT's potential to enhance visuospatial and executive functions in PD, underscoring its role as a promising adjunct to neurorehabilitation. Future research should explore AT's broader applications to establish its efficacy in integrated care strategies for PD.

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P188

Role of CITIcoline as supportive therapy in PARKinson's disease: the CITIPARK trial

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Introduction: Experimental studies suggest citicoline has neuroprotective and symptomatic benefits in neurodegenerative models. Long-term use positively affects dopaminergic metabolism and alleviates motor and non-motor symptoms of Parkinson's Disease (PD). However, clinical evidence is outdated and stems from old studies with weak designs.

Objectives: The CITIPARK trial evaluates citicoline as a supportive therapy for PD alongside levodopa. The primary goal is to confirm citicoline's clinical efficacy after six months. Secondary objectives include assessing its impact on motor and non-motor symptoms and quality of life.

Methods: CITIPARK is a double-blind, placebo-controlled, randomized trial with a 2:1 treatment-to-placebo ratio. Patients receive 1000 mg of citicoline or a placebo via intramuscular injection. The primary endpoint is the change in MDS-UPDRS total scores at 24 weeks. Secondary outcomes include motor and non-motor symptoms, and quality of life. The study enrolled 474 patients with PD, aged ≥55, at Hoehn and Yahr stages 1.5–3, on stable dopaminergic therapy without motor fluctuations or dementia.

Results: Of 474 patients enrolled, 368 completed the study (citicoline n=235, placebo n=133). Final analyses included 242 fully compliant patients. Citicoline patients showed a significant MDS-UPDRS reduction (-5.2 vs -1.6, $p<0.01$), driven by motor improvement (MDS-UPDRS III: -3.3 vs 0.25, $p<0.01$). Baseline scores and age influenced outcomes (OR 1.04 and OR 0.93, $p<0.01$). Minor improvements in quality of life were noted in the citicoline group. Adverse events were similar across groups.

Conclusions: In this randomized trial, intramuscular citicoline was safe and effective, improving symptom management in PD patients on stable dopaminergic therapy.

P189

Clinical-radiological differences in hyperkinetic movement disorders associated with acute and chronic cerebrovascular disease

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Background: Cerebrovascular disease is one of the principal cause of movement disorders (MD) and hyperkinetic MD emerge in about 4% of stroke cases, being reported acutely or chronically as delayed-onset progressive MD [1]. However, association between stroke localization and phenomenology is still less than 30% [2].

Objective: To evaluate differences in hyperkinetic MD in patients with acute and chronic cerebrovascular disease.

Methods: Patients with hyperkinetic MD and evidence of cerebrovascular disease on MRI were enrolled. Patients were divided into two groups according to onset of associated cerebrovascular events.

Results: Thirty-three patients (18 men, 54.5%) with hyperkinetic MD associate with cerebrovascular diseases, mostly ischemic (90.1%), were enrolled. Out of these, the first group was composed by 9 patients (27.3%) who presented cerebral stroke preceding MD. The second group was composed by 24 patients (72.7%) with chronic cerebrovascular disease, characterized by subcortical white matter and basal ganglia lesions.
The most observed hyperkinetic MD in both acute and chronic groups were tremor (55.6% vs 25%) and dystonia (33.3% vs 45.8%), followed by chorea, ballism and myoclonus. No differences between groups were observed. Upper limbs localization of MD was more frequent in the acute group (100% vs 62.5%; $p=0.038$), while cranial onset was more frequent in the chronic group (75% vs 22.2%; $p=0.013$).
Regarding MRI vascular lesions, cortical areas were more affected in acute group (88.9% vs 8.3%; $p<0.001$), mainly unilaterally (77.8% vs 25%; $p=0.013$), while subcortical white matter lesions were mainly observed in chronic group (95.8% vs 66.7%; $p=0.05$). Basal ganglia were involved in 22.2% of the acute patients vs 41.7% of the chronic patients, while brainstem in 11.1% vs 33.3% and cerebellum in 22.2% vs 12.5%.

Conclusion: Hyperkinetic MD in patients with acute cerebrovascular event seem to have stronger correlation with cortical lesions than patients with chronic cerebrovascular disease, principally affecting upper limbs.

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P190

Infusion test result associations with cognitive and motor outcomes of ventriculoperitoneal shunt in normal pressure hydrocephalus

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Introduction: Normal pressure hydrocephalus (NPH) is a frequent but poor recognized and treated disease. Its pathophysiology is still debated, but ventriculoperitoneal shunting (VPS) improved the clinical syndrome in selected patients.

Objectives: Investigate the predictive value of the infusion test on VPS cognitive and motor outcome.

Methods: This is a prospective study conducted on 26 patients with clinically and radiologically confirmed NPH undergoing infusion test and VPS. Kinematic gait parameters (G-Walk system) and neuropsychological tests were collected. Patients were evaluated at baseline and 1 month after shunting.

Results: Subjects undergoing surgery showed improvement at both neuropsychological batteries and gait analysis. Infusion test results (Rout, Elastance, waveforms) were associated with MMSE, Ray word list, Trail Making Test and Stroop test ($p<0.01$). Waveforms associated with gait parameters (single and double stance, swing time, propulsion) ($p<0.05$).

Conclusion: Infusion test correlate with cognitive and gait outcomes at 1 month, with a possible selectivity of specific test domain with cognitive or motor functions. Possible pathophysiologic underpinnings warrant further investigations.

P191

Paralytic ileus in Huntington's disease: a case report of an uncommon gastrointestinal manifestation

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Introduction: Huntington's disease (HD) is a neurodegenerative disorder characterized by pathological involvement extending beyond the striatum to include the autonomic nervous system. Bowel dysfunction is a recognized but underreported complication in HD patients, with its underlying mechanisms remaining poorly understood [1]. This report describes a unique case of a 55-year-old woman with advanced HD who developed paralytic ileus, highlighting the need for further investigation of gastrointestinal dysfunction in this population.

Objective: This case concerns a 55-year-old woman with advanced-stage HD, diagnosed in 2013. She was non-ambulatory, fully dependent on caregivers, and exhibited moderate dysarthria and dysphagia. In Luly 2024 a upper digestive endoscopy (UDE) was negative for organic lesions. Liquid thickeners where recommended and percutaneous endoscopic gastrostomy was deemed unnecessary. In October 2024 the patient was admitted to the Emergency Room after experiencing over three weeks of persisting vomiting, primarily post-prandial and nocturnal. Clinical evaluation revealed a painful, hyper-tympanic abdomen. Abdominal imaging (ultrasound and X-ray) showed stomach and distal esophagus distension with fluid retention and coprostasis. UDE revealed grade B esophagitis. A nasogastric tube was placed for decompression. An upper GI X-ray detected gastric atony and absence of small bowel peristalsis, leading to a diagnosis of paralytic ileus. To address the condition, mechanical distension of the pylorus and nasojejunal tube placement were performed to enable pharmacological therapy and initiate enteral nutrition. However, the patient poorly tolerated enteral feeding, necessitating the continuation of parenteral nutrition. A contrast CT scan of the abdomen demonstrated a slight improvement of gastric ectasia but no effect on the small bowel dilation and intestinal atony. The patients was discharged with nursing care and proton pump inhibitor therapy.

Conclusion: Paralytic ileus has not yet been documented as a gastrointestinal manifestation of HD. Emerging evidence shows that HD affects not only the brain but also the autonomic nervous system and gastrointestinal tract. Studies in HD mouse models suggest that huntingtin inclusions in enteric neurons may contribute to bowel dysfunction, particularly in advanced stages [2,3]. Further studies are needed to better understand the pathophysiology and develop effective treatments.

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P192

Anti-IgLON5 encephalitis with coexisting chorea and sleep apnea: a case with distinct FDG PET/CT findings

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Introduction: Anti-IgLON5 disease is a rare neurological disorder combining autoimmune and neurodegenerative features, first described in 2014. It manifests through diverse clinical syndromes, including sleep disturbances, bulbar dysfunction, progressive supranuclear palsy-like symptoms, cognitive decline, and movement disorders. The disease is associated with distinct, though incompletely characterized, brain metabolic and structural changes [2].
We present a 64-year-old man with anti-IgLON5 disease, highlighting an atypical FDG PET/CT metabolic pattern and the rare coexistence of chorea and obstructive sleep apnea (OSA).

Case: The patient presented a one-year history of progressive involuntary movements, predominantly affecting the right limbs, along with postural and gait instability, mood changes, dysphagia, weight loss, speech disturbances. His medical history included smoking, previous alcohol abuse, type 2 diabetes mellitus, hypertension, and a prior polysomnographic diagnosis of OSA. Neurological examination revealed dysarthria, choreoathetosis with right-sided predominance, dystonic neck posture, blepharospasm, oral dyskinesias. Diagnostic workup, including brain MRI, CT, nerve conduction studies, rheumatological screening, genetic testing for Huntington's disease and cerebrospinal fluid analysis, showed no abnormalities. However, FDG PET/CT demonstrated mild thalamic hypermetabolism with bilateral prefrontal cortex and right temporo-lateral hypometabolism. The detection of serum anti-IgLON5 antibodies directed the diagnosis toward IgLON5 encephalitis. High-dose steroid therapy provided transient improvement, but plasmapheresis was poorly tolerated due to significant dysautonomia. Rituximab was initiated. Despite treatment, symptoms worsened, influenced by comorbidities and poor therapy tolerance.

Conclusion: This case highlights the clinical heterogeneity of anti-IgLON5 disease and underscores the diagnostic value of FDG PET/CT in identifying unique metabolic patterns. The coexistence of chorea and OSA broadens the spectrum of motor and sleep disturbances linked to the disease [1]. Further research is needed to elucidate the pathophysiology and optimize therapeutic strategies.

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P193

Psychometric properties and clinical correlates of the short version of carers' quality-of-life questionnaire for parkinsonism (PSP ShoQoL carer) in progressive supranuclear palsy: data from the PSP-NET

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Introduction: Caregivers of Progressive Supranuclear Palsy (PSP) patients frequently show quality of life deterioration which can be assessed with the carers' quality-of-life questionnaire for parkinsonism [1] (PSP-ShoQoL carer).

Objectives: The aims of this study are to develop a short version of the carers' quality-of-life questionnaire for parkinsonism (PSP-ShoQoL carer) and to describe its psychometric properties and clinical correlates in PSP caregivers, as well as to have a time-saving tool in caregiver assessment.

Methods: PSP-ShoQoL carer was administered within the PSP-NET study group [2]. Patients, diagnosed according to the Movement Disorder Society criteria, and their caregivers underwent a clinical interview, a motor, extensive cognitive and behavioural evaluation. Based on the PSP-ShoQoL carer, the PSP-ShoQoL carer was created using a three-factor solution and item-total correlation. Psychometric properties of the PSP-ShoQoL carer were explored.

Results: Data from 563 patients and 344 caregivers were included in this study. The final scale included 14 items. The internal consistency was high (Cronbach's alpha = 0.930) and no improvement of this value was noted upon removal of any items. The PSP-ShoQoL carer showed good acceptability, reliability and validity. The standard error of measurement (SEM) value for the PSP-ShoQoL carer total score was 0.685 [SEM = SD √ (1 – Cronbach's alpha)]. The PSP-ShoQoL carer showed a significant correlation with EQ 5D Index and its domains, except self-care one. It demonstrated a significant correlation with both patients' clinical characteristics, such as quality of life, PSP-Rating scale and Montreal Cognitive Assessment, and with caregivers' variables, i.e. Hospital Anxiety and Depression Scale, Resilience Scale 1 and Zarit Burden Inventory. Linear regression analysis showed that the impairment of PSP patients' quality of life and the presence of neuropsychiatric symptoms significantly affects caregivers' quality of life.

Conclusions: In conclusion, the PSP-ShoQoL carer is a reliable and valid time-saving tool for the assessment of PSP caregivers' quality of life.

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P194

Diagnostic outcomes of acute/subacute chorea: a retrospective analysis with a systematic literature review

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Aim: This study aims to review the clinical features, causes, and outcomes of (sub)acute chorea in patients from our department and through a systematic literature review.

Materials and Methods: We used a standardized pro-forma to collect demographic (age and sex), clinical (chorea distribution, etiology), treatment (causative and/or symptomatic therapy), and outcome data from patient records at our department (January 2023 - April 2024) and via a systematic literature review. Searches were conducted on PubMed using the terms: "acute", "subacute", "chorea", "emergency department." All paper types were included except those lacking original data. Chronic chorea cases were excluded. Descriptive analyses were performed.

Results: Seventy-eight patients (59 females, 75.6%) with (sub)acute chorea were evaluated, comprising 72 published cases and 6 from our department. The mean age was 67.5 years (SD: ~7.69 yrs). Chorea was generalized in 57.69% of cases (45 patients) and hemichorea in 42.31% (33 patients). The etiology were vascular (44.9%), metabolic (17.8%), drug-related (14.1%), infectious (6.4%), inflammatory (10.3%), with other causes at 5.1%. In 1.3% of cases, the etiology was undetermined. Vascular causes were significantly linked to hemichorea, while drug-induced chorea was associated with generalized distribution ($p < 0.001$) [1]. Among 40 patients with available data, 18 (45%) received causative treatment only, 19 (47.5%) needed additional symptomatic treatment (mostly Haloperidol up to 3 mg/day), and spontaneous resolution occurred in 3 (7.5%) [2]. Overall, outcomes were positive in 74% of cases, with negative outcomes in the remainder.

Discussion: Despite the limited sample size, our findings are consistent with previous reports, indicating vascular causes as the most common for subacute chorea. Rarer conditions like Huntington's disease were also noted even without family history. Timely identification of treatable causes is crucial, especially given one patient's exitus [3]. Some cases required additional symptomatic treatment without clear links to underlying etiology.

Conclusions: The etiologies of (sub)acute chorea are varied, and outcomes may be poor if not promptly recognized. We recommend a checklist of diagnostic procedures for clinical practitioners to follow.

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P195

Observational cross-sectional study of the prevalence of movement disorders in a population of adults with intellectual disabilities belonging to a local disability service

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Introduction: Movement disorders (MD) are common among adult patients with intellectual disability. Most of observed MD are due to use/overuse of antipsychotic drugs but sometimes the drugs themselves can mask the onset of movement disorders due to other causes.

Objective: To assess the prevalence and the pattern of movement disorders among out patients and in-patient belonging a Service for Adult Disability of local health authority of Viterbo.

Methods: A cross sectional study was conducted on a cohort of 645 in- and out -patients with intellectual disability in the period 2022-2024. Charts of patients were rewieved and those who reported a movement disorder were further assessed by a multidisciplinary team to characterize history, putative risk factors and phenomenology of MD.
MD were measured by clinical appropriate scales.

Results: The overall prevalence of MD in our cohort was of 40.4%. Parkinsonism, dyskinesia, akathisia, and dystonia were respectively 65,4%, 25.2%, 10 %, and 1.7% of patients with ID. Mixed phenomenology were observed in the 35%. All patients used at least one antipsychotic drug, in the 50% of patients more than one antipsychotic drug and in the 18% more than 3.
In at least half of the patients taking drugs and presenting with MD it was not possible to trace the clinical indication for the prescription over time, probably challenging behaviors A postural bilateral tremor was present in those patients using valproate often associated to other MD. Those patients presenting a greater degree of ID severity were those using more than two antipsychotic drugs and presented more complex MD. Only 65 patients (0.1%) had undergone tests carried out to exclude non-iatrogenic causes of MD.

Conclusions: Although cross sectional and single center, our study confirm current literature for the high prevalence of MD among people with ID. However, it remains difficult to understand the role of antipsychotic and other psychotropic drugs in the development and maintenance of MD The limited possibility of accessing third level exams in the past, has masked MD of other etiology.
The abuse of antipsychotic drugs worsens people's quality of life and reduces the already reduced life expectancy of these patients.

P196

Multiple system atrophy with postganglionic cardiovascular denervation: a different subtype?

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Introduction: Cardiovascular autonomic dysfunction in Multiple System Atrophy(MSA) is mostly related to preganglionic degeneration, which corresponds to normal iodine-123-metaiodobenzyl-guanidine(123I-MIBG) cardiac scintigraphy [1]. However, reduced tracer uptake, reflecting postganglionic compromise, has been reported in up to one third of MSA patients [2]. Whether this is associated with a different clinico-pathological phenotype is still unclear. The aim of this study is to outline clinical/investigational features and autonomic profile of patients affected by MSA associated with postganglionic sympathetic denervation.

Methods: A retrospective study on patients affected by probable or established MSA [3], who underwent cardiac 123I-MIBG scintigraphy, was performed. Clinical features, scale scores, MRI markers, plasma catecholamine values and cardiovascular autonomic tests findings were compared among patients with and without cardiac postganglionic sympathetic denervation.

Results: Fifty-three patients were included, 42 (79.2%) with normal (N) and 11 (20.8%) with reduced (R) cardiac sympathetic innervation. 43 patients had parkinsonian and 10 had cerebellar phenotype. Clinical-demographic features were similar between N and R except for hyposmia (patient-reported) which was associated with R. Heart rate variability analysis revealed that patients with R had reduced LF/HF (low frequencies/high frequencies) ratios while standing on tilt-test. A sub-analysis on patients with MSA-P diagnosis confirmed the association between R and hyposmia and also with delayed orthostatic hypotension, while patients with MSA-P and N had more severe and earlier incidence of dysphagia. Results from the remaining investigations (neuroimaging, laboratory, autonomic) were comparable among groups.

Conclusion: In our cohort postganglionic cardiovascular denervation in patients affected by MSA was associated with self-reported hyposmia, which is atypical for the disease. Preganglionic degeneration was associated with earlier and more severe occurrence of dysphagia, a condition typical of “pure” MSA. Patients with R had reduced LF/HF ratios while standing on tilt-test, which reflects sympathetic dysfunction. MSA associated with postganglionic sympathetic denervation may therefore constitute a distinct subtype. The mechanism underlying postganglionic denervation in MSA remains unclear and needs further investigations.

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P197

Retinal thickness in essential tremor plus (et plus): correlation with clinical variables

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Objective: Retinal thickness measured thought optical coherence tomography (OCT) has been discovered to be low in several neurodegenerative diseases such as Parkinson Disease, Alzheimer's Disease and others [1]. We have studied retinal thickness in ET plus with rest tremor.

Materials: Eighteen ET plus patients have been recluted. Clinical features and cognitive assessment have been evaluated with The Tremor Research Group Essential Tremor Rating Scale (TETRAS) and Montreal Cognitive Assessment battery (MoCA), respectively. All patients performed OCT.

Methods: We have used non parametric test as Mann-Whitney and Spearman rank correlation.

Results: Total macular thickness in the parafoveal zone (3mm) and total macular volume in the parafoveal zone (3mm) correlated with TETRAS in particular activities of day living sections (ADL) (p-value 0.004 and p-Value 0.007). Also TETRAS-ADL correlated with MoCa and with visuospatial subscore (p.value 0.033 and 0.031).

Conclusion: Despite being preliminary, our data suggest that retinal thickness may be a marker of more severe phenotype of ET plus.

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P198

Autonomic dysfunction in patients with Huntington's disease

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Introduction: Autonomic dysfunction has been described Huntington's disease (HD), but the involvement of the autonomic nervous system has not been clarified yet.

Objective: Our aim was to assess the autonomic control of the cardiovascular reflexes in HD.

Methods: It is a prospective monocentric study, including 16 manifest subjects, compared with 16 age- and sex-matched healthy controls. All subjects underwent to clinical assessment and a complete cardiovascular reflex tests session (CRTs).

Results: During the Tilt Table Test, patients with HD showed a lesser increase in blood pressure (BP) values at the 3rd and 10th min after standing, statistically significant for both systolic BP (SBP) and diastolic BP (DBP) at the 3rd min and for SBP at the 10th min. During Valsalva Maneuver, patients showed a statistically significant lower overshoot (mean value, range; 28, 20.8-34) compared to controls (43.5, 35-55.3). During the sustained handgrip test, the increase in SBP values was lower (21.5, 15.5-32.8) compared to controls (35.5, 29.3-41.8), with a trend towards significance (p-value = 0.053).

P199

The syndrome of sustained shoulder elevation: a functional movement disorder

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Background: Fixed postures without mobile components are often observed in patients with functional movement disorders. We describe a form of pseudodsystonia primarily affecting the shoulder and often involving neighboring body regions.

Methods: We analyzed the clinical records of patients with dystonia and retrieved data of patients with sustained or fixed shoulder elevation, whether with or without involvement of the neck or trunk. Genetic or acquired forms were excluded. The selected patients underwent a battery of clinical, neurophysiologic, and neuropsychologic tests. In addition, a PubMed search of cases with similar phenomenology was performed.

Results: In a series of more than 1200 records, six fulfilled the inclusion criteria. Their phenomenology was: sustained postural abnormalities involving one shoulder that was usually elevated, often involving also neighboring regions; frequent occurrence of local pain; absence of alleviating maneuvers, mirroring, or overflow. A preceding local trauma was reported by two patients; the onset was acute or gradual. There was poor benefit from oral medications and BoNT treatment. GPi DBS was performed in one patient without benefit; motor cortex stimulation was applied to two patients with partial improvement. All the patients met DSM-5 criteria for functional neurological symptom (conversion) disorder with abnormal movements.
Our search strategies identified 18 publications encompassing 75 cases whose clinical descriptions matched the syndrome. In 75% of the cases, there was a previous minor single traumatic event. Response to oral therapies, BoNT, and physical therapy was poor in all cases. Some earlier observations suggested a functional or psychiatric etiology, while others considered an organic cause.

Conclusions: These observations are in agreement with reported cases describing a rare syndrome with sustained shoulder elevation and involvement of neighboring structures. We provide evidence to indicate that this is a functional movement disorder with a typical syndromic aggregation and a recognizable identity.

P200

Treatment of essential tremor with combined stimulation using cTBS on M1 and cerebellar tDCS: a single-session pilot study

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Introduction: Essential tremor (ET) is one of the most common movement disorders, often poorly responsive to pharmacological therapy [1]. Non-invasive neurostimulation is emerging as a valid treatment for different neurological and psychiatric conditions.

Objective: we analyzed the rapid effects of a combined single-session transcranial magnetic (TMS) and electrical (TES) stimulation in a group of patients with ET.

Methods: Twelve patients with ET were recruited. The patients underwent a single session of continuous Theta Burst Stimulation (cTBS) on the left motor area M1 [2], immediately followed by cathodal transcranial direct current stimulation (tDCS) over the cerebellum [3]. Clinical, neurophysiological, and kinematic evaluations were performed before and after 30 minutes of stimulation to assess the short-term therapeutic effect. Clinical response was evaluated using the Essential Tremor Rating Assessment Scale (TETRAS). Neurophysiological changes were assessed through band-specific functional connectivity (FC) analysis using HD-EEG [4] and cortical-brain inhibition (CBI) evaluation [5]. Finally, kinematic tremor analysis was performed using accelerometers placed on the patient's hands to quantify tremor frequency and amplitude before and after the intervention.

Results: A significant reduction in TETRAS scores, indicative of clinical response, was documented in ET patients after treatment. Moreover, kinematic analysis revealed a marked reduction in tremor amplitude in both hands following stimulation. Concurrently, significant increases of FC in the β (13-30 Hz), low-γ (30-50 Hz), and high-γ (50-100 Hz) bands in sensorimotor regions, and a significant improvement in CBI were observed 30 minutes after stimulation.

Conclusions: These findings highlighted the potential efficacy of combining cTBS on M1 and cerebellar cathodal tDCS in modulating dysfunctional cortico-cerebellar circuits in ET. The observed reduction in tremor amplitude, alongside increased FC and CBI, suggests that this approach may positively influence the balance of sensorimotor-cerebellar networks. This pilot study demonstrated that combined treatment could represent a valid strategy for managing drug-resistant ET.

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P201

Gait patterns in iatrogenic parkinsonism and Parkinson's disease

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Introduction: Drug-induced parkinsonism (DIP) is often indistinguishable from Parkinson Disease (PD) on a clinical basis alone. Supportive instrumental exams, such as ^{123}I-ioflupane dopamine transporter (DaT) single-photon emission computer tomography (SPECT), are not always conclusive due to poor standardization in interpretation of results and to possible drug interference.

Objectives: To evaluate the contribution of gait analysis in the differential diagnosis between DIP and PD.

Methods: We consecutively enrolled patients affected by PD patients and patients affected by Bipolar Disorder (BD) with DIP. In the latter group, nigral degeneration was excluded through a normal DaT SPECT imaging [1]. Each patient was clinically assessed and evaluated with gait analysis acquired in three different conditions (normal gait and two dual-tasks). Spatiotemporal parameters were extracted and computed using univariate statistical analysis (parametric t-test or non-parametric Mann-Whitney U test, as appropriate). Significance was set a $p<0.05$.

Results: Data were obtained from 14 BD and 16 PD patients, matched for age, sex, motor symptoms duration and MDS-UPDRSIII scores. Compared to PD, BD patients had significant longer mean stance phase and double support phase, shorter mean oscillation phase and single support phase, lower cycle length and increased step width, both in single and dual tasks.

Conclusions: In our study, gait analysis revealed that BD patients with iatrogenic parkinsonism displayed worse gait parameters than PD patients. In particular, BD patients showed increased dynamic instability, as revealed by increased double stance phase duration and greater step width. Future comparison with a more heterogenous population with DIP could further elucidate whether these alterations may be attributed to drug exposure or to the underlying psychiatric disease.

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P202

A window into the mind-brain-body interplay: development of diagnostic, prognostic biomarkers and rehabilitation strategies in functional motor disorders (pnrr-mad-2022-12376826)

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Introduction: Functional motor disorders (FMD) are disabling conditions characterized by abnormal movements (functional weakness, tremors, and dystonia) distinguished by distractibility and incongruence with organic neurological conditions [1,2]. Despite their prevalence and impact on independence and healthcare costs, FMD remains poorly understood, with delayed diagnoses and inadequate treatments underscoring the need for diagnostic and prognostic biomarkers [2,3]. This research, funded by the European Union – Next Generation EU (NRRP M6C2 – Investment 2.1, PNRR-MAD-2022-12376826), aims to address this gap.

Objectives: To develop diagnostic and prognostic disease-specific biomarker algorithms in motor, exteroceptive, and interoceptive domains through advanced behavioural, neurophysiological, and MRI assessments supported by explainable artificial intelligence (XAI).

Methods: This cross-sectional and longitudinal study involves FMD patients, healthy controls (HC), and patients with "organic" motor disorders. Behavioural, neurophysiological, and MRI assessments targeting motor, exteroceptive, interoceptive, and cerebral domains followed a published protocol [4].

Results: Preliminary analyses comparing 115 HC (mean age 39.62±11.5 years) and 41 FMD patients (mean age 45.5±13.3 years) revealed non-motor symptom burdens (alexithymia, anxiety, depression, fatigue, and pain) and reduced quality of life in FMD patients ($p<0.05$, for all). Age-matched subgroup analysis showed significant motor impairment in FMD, including reduced stride length and slower walking speed ($p<0.001$, for all), with improved gait metrics in dual-task visual conditions. Balance challenges were evident in Romberg index performance under single-task conditions

($p<0.003$) but not during dual-task conditions. Blink reflex R2 response modulation between baseline and prepulse conditions differed significantly in FMD ($p<0.021$), partially aligning with HC patterns. Exteroceptive assessments showed altered laser-evoked potentials in FMD, with N2P2 amplitude reductions during Diffuse Noxious Inhibitory Controls (DNIC) returning to baseline post-DNIC ($p<0.05$), mirroring HC patterns. Interoceptive and MRI findings remain under analysis.

Conclusions: Preliminary results reveal distinct motor and exteroceptive biomarkers in FMD, offering insights into mechanisms and diagnostic tools. Findings support multimodal assessments to improve FMD diagnosis.

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P203

Personality profile in patients with multiple system atrophy: a preliminary study

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Introduction: Multiple System Atrophy (MSA) is a rare neurodegenerative disorder characterized by autonomic dysfunction, parkinsonism (MSA-P), and/or cerebellar ataxia (MSA-C). Despite motor and non-motor symptoms are well-established, the personality features of MSA patients remain underexplored.

Objective: This study aims to identify specific personality profile in MSA patients.

Methods: A cohort of 26 MSA patients (12 female, mean±SD: age 60.6±5.7 years, disease duration 3.9±2.4 years) was evaluated using the Minnesota Multiphasic Personality Inventory-2-RF (MMPI-2-RF). Cognitive decline was excluded via the Montreal Cognitive Assessment screening. Demographic and clinical variables were collected. To identify prevalent and absent personalityfeatures, we focused on MMPI-2-RF scales with significant score elevations (≥65) in at least 35% of the cohort and on those with no elevations (0%). Nonparametric statistical methods examined correlations between scales and demographic/clinical variables, and comparisons were made between MSA-P and MSA-C phenotypes.

Results: MSA patients frequently reported different somatic complaints, including neurological symptoms (NUC: 85%), general somatic issues (MLS: 58%), and somatic preoccupations (RC1: 38%). Emotional difficulties were prevalent, with notable elevations in introversion (INTR_r: 46%), suicidal ideation (SUI: 46%), reduced positive emotions (RC2: 38%), and helplessness (HLP: 54%). However, stress (STW) and aggressive behavior (AGGR_r) were absent, indicating passivity and low stress awareness. Strong correlations were observed between somatic and emotional domains, including MLS with RC2 ($r=0.656$; $p<0.001$) and NUC with disease duration ($r=0.700$; $p<0.001$). No significant differences emerged between phenotypes ($p>0.05$).

Conclusions: MSA patients display a personality profile marked by somatic complaints, emotional difficulties, and social withdrawal. Despite this, no clinically significant stress or aggressive behavior was observed, suggesting underreporting and passivity. The interplay between somatic and emotional factors highlights how reduced positive emotionality and helplessness exacerbate somatic symptoms, while physical burdens deepen psychological distress. These findings underline the importance of a multidisciplinary approach addressing both explicit and unexpressed challenges to improve patients' quality of life.

P204

The relation between upper limbs action tremor asymmetry, midline tremor and gait disorders in essential tremor: an exploratory study

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Introduction: Upper limbs action tremor represents the clinical hallmark of Essential Tremor (ET), which showed varying degrees of asymmetry. However, the possible role of the upper limbs action tremor asymmetry in the context of the broader ET motor phenotypical spectrum has never been addressed to date.

Objective: The aim of the present study was to assess the possible relation between upper limbs action tremor asymmetry and other motor aspects which may characterize the ET syndrome.

Methods: Clinical tremor scores and instrumental kinematic gait parameters were assessed. An asymmetry index (AI) was computed based on clinical severity of each upper limbs action tremor component. Symmetric (S-ET, AI=0) and Asymmetric (A-ET, AI>0) patients were defined and compared based on the most asymmetric action tremor component.

Results: Thirty-seven tremor patients [8 pure ET (21.6%) and 29 ET-plus (78.4%)] were enrolled. Forward outstretched (FO) postural tremor represented the action tremor subtype showing the greater clinical asymmetry across the whole tremor population. No significant differences on action tremor AIs were reported between pure ET and ET-Plus. Based on FO tremor AI, two patients' subgroups were defined: A-ET (N=21, 56.8%) and S-ET (N=16, 43.2%), the latter showing higher midline tremor severity (i.e. head and voice) and worse instrumental gait parameters.

Conclusions: The study highlights the possible role of upper limbs action tremor asymmetry as an adjunctive feature to be considered in ET clinical phenotyping.

P205

Markers of autonomic dysfunction in patients with Parkinson's disease and multiple system atrophy

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Introduction: In Parkinson's disease (PD) and multiple system atrophy (MSA), autonomic dysfunction has a significant impact on quality of life and overall survival. When overlooked, it may delay the differential diagnosis and limit the access to clinical trials and newer treatments.

Objective: To characterize autonomic dysfunction in PD and MSA and to identify possible markers supporting the differential diagnosis, focusing on the involvement of the cardiovascular and urinary domains.

Methods: 40 patients diagnosed with PD and MSA (13 and 27, respectively) underwent a standardized clinical evaluation (MDS-UPDRS, UMSARS scales). Autonomic symptoms were assessed using the COMPASS-31 score. A subgroup underwent a neuropsychological evaluation and structural and functional neuroimaging (i.e. brain MRI, PET-MRI/PET-CT). Bladder post-void residual volume was quantified using ultrasound. Cardiovascular involvement was assessed with Holter EKG 24h, ambulatory blood pressure monitoring (ABPM), [123I] MIBG cardiac scintigraphy and cardiovascular autonomic tests. Skin biopsies were performed in a subgroup for biological characterization.

Results: ABPM disclosed abnormal blood pressure circadian rhythms in PD (85.7%) and MSA (70%). A significant correlation emerged between the systolic/diastolic blood pressure values in the supine position and the OH domain score of the COMPASS-31. Among MSA, 37.5% disclosed abnormal results in the cardiac scintigraphy. Skin biopsy immunohistochemistry did not detect phosphorylated α-synuclein (p-syn) deposits in 33.3% of the MSA patients (all presenting a longer disease duration). The autonomic fibers in the skin resulted positive for p-syn in 44.4% of MSA patients.

Conclusions: Abnormalities in blood pressure circadian rhythm are a common finding in patients with PD and MSA, but tools focusing on symptoms are not helpful, due to their poor relationship with the magnitude of the pressure drop. This finding, together with the frequency and clinical impact of the autonomic dysfunction, highlights the need to routinely introduce a standardized approach, including a biological characterization.

P206

Diabetic striatopathy: a clinical case and reflections on the neurological management of diabetes

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Introduction: Diabetic striatopathy (DS) is a neurological complication associated with diabetes mellitus, also known as hyperglycemic hemichorea-hemiballismus, characterized by acute involuntary movements and striatal abnormalities visible on neuroimaging [1]. Pathophysiology is not fully understood but may involve hyperviscosity, ischemia, and alterations in basal ganglia neurotransmitters [2]. DS is more frequently reported in Asian countries but is underdiagnosed in Western populations.

Case report: We report a case of 77 years-old caucasian male patient, with history of diabetes mellitus type II for which does not take specific therapy due to severe episodes of lipothymia. Symptoms developed are hemicorea-hemibllism at the left hemisome, with a progressive trend in the first three weeks. After this period, the patient presented to the emergency department, where laboratory tests revealed normal values, including blood glucose, and a brain computed tomography scan that showed no evidence of any suspected lesions. During hospitalization, more detailed examinations revealed glycated haemoglobin with a value of 14.3%. Magnetic resonance imaging revealed hyperintensity on T1-weighted images and hypointensity on T2-weighted images in the right putamen. Therapy with tetrabenazine 25 mg per day was started, then has been increased after 4 days to 50 mg per day. Of course, insulin therapy has also been set. At the follow-up at 45 days, symptoms were almost completely reversed, with the patient regaining control of the movements.

Conclusion: Hyperglycemic hemichorea-hemiballismus without ketoacidosis is a rare movement disorder that can occur in patient with poorly controlled diabetes [3]. The pathophysiological mechanisms are still unclear, given the low number of cases in literature, so it is necessary a further study. Close glycemic control should be the first target to achieve. Symptoms, if not spontaneously reversed, may require use of drugs acting on the CNS such as tetrabenazine.

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P207

Long-term outcome and relapse risk in Sydenham Chorea: evidence from a large corticosteroid-treated cohort

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Introduction: Sydenham chorea (SC) is the most common cause of acquired chorea in children. Although commonly described as a monophasic, spontaneously resolving disorder, motor symptoms may persist for more than two years in 25-50% of patients, 16-42% experience chorea relapses, and psychiatric symptoms may persist beyond chorea resolution.
Recently, a meta-analysis of retrospective studies showed that corticosteroid treatment is associated with faster chorea resolution and a reduced risk of relapse [1]. However, several uncertainties remain regarding the optimal treatment regimen, the impact of corticosteroid use on psychiatric symptoms, and factors associated with corticosteroid failure in preventing the persistence or recurrence.
In this study, we retrospectively analyzed the motor and non-motor outcomes of a large cohort of corticosteroid-treated patients with SC, in order to define treatment regimens and clinical features associated with a less favorable course.

Methods: A retrospective analysis of SC patients diagnosed between 2009 and 2023 at two Italian referral centers was performed. Inclusion criteria were: SC diagnosis according to the modified Jones criteria, age under 18 years at onset, and a minimum follow-up of six months. Data collected included clinical features, brain imaging, pharmacological treatment, and the course of motor and non-motor symptoms over time. Kaplan-Meier curves were used to analyze chorea resolution and relapse risk, and a logistic regression model was applied to identify clinical features associated with an increased risk of relapse.

Results: Sixty-eight patients were included, with a mean age of 9.5±2.25 years. Chorea was generalized in 55.6% and unilateral in 44.3%. Motor symptoms were classified as mild in 29%, moderate in 68%, and severe in 3%. Thirty-five percent of the patients showed hyperintense white matter lesions on brain MRI. The mean time to chorea resolution was 2.4 months. Non-motor symptoms occurred in 41.2% of patients at onset, gradually decreasing to 25% at one month, 17% at six months, 16.2% at one year, and 7.35% after three years. All patients received corticosteroids, either oral prednisone alone (47%) or intravenous methylprednisolone followed by oral prednisone (53%). The mean equivalent prednisone dose was 100.8 ± 51.8 mg/kg, with a mean treatment duration of 62.27±19.92 days. Nineteen percent of the patients experienced SC relapse (77% of relapses occurred within six months from onset). Logistic regression showed that prolonged steroid therapy (>60 days, odds ratio [OR] 1.086, $p = 0.048$), white matter hyperintensities on brain MRI (OR 11.629, $p = 0.042$), and the use of antidopaminergic medications (OR 33.989, $p = 0.035$) were significantly associated with a higher risk of relapse.

Conclusions: In corticosteroid-treated patients, chorea duration is shorter compared to historical cohorts. However, white matter abnormalities on MRI are associated with a higher relapse rate, possibly reflecting more severe neuroinflammation and a more aggressive course. Antidopaminergic treatment and prolonged steroid therapy are also associated with an increased relapse risk, possibly

reflecting treatment-induced long-term modifications of basal ganglia circuitry. Our data suggest that prolonged steroid regimens should be avoided, and brain MRI is a useful prognostic tool for relapse risk stratification at SC onset.

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P208

Cognitive responses to the Tap Test and biomarker analysis: a retrospective study of patients with suspected normal pressure hydrocephalus

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Introduction: Normal Pressure Hydrocephalus (NPH) shares features with neurodegenerative diseases, complicating diagnosis. Combining cerebrospinal fluid (CSF) tap test (CSFTT) results, biomarker data, and cognitive assessments, including Montreal Cognitive Assessment (MoCA) scores, provide insight into cognitive responses and partially reversible decline following CSF drainage [1,2,3].

Objective: This retrospective study analyzed clinical responses to CSFTT and associated biomarkers in patients with suspected NPH, differentiating responders from non-responders through pre- and post-test assessments.

Methods: A retrospective analysis was conducted on twenty patients who underwent CSFTT for suspected NPH. Patients were classified into responders (RE, n=11; mean age±SD, 75.50±6.85 years) and non-responders (nRE, n=9; mean age±SD 80.00±5.17 years) based on motor outcomes post-CSFTT. Clinical assessments included MoCA, simple reaction times (sRT), and Go-No-Go-Rt tasks, measured pre- and post-CSFTT. The CSF biomarkers analyzed were Tau, p-Tau, Aβ-42, and Aβ-40. Statistical analyses compared group results.

Results: No significant differences were observed between demographic groups or cognitive performance at baseline (MoCA p=0.25, sRT p=0.76, Go-No-Go-Rt p=0.71). RE showed a 10% improvement in MoCA scores (p=0.002) and a trend toward improvement in sRT (p=0.06) after CSFTT, while nRE experienced a 10% decrease in MoCA (p=0.002). CSF biomarker analysis revealed significant differences in Tau (p=0.047) and p-Tau (p=0.019), but not in Aβ-42, Aβ-40, Aβ-42/Aβ-40 ratio, or p-Tau/Aβ-42 ratio (p>0.05) between RE and nRE. The change in MoCA scores was negatively correlated with Tau (r= -0.540, p=0.014) and p-Tau (r= -0.569, p=0.009), indicating worse outcomes with higher biomarker levels.

Conclusions: CSFTT demonstrated its utility in stratifying patients based on clinical response, with responders showing improvement in MoCA scores and lower CSF Tau and p-Tau levels. The correlation between Tau levels and cognitive changes suggests that the improvement after drainage may be due to a reduction in neuronal damage, highlighting the value of cognitive and biomarker assessments in suspected NPH, and warranting further prospective studies.

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P209

The 8Item-4RTau Symptoms Checklist: an informant-based tool for the differential diagnosis between Parkinson's disease and CBS/PSP parkinsonisms

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Introduction: The differential diagnosis between Parkinson's Disease (PD) and Corticobasal Syndrome (CBS) and Progressive Supranuclear Palsy (PSP) remains a significant challenge.

Objective: This study aimed to develop a concise and simple symptom checklist to assist movement disorder specialists in distinguishing PD from 4-repeat (4R) tauopathies.

Methods: The study included 35 nondemented PD patients and 44 patients with CBS/PSP. The two groups were matched for age (73.8 yrs ±6.4 and 72.9 yrs ±6.4, respectively), education (10.1 yrs ±4.7 vs. 11.0 yrs ±3.8), sex (percentage men: 41% vs. 57%) and, importantly, for disease duration (4.0 yrs ±2.5 vs. 4.8 yrs ±3.6). We identified eight clinical features commonly associated with 4R tauopathies, but rare in the first stages of PD: imbalance, dysphagia, motor speech impairment, attention/orientation deficits, difficulty performing complex tasks, inappropriate behavior, agraphia and repetitive behaviours. Both the patient and an informant were asked to rate the severity of each symptom on a 5-point Likert scale (from 0 = absent to 4 = severe). The total Checklist score ranged from 0 to 32, with higher values indicating more severe symptoms.

Results: The mean 8Item-4RTau Symptoms Checklist score was significantly worse in CBS/PSP patients (10.3±6.4) compared to PD patients (3.2±2.9) ($p < 0.00001$). ROC curve analysis showed excellent diagnostic performance: at a cutoff point > 5, the Area Under the Curve (AUC) was 0.87 (95% CI: 79.5 – 94.8), with a Youden Index of 0.64, and 84.1% sensitivity and 80.0% specificity.

Conclusion: Our 8Item-4RTau Symptoms Checklist provides a simple, quick and effective informant-based tool which may raise the suspicion of a 4R tauopathy in patients with degenerative parkinsonism. Further validation in larger, diverse cohorts will be needed to confirm its utility and reliability.

P210

A survey on the onset of non-motor symptoms in multiple system atrophy

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Objective: To investigate the presence and onset of non-motor symptoms in MSA.

Background: In addition to the characterising dysautonomic features, non-motor manifestations in Multiple System Atrophy (MSA) are increasingly recognized. Several studies highlighted manifestations in the gastrointestinal, cognitive, mood, sleep and pain domains [1-5]. Recent studies on the progression of MSA manifestations highlighted that about 50%-70% of patients show significant urinary manifestations, 50% orthostatic hypotension, and almost 90% showed videopolysomnography-confirmed REM sleep behaviour disorder (RBD) [3,6]. Subjective memory complaints and depressive symptoms were also common [3].

Method: The presence and onset of non-motor symptoms was assessed through a previously published, modified 33-item questionnaire, with the additions of items investigating recognised MSA manifestations. Several domains were investigated, including gastrointestinal, genital and urinary, thermoregulation, cardiac and blood pressure changes, sleep, mood, memory and pain. 11 probable or possible MSA participants were enrolled in this preliminary phase of the study.

Results: All subjects reported the presence of at least one manifestation in the urinary, RBD and mood domains at some point throughout the disease. All but one reported at least one manifestation in the sexual and sleep (other than RBD) domains. 9 out of 11 (82%) reported orthostatic symptoms. More than 50% of participants reported manifesting non-motor symptoms prior to the onset of motor symptoms in domains related to RBD (82%), mood or anxiety (82%), sexual dysfunction (73%), insomnia or excessive daytime sleepiness (64%), urinary, thermoregulatory and GI problems (55%); orthostatic symptoms before the onset of motor symptoms were reported in 45% of participants.

Conclusion: Non-motor manifestations other than dysautonomia are common in MSA and could appear before the onset of motor symptoms. A larger survey with early and prospective enrolment is needed to further elucidate the timing of onset of non-motor symptoms.

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P211

Short-term effects of continuous theta burst stimulation in treating a young patient affected by post-ischemic hemidystonia

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Introduction: Hemidystonia is a rare post-ischemic manifestation, observed in approximately 1% of movement disorders post-stroke [1]. Symptoms often resist medical therapy, with structural basal ganglia damage limiting recovery. Repetitive transcranial magnetic stimulation (rTMS) has emerged as a non-invasive intervention for neurological disorders, including dystonia, by modulating cortical excitability and neuronal plasticity [2].

Objective: This case study aimed to evaluate the efficacy of continuous theta burst stimulation (cTBS) in treating drug-resistant post-ischemic hemidystonia in a 23-year-old male patient.

Methods: The patient, diagnosed with post-ischemic hemidystonia, presented a limited response to conventional pharmacological therapy. He underwent 10 sessions of cTBS targeting motor cortical regions for the affected arm and leg, delivered consecutively over 10 days. Clinical outcomes were assessed using the Unified Dystonia Rating Scale (UDRS). Moreover, single-pulse TMS was used to analyze corticospinal excitability, while short-interval intracortical inhibition (SICI) was assessed through paired-pulsed TMS before and after the treatment cycle [3].

Results: The UDRS score decreased from 13 at baseline to 11 after treatment, indicating a significant improvement, particularly in the arm. Corticospinal excitability showed a slight increase in motor thresholds post cTBS. SICI improved significantly at interstimulus intervals of 1–6 ms. No significant adverse effects were observed.

Conclusion: This case highlights the potential role of cTBS in alleviating cortical hyperexcitability associated with post-ischemic hemidystonia. Although clinical improvement was modest and variable between the arm and leg, the findings underscore the safety and therapeutic promise of rTMS as an adjunctive treatment for refractory dystonia. Further studies are needed to optimize stimulation parameters and clarify the neurophysiological mechanisms underlying its effects.

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P212

Misdiagnosis of functional neurological symptom disorders in pediatrics

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Content: Functional neurological symptom disorders (FNSD) pose a common challenge in clinical practice, particularly in pediatric cases where the clinical phenotypes can be intricate and easily confused with structural disturbances [1-3]. The frequent coexistence of FNSDs with other medical disorders often results in misdiagnosis [2]. We highlight the distinctions between FNSD and various psychiatric and neurological conditions. Contrary to the misconception that FNSD is a diagnosis of exclusion, we underscore its nature as a diagnosis of inclusion, contingent upon recognizing specific clinical features [1]. However, our focus is on a critical learning point illustrated by the case of a 14-year-old male initially diagnosed with FNSD, but subsequently found to have a rare primary monogenic movement disorder (paroxysmal kinesigenic dyskinesia, PKD). The crucial takeaway from this case is the importance of avoiding an FNSD diagnosis based solely on psychiatric comorbidity and suppressible symptoms [3]. Instead, clinicians should diligently assess for specific features indicative of FNSD, which were absent in this case. This emphasizes the importance of making a diagnosis of inclusion. Extended follow-up and clinical-oriented genetic testing might help identify comorbidities, prevent misdiagnosis, and guide interventions in complex cases, which cannot be simply classified as “functional” solely because other conditions can be excluded.

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P213

Is the motor reserve always a protective factor in movement disorders?

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Introduction: Cognitive reserve (CR) refers to the ability to cope with the effects of age and disease on cognition. More recently, the concept of motor reserve (MR) has been proposed as the ability to counteract the effects of disease on motor abilities. Involvement in motor activity predicts lower functional motor impairment in Parkinson's Disease (PD). Similarly, specific cerebellum brain networks in subjects with spinocerebellar ataxia type 2 correlated significantly with MR measures [1]. Aberrant connectivity has been shown in hyperkinetic motor symptoms, including dystonia [2].

Objective: Excessive repetitive movements in a particular setting may correlate with the onset of task specific dystonia even if no data are available for other dystonia syndromes; however, on this base we hypothesized that dystonia may be associated with increased MR.

Methods: MR was assessed by the MR Index questionnaire-MRIq [3]. Nineteen patients with isolated idiopathic cervical dystonia (iCD) were compared with 19 PD patients. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and the Unified Parkinson's Disease Rating Scale (UPDRS) were used to assess the severity of the motor disorder in iCD and PD, respectively.

Results: iCD had significantly higher MR than PD. In iCD group, MRIq total score, MRIq domestic activities and MRIq leisure activities subscales were positively correlated with the TWSTRS disability subscale. Moreover, TWSTRS total score was positively correlated with MRIq domestic activity subscale. In PD the MRIq leisure activities subscale was positively correlated with disease duration when keeping constant the motor disorder severity as measured by the UPDRS. Ultimately, only in iCD higher MR predicts more severe disability.

Conclusions: MR may be a protective factor for PD symptoms; in iCD, MR may be a predisposing factor for at least some of the symptoms. MR is a new concept whose relationship with movement disorders needs to be further investigated.

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P214

Spectral domain and angiography optical coherence tomography in atypical parkinsonisms and Parkinson's disease: an explorative study

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Introduction: Research recently focused on identifying early and accurate biomarkers to differentiate Parkinson's Disease (PD) from other degenerative parkinsonisms, as Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA) [1-3].

Objective: We aimed to investigate changes in the retinal structure and choroidal vascular network (CVN) in PSP and MSA patients in comparison to PD and controls (Ctrl).

Methods: Spectral Domain-Optical Coherence Tomography (SD-OCT) was used to examine the ganglion cell complex (GCC), retinal nerve fiber layer (RNFL) and subfoveal choroidal thickness, and OCT Angiography (OCTA) for the vessel density (VD) of retinal and CVN assessment.

Results: We analyzed 22 eyes from 11 PSP, 14 from 7 MSA, 48 from 24 PD patients, and 50 from 25 Ctrl. In comparison to Ctrl, we observed decreased GCC thickness among PSP ($p=0.001$) and PD patients ($p=0.003$), and reduced RNFL thickness in all three groups of patients (PD $p=0.043$; PSP $p<0.001$; MSA $p<0.001$). PD subjects showed lower values in VD of superficial capillary plexus ($p=0.013$) and radial peripapillary capillary (RPC) plexus ($p=0.014$) in comparison to Ctrl, whereas MSA and PSP patients did not differ from them. Both groups presented significantly decreased RNFL thickness and higher VD of RPC plexus in comparison to PD group ($p<0.001$).

Conclusions: Compared to PD, the retina structural damage in PSP and MSA appears to be similar but more severe, whereas the CVN appears to be preserved. Our preliminary results should be confirmed in a larger series of patients to test whether OCTA can be used to differentiate degenerative parkinsonisms early.

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P215

Creutzfeldt-Jakob disease presenting as corticobasal syndrome

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Background: Creutzfeldt-Jakob disease (CJD) is a rare and fatal prion disorder characterized by rapid neurological decline [1]. Its heterogeneous clinical presentations can mimic other neurodegenerative diseases, complicating early diagnosis. While typical features include cognitive impairment, cerebellar ataxia, and myoclonus, atypical presentations pose significant diagnostic challenges.

Case Presentation: We report the case of a 72-year-old woman evaluated for progressive gait impairment. Neurological examination revealed mild dysarthria, dystonic posturing, action-sensitive myoclonus, parkinsonism, and cortical sensory deficits. Cognitive assessment showed borderline impairment (MoCA 24). Investigations performed at two months from the clinical onset were inconclusive: MRI demonstrated mild nonspecific leukoencephalopathy, while brain SPECT and PET revealed hypoperfusion and hypometabolism in the right frontoparietal and temporal cortices. Initially, the clinical features strongly aligned with probable Corticobasal Syndrome (CBS) based on Armstrong criteria [2]. However, rapid clinical deterioration led to further investigations. EEG revealed periodic sharp waves in the right parietal derivations, and a second MRI showed cortical hyperintensity in diffusion-weighted scan. RT-QuIC confirmed sporadic CJD weeks after symptom onset. The patient developed clonic seizures and entered a comatose state, ultimately succumbing to the disease within months.

Conclusions: This case underscores the diagnostic complexity of CJD, particularly its potential to mimic CBS both clinically and on neuroimaging. Notably, in this case, hallmark EEG and MRI findings emerged only late in the disease course, emphasizing the importance of a thorough clinical evaluation and patient history in raising early suspicion of CJD. The rapid progression observed necessitates heightened vigilance and consideration of prion disease in atypical, rapidly progressive neurological syndromes. Advanced diagnostics such as RT-QuIC and diffusion MRI play a critical role in confirming the diagnosis and distinguishing CJD from other neurodegenerative conditions [3].

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P216

GATA1LOW mice: a new model for synucleinopathies?

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Introduction: GATA1 is a transcription factor involved in erythropoiesis for which there is no clear evidence in neuronal lineage, in contrast to GATA2. Current studies have demonstrated its role in the transcription of SNCA (alpha synuclein gene), Olig2 and TCF3, suggesting its involvement in myelination, inflammatory activity, autophagy homeostasis and glial cell development.

Objectives: The present study aims to determine the GATA1 expression in the brain, the effects of GATA1 knocking down on the expression of a-syn and on the survival of different neuronal subtypes and its subsequent role in neuronal processes.

Methods: The study was performed using control mice with CD1 background and a mice model of GATA1 knock down (STOCK GATA1tm2Sho/J). Following cyto-morphological comparison through Transmission Electron Microscopy, immunohistochemistry (IHC), immunofluorescence (IF) and RNAscope were used to analyze the expression of GATA1 protein and its co-expression with several markers of neuronal populations. Myelin was studied through Luxol fast blue and in IF. The expression levels of a-syn were analysed by ELISA.

Results: GATA1 is expressed in the peri-glomerular layer of the OB. The myelin fibers were significantly increased in the GATA1low mice, while the colocalization between MBP and MAPLC3β in the model indicated increased autophagy at the myelin fibers. TGFβ have shown colocalization with GATA1. Interestingly, the expression of GATA1 correlates with altered expression and aggregation of a-syn.

Conclusions: Our results prove, for the first time, that GATA1 is expressed in the brain. The observation of myelin and autophagic alterations in mice together with the TGFβ and GATA1 colocalization suggest a potential role for GATA1 in maintaining myelin integrity possible influence in neuroinflammatory or neurodegenerative pathways. Regulation of SNCA gene and contribution to maturation and survival of DA neurons, represent key biological functions of GATA1, which require further exploration to link GATA1 in the context of synucleinopathies.

P217

The diagnostic challenge of juvenile-onset Huntington disease

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Introduction: Juvenile-onset Huntington disease (JHD) is defined by onset of symptoms before the age of 21. Clinical manifestations mainly include behavioral disturbance, cognitive impairment and parkinsonian features [1,2].

Methods: We report a case of JHD in a patient with long-lasting severe psychiatric symptoms, cognitive dysfunction and a mild concomitant complex movement disorder.

Results: This 33 y.o. woman had a history of juvenile-onset major depressive episodes, with suicide attempts at the age of 18 and 29. Since age 29 she complained of generalized purposeless involuntary movements. In the next four years she experienced cognitive difficulties, with multidomain cognitive impairment revealed by neuropsychological evaluation. She had no developmental delay. Family history was unavailable, as the patient had been adopted. Clinical evaluation revealed cortical dysfunctions (apraxia, aphasia), upper motoneuron signs (hyperreflexia), mild complex movement disorder (choreoathetosis, oromandibular dystonia, bradykinesia) and brainstem dysfunction (downward gaze paralysis). General physical examination revealed a large abdominal mass, which was characterized as leiomyoma through further instrumental investigations. Hepatosplenomegaly was excluded. Biochemical analyses (blood, urine, CSF) were unremarkable for neoplastic markers, anti-neuronal surface antibodies, onconeural antigen-specific antibodies and metabolic alterations. T2-weighted brain MRI showed putaminal atrophy and hyperintensity. 18F-FDG brain PET-MRI documented bilateral hypometabolism in the striatal, parietal and temporo-occipital regions. DaT-SCAN showed bilateral marked hypoactivation of the striatum. An extensive genetic analysis for neurodegenerative diseases and movement disorders identified a 17/50 CAG repeat expansion in the HTT gene.

Conclusion: Diagnosis of JHD is often difficult due to the variety of clinical signs and symptoms, especially if family history is unavailable. Brain imaging can be key to formulate the correct diagnosis.

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P218

Anti-GAD65 antibodies: an atypical presentation of asymmetric movement disorder

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Introduction: Anti-GAD65 (Glutamic Acid Decarboxylase) antibodies are linked to autoimmune neurological disorders such as Stiff-Person Syndrome, cerebellar ataxia, epilepsy, and limbic encephalitis [1,2]. Their clinical presentations are diverse and can overlap with other neurological conditions, complicating diagnosis [3]. This report describes an atypical case of an asymmetric movement disorder associated with anti-GAD65 antibodies.

Case Report: A 65-year-old right-handed white man experienced a subacute onset of stiffness in his lower limb, leading to difficulty walking. A month later, he developed micrographia and tremor in his right hand, especially during prolonged tasks. Over the same period, he experienced involuntary weight loss of approximately 10 kg. His medical history included arterial hypertension and autoimmune thyroiditis. Neurological examination revealed mild dysarthria, nystagmus with slight vertical components, mild bradykinesia, moderate dysmetria, spastic hypertonia, and brisk reflexes in the right limbs, along with spastic-dystonic gait and dystonia in the right foot. Bilateral extension plantar reflexes were observed. Brain MRI showed mild chronic microangiopathy and cerebellar atrophy. 18F-FDG PET revealed subtle hypometabolism in the right cerebellum and anterior cingulate. Dopamine transporter SPECT was unremarkable. Neuropsychological testing indicated initial cognitive decline and ideomotor apraxia in the right hand. Cerebrospinal fluid analysis showed no significant abnormalities except a slight elevation in tau protein. High titers of anti-GAD65 antibodies were detected in both serum and cerebrospinal fluid. Neurophysiological studies confirmed nervous hyperexcitability in the right lower limb. A diagnosis of Stiff-Limb Syndrome was hypothesized, and treatment with high-dose IV steroids (Methylprednisolone 1 g/day for 5 days) and diazepam was initiated, resulting in improved gait and reduced stiffness. Chest-abdomen CT excluded paraneoplastic origins.

Conclusion: This case underscores the need to include anti-GAD65-related disorders in the differential diagnosis of asymmetric movement disorders [4,5]. Early diagnosis and tailored treatments, such as immunotherapy, can significantly improve outcomes. Follow-up is ongoing to monitor clinical progression and optimize therapy.

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P219

Disentangling long-standing psychiatric disorder from neurodegenerative disease in a complex case of parkinsonism and cognitive decline: a diagnostic challenge

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Objective: To present the case of a 68-year-old woman manifesting an atypical movement disorder associated with long-lasting psychiatric symptoms and progressive cognitive decline.

Case report: A 68-year-old woman came to our attention due to increasing gait difficulties, psychomotor slowing, and involuntary movements of the trunk and limbs, accompanied by buccolingual stereotypy, which had started three years earlier. Additionally, she reported memory and attention disturbances. She had been treated for approximately twenty years with various antidepressants and antipsychotics for a complex neuropsychiatric disorder characterized by persecutory delusions, misperceptions, depressed mood, dysphoric disorder, anxiety and insomnia. She had a family history of Alzheimer's disease. Neurological examination showed: hypomimia, hypophonic speech, vertical gaze limitation, bradykinesia, rigidity, choreiform movements and short steps in walking. Brain MRI showed severe bilateral frontal-temporo-parietal atrophy. Cerebrospinal fluid showed low amyloid-beta42. Serial neuropsychological evaluations documented multidomain deficits, with predominant impairment in memory and executive functions. The genetic test ruled out Huntington's disease. Further diagnostic investigations were not performed due to the patient's poor compliance.

Discussion: Tardive dyskinesia (TD) is a syndrome characterized by a constellation of iatrogenic movement disorders resulting from dopamine receptor antagonism. Long-term antipsychotic treatment is associated with the development of TD, which may result from aberrant dopamine transporter activity and is linked to an increased risk of cognitive impairment in psychiatric patients. In the presented case, TD due to long-term antipsychotic use likely compounded an underlying neurodegenerative disease, most probably Alzheimer's disease with suspected concomitant non-Alzheimer's pathology. This is supported by low CSF amyloid levels and cortical atrophy observed on MRI. However, a detailed differential diagnosis should exclude other causes of parkinsonism and cognitive decline, such as Lewy body dementia and corticobasal degeneration. The chronic use of antipsychotics may have both masked and exacerbated the clinical presentation, complicating the distinction between iatrogenic effects and primary neurodegenerative pathology.

P220

The tabetic hand: an ancient movement disorder not to be forgotten

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Introduction: Acute onset movement disorders among the many other causes can be symptomatic of lesions more frequently placed in the cerebral peduncles, internal capsule, thalamus or basal ganglia.

Case presentation: A 17 y.o. man presented to the ER complaining abrupt onset of weakness and motor impairment of the right hand during a period of emotional stress. One month earlier, he experienced transient paresthesia in upper and lower limbs, resolving within two weeks.
Neurological examination revealed fluctuating, slow, irregular involuntary fingers movements in both hands, worsened during eye closure and partially distractible. Remaining examination was unremarkable. Initially a psychogenic disorder was suspected.
Brain CT scan and blood examination were normal. Symptoms progressively resolved within a week.

Results: MRI showed T2 hyperintensities in the periventricular white matter, a contrast-enhancing lesion with predominant involvement of the posterior cord at C2 and in the cervical cord at C6.
CSF analysis was positive for oligoclonal bands.
The neurophysiological study only showed a reduction in amplitude and disorganized morphology of SEP from the left tibial nerve.
Our patient was diagnosed with Multiple Sclerosis (MS) according to the 2017 McDonald criteria and was treated with high dose methylprednisolon for 5 days and then started on fingolimod.

Discussion: Our patient had a tabetic hand, historically linked to syphilis and posterior column damage, which can present with ataxia, hypoesthesia, dystonia, handwriting alterations, involuntary movements and impaired fine motor skills. Isolated lesions of the posterior columns can mimic this condition. Movement disorders in MS arising from lesions in the posterior columns are rare. In this case, involuntary movements likely originated from altered descending projections with reduced proprioceptive control input to the motor system. Our patient emphasizes the need to recognize tabetic hand feature as important localizing neurological sign.

P221

An unusual case of cerebellar atrophy and palatal myoclonus: a case report

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Objective: Palatal myoclonus, also known as palatal tremor, is a rare neurological disorder characterized by rhythmic movements of the soft palate, typically within the 1–4 Hz range. These movements may be sinusoidal or jerk-like, resulting in the classification as either "tremor" or "myoclonus" based on clinical presentation. Palatal myoclonus is divided into two categories: essential (EPM), which lacks identifiable MRI lesions, and symptomatic (SPM), associated with structural abnormalities, often involving the Guillain-Mollaret circuit.

Objective: To investigate the etiology of a rare hyperkinetic movement disorder linked to cerebellar injury following trauma.

Methods: A comprehensive evaluation, including genetic testing, neurophysiological studies, and imaging, was performed to determine the cause of palatal tremor in a 25-years-old male.

Results: The patient presented with an ataxic gait, marked dysmetria in all limbs, diffuse hypotonia, divergent strabismus, cerebellar dysarthria, asymmetric reflexes, and flexed great toes. His medical history revealed a severe head trauma at the age of 15, one year before symptom onset. A head CT scan immediately after the trauma showed brain edema and a haemorrhagic contusion, with normal posterior fossa structures. An MRI one year later revealed mild hydrocephalus, cerebellar and corpus callosum atrophy, and sequelae of a right temporal contusion. Genetic testing via next-generation sequencing (NGS) was negative. Electromyography (EMG) and somatosensory evoked potentials (PESS) were also normal. A follow-up MRI confirmed hypertrophy and signal changes in the inferior olivary nuclei, along with a lesion in the right superior cerebellar peduncle and additional cerebellar damage. These findings supported a diagnosis of cerebellar atrophy and palatal tremor secondary to traumatic brain injury.

Conclusions: This case highlights an uncommon case of post-traumatic cerebellar atrophy with palatal tremor. Genetic testing excluded a primary etiology while, following an initial progression, the symptoms subsequently stabilized. Imaging demonstrated trauma-induced lesions in the Guillain-Mollaret circuit with typical hypertrophy of olives, demonstrating the etiology.

P222

Age-matched comparison of focused ultrasound thalamotomy for tremor in Parkinson's disease and essential tremor: a two-center study

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Background: Focused ultrasound (MRgFUS) thalamotomy is a proven and safe treatment for medically refractory tremors in both essential tremor (ET) and Parkinson's disease (PD). Few studies have compared outcomes between these two conditions, with some suggesting a lower long-term effectiveness in PD [1]. Recent research has identified age as a potential predictor of treatment response, but with divergent trends in PD [2] and ET [3]. This age-related variability may contribute to observed differences in outcomes.

Objectives: This study aimed to compare the treatment response to unilateral MRgFUS thalamotomy in age-matched populations of PD and ET patients, treated at two tertiary care centers.

Methods: We included patients matched by age, who were clinically assessed at baseline and at 6-month follow-up. A positive response was defined as a >30% reduction in the tremor score on the treated side at 6 months. Tremor severity was assessed using TETRAS for ET patients and MDS-UPDRS-III for PD patients. Adverse events were monitored at 48 hours and 6 months.

Results: We included 40 ET patients and 24 PD patients. ET patients experienced a reduction in tremor score of 49.2% (IQR, 38%–73%), while PD patients showed a reduction of 73.3% (IQR, 50%–97%) on the treated side. At 6-month follow-up, 32 out of 40 (80%) ET patients and 22 out of 24 (91%) PD patients had a >30% tremor improvement on the treated side (p=0.297). All adverse events were mild and transient.

Conclusions: A head-to-head comparison of unilateral MRgFUS thalamotomy outcomes in age-matched ET and PD patients revealed no significant differences in treatment effectiveness. Both groups demonstrated substantial tremor improvement, with no major adverse events.

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P223

Effects of combined theta-gamma frequency stimulation of the subthalamic nucleus on verbal fluency in Parkinson's disease: a randomized, double-blind, crossover study

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Introduction: High-frequency (gamma, 130-180 Hz) Deep Brain Stimulation (DBS) targeting the subthalamic nucleus (STN) is a well-established treatment for motor complications in Parkinson's disease (PD) [1]. However, evidence suggests that it may lead to cognitive decline, particularly in verbal fluency (VF) [2]. Low-frequency (theta, 4-10 Hz) stimulation has shown potential benefits for cognition but may worsen motor symptoms [3,4].

Objectives: This randomized, double-blind, cross-over trial aimed to evaluate the efficacy on VF and the safety of combined theta-gamma frequency stimulation in PD patients treated with STN-DBS.

Methods: Patients were randomly assigned 1:1 to start with either standard or theta-gamma STN stimulation, followed by the reverse. Each treatment period lasted one month. VF (including phonemic, episodic and non-episodic category, and switching VF) was assessed at baseline, one hour, and one month after each stimulation change. Secondary endpoints included adverse events (AEs), motor and non-motor symptoms (including mood and impulsivity) and their complications. Data were analyzed using a linear mixed-effects model, considering fixed effects for visit time, stimulation setting, and their interaction.

Results: Twelve patients completed the study. No significant effects of the stimulation settings were observed one hour after stimulation change for each VF tasks. After one month, theta-gamma stimulation significantly improved non-episodic category VF ($p = 0.037$) and episodic category VF ($p = 0.034$) over standard stimulation. No significant differences were found in phonemic fluency or category switching. Motor and non-motor outcomes were not significantly affected by the stimulation setting. AEs were mild and evenly distributed between conditions.

Conclusions: Combined theta-gamma frequency stimulation may improve VF in PD patients treated with STN-DBS safely and without worsening motor symptoms. This approach could be integrated into existing stimulation paradigms, though further studies are needed to confirm these findings and explore broader clinical implications.

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P224

Effects of deep brain stimulation on swallowing function in Parkinson's disease: a comparison between STN and GPi targets

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Introduction: Dysphagia is a common and debilitating non-motor symptom of Parkinson's Disease (PD), significantly affecting quality of life and increasing the risk of respiratory complications, including aspiration pneumonia. Deep brain stimulation (DBS) is an established treatment for advanced PD, and evidence suggests that DBS may influence the brain circuits involved in swallowing regulation. However, the precise effects of DBS on swallowing in dysphagic PD patients remain unclear.

Objectives: This study aimed to evaluate the effect of DBS stimulation on swallowing function in PD patients with dysphagia who already have DBS implanted, comparing outcomes between those with stimulation targeting the subthalamic nucleus (STN) or the globus pallidus internus (GPi). Swallowing was assessed both clinically and using instrumental methods, in both the 'on' and 'off' DBS states.

Patients and Methods: PD patients with DBS were evaluated through a multidisciplinary approach, including neurological, speech-language, and otolaryngological assessments. Various scales were used, including MDS-UPDRS III, Hoehn & Yahr stage, Dysphagia Outcome and Severity Scale (DYMUS), Mann Assessment of Swallowing Ability (MASA), and others. Fiberoptic Endoscopic Evaluation of Swallowing (FEES) was used for otolaryngological evaluation. Swallowing was assessed in the "on" medication state both during DBS "on" and "off" states.

Results: Fourteen PD patients (8 with DBS-STN, 6 with DBS-GPi) participated in the study. Preliminary results showed significant improvement in swallowing function in the DBS-GPi group during the 'on' stimulation phase, with a notable improvement in YALE valleculae scores ($p = 0.035$) and a significant increase in tongue strength ($p = 0.025$). In contrast, the DBS-STN group exhibited worsening in YALE pyriform sinus scores ($p = 0.039$) in the 'on' vs. 'off' state.

Conclusions: These preliminary findings suggest that DBS may affect swallowing function, with the implantation site playing a key role in modulating non-motor symptoms. Specifically, DBS targeting the GPi could improve swallowing, while DBS targeting the STN might have detrimental effects. However, these results need to be confirmed in larger studies.

P225

GBA1 status and deep brain stimulation in Parkinson's disease: a single-center retrospective longitudinal study

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Background: Effects of subthalamic nucleus deep brain stimulation (STN-DBS) in patients with Parkinson's disease (PD) carrying GBA1 variants has recently gained attention due to a possible more rapid cognitive decline than in non-carriers. The aim of this study was to evaluate motor and cognitive outcomes in STN-DBS patients according to their GBA1 status (GBA1+ vs GBA1-).

Methods: A single-center retrospective longitudinal study was conducted. Available clinical data were collected before (T0) and at several follow-ups after STN-DBS up to 10y (T5). Repeated measures analysis of variance (ANOVA) was performed to establish STN-DBS efficacy considering also levodopa equivalent daily dose (LEDD) reductions. Univariate and multivariate survival analysis (adjusted for sex, age-at-DBS, PD-duration-at-DBS) were performed to estimate the post-DBS risk of dementia.

Results: One-hundred-three STN-DBS patients were included (42 GBA1+, 61 GBA1-), with a mean age-at-last-follow-up of 64.1±9.2y, age-at-PD-onset of 43.2±7.5y, and age-at-DBS of 56.3±8.1y. Considering LEDD reductions, both groups benefited from STN-DBS up to T5 ($p<0.001$). Dementia occurred more frequently in GBA1+ patients ($p<0.001$) with an earlier age-at-diagnosis ($p=0.005$) and shorter DBS duration ($p=0.005$). GBA1+ status conferred a hazard ratio for dementia of 3.49 (1.49-8.18, adjusted-$p=0.004$), with half of GBA1+ with cognitive decline after a median of 10y after DBS (19y for GBA1-).

Conclusions: STN-DBS is effective for the management of advanced PD in GBA1 carriers, despite possible earlier cognitive burden than non-carriers. Future studies should focus on life quality of patients and caregivers to better elucidate the risk-benefit ratio of STN-DBS in this type of patient.

P226

Subcutaneous foslevodopa-foscarbidopa infusion: results at six months, pitfalls and hints

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Introduction: Subcutancous foslevodopa-foscarbidopa is an innovative therapeutic approach used in the management of advanced Parkinson's disease, particularly for patients experiencing motor fluctuations despite optimized oral dopaminergic therapy [1]. The treatment has been shown to improve motor symptoms, reduce off-time. and enhance overall quality of life in patients with fluctuating responses to oral medications [2]. Additionally, patients report improved quality of life. including greater mobility, reduced pain, and a decrease in the severity of non-motor symptoms [2].

Objectives: To report the experience of our Movement Disorder Center over a follow up period of six months.

Results: 12 patients were enrolled from May 2024 with 3 drop out due to the following: 1 patient for unmanageable dyskinesia, 1 patient for complications of concomitant neoplastic condition, and 1 patient for severe site reaction. Nine patients (6M/3F) were evaluated at baseline and after three and six months. Unmanageable motor fluctuations were the main inclusion criteria for 5 patients. while 4 patients with minor daytime fluctuations where enrolled due to severe nocturnal hypokinesia.
Mean age was 61.58 (range 53-81), mean disease duration was 8.5 (range 5-17). mean MoCA score was 25.28 (range 20-28), mean MDS-UPDRS I score was 12 (range 4-23), mean MDS-UPDRS II score was 22.8 (range 12-32), mean MDS-UPDRS Ill score was 56.57 (range 32-87). mean UPDRS IV score was 5.43 (range 4-15). All patients received a 24-hours infusion at an infusion rate ranging from 0.34 to 0,57 ml/h (mean 0,46 ml/h). 2 patients discontinued all the oral medications, while 7 paitents continued to assume opicapone. MDS-UPDRS scores significantly improved at three months follow up (p-0.001 for the I-I-III-IV parts). At six months the improvement remained stable, MoCA scores remained stable.

Conclusions: Pitfalls: the titration period ranged between few days to several weeks to reach a good quality of ON time; site reactions may temporary decrease the drug absorption with transient worsening and reoccurrence of OFF time.
Hints: management of site reactions is crucial to the response to treatment; the daily doses of foslevodopa-foscarbidopa is generally higher than the previous oral LED, but this should be considered in order to prevent worsening of quality of life in the titration period.

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P227

Opicapone as add on to subcutaneous foslevodopa-foscarbidopa infusion: preliminary results

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Introduction: The use of subcutaneous foslevodopa-foscarbidopa in the management of advanced Parkinson's disease has shown promising outcomes. Clinical studies demonstrate significant improvements in motor fluctuations, with a reduction in off-time and enhanced on-time without dyskinesia.

Objectives: To report the experience of our Movement Disorder Center with opicapone as add on therapy to subcoutaneous foslevodopa-foscarbidopa.

Results: Twelve patients were enrolled from May 2024 with 3 drop out. Nine patients (6M/3F) were enrolled. Mean age was 61.58 (range 53-81), mean disease duration was 8.5 (range 5-17), mean MoCA score was 25,28 (range 20-28), mean MDS-UPDRS I score was 12 (range 4-23), mean MDS-UPDRS II score was 22,8 (range 12-32), mean MDS-UPDRS III score was 56,57 (range 32-87), mean UPDRS IV score was 5,43 (range 4-15). All patients received a 24-hours infusion at an infusion rate ranging from 0,34 to 0,57 ml/h (mean 0,46 ml/h). In all patient motor fluctuations completely disappeared within 2-28 days of treatment. Quality of ON, measured by UPDRS II mean score 18,25 (range 11-26) and reported by patients in their daily activities was still not adequate in 8 patients after a titration period of 4-6 weeks, so opicapone 50 mg was added at a variable doses of 1 tb/daily to 1/tab every other day in order to control reoccurence of dyskinesia. All these patients showed significant rapid improvement in the quality of ON time, with UPDRS II mean 11,12 (range 9-18) with no need of further increases of the foslevodopa-foscarbidopa dose.

Conclusions: Opicapone could be a useful add on to subcoutaneous foslevodopa-foscarbidopa in order to improve the quality of ON time and in order to limit the daily dose of foslevodopa-foscarbidopa, with a containment in the treatment costs per patient.

P228

Long-term efficacy of MRgFUS VIM thalamotomy for essential tremor and tremor-dominant Parkinson's disease: a 5-year follow-up

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Introduction: Essential tremor (ET) and Parkinson's disease (PD) have a significant impact on quality of life. Tremor affects 92% of PD patients, and tremor-dominant Parkinson's Disease (TDPD) severely impacts daily activities. [1] Magnetic resonance image-guided focused ultrasound (MRgFUS) thalamotomy targeting the ventral intermediate nucleus (VIM) has been proved effective for medically refractory tremor. [2] Although pivotal trials have demonstrated significant tremor and disability reduction at five years in ET patients, [3] long-term data on MRgFUS in TDPD are lacking. We present our center's long-term findings.

Objective: To assess the sustained efficacy and safety of MRgFUS VIM thalamotomy in patients with ET and TDPD over five years.

Methods: We included 12 patients (8 with ET, 4 with TDPD) who underwent unilateral MRgFUS-VIM thalamotomy. Efficacy was assessed using the Essential Tremor Rating Assessment Scale (TETRAS) and hand tremor scores from the Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III), with patients off anti-Parkinson medications. Evaluations were performed at baseline, 1, 6, 12 months post treatment and up to 5 years.

Results: At five years tremor remained significantly improved compared to baseline in both ET and PD patients, demonstrating sustained benefits of MRgFUS.
In ET patients, mean tremor scores improved by 64±25% at six months and 47±24% at five years. ADL improvements were observed in all ET patients, with a 64±20% reduction in ADL score at six months, maintaining a 40±11% improvement at five years.In PD patients, tremor scores improved by 58±19% at six months and 61±45% at both twelve months and five years.

Conclusions: We confirm the long-term outcomes of MRgFUS VIM in ET patients [3] and, for the first time, present long-term data on its effects in TDPD patients, although based on a limited cohort. Studies with larger sample size are needed to confirm these preliminary findings.

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P229

Foslevodopa infusion in Parkinson disease: a 20-week observation

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Background: Subcutaneous foslevodopa/foscarbidopa infusion is a promising treatment option for Parkinson's disease (PD) patients experiencing motor fluctuations that cannot be adequately managed with optimized oral therapy.

Methods: Patients were selected from two tertiary movement disorder centers and followed for 20 weeks (T1). Assessments included Parts III and IV of the MDS-UPDRS, BMI, MOCA test, and the calculation of the levodopa equivalent dose (LED) [1]. At baseline, the starting foslevodopa/foscarbidopa hourly infusion rate was determined based on previous reports [2]. All enrolled patients were evaluated for safety, while only those who completed the study were assessed for treatment efficacy.

Results: A total of 34 patients were enrolled, of whom 21 completed the 20-week observation period. Although there was no substantial change in the MDS-UPDRS motor score at week 20 compared to T1, most patients reported a significant reduction in motor fluctuations. During the study, foslevodopa infusion was initiated and progressively increased from 1688.34 mg (±523.89) at week 1 to 2319.77 mg (±754.37) at week 20. The daily LED also increased by 33% at week 20. Adverse events were reported in 70.5% of patients, with infusion site reactions being the most common. Additionally, three patients experienced worsening cognitive and psychiatric symptoms.

Conclusion: This study confirms that foslevodopa/foscarbidopa infusion effectively reduces motor fluctuations, while MDS-UPDRS motor scores remained stable. Foslevodopa doses and LED progressively increased over 20 weeks, likely influenced by 24-hour administration and an underestimated conversion factor. Most adverse events were infusion site-related. Overall, this study supports the efficacy of foslevodopa/foscarbidopa in patients with advanced PD.

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P230

Impact of low vs. high-frequency STN-DBS on PD motor symptoms: results from a two-center, randomized, double-blind, crossover trial

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Introduction: Subthalamic nucleus deep brain stimulation (STN-DBS) is an effective treatment for Parkinson's disease (PD). However, whether low-frequency stimulation (LFS) (i.e., 60 Hz) is more effective than high-frequency stimulation (HFS) (i.e., 130 Hz) on gait and postural disturbances is not entirely elucidated yet [1].

Objective: To explore whether LFS and HFS STN-DBS exert different effects on PD motor symptoms.

Methods: We conducted a two-center, randomized, double-blind, crossover trial on sixteen STN-DBS patients (7 females; age 69.7±7.2). Of them, 7 were tremor predominant (TD), and 9 were postural instability/gait disorder (PIGD) [2]. Participants were randomly assigned to receive either LFS (60 Hz) or HFS (130 Hz) during two separate visits, conducted one week apart, while in OFF-medication state. Stimulation amplitude was adjusted to maintain a stable total electrical energy delivered. The MDS-UPDRS part III, the Berg Balance Scale (BBS), and the Time Up-and-Go (TUG) tests were performed in OFF- and ON-stimulation states.

Results: A significant time, frequency, and motor subtype interaction was found for MDS-UPDRS part III total ($F_{2,13}=7.19$, $p=0.007$), tremor ($F_{2,13}=10.5$, $p<0.001$) and gait score ($F_{2,13}=4.27$, $p=0.03$), and BBS ($F_{2,13}=4.16$, $p=0.04$). Post-hoc tests for the tremor score indicated that in TD patients HFS ON state was significantly different from its OFF state ($p<0.001$) and LFS ON state ($p=0.02$). In contrast, for the gait score and BBS in PIGD patients both LFS and HFS ON states were significantly different from their OFF states ($p=0.02$ and $p=0.007$, $p=0.006$ and $p<0.001$, respectively), but not from each other ($p=0.77$). A significant effect of time ($F_{1,15}=5.73$, $p<0.03$), but not a significant time, frequency, and motor subtype interaction was found for TUG test duration.

Conclusions: LFS is equally effective to HFS in improving gait and postural stability in PIGD patients, whereas HFS is more effective than LFS for the management of PD resting tremor.

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P231

The effect of subcutaneous foslevodopa/foscarbidopa on non-motor symptoms and non-motor fluctuations: preliminary data

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Introduction: Non-motor symptoms (NMS) and non-motor fluctuations (NMF) are common complications of Parkinson's disease (PD) and occur since early stages, but their impact on patients' quality of life and disability increases in more advanced PD stages. Subcutaneous foslevodopa/foscarbidopa has recently been introduced as an innovative treatment for motor fluctuations and troublesome dyskinesia in PD patients [1].

Objective: To explore the effect of subcutaneous foslevodopa/foscarbidopa on NMS and NMF in PD patients.

Methods: Consecutive PD patients receiving subcutaneous foslevodopa/foscarbidopa at our institution were evaluated using the Non-Motor Symptoms Scale (NMSS) [2] and the Non-Motor Fluctuation Assessment questionnaire (NoMoFa) [3] at baseline and after 3, 6 and 12 months of therapy.

Results: A total of 14 patients were enrolled; a subset of 8 patients completed the baseline and 3-month follow-up assessments. At baseline, all patients (100%) reported at least one NMS, with a mean total NMSS score of 84.5 (46.4); furthermore, all patients (100%) reported at least one NMS in the OFF or ON state and were then considered as non-motor fluctuating, with a mean total NoMoFa score of 26.7 (18.3). The total NMSS score, gastrointestinal and mixed subscores improved significantly at the 3-month follow-up (all $p < 0.05$). A trend towards improvement was also found for total NMF score in the OFF condition ($p = 0.06$), miscellaneous - total number of symptoms ($p = 0.088$), dysautonomia – static score ($p = 0.076$) and memory in the ON phase ($p = 0.087$).

Conclusions: PD patients receiving subcutaneous foslevodopa/foscarbidopa may show improvements in NMS and NMF-related burden within a short time (3 months) after treatment initiation. Further data are needed to confirm these preliminary results.

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P232

Cognitive outcomes of advanced therapies in Parkinson's disease: A systematic review of apomorphine and levodopa-carbidopa intestinal gel therapies

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Background: Parkinson's Disease (PD) treatments, such as Apomorphine (APO) and Levodopa-Carbidopa Intestinal Gel (LCIG), represent advanced therapeutic options for managing motor symptoms [1]. However, clear selection criteria and well-defined cognitive outcomes remain lacking.

Objective: This systematic review specifically aims to address these gaps by assessing the cognitive impact of APO and LCIG in PD patients.

Methods: A systematic review followed PRISMA guidelines, with searches in PubMed, Web of Science, Scopus, and Embase. Two authors screened studies based on key inclusion criteria, including at least two cognitive tests, and a follow-up of 6 months or more. The risk of bias was evaluated using the Newcastle-Ottawa Scale (NOS).

Results: Fifteen studies were identified (7 APO, 8 LCIG). APO generally preserved cognitive function over a 12-month follow-up, with some declines in visuospatial memory and executive functions. LCIG, with a 28-month follow-up, showed a more extensive cognitive decline, particularly in patients with pre-existing impairments. Variability in cognitive tests made direct comparisons difficult.

Discussion: APO may have a more favorable cognitive profile than LCIG. However, differences in follow-up duration, moderate risk of bias, and inconsistent cognitive assessments warrant cautious interpretation. Improved patient selection and comprehensive cognitive evaluations are recommended for future practice.

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P233

A 12-month single-center experience with continuous subcutaneous infusion therapies for Parkinson's disease: the impact of proper patients and caregivers selection

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Objective: Subcutaneous continuous infusion (SCI) of levodopa/carbidopa and apomorphine are second-line treatments for Parkinson's disease (PD) patients with severe motor fluctuations unresponsive to conventional therapies. Due to the risk of treatment discontinuation, real-world data are crucial for optimizing treatment strategies.

Background: Foslevodopa/foscarbidopa is a soluble formulation of levodopa/carbidopa administered as 24h continuous subcutaneous infusion. Due to its recent commercialization, real-life studies and practical guidelines are still lacking. Apomorphine is a widely used advanced therapy for PD, but its use in Italy has been limited recently.

Methods: We report the experience of a single center (Parkinson Institute of Milan, ASST G.Pini-CTO, Italy), during the first 12 months after the commercialization of foslevodopa/foscarbidopa in Italy. The indication to an advanced therapy was decided during a multidisciplinary discussion, involving neurologists, neuropsychologists and nurses. A personalized decisional flowchart, including all different device aided therapies, was discussed for each patient, depending on the clinical history, specific contraindications and the presence of a caregiver.

Results: Between February 12th 2024 and January 22th 2025, foslevodopa/foscarbidopa therapy was offered to 30 patients. Two patients were unable to continue the treatment at discharge due to practical reasons (concomitant pulmonary infection and the lack of caregiver, respectively). One patient discontinued the therapy after 3 months due to the lack of familial support. The other patients continued the therapy with great motor benefit and improvement of the quality of life. We observed a worsening of hallucinations/psychosis in 3 patients, all responsive to reduction of the dose. In the same timeframe, we offered apomorhine SC infusion to 13 patients, of which 1 refused it at discharge. Among them, we had 2 drop out due to insufficient symptom control and 1 patient died for reasons unrelated to the treatment.

Conclusions: Subcutaneous infusions offer a safe and effective treatment option for patients with advanced PD. Our findings emphasize the importance of a multidisciplinary approach, including careful patient selection and ongoing support, to optimize treatment outcomes. Long-term follow-up and larger studies are needed to further refine treatment strategies.

P234

Monitoraggio domiciliare dei pazienti con malattia di Parkinson e terapie a infusione sottocutanea continua: migliorare il follow-up e le decisioni terapeutiche con le tecnologie indossabili

Home monitoring of patients with Parkinson's disease and continuous subcutaneous infusion therapies: improving follow-up and therapeutic decisions with wearable technology

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Objective: Subcutaneous continuous infusion of fosflevodopa/foscarbidopa and apomorphine is a valid treatment for patients with Parkinson's disease (PD) and severe motor fluctuations unresponsive to conventional oral therapy. Due to the risk of drop out, clinical monitoring is critical for appropriate and cost-effective care [GL1].

Background: Foslevodopa/foscarbidopa is a novel formulation of levodopa/carbidopa for patients with PD as a daily continuous subcutaneous infusion, Due to its recent commercialization, real-life studies are lacking, while apomorphine is an already widely used advanced therapy for PD.
Wearable devices for parkinsonian patients are widely available and can help in monitor symptoms for appropriate treatment and follow-up.

Methods: We report 1-week home monitoring data of the first 3 patients who received fosflevodopa/foscarbidopa infusion at the Parkinson Institute of Milan (ASST G. Pini-CTO, Italy) and 4 patients receiving apomorphine subcutaneous infusion in the same timeframe. Patients were assessed with clinical scales (UPDRS and UDYRS) and the STAT-ON device [1] before the start of the infusion and at 3-months follow-up. This device provides objective information on motor symptoms, like bradykinesia, dyskinesia, on/off fluctuations, freezing of gait, gait parameters, quantity of movement, postural activity. Concomitant oral drugs and side effects were collected.

Results: All patients report an increase in "good on time" compared with conventional therapy, with a significant reduction of peak-dose dyskinesia, with a mean reduction of UPDRS IV of 19%. This beneficial effect was confirmed at follow up visits. Symptom stratification based on wearable inertial sensors confirms symptom improvement, with a mean reduction of off time of 28% and of time with dyskinesia of 22%.

Conclusions: Subcutaneous infusions are a safe and effective treatment for patients with advanced PD. Home monitoring with wearable devices supports clinicians in understanding real-life motor status for appropriate patient follow-up in the domestic setting, which is critical for future cost-effectiveness studies and to reduce the dropout rate.

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P235

Can local-field potentials fast survey guide deep brain stimulation clinical programming in Parkinson's disease? A longitudinal study

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Introduction: Stimulation programming represents a critical step in DBS optimization and it is currently based on clinical assessment, it is time-consuming and prone to errors. DBS systems allowing Local Field Potentials (LFPs) recordings may represent a relevant tool to guide stimulation programming by assessing beta-band activity in Parkinson's disease (PD) [1,2].

Objective: Assess if LFP-based programming can reliably identify the best stimulating contact clinically assessed with monopolar review (MR) and with >6 months clinical follow-up (cFU).

Methods: Bipolar LFP recordings were obtained in nineteen PD patients treated with sensing-enabled DBS systems targeting the Subthalamic Nucleus or Globus Pallidus internus. LFPs were collected blindly with respect to clinical evaluation at MR (T0) and cFU (T1). After detecting beta-band peaks, three different methods were applied to identify the best contact between segmented rings (1 vs. 2), including non-adjacent rings (Method A), contiguous rings (Method B), and segments (Method C). Levels selected with each method were then compared to clinical and imaging-based contact selection by applying a similarity function and assessing the stability of the selection over time. A bootstrap hypothesis testing approach was also employed to compare the different methods with random contact choice.

Results: Among LFP-based programming strategies, Method B showed the highest concordance with clinical-based contact selection at both T0 and T1 (correlation coefficient of 0,5 and 0,6, respectively) and the highest selection stability over time (80,6%). In addition, Method B was superior to imaging-based and random selection in detecting the clinically selected stimulation level at both timepoints. When assessing the predictive value of the selection at T0, Method B showed a statistically significant similarity (91%) to clinical contact selection.

Conclusions: LFP-guided contact selection using a specific method can reliably detect clinical-based DBS stimulating contacts. Our observations support the application of Brainsense Survey in selecting the optimal stimulation site to reduce programming times.

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P236

Effects of subcutaneous foslevodopa-foscarbidopa on motor and nonmotor symptoms in Parkinson's disease patients: a prospective longitudinal study

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Introduction: Foslevodopa/foscarbidopa is a new, soluble prodrug combination administered as a 24-hour/day continuous subcutaneous infusion (CSCI) to treat Parkinson's disease (PD) patients who are not well controlled on oral medication.

Objective: We aimed at analyzing the effect of the switch from oral treatment with L-dopa to CSCI on motor and nonmotor symptoms over a 3-month treatment period.

Methods: From April to December 2024, 28 PD patients were implemented on CSCI in our site. Longitudinal data were available for 20 PD patients. At baseline and at the 3-month follow-up, motor symptoms severity was assessed using the Unified Parkinson's Disease Rating Scale part III (UPDRS III). Severity of treatment-related motor and nonmotor complications were assessed by means of the UPDRS part IV and the Nonmotor Fluctuation Assessment questionnaire (NoMoFa), respectively. Nonmotor symptoms burden was assessed using the NonMotor Symptom Scale (NMSS). Sleep quality was assessed by means of the Parkinson's disease sleep scale 2 (PDSS-2). Patient-reported Quality of Life (QoL) was evaluated using the Parkinson's Disease Questionnaire 8 (PDQ-8). At each visit, the total levodopa equivalent daily dose (LEDD) was calculated. Within-subject longitudinal differences on demographic and clinical variables between the two timepoints were assessed by means of one-way repeated-measures ANOVA analyses.

Results: Compared to baseline, significant improvement was found in NMSS – sleep and mood/cognition domain after 3 months of treatment with CSCI. Significant effects were also observed in PDSS-2 and PDQ-8 scores. As expected, significant increase in total wake-up time spent in OFF state without troublesome dyskinesia was also observed at follow-up. No significant changes were found in terms of total LEDD (oral vs CSCI). Infusion site adverse events were common and generally well-tolerated after 3 months of treatment.

Conclusion: Our data reveal that, along with motor fluctuation stabilization, treatment with CSCI may significantly improve nonmotor symptoms burden in PD patients.

P237

Voice tremor improvement following MRgFUS thalamotomy. An artificial intelligence study

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Introduction: The efficacy of Magnetic Resonance Imaging-guided Focused Ultrasound (MRgFUS) in treating upper limb essential tremor (ET) is well established [1]. Less evidence is available regarding the impact of MRgFUS on vocal tremor.

Objectives: The aim of this study was to investigate short-term (24-hour) changes in vocal tremor in ET patients undergoing MRgFUS, through objective artificial intelligence procedures.

Methods: All consecutive patients undergoing MRgFUS for medically refractory tremor over a two-year period were assessed for inclusion in the study. The inclusion criteria were a diagnosis of ET, with or without clinically overt voice tremor (ETVT+/ETVT-), and the availability to comply with the study protocol. Included patients were clinically and instrumentally assessed using a specific voice recording protocol [2] both before and 24 hours after MRgFUS targeting the ventral intermediate nucleus (Vim). Healthy subjects (HS), matched for age and sex, were also recruited and served as a control group. Sustained vowel /e/ emissions were collected through smartphones and processed with support vector machine algorithms to obtain receiver operating characteristic (ROC) curves. Lastly, likelihood ratios (LRs) were calculated to achieve clinical-instrumental correlations.

Results: 83 patients were included (44 ETVT+, 13 females, 31 males, mean age±SD 69.5±8.1 years, range 51-86 years and 39 ETVT-, 7 females, 32 males, mean age±SD 70.6±10.2 years, range 31-86 years). ROC curve analysis showed high statistical performance in discriminating HS from ET patients after MRgFUS (Acc: 95.2%). A similarly high level of statistical significance was observed when analyzing ET patients before and after MRgFUS (Acc: 80.4%). The artificial intelligence protocol demonstrated that MRgFUS targeting the Vim significantly improved voice performance in all ET patients, with a more pronounced effect in ETVT+ patients.

Conclusions: This study demonstrates, for the first time, a short term voice improvement following MRgFUS thalamotomy in ET patients. Longitudinal follow-up is necessary to confirm this evidence.

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P238

Parkinson MRgFUS L'Aquila registry: clinical characteristics and outcomes

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Introduction: Parkinson Disease's (PD)-related tremor is often resistant to conventional pharmacological treatments. Magnetic resonance-guided focused ultrasound (MRgFUS) offers a minimally invasive therapeutic option that uses high-intensity focused ultrasound for targeted thermoablation under real-time MRI guidance [1,2].

Objective: The aim of this study was to investigate the clinical characteristics and outcomes of patients included in the PD MRgFUS L'Aquila Registry.

Methods: All consecutive patients undergoing MRgFUS for PD-related tremor over a five-year period were included in the study registry. Clinical assessments were performed pre-treatment, and at 24 hours, 1 month, and 6 months post-treatment, using standardized scales such as the Clinical Rating Scale for Tremor (CRST) and the Unified Parkinson's Disease Rating Scale (UPDRS) Part III.

Results: 125 patients were included (98 males and 27 females, mean age±SD 68.93±8,85). The results demonstrated significant tremor improvement at all follow-up points, with the most pronounced benefits observed at 24 hours post-treatment (CRST pre-treatment: 32.71±13.34 vs. 16.45±9.20 at 24 hours, $p < 0.001$). These benefits potentially extended beyond tremor control, with significant improvements in overall motor symptoms as measured by UPDRS-III scores (UPDRS pre-treatment: 32.32±12.27 vs. 21.97±9.27 at 24 hours, $p < 0.001$). The procedure was well tolerated by most patients, with minimal and transient adverse events. Although a slight decline in efficacy was observed over time, significant improvements compared to baseline were maintained throughout the 6-month follow-up period (CRST: 21.99±10.32; UPDRS: 27.91±10.02, $p < 0.001$).

Conclusions: This technique provides improved motor control and enhances the quality of life for PD patients. Further studies are necessary to investigate whether the overall effect of MRgFUS thalamotomy on motor behavior is primarily driven by tremor improvement or if it is also associated with potential improvements in bradykinesia and hypertonia.

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P239

Advanced levodopa-carbidopa gel therapy management in Parkinson's patients: the key role of the nurse Case Manager

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Introduction: The intestinal gel of levodopa-carbidopa is used in patients with Parkinson's disease (PD) to alleviate symptoms of advanced PD and improve quality of life (QoL) compared to conventional therapy [1]. Since 2018, the Fondazione IRCCS Istituto Neurologico Carlo Besta, in Milan, has organized specialized visits to ensure optimal care for patients undergoing this treatment. In 2020, a dedicated multidisciplinary outpatient clinic was established, where the Nurse Case Manager (CM) plays a central role in the care and management of these patients.

Objective: This work focuses on the activities of the CM in evaluating patients undergoing advanced therapy with levodopa-carbidopa gel, aiming to provide personalized nursing care.

Methods: With the increase in outpatient activities, it was deemed necessary to establish a Diagnostic-Therapeutic Care Pathway (PDTA) that clearly outlines roles, responsibilities, timelines, and processes for managing this patient population, from the screening phase to hospitalization for J-PEG implantation.

Results: The PDTA is currently under development. During the screening phase, the CM assesses non-motor symptoms and social aspects to ensure the patient has the necessary support and resources to undergo therapy. This specific assessment includes evaluating caregivers using specific scales, addressing aesthetic concerns related to the device, assessing the patient's and caregiver's potential capabilities, evaluating living conditions, autonomy, and providing targeted therapeutic-health education. In 2023-2024, 18 patients were admitted and subsequently underwent J-PEG implantation, out of a significantly larger number of patients screened.

Conclusions: Given the invasive nature of the therapy, the presence of a caregiver and a well-structured social framework is essential to ensure the compliance and effectiveness of the therapeutic pathway.

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P240

Multidimensional evaluation of subthalamic deep brain stimulation outcomes

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Introduction: Subthalamic nucleus deep brain stimulation (STN-DBS) is a widely regarded surgical treatment for Parkinson's disease (PD). However, questions persist about its effects on cognition, behavior, and other non-motor features, emphasizing the importance of tailoring surgical indications to optimize outcomes.

Objective: To describe STN-DBS effects through a comprehensive evaluation of motor and non-motor outcomes while exploring the interconnections among these aspects.

Methods: This longitudinal cohort study included 98 PD patients, extensively evaluated before and 6 months after surgery. Comprehensive clinical assessments covered motor, cognitive, neuropsychiatric, sleep, autonomic, and quality of life aspects. Pre and post-DBS scores were compared using the Wilcoxon signed-rank test, and then reliable change indexes (RCI) were calculated. Logistic regression analysis was conducted to identify the predictive feature of stimulation outcomes, followed by a cluster analysis based on RCI to capture inter-variability in clinical outcomes.

Results: Motor symptoms and quality of life improved by a median of 48% and 29%. Cognitive functions remained normal in 76% of individuals, with an incidental risk of developing mild cognitive impairment estimated at 11%. Behavioral assessment showed a significant reduction in neuropsychiatric fluctuations after surgery. Cluster analysis revealed three distinct patient groups: one with mild PD and limited motor benefits post-DBS, one with severe cognitive deficits showing further cognitive and functional declines, and a third group with severe motor symptoms but better cognition that achieved the highest post-operative improvements.

Conclusion: This study introduces a multidimensional approach for assessing STN-DBS outcomes, highlighting the varied motor and non-motor benefits across patient profiles and underscoring the importance of personalized approaches.

P241

Continuous subcutaneous foslevodopa/foscarbidopa infusion: efficacy and safety in patients with advanced Parkinson's disease, the real-life experience of a single centre

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Introduction: Continuous subcutaneous infusion of foslevodopa-foscarbidopa represents the latest advancement among device-aided therapies for patients with advanced Parkinson's disease (PD), with proven safety and efficacy.

Objectives: The aim of the present study was to investigate the clinical profile and response of PD patients initiating continuous subcutaneous infusion of foslevodopa-foscarbidopa.

Methods: Patients with advanced PD (requiring at least 5 doses of levodopa per day, experiencing motor fluctuations, ≥1 hour of troublesome dyskinesia per day, and ≥2 hours of OFF symptoms per day) who were consecutively selected to start therapy with foslevodopa-foscarbidopa at the Movement Disorders Center, San Salvatore Hospital, L'Aquila, were longitudinally evaluated. The hourly infusion rate was calculated based on the patient's previous oral therapy. Patients were assessed using the UPDRS scale and initiated the new therapy during the OFF phase. Follow-up evaluations were conducted on days 7, 15, and at 1 month.

Results: 21 patients (median age±SD 71.9±7.8 years, 19% females, mean disease duration 14 ±6 years, median Hoen and Yahr score 3 (range 2-4), mean UPDRS III in the off phase 46.5±21). The mean starting infusion rates were as follows: basal 0.33±0.06, high 0.35±0.03, and low 0.21±0.04. The mean UPDRS III score after 2 hours of treatment was 35.8±16.8. At the 1-month follow-up, the mean infusion rates were: basal 0.37±0.09, high 0.39±0.09, and low 0.25±0.0. UPDRS III score improved significantly (29.4±20.1, $p < 0.001$) independently from sex ($p=0.23$) and years of disease (10 vs 25 years; $p=0.65$). Six patients dropped out due to inefficacy (n=2), adverse events (n=2, electric shock sensation in the lower limbs), and difficulties in managing the device (n=2). Significant improvement of non-motor symptoms such as sleep quality, pain control and gastrointestinal symptoms. Improved quality of life for both patients and care givers.

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P242

Evaluating Beta-Sensing for the optimization of deep brain stimulation in Parkinson's disease

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Introduction: Deep brain stimulation (DBS) is a well-established treatment for advanced stage Parkinson's disease (PD). Different approaches have been proposed to optimize stimulation parameters, including clinical monopolar review, 3D-radiological reconstructions and beta-sensing.

Objective: To compare beta-sensing with other approaches to optimize DBS stimulation parameters in PD patients.

Methods: We included DBS-PD patients with beta-band sensing devices. Baseline motor performances were evaluated using the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III in OFF-stimulation/OFF-medication state. Non-motor symptoms and motor fluctuations using MDS-UPDRS part I, II and IV, quality of life using Parkinson's disease Questionnaire (PDQ-39). Levodopa equivalent daily dose (LEDD) was calculated. First, DBS was activated using parameters pre-established through clinical monopolar review and 3D-reconstructions. Three hours later, patients were clinically examined using MDS-UPDRS-III in an OFF-med state, and new parameters were set based on beta-sensing. At follow-up visits, we reassessed the patients and examined beta-band sensing recording. We also calculated Total Electrical Energy Delivered (TEED) at every timepoint.

Results: Eight PD patients (5 males, 3 females, mean age at onset of 53.5±5.5 years) underwent DBS surgery at a mean age of 63.4±4.1 years. Seven received STN-DBS and one GPi-DBS. Baseline mean MDS-UPDRS part III scores were 35.3±7.0 (OFF-med/OFF-stim) and 23.3±5.4 (OFF-med/ON-stim). Scores for parts I, II, IV, and PDQ-39 were 8.0±5.1, 7.3±3.7, 3.9±3.3, and 29.6±27.9, respectively. Mean LEDD was 827.3±276.9 mg/die. Beta-sensing suggested new parameters in six patients. Three attended the first follow-up visit, showing trends toward improved MDS-UPDRS and PDQ-39 scores, though differences were not significant, with reduced TEED.

Conclusions: Our results show that beta-sensing is as effective as clinical monopolar review and 3D-reconstructions for short-term DBS optimization. Further data are needed to establish the long-term efficacy of the beta-sensing approach. For this purpose, long-term follow-up data on a larger sample of patients are currently being collected.

P243

Sex-related differences in a large cohort of patients with essential tremor and tremor-dominant Parkinson's disease treated with MRgFUS VIM thalamotomy

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Introduction: No studies so far have systematically explored sex-based differences in terms of clinical-demographic parameters, execution of the procedure, lesion's characteristics and outcomes between males and females undergoing magnetic resonance-guided focused ultrasound (MRgFUS) Vim thalamotomy for tremor control, both in the context of essential tremor (ET) and tremor-dominant Parkinson's disease (TdPD) [1].

Objectives: To identify the presence of possible sex-related differences in the outcome of the procedure; to compare by gender clinical-demographic (disease duration, age at the procedure, skull density ratio SDR), intra-procedural (duration, energy, power, average and maximum temperature reached), lesion volumes 1 day after procedure, effectiveness of the procedure and relapse rate, both within patients with the same pathological condition and between the different clinical entities treated with MRgFUS Vim thalamotomy (ET vs TdPD).

Methods: We retrospectively analyzed outcome and clinical-demographic, procedural and lesion-related variables of 108 subjects with ET (84 men, 24 women) and 86 patients (70 men, 16 women) with TdPD who underwent MRgFUS VIM thalamotomy for treating tremor. To assess baseline and 6 moths follow-up tremor severity, we used the TETRAS scale and the tremor-referred items of the MDS-UPDRS part- scale respectively in ET and TdPD patients.

Results: In the group of 108 patients with ET, we did not find significant differences between men and women in terms of disease duration, age at the procedure, tremor severity or SDR; the execution of the procedure and lesion volume 1 day after were not influenced by sex, nor were effectiveness of the procedure at 6-months follow-up and the relapse rate. Similar results were obtained in the group of 86 patients with TdPD.

Conclusions: Analyzing a large cohort of patients with ET and TdPD treated with MRgFUS Vim thalamotomy, it appears that sex is not a variable that determines differences in the characteristics of patients accessing the treatment, in the execution or results of the procedure itself [2].

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P244

Conventional and adaptive deep brain stimulation in Parkinson's disease: evidence from oxidative stress and inflammation biomarkers.

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Background: Parkinson's Disease (PD) progression involves oxidative stress (OxS) and neuroinflammation, contributing to neuronal degeneration. Conventional Deep Brain Stimulation (cDBS) improves motor symptoms but may exacerbate OxS. Adaptive DBS (aDBS), a closed-loop approach, modulates stimulation parameters in real-time, potentially mitigating oxidative damage.

Methods: The study enrolled eight PD patients (5 males, 3 females; mean age: 57.1±7.9 years; mean disease duration: 12.4±3.2 years). Patients underwent both cDBS and aDBS stimulations in a controlled, randomized cross-over design. Blood samples were collected pre-stimulation and in on and off stimulation conditions to assess biomarkers: reactive oxygen species (ROS) via electron paramagnetic resonance (EPR); total antioxidant capacity (TAC), inflammatory cytokine (IL-6) and Transthyretin (TTR) by Enzyme-Linked Immunosorbent Assay methods; thiol redox status measured through high-performance liquid chromatography (HPLC). Each modality was administered for 8 hours under controlled conditions.

Results: DBS, regardless of modality, has no effect on OxS markers ($p > 0.05$). ROS production rate and TAC remained stable compared to baseline with both types of stimulation. Thiol redox status remained unaltered post-stimulation. IL-6 showed a decrease of 34% in cDBS "on" compared with "off" condition and an increase of 13% with aDBS "on" vs "off" condition. TTR decreased by 34% when comparing cDBS "off" to cDBS "on" and increased by 10% comparing aDBS "on" to aDBS "off.".

Conclusions: Oxidative stress persists despite DBS interventions. Although no significant effects on OxS biomarkers were observed in this study, the observed opposing directions of IL-6 decrease and TTR changes suggest a complex interaction of underlying phenomena; suggesting a role for TTR as a modulator of alterations occurring during deep brain stimulation in PD patients. These findings warrant further investigation in longitudinal studies to better understand the dynamics of oxidative stress and the potential long-term effects of DBS on neuroprotection.

P245

Subcutaneous foslevodopa/foscarbidopa for advanced Parkinson's diseases: preliminary data on the experience of the Verona Parkinson Centre

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Introduction: Subcutaneous foslevodopa/foscarbidopa has recently been introduced as an innovative advanced non-invasive treatment for motor fluctuations and troublesome dyskinesia in Parkinson's disease (PD) [1].

Objectives: To report the experience of the first 15 PD patients treated with subcutaneous foslevodopa/foscarbidopa at the Parkinson Centre at the University of Verona.

Methods: Consecutive patients with levodopa-responsive advanced PD, inadequately controlled on current therapy, receiving subcutaneous foslevodopa/foscarbidopa at our institution were included. On time without troublesome dyskinesia, off time, safety and tolerability were assessed at baseline and after 3 and 6 months.

Results: A total of 15 patients (8 women, 7 men; age: 68.9, SD 8,5; disease duration: 19.4, SD 7.2) were enrolled. Three of them were previously treated with subcutaneous apomorphine infusion, three with continuous intrajejunal levodopa/carbidopa intestinal gel infusion, and one with deep brain stimulation that was removed because of infection. On time without troublesome dyskinesia and off time were significantly improved at 3 months (+2.2 h, SD 0.7 and -1.8, SD 0.6; $p < 0.05$) and 6 months (+2.4 h, SD 0.6 and -1.5, SD 0.4; $p < 0.05$). No serious adverse events were reported. Four patients reported infusion site adverse events (erythema and pain) that were treated with education of the caregivers and did not lead to discontinuation. Hallucinations and mild psychosis were reported by one patient who dropped out.

Conclusions: Our data confirmed that foslevodopa-foscarbidopa improves motor fluctuations, with benefits in both on time without troublesome dyskinesia and off time in patients with advanced PD. Further and longer follow up data are needed to confirm these preliminary results, as well as the long-term safety of this innovative treatment.

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P246

Advanced therapies for Parkinson's disease: the experience of the Parkinson Unit of AOU Careggi of Florence in the initiation of subcutaneous foscarbidopa/foslevodopa administration

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Introduction: The "complex phase" of Parkinson's Disease (PD) is characterized by the appearance of motor and non-motor fluctuations which significantly impact the patient's quality of life. One of the hypotheses underlying the onset of fluctuations concerns oscillation of dopamine concentration at the striatal level, correlated with the intermittent intake of oral L-dopa. It was hypothesized that a continuous administration of L-dopa could reduce fluctuations in striatal dopamine concentration and the appearance of motor fluctuations. Subcutaneous Fosflevodopa/Fosfcarbidopa administration has recently been approved as an effective therapy for the complex phase of PD. Here we expose the experience of our center.

Objective: Evaluate the tolerability and efficacy of Foslevodopa/Foscarbidopa therapy in a cohort of patients suffering from "complex-phase" of PD.

Methods: 15 subjects were enrolled among patients of the Parkinson Unit of Careggi Hospital, with a diagnosis of complex-stage PD and were screened for advanced therapy. Screening included motor, cognitive, behavioural assessment and questionnaire about quality of life: motor fluctuations were assessed by the MDS-UPDRS part IV. Cognitive assessment included Montreal Cognitive Assessment and Frontal Assessment Battery. At the screening examination subjects had a mean duration of illness of 14.5 years and a mean age of 66,8 y/o. Before the beginning of Foslevodopa/Foscarbidopa therapy patients were taking polytherapy with a mean LEDD of 1029 mg/die. Patients started Foslevodopa/Foscarbidopa therapy between May 2024 and January 2025 and underwent neurological follow-up.

Results: 13 of 15 patients reported a reduction in fluctuations and dyskinesia, improvement in quality of life without significant side effects. We only recorded two discontinuations of therapy, one for ineffectiveness and one for switching to Deep Brain Stimulation. Clinical follow-up is still ongoing.

Conclusion: Preliminary data on the use of subcutaneous Foslevodopa/Foscarbidopa therapy confirms the good tolerability of the therapy, low number of adverse events and an improvement in quality of life.

P247

Neurophysiological and clinical effectss of deep brain stimulation in Parkinson's disease: studying the local field potentials of the subthalamic nucleus

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Introduction: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established treatment for complex-stage Parkinson's disease. Besides its therapeutic utility, new generation neurostimulators allow chronic recording of the STN Local Field Potential (LFP) simultaneously with current delivery. Previous studies demonstrated that excessive oscillatory activity within the beta band (13-35 Hz) is related to motor symptoms; conversely, it is reduced by therapeutic interventions such es L-DOPA and DBS. Moreover, it has recently been observed that beta activity fluctuates over time according to a 24-hour periodicity.

Objective: To study how the beta band activity is modulated according to intake of medication, time of the day and clinical state (on, off, dyskinesias) in patients with Parkinson's disease implanted with DBS in a real-life scenario.

Materials and methods: 8 patients implanted with sensing-enabled Percept™ stimulator at Parkinson Unit AOU Careggi Florence were included to achieve long-term recordings of the STN-LFP during chronic DBS.

Results: Data analysis showed a significative relationship between medication and beta power reduction. Furthermore, a clear fluctuation of beta power according to a 24-hour periodicity was observed, assessing that beta activity was consistently greater during wake time and lower during sleep time.

Conclusion: As well as being effective therapeutic tools, new sensing-enabled stimulators are useful for the clinical management of patients with Parkinson's disease and for research purposes. Firstly, they provide remarkable information for optimizing medical treatment and adjusting DBS parameters, in order to stabilize the clinical benefit of patients. Secondly, they allow to explore the neural correlates of the complex interaction between DBS, drugs, clinical states and time of the day in the every-day life of patients, to achieve a better characterization of the behaviour of beta power, which is used as the main feedback biomarker for a-DBS algorithms.

P248

Implementation of sub-cutaneous foslevodopa-foscarbidopa in advanced Parkinson's disease: experience in real-life

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Introduction: Foslevodopa-foscarbidopa has been recently approved for treatment of motor fluctuation in advanced Parkinson's disease (PD) [1]. Little is known on the implementation of Foslevodopa-foscarbidopa in real-life settings.

Objective: The aim of this study is to describe our single center experience with implementation of foslevodopa-foscarbidopa in advanced PD.

Methods: Foslevodopa-foscarbidopa has been implemented in 14 patients so far of whom 2 dropped out. All patients underwent motor and non-motor evaluation before and after 6 months since the implementation including the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part I-II-III-IV and the Questionnaire for impulsive-compulsive disorder in Parkinson's disease rating scale (QUIP-RS). To date, six out 12 patients on foslevodopa-foscarbidopa completed the 6-month follow-up. Comparison between baseline and follow-up data was run with paired sample t-test.

Results: Twelve patients remained on foslevodopa-foscarbidopa. Mean age (standard deviation) and disease duration at implementation were 68.38 (8.07) and 15.33 (5.86) years, respectively. Before the implementation, Total Levodopa Daily Dosage was 981.32 (301.68) mg. The MDS-UPDRS part I [1.16 (4.02), p=0.509], II [-0.16 (2.63), p=0.883], III [-1.75 (4.85), p=0.523], IV [1.40 (2.60), p=0.296] remained stable over time. The QUIP-RS presented a trend towards significance for an increase over time [7.00 (5.35) p=0.079]. All daily dosages (low, intermediate and high) presented an increase over the follow-up (+14.13%, +12.69% and +21.38%, respectively).

Conclusions: Our data support the need to increase the foslevodopa-foscarbidopa dosages over the follow-up. Follow-up evaluations of the remaining patients are ongoing.

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P249

Real-life experience with continuous subcutaneous foslevodopa/foscarbidopa infusion in advanced stage of Parkinson's disease at Villa Margherita, a leading institution in patient care

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Introduction: Continuous subcutaneous infusion (CSCI) is a novel treatment for advanced-stage Parkinson's disease (PD) [1]. Since its approval by the Italian regulatory agency (AIFA) in 2024, we have adopted this therapy in our clinical practice. Here, we present the results of our case series, focusing on tolerability and efficacy, in line with clinical trial findings.

Methods: Twenty patients (6 females, 14 males) with levodopa-responsive PD and morning akinesia, meeting the Delphi panel criteria [2], were treated with 24-hour CSCI at individually optimized doses determined during a 10-day hospitalization period. The primary objectives included assessing improvements in morning akinesia, evaluating changes in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS III and IV) and documenting any additional clinical observations.

Results: Between March and November 2024, we enrolled 20 patients with a mean age of 70 years (62–80), MMSE scores of 27/30 (25–30), disease duration of 10.4 years (5–17), and total daily levodopa intake of 806 mg (350–1200). Two patients discontinued treatment: one due to a depressive reaction and one due to a severe localized skin infection. The most frequent adverse events were mild non-serious infusion site reactions. All patients reported significant improvement in morning akinesia, however, 4 out of 18 patients still required oral medication for early morning administration. At three months, preliminary data showed global improvement in UPDRS III and IV scores compared to baseline (data collection ongoing). At the end of hospitalization, the mean CSCI infusion rates were 0.30 mL/h during the day (0.15–0.47) and 0.17 mL/h at night (0.15–0.30). Seven patients tested self-administered bolus doses (0.30 mL) but found them less effective than oral rescue therapy. Three patients temporarily suspended CSCI due to mild infusion site reactions: during the interruption, they reported improved therapeutic coverage with the same oral medication regimen used prior to CSCI initiation, suggesting a potential residual benefit of continuous infusion on oral pulsatile administration.

Conclusion: We confirm that in a real-life setting CSCI is a safe and efficacious treatment for patients with advanced PD.

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P250

Life before and after Deep Brain Stimulation in Parkinson's disease patients: evolving needs, expectations, and perceived outcomes

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Introduction: The integration of neurotechnology, such as deep brain stimulation (DBS), into clinical practice, gives rise to challenges for translational ethics in healthcare. DBS for Parkinson's disease (PD) has been shown to mitigate motor symptoms effectively. At the same time, however, it can also substantially impact psychological and psychosocial domains [1]. These are areas that remain underexplored in research. Post-DBS patients face new challenges, including adapting to the device and coping with progressing disease stages [2], [3]. These aspects necessitate a more comprehensive approach to patient care that values individual experiences and perceptions, moving beyond disease management to encompass holistic well-being.

Objectives: To investigate patients' and informal caregivers' perspectives, needs, and experiences before and after DBS.

Methods: We conducted semi-structured interviews with PD patients (P) and their informal caregivers (C) at three time points: 4.1 months preoperatively (P: n=9; 2 females; C: n=8; 6 females), 8.9 months after stimulation, and 16 months post-DBS (P: n=4; 1 female; C: n=3; 1 female). Thematic analysis identified patterns in evolving expectations, challenges, and perceptions.

Results: Before surgery, many reported feeling adequately informed when making the decision. Still, unrealistic expectations were also reported, as well as anxiety regarding the delicacy of the surgical procedure and its outcomes. Post-operative interviews revealed dynamic shifts in patients' perceptions of benefits, with new needs and expectations emerging as they adjusted to the device and its long-term effects. Importantly, caregivers did not always share complementary perspectives, highlighting the interdependence of patient and family experiences in adapting to DBS.

Conclusions: Our results offer practical insights that can be used to enhance patient-centred care, facilitate realistic expectation management, and improve shared decision-making processes. The conclusions of this study contribute to a more comprehensive understanding of the long-term impact of DBS, advocating for a model of care that moves beyond isolated symptom management to promote comprehensive well-being.

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P251

Switching from subcutaneous apomorphine to subcutaneous foslevodopa/foscarbidopa infusion: in advanced Parkinson's diseases: a case report

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Introduction: Subcutaneous foslevodopa/foscarbidopa has recently been introduced as an innovative advanced non-invasive treatment for motor fluctuations and troublesome dyskinesia in Parkinson's disease (PD) [1].

Objective: To report a single advanced PD patient who was previously treated with subcutaneous apomorphine infusion and switched to subcutaneous foslevodopa/foscarbidopa.

Case report: An 81-year-old woman with levodopa-responsive advanced PD (disease duration 25 years) was treated with subcutaneous apomorphine infusion (90 mg/day) for 10 years, pramipexole extended release 3.15 mg/day and on-demand melevodopa. The control of motor fluctuations and dyskinesia was incomplete and various therapeutic schemas with levodopa/melevodopa were not tolerated or worsened symptoms. Sleep quality and cognition were poor with hallucinations and delusions. Additionally, nausea and reduced food intake were reported. She refused deep brain stimulation in the past and repeatedly refused continuous intrajejunal levodopa/carbidopa intestinal gel infusion because she considered both treatments as too invasive. The patient was switched to subcutaneous foslevodopa/foscarbidopa that resulted in improvement of sleep quality, reduced hallucinations/delusions, reduced nausea and increase food intake leading to weight gain. The dosage of subcutaneous foslevodopa/foscarbidopa was slowly increased to 10 ml/day and the patient reported complete disappearance of dyskinesia and consistent improvement of off stages. No side effects were reported.

Conclusions: The patient here reported was on high-dose subcutaneous apomorphine infusion and the switch to subcutaneous foslevodopa/foscarbidopa was feasible, safe and effective, resulting in consistent improvement of motor and non-motor PD symptoms. Reaching the optimal dosage required a long time, probably because of the switch from a post-synaptic to a pre-synaptic drug and the reduced absorption of foslevodopa/foscarbidopa due to subcutaneous effect of previous apomorphine infusion.

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P252

Long-term pallidal deep brain stimulation for VPS13A chorea-acanthocytosis: a case study and meta-analysis

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Background: Chorea-acanthocytosis (ChAc) is a rare neurodegenerative disorder caused by autosomal recessive VPS13A mutations, leading to progressive movement and neuropsychiatric symptoms. The disease primarily affects the striatum and globus pallidus, with chorea, dystonia and neuropsychiatric disorders as hallmark features. Deep brain stimulation (DBS) of the globus pallidus internus (GPi) has been proposed as a symptomatic treatment, but its long-term efficacy remains unclear.

Objectives: We evaluated the long-term effects of bilateral GPi-DBS in a patient with genetically confirmed VPS13A-ChAc, focusing on motor symptom control and disease progression. Additionally, a meta-analysis focused on VPS13A-ChAc patients treated with DBS was provided to contextualize these results.

Methods and Results: A 29-year-old female presented with behavioral disturbances, tics, chorea-dystonia, and self-mutilation. Genetic analysis confirmed VPS13A mutations, and neuroimaging revealed basal ganglia atrophy and dopaminergic dysfunction. At age 39, she underwent bilateral GPi-DBS due to severe motor impairment. Preoperative assessment showed oromandibular and feeding dystonia, dystonic tongue protrusion, self-mutilation, and gait disturbances. Electrode placement was confirmed using neuroimaging and intraoperative neurophysiology. Following DBS, the patient showed sustained improvement in chorea, dystonia, and self-mutilation, particularly oromandibular symptoms, for 8 years. However, by year 9, she developed progressive gait dysfunction and postural instability (PIGD-like phenotype), worsening at 11 years post-implantation, despite DBS adjustments and dopaminergic therapy. A systematic review of 20 VPS13A-ChAc cases treated with DBS revealed variable motor outcomes, particularly for dyskinesia control.
Conclusions: Our case demonstrates that GPi-DBS provided long-term improvement in chorea-dystonia, particularly oromandibular symptoms, but less effective on axial symptoms. This case represents the longest documented DBS follow-up in VPS13A-ChAc (11 years) and the first with detailed neuroimaging and neurophysiological validation of electrode placement. The emergence of PIGD-like symptoms suggests disease progression rather than DBS failure. Given heterogeneous DBS response, further studies should standardize implantation protocols, explore neurophysiological biomarkers, and investigate disease progression to refine therapeutic strategies for VPS13A-ChAc.

P253

Subcutaneous infusion of foslevodopa/foscarbidopa: the importance of a standardized assessment, preliminary data from a movement disorders centre in Southern Italy

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Introduction: Foslevodopa/foscarbidopa subcutaneous infusion is a new device-aided therapy (DAT) for Parkinson's Disease [1-4]. Patients should be selected according to precise inclusion criteria [2].

Objectives: Propose a standardized clinical protocol of evaluation of the patients before and after the beginning of the infusion.

Methods: Motor and non-motor evaluation (UPDRS III in ON and OFF phases, UPDRS I, II and IV, Addenbrooke's Cognitive Examination – III) before treatment;
Education of the caregivers and the patient in a 3day period after the beginning of the treatment;
Follow-up visits (7 days: motor assessment; 1, 3, 6, 12 months: motor and non-motor assessment).

Inclusion criteria: HY ≤ 3, Addenbrooke's Cognitive Examination – III MMSE ≥ 24, good levodopa response (improving of UPDRS III by at least 25%); OFF state ≥ 2h/daily; levodopa doses ≥ 5 daily; presence of a caregiver.

Results: We evaluated 8 patients (4 males, 4 females), mean age 70years, mean HY 2, of which: 2 did not meet the inclusion criteria, 2 missed their 7days follow-up visit and discontinued the treatment and 1, though eligible, chose to wait before receiving the treatment. The three patients who are currently under treatment are 2 females, 1 male. All three of them experienced a worsening in UPDRS III (of 20, 30 and 10 points respectively) after one week from the implementation of therapy and required a dose adjustment. Data at 1 and 3 month-follow up have been collected for two patients.

Conclusion: The most important follow-up assessment is the 7 days one, since all the patients experience a worsening of their motor function, and therefore a dose adjustment is required. Our study is a preliminary one, and we plan to extend the number of patients and to present follow-up data at 3, 6 and 12 months after the implementation of therapy.

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P254

Differences in beta-band dynamics between STN and GPi in Parkinson's disease and their clinical correlates

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Introduction: Abnormal beta synchronization in the basal ganglia is a hallmark of Parkinson's disease (PD) [1,2]. However, while consistent Local Field Potentials (LFPs) data from the Subthalamic Nucleus (STN) are available, beta dynamics in the Globus Pallidus internus (GPi) are poorly defined.

Objective: We aimed to characterize and compare chronic LFP recordings from STN and GPi.

Methods: Eighteen PD patients implanted with a sensing-enabled deep brain stimulation (DBS) system (10 STN-DBS, 8 GPi-DBS, 36 nuclei) were evaluated >6 months after surgery. LFPs were recorded using the BrainSense Streaming. Cardinal motor symptoms were assessed using MDS-UPDRS-III. Patients were evaluated in the clinical OFF condition (MED-OFF) and 1 hour after L-Dopa administration (MED-ON) with DBS switched off (DBS-OFF) and on (DBS-ON). LFP power spectra were computed and activity in the beta band analysed. Also, beta bursts were identified and characterized.

Results: Beta peak amplitude was higher in the STN than GPi, while mean power in the beta, low- and high-beta bands were similar between nuclei. The total number of beta bursts, bursting rate and amplitude were similar between targets. In both nuclei, the severity of bradykinesia in the MED-OFF/STIM-OFF condition correlated with the beta peak amplitude, low-beta power and the number of beta bursts. L-Dopa and DBS stimulation reduced beta peak amplitude, the total number and long beta bursts and increased the number of short bursts in both nuclei [2,3]. However, L-Dopa and DBS alone were able to reduce the low-beta power in the STN [3], while the combination of the two was required to obtain the same effect in the GPi, paralleling bradykinesia amelioration.

Conclusions: Overall, our results demonstrate similar beta-band dynamics between STN and GPi. The differential modulation of low-beta activity by L-Dopa and DBS between the two nuclei may be the neurophysiological substrate explaining differences observed in clinical practice.

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P255

The mapping of the subcutaneous adipose tissue improves foslevodopa/foscarbidopa subcutaneous delivery and its therapeutic outcome

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Introduction: Foslevodopa-foscarbidopa is a soluble formulation of levodopa and carbidopa prodrugs delivered as a 24-h/day continuous subcutaneous infusion (CSCI) for people with Parkinson's disease (PwPD) and motor fluctuations. It undergoes to rapid enzymatic conversion via alkaline phosphatases to the pharmacologically active forms of levodopa-carbidopa. The selection of the best site of infusion represents a priority to ensure its absorption, and an inadequate thickness of the subcutaneous adipose tissue (SAT) can cause a therapeutic failure.

Objectives: To assess the utility of ultrasound (US) measurement of the SAT before treatment.

Methods: The US protocol was performed with a 5-11 MHz linear probe on six sites per side: upper abdomen (UA), lower abdomen (LA), lumbar region (LR), lateral thigh (LT), upper gluteus (UG) and shoulder region (SR). We built a map of SAT thickness for each subject, to chose the best site of infusion.

Results: Seven PwPD were enrolled for CSCI with foslevodopa/foscarbidopa. Four of them (58%) were slim and had a body mass index (BMI) between 18 and 25. We first applied our US protocol, and among the slim cohort the mean SAT thickness mapping was: UA 5,75 mm (± 0,96), LA 6,50 mm (± 1,29), LR 11,75 mm (± 0,96), LT 7,00 mm (± 0,82), UG 11,00 mm (± 0,82), DR 6,50 mm (± 0,58). The best sites of infusion in those subjects were LR and UG, then we started infusion with a 6 mm length needle, and they improved within one our. For all subjects with low BMI, this technique avoided inadequate site of infusion. At the 3-months follow-up they still were on effective therapy.

Conclusions: The preliminary US mapping of the SAT thickness represents a useful tool to avoid failure of CSCI. This technique ensures an adequate absorption of subcutaneous foslevodopa/foscarbidopa and its therapeutic outcome.