ABSTRACTS

The 2026 Fresco International Workshop on Synaptic Plasticity and Advances in Parkinson's Disease

Wednesday–Friday, November 4–6, 2026

Florence, Italy

www.frescoparkinsoninstitute.com

Fresco Parkinson Institute

NYU Langone Health

CENTRO NEUROLESI BONINO PULEJO IRCCS MESSINA

CUNY School of Medicine



Poster Number	Author	Title
1	Ambrogi Virginia	Impairment in Complex Emotion Recognition in Parkinson's Disease: Cognitive and Clinical Correlates
2	Barbaro Andrea	Effects of transcranial Electrical Stimulation (tES) on Theory of Mind (ToM) and Facial Emotion Recognition (FER) performance: A systematic review and meta-analysis
3	Culicetto Laura	Visuospatial and Alexithymia Dimensions of Resting-State EEG Connectivity in Parkinson's Disease
4	Maggio Maria Grazia	Immersive Dual-Task Virtual Reality in Parkinson's Disease: Linking Body Uneasiness to Cortical Connectivity.
5	Giglia Giuseppe	Feel the Grove, Reduce the Pain. Effects of Music on Pain related Changes in Motor Corticall Excitability
6	Marra Anna	Parkinson's disease influences processing of emotional action-related sentences
7	Cazzato Valentina	Beyond the masked face: dissociable components of facial emotion processing in Parkinson's disease
8	Lencioni Tiziana	Effects of Emotional Auditory Stimuli on Gait Termination and Re-initiation in Parkinson's Disease With and Without Freezing of Gait
9	Giovannelli Fabio	Proactive inhibition and action preparation as a function of impulsivity traits: a TMS study
10	Lombardi Giovanni	Impaired cortical inhibitory control in levodopa-induced dyskinesia
11	De Riggi Martina	The Shape of Sequence Effect in Parkinson's Disease
12	Ferraioli Francesca	Dissociated Corticospinal and Corticobulbar Responses to Levodopa in Parkinson's Disease
13	Lo Buono Viviana	Beyond Tremor Control: Multidimensional Functional and Emotional Recovery after MRgFUS VIM Thalamotomy in Tremor-Dominant Parkinson's Disease
14	De Santis Tiziana	Post-hypoxic myoclonus and Deep Brain Stimulation. Experience from a small patient cohort and literature review highlighting variable outcomes
15	Boccia Vincenzo Daniele	Thalamic Lesion Topography and Clinical Outcomes after MRgFUS in Tremor-Predominant Parkinson's Disease
16	Boccia Vincenzo Daniele	A Novel XPR1 In-Frame Deletion in Primary Brain Calcification: Clinical and Systems Neuroscience Insights
17	Di Vico Ilaria	Prevalence and Clinical Correlates of Fatigue in Parkinson's Disease: A Multicenter Case-Control Study
18	Formica Caterina	Resting-State High-Density EEG Biomarkers of Cognitive Dysfunction and Fatigue in Multiple Sclerosis: A Preliminary Study
19	Simeon Rachele	Short-latency Afferent Inhibition as a Potential Neurophysiological Biomarker of Fatigue in Parkinson's Disease
20	*Ielo Augusto*	Brain fingerprinting as a predictive biomarker of art therapy outcomes in Parkinson's disease
21	Di Rauso Giulia	In-Depth Insight into Young-Onset Parkinson's Disease: Demographic, Clinical, and Genetic Features
22	Del Gamba Claudia	Implementing genotype-guided Parkinson's disease care in clinical practice: the NEXT-GEN-PRATO ongoing multicenter targeted NGS study
23	Santurelli Pierpaolo	Botulinum Toxin for Musician's Dystonia: Clinical and Epidemiological Findings from a Two-Center Retrospective Cohort
24	Castagna Anna	Is Raman Spectroscopy salivary test useful in differentiating isolated cervical dystonia patients from healthy controls? Results from a preliminary pilot study
25	Lus M. / Castagna Anna	Goal Attainment Scaling in Isolated Cervical Dystonia Treated with Botulinum Neurotoxin: A Patient-Centred Group-Level Analysis
26	De Iaco L. / Castagna Anna	Long-Term Effect of Repeated Botulinum Toxin-A injections performed with Ultrasound and EMG guides in Professional Musicians: A Case Series
27	Montomoli Martino	Expanding the Motor and Molecular Spectrum of NAA15-Related Disorder: A Clinically Recognizable Pediatric Gait Dystonia.
28	Canonichesi Jacopo	Nanomedicine-based cholesterol delivery approach to counteract cortico-striatal disconnection in a prodromal Huntington's disease model
29	Çağlar Hilal	Seasonal Variations and Air Pollutant Associations in Ischemic and Hemorrhagic Stroke: A Retrospective Analysis
30	Frattini Emanuele / Magni Manuela	Modeling Multiple System Atrophy pathology in striatum organoids
31	Guell Paradis Xavier	A Novel 2D Synthesis of Cerebellar Anatomy
32	Mancini Maria	Alpha-synuclein effects in GBA Parkinson's model: early striatal circuit remodeling
33	Genovese Danilo	Unraveling the role of GBA1 genotype in axial signs response to subthalamic deep brain stimulation
34	Bellingacci Laura	Distinct roles of α-synuclein aggregates in synaptic dysfunction and therapeutic potential of novel anti-aggregating compounds
35	Restuccia Giovanni	APOE ε4 carriage is associated with basal ganglia microstructural alterations in early Parkinson's disease
36	Crolla Pio	Levodopa-responsive parkinsonism with early cognitive impairment in a carrier of the PSEN1 p.Tyr154Cys variant
37	Minuti Aurelio	Integrated Gene-Expression and Alternative-Splicing Analysis Reveals Molecular Dysregulation Associated with P301L Tau
38	Silvestro Serena	Synergistic neurotoxicity and transcriptomic profiling of PCB co-exposure with MPP+ in SH-SY5Y and SH-TAU Parkinson's disease models
39	Bastioli Guendalina	Investigation of Early Synaptic Dysfunction in PrknR275W Mouse Model: Effects of Pharmacological Kainate Receptor Blockade
40	Susca Gianmarco	Opicapone in advanced Parkinson's disease: a real-world longitudinal retrospective study
41	Gambelli Jasmine	Physical activity and rTMS modulate inflammatory pathways and improve clinical outcomes in Parkinson's disease
42	Gjonaj Elvira	High-Density EEG markers of neuroplasticity following intensive rehabilitation in Parkinson's disease
43	Saibene Francesca Lea	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.
44	Tenerini Carlotta	Casa Parkinson: An Integrated Multidisciplinary Territorial Model of Spe- cialized Care for Parkinson's Disease and Parkinsonisms
45	Polito Cristina	Cognitive training with a bio-cooperative robotic platform in Parkinson's Disease with Mild Cognitive Impairment: pilot findings from the OPERA project
46	Di Leo Maria Tiziana	Camptocormia in Parkinson's disease: An integrated rehabilitation approach and instrumental monitoring
47	Tatti Elisa / Ghilardi M. Felice	Intense multimodal outpatient training camp in Parkinson disease (PD): Preliminary results from a pilot study
48	Elayan N. / Ghilardi M. Felice	Inpatient Rehabilitation programs' impact on motor and non-motor signs of Parkinson's Disease
49	Maione Raffaela / Maggio Maria Grazia	Subjective-objective cognitive mismatch in Parkinson's disease: relationships with cognitive reserve and subjective cognitive complaints during home-based cognitive telerehabilitation
50	Siri Chiara	CREC (Creativity in Everyday Life Challenges): A Pilot Study of a Divergent Thinking-Based Cognitive Intervention in Patients with PD-MCI
51	Impellizzeri Federica	When Movement Becomes Music: Investigating Motor Agency Through Interactive Musical Feedback in Parkinson's Disease
52	Bonanno Mirjam	A Technology-Assisted Upper-Limb Rehabilitation Pathway in Parkinson's Disease: A Pilot Randomised Controlled Study Integrating Robotic Devices and Virtual Reality
53	Federica Campanelli	IL-1β Signaling Drives Early Hippocampal Dysfunction and Social Cognitive Deficits in Experimental Parkinson's Disease
54	De Carluccio Maria	Aerobic exercise reshapes inflammatory responses in Parkinson's disease: emerging role of perivascular macrophage-microglia crosstalk
55	Servillo Federica	Long-lasting and neuroprotective effects of intensive treadmill exercise on synaptic and behavioral outcomes in an α-synuclein model of Parkinson's disease
56	Floramo Alessia	Bioactivated Glucoraphanin exerted neuroprotective effects in an In Vitro Model of Parkinson's Disease
57	Zanetti Letizia	The autoimmune hypothesis: understanding neurodegeneration across idiopathic and genetic models of Parkinson's Disease
58	Bellini Gabriele	Gut epithelial-vascular barrier impairments and NLRP3 inflammasome activation across early Parkinson's disease and isolated REM sleep behavior disorder subjects
59	Marino Gioia	Ex vivo Alpha-Synuclein Effects Mimic Pesticides, Inducing Alterations in Glutamate AMPA Receptor Subunits
60	Grillo Piergiorgio	Physical exercise modulates plasma irisin levels in endurance athletes: implications for Parkinson's Disease
61	Grillo Piergiorgio	Data-Driven Biological Subtypes of Parkinson's Disease
62	Grillo Piergiorgio	The Prokineticin System Is Downregulated in Idiopathic Rapid Eye Movement Sleep Behavior Disorder: Evidence from Olfactory Neurons
63	Grillo Piergiorgio	Parameters of the Alpha-Synuclein Seed Amplification Assay on CSF predict the clinical subtype of Parkinson's Disease at 10-year follow-up
64	Melani Riccardo	Effects of voluntary physical activity on nigrostriatal DA release and nigral physiology in a mouse model of Parkinson's Disease
65	Sergi Gabriele	A Multisite ULTrasound Investigation of Vagus nerve Echostructure, Regional Substantia nigra, and Extra-neural markers in Parkinson's Disease: the MULTIVERSE-PD project.
66	Giacomina Carlo	Application of a framework for digital analysis in the longitudinal profiling of Muhammad Ali's voice, early Parkinson's disaese and matched controls
67	Marano Massimo	VAgus nerve Non-Invasive Stimulation Home trial for Parkinson's disease: the VANISH-PD trial

1. Impairment in Complex Emotion Recognition in Parkinson's Disease: Cognitive and Clinical Correlates

Authors
Virginia Ambrogi, Francesca Cecchi, Giulio Cherubini, Andrea Bellucci, Chiara Pedrini, Alice Gualerzi, Francesca L. Saibene, Anna Salvatore, Martina G. Turinelli, Angelo Bellinvia, Elisabetta Farina, Anna Castagna, Cristina Polito, Jorge Solano Navarro, Silvia Ramat, Marzia Bedoni, Benedetta Nacmias

Introduction
Parkinson's disease (PD) is characterized by motor and non-motor symptoms that affect disability and quality of life. Among non-motor manifestations, social cognition impairments, including difficulties in recognizing and interpreting others' mental and emotional states, are of growing clinical interest.

Objective
To assess complex mental state recognition in people with PD and explore its associations with cognitive and clinical characteristics.

Methods
Thirty-eight patients with PD, recruited at IRCCS Fondazione Don Carlo Gnocchi, Florence, within the SANDY study (ClinicalTrials.gov ID NCT06875739), were assessed using the FACE Test. Cognitive functioning was evaluated using the MoCA, FAB, Stroop Test, TMT, Rey Auditory Verbal Learning Test, and Rey Complex Figure. Clinical and motor data were also collected. Groups defined according to FACE Test performance were compared using Mann–Whitney tests.

Results
Twelve participants (31.6%) showed impaired or borderline performance. No significant differences were found in global cognition, executive functions, memory, visuospatial abilities, or motor measures. A significant difference emerged only in the MoCA Language subscore, with lower scores in participants with impaired FACE Test performance (U=93.00; p=0.026).

Conclusions
Difficulties in complex mental state recognition were relatively frequent and were not associated with the main cognitive or motor measures. The finding in the language domain suggests a possible involvement of cognitive-semantic processes and supports the potential value of including social cognition assessment in the multidimensional characterization of people with PD.

References
Aarsland, D., Creese, B., Politis, M., Chaudhuri, K. R., Ffytche, D. H., Weintraub, D., & Ballard, C. (2017). Cognitive decline in Parkinson disease. In Nature Reviews Neurology (Vol. 13, Number 4, pp. 217–231). Nature Publishing Group. https://doi.org/10.1038/nrneurol.2017.27
Argaud, S., Vérin, M., Sauleau, P., & Grandjean, D. (2018). Facial emotion recognition in Parkinson's disease: A review and new hypotheses. In Movement Disorders (Vol. 33, Number 4, pp. 554–567). John Wiley and Sons Inc. https://doi.org/10.1002/mds.27305
Terruzzi, S., Funghi, G., Meli, C., Barozzi, N., Zappini, F., Papagno, C., & Dodich, A. (2023). The FACE test: a new neuropsychological task to assess the recognition of complex mental states from faces. Neurological Sciences, 44(7), 2339–2347. https://doi.org/10.1007/s10072-023-06697-w

2. Effects of transcranial Electrical Stimulation (tES) on Theory of Mind (ToM) and Facial Emotion Recognition (FER) performance: A systematic review and meta-analysis

Authors
Andrea Barbaro1, A. D'Iorio1, G. Santangelo1

Affiliation
1 Department of Psychology, University of Campania "Luigi Vanvitelli", Caserta

Background
Transcranial Electrical Stimulation (tES) is a promising non-pharmacological approach for modulating social-cognitive processes such as Theory of Mind (ToM) abilities and facial emotion recognition (FER) [1, 2, 3, 4]. These related but non-interchangeable processes are often assessed together in the tES literature [5, 6]. This systematic review and meta-analysis therefore examined tES effects on cognitive and affective ToM and on FER in healthy and clinical populations

Methods
Randomized controlled parallel and crossover studies were identified in PubMed, Scopus and Web of Science. Quality was evaluated with RoB 2. Meta-analyses used Hedges' g.

Results
Thirty-six studies were included in the systematic review, of which 7 were eligible for meta-analysis. Studies varied in participant characteristics, stimulation technique, target brain region, task type, current intensity, duration and number of tES sessions. Qualitative findings indicated that tES-related changes occurred more in both affective ToM and FER than in cognitive ToM and were more consistently observed for reaction times (RTs) than for accuracy. The meta-analysis based on accuracy scores showed a significant pooled effect favoring tES ($g=0.68$, $p=0.045$), with substantial heterogeneity ($I^2=77.75\%$). The meta-analysis based on RTs outcomes showed $g=0.47$ ($p=0.041$, $I^2=0\%$). Because the task measures were conceptually heterogeneous, these pooled estimates should be interpreted as broad, exploratory indices of social-cognitive task performance

Conclusions
tES may influence performance on cognitive and affective ToM task and on FER. Methodological and conceptual heterogeneity substantially limits comparability and generalizability. Larger preregistered trials using clearly differentiated outcome measures, standardized protocols and cautious clinical end points are needed.

Bibliography
[1] M. Cotelli *et al.*, «Enhancing theory of mind in behavioural variant frontotemporal dementia with transcranial direct current stimulation», *Cogn. Affect. Behav. Neurosci.*, vol. 18, fasc. 6, pp. 1065–1075, dic. 2018, doi: 10.3758/s13415-018-0622-4.
[2] X. Mai *et al.*, «Using tDCS to Explore the Role of the Right Temporo-Parietal Junction in Theory of Mind and Cognitive Empathy», *Front. Psychol.*, vol. 7, mar. 2016, doi: 10.3389/fpsyg.2016.00380.
[3] V. Nejati, M. Sharifian, Z. Famininejad, M. A. Salehinejad, e S. Mahdian, «The neural structures of theory of mind are valence-sensitive: evidence from three tDCS studies», *J. Neural Transm.*, vol. 131, fasc. 9, pp. 1067–1078, set. 2024, doi: 10.1007/s00702-024-02808-9.

[4] F. Ruggiero *et al.*, «Anodal Transcranial Direct Current Stimulation over the Cerebellum Enhances Sadness Recognition in Parkinson's Disease Patients: a Pilot Study», *The Cerebellum*, vol. 21, fasc. 2, pp. 234–243, apr. 2022, doi: 10.1007/s12311-021-01295-y.
[5] P. Fitzpatrick, J. A. Frazier, D. Cochran, T. Mitchell, C. Coleman, e R. C. Schmidt, «Relationship Between Theory of Mind, Emotion Recognition, and Social Synchrony in Adolescents With and Without Autism», *Front. Psychol.*, vol. 9, lug. 2018, doi: 10.3389/fpsyg.2018.01337.
[6] P. H. Donaldson, M. Kirkovski, N. J. Rinehart, e P. G. Enticott, «A double-blind HD-tDCS/EEG study examining right temporoparietal junction involvement in facial emotion processing», *Soc. Neurosci.*, vol. 14, fasc. 6, pp. 681–696, nov. 2019, doi: 10.1080/17470919.2019.1572648.

3. Visuospatial and Alexithymia Dimensions of Resting-State EEG Connectivity in Parkinson's Disease

Authors
Laura Culicetto, Elvira Gjonaj, Fabiana Maria Bonasera, Serena Dattola, Lilla Bonanno, Simona De Salvo, Nunzio Muscarà, Viviana Lo Buono, Fabio Mauro Giambò, Chiara Sorbera, Giuseppe Di Lorenzo, Angelo Quartarone, Silvia Marino

Affiliation
IRCCS Centro Neurolesi Bonino Pulejo, Messina, Italy

Abstract
Visuospatial dysfunction and alexithymia are non-motor features of Parkinson's disease (PD)[1-2].
This study investigated their associations with resting-state EEG activity.
Thirty patients with PD (mean age 66.27 ± 9.51 years; 10 women) underwent 256-channel resting-state EEG and completed measures of visuospatial performance (BIT; Clock Drawing Test) and alexithymia (TAS-20; PAQ). Spectral power was estimated in the alpha, beta, and gamma bands. Source activity was reconstructed using eLORETA, and between-network functional connectivity was quantified through absolute imaginary coherency across eight networks. Associations were assessed using Spearman correlations with false-discovery-rate correction.
Better line-cancellation performance was associated with greater alpha-band connectivity between frontoparietal and visual networks ($\rho = 0.475$, $p = 0.008$), frontoparietal and default-mode networks ($\rho = 0.469$, $p = 0.009$), and limbic and visual networks ($\rho = 0.459$, $p = 0.011$). Letter-cancellation performance was positively associated with beta- and gamma-band connectivity, particularly frontoparietal–visual ($\rho = 0.498$, $p = 0.005$) and default-mode–visual connectivity ($\rho = 0.495$, $p = 0.005$). Greater difficulty identifying bodily sensations was associated with reduced beta- and gamma-band connectivity, especially limbic–auditory ($\rho = -0.499$, $p = 0.005$) and limbic–temporal connectivity ($\rho = -0.469$, $p = 0.009$). Poorer line-cancellation performance was associated with increased frontal alpha and beta power and central-parietal alpha power, whereas alexithymia dimensions showed positive associations with spectral power.
These exploratory findings suggest that visuospatial-attentional performance and alexithymia are associated with distinct resting-state EEG patterns in PD. Visual, frontoparietal, default-mode, and limbic networks represent candidate neural substrates requiring confirmation in larger samples.

References
[1]Assogna, F., Palmer, K., Pontieri, F. E., Pierantozzi, M., Stefani, A., Gianni, W., Caltagirone, C., & Spalletta, G. (2012). Alexithymia is a non-motor symptom of Parkinson disease. The American Journal of Geriatric Psychiatry, 20(2), 133–141.

[2]Shao, X., Wang, K., Zhang, Y., Zhen, X., Dong, F., Tian, H., & Yu, Y. (2023). Outcome of visuospatial dysfunction assessment in patients with Parkinson's disease using mobile application software. *Frontiers in Aging Neuroscience, 15*, Article 1108166.

4. Immersive Dual-Task Virtual Reality in Parkinson's Disease: Linking Body Uneasiness to Cortical Connectivity.

Authors
Maria Grazia Maggio, Serena Dattola, Antonino Lombardo Facciale, Simona De Salvo, Elvira Gjonaj, Rachele Burrascano, Alessandra Benenati, Raffaela Maione, Piero Buonasera, Paolo De Pasquale, Mirjam Bonanno, Angelo Quartarone, Rocco Salvatore Calabrò.

Background
Adaptive movement relies on updating the body relative to the environment through multisensory networks [1]. In Parkinson's disease (PD), disruption of this process may affect motor control [2,3]. We examined covariation between cortical connectivity and body uneasiness following CAREN dual-task rehabilitation.

Methods
Ten participants completed 20 CAREN sessions targeting gait, attention, executive control, and multisensory body processing. Body uneasiness was assessed using the BUT-A/B. Resting-state 256-channel EEG were acquired pre/post rehabilitation. Source-level lagged linear connectivity was compared across band-specific ROI pairs using paired Wilcoxon tests with FDR correction. Spearman correlations tested T1–T0 BUT changes against nominally changed connectivity features; correlation p-values were FDR-corrected.

Results
Six connections showed nominal post-treatment increases: left frontotemporal delta, right frontoparietal alpha, left parietotemporal beta/gamma, bilateral occipital beta/gamma. None survived FDR correction. Eight significant BUT–connectivity associations emerged. Increased bilateral occipital and left frontotemporal connectivity was predominantly associated with reduced body-image concerns (BIC, gamma: $\rho = -0.795$), compulsive self-monitoring (CSM, beta: $\rho = -0.649$), body-related avoidance (A, delta: $\rho = -0.635$; PST, delta: $\rho = -0.651$), and distress related to specific bodily features and functions (VIII, beta: $\rho = -0.696$). Left parietotemporal associations were frequency-dependent and directionally mixed (WP, beta: $\rho = 0.694$; III, beta: $\rho = 0.683$; VIII, gamma: $\rho = -0.662$). No correlation survived FDR correction.

Discussion
These findings involve regions supporting visual, spatial, and body-related networks. CAREN may act as an ecological multisensory perturbation, potentially modulating plasticity within a body–space–action network. Despite their exploratory nature, the dynamic updating of body representations could be an underexplored component of motor adaptation in PD.

References
1) Ionta S, Martuzzi R, Salomon R, Blanke O. The brain network reflecting bodily self-consciousness: a functional connectivity study. Soc Cogn Affect Neurosci. 2014;9(12):1904–1913. doi:10.1093/scan/nst185
2) Roytman S, Paalanen R, Carli G, et al. Multisensory mechanisms of gait and balance in Parkinson's disease: an integrative review. Neural Regen Res. 2025;20(1):82–92. doi:10.4103/NRR.NRR-D-23-01484

3) Scarpina F, Cau N, Cimolin V, et al. Defective tool embodiment in body representation of individuals affected by Parkinson's disease: a preliminary study. Front Psychol. 2019;9:2489. doi:10.3389/fpsyg.2018.02489.

5. Feel the Grove, Reduce the Pain. Effects of Music on Pain related Changes in Motor Corticall Excitability

Authors
Fabrizio Di Giovanni, Marzia Magnanini, Antonio Cangelosi, Giuditta Gambino*, Filippo Brighina and Giuseppe Giglia

Affiliations
Department of Biomedicine, Neuroscience and Advanced Diagnostics (BIND),
Section of Human Physiology
University of Palermo.

Abstract
Music has been proposed as a non-pharmacological tool for pain relief, but whether and how it counteracts pain-induced changes in motor cortex physiology remains poorly understood. Pain is known to alter corticospinal excitability and intracortical inhibition, and some analgesic interventions can restore these changes. Given that music may also modulate motor cortex physiology, whether these neurophysiological effects may be related to music-induced analgesia, and whether they depend on specific musical features such as groove, has not been established. Twelve healthy non-musicians (6 female) underwent transcranial magnetic stimulation (TMS) to assess corticospinal excitability (motor evoked potential, MEP; input-output curve, IOC) and intracortical inhibition (cortical silent period, CSP) in 4 conditions: baseline, capsaicin-induced pain, and pain combined with high-groove (HG) or low-groove (LG) music. Pain was rated on a visual analogue scale (VAS). VAS ratings did not differ significantly between music conditions, although only HG showed a nonsignificant trend toward lower pain. Capsaicin-induced pain reduced MEP amplitude ($p < 0.001$) and CSP duration ($p < 0.01$), indicating decreased excitability and inhibition. Crucially, both HG and LG music restored these parameters toward baseline, regardless of groove content. These findings suggest that music can counteract pain-related changes in motor cortex excitability independently of groove, even when effects on subjective pain are limited.

6. Parkinson's disease influences processing of emotional action-related sentences

Authors
Anna Marra2*, Sara Terranova1*, Giovanna Lagravinese3, Maria Catena Silvestri4, Alessandro Botta1, Martina Putzolu2,3, Gaia Bonassi2,3, Rachele Simeon2, Elisa Pelosin2,3, Carmelo Mario Vicario4, Laura Avanzino1,3.

Affiliations
1Department of Experimental Medicine, Section of Human Physiology, University of Genoa, Viale Benedetto XV 3, Genoa, 16132, Italy.
2Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Largo Daneo 3, Genoa, 16132, Italy.
3Ospedale Policlinico AOM San Martino, IRCCS, Genoa, Italy.
4Dipartimento di Scienze Cognitive, Psicologiche, Pedagogiche e Degli Studi Culturali (COSPECS), Università di Messina, 98121 Messina, Italy.
*****Both authors contributed equally to this work.

Background
This study tested the "embodied semantics" theory — that language meaning, especially action-related meaning, partly reuses motor-system circuitry — examining how Parkinson's disease (PD) patients process action-related versus abstract sentences with positive, negative, or neutral emotional content.

Objectives
We investigated whether accuracy and response times in discriminating emotional sentences differed between abstract-content (non-embodied) and action-related (embodied) sentences in PD patients.

Methods
Thirty-five PD patients (Hoehn C Yahr 1–2.5) and 20 age- and gender-matched healthy controls (HC) performed an emotion discrimination task on 36 sentences: 18 action-related and 18 abstract-content, each split into neutral, positive, and negative subsets. Accuracy and response times (RTs) were recorded.

Results
PD patients were less accurate and slower than controls ($p < 0.001$). Relative to RTs, an interaction emerged between group, sentence type, and emotion. Patients were slower than controls on all sentences except negative action-related ones ($p > 0.05$); for these, both groups slowed relative to positive action-related sentences ($p < 0.05$), but the slowing was greater in controls, eliminating the group difference. HC also responded faster to positive action-related than positive abstract sentences ($p < 0.01$) and slower to negative action-related than negative abstract sentences ($p < 0.01$) — a modulation absent in PD.

Discussion
Although PD patients lost the action-vs-abstract modulation, emotional-content modulation persisted, with a relative motor advantage on negative action-related sentences. We speculate that PD patients recruit a compensatory emotional-motor pathway for negative emotion, bypassing impaired motor circuits, offering insight into how embodiment and emotion interact when the motor system is damaged.

7. Beyond the masked face: dissociable components of facial emotion processing in Parkinson's disease

Authors
Valentina Cazzato[1,2], Salvatore Bertino[3], Paolo De Pasquale[3], Emanuele Gentile[1], Andreina Giustiniani[3], Maria Grazia Maggio[3], Raffaela Maione,3 Antonella Maselli[4], Angelo Quartarone[3,4], Stergios Makris[5]

Affiliations
[1] Department of Cognitive, Psychological, Pedagogical and Cultural Studies (COSPECS), University of Messina, Messina, Italy
[2] School of Psychology, Liverpool John Moores University, Liverpool, UK
[3] IRCCS Centro Neurolesi "Bonino Pulejo", Messina, Italy
[4] Department of Biomedical, Dental Sciences and Morpho-Functional Imaging (BIOMORF), University of Messina, Messina, Italy
[5] Department of Theoretical and Applied Sciences, Università degli Studi eCampus, Novedrate (CO), Italy

Background
Hypomimia in Parkinson's disease (PD) can disrupt communication and social interaction, yet the MDS-UPDRS assesses facial expression using a single ordinal item, potentially obscuring motor and socio-emotional alterations. We used automated facial analysis to examine facial dynamics across voluntary, imitative and spontaneous expression, alongside emotion recognition.

Methods
Eight patients with PD completed four protocols assessing graded voluntary expression (smile versus grin), acted versus imitated production of six emotions and a neutral condition, spontaneous responses to emotional films, and dynamic facial-emotion recognition with facial recording (1,110 video clips; 392 recognition trials). Py-Feat extracted frame-wise action-unit intensities, facial landmarks and head pose.

Results
Six of eight patients increased expressive intensity when asked to grin rather than smile (p=.005). Time-course analyses distinguished patients who initiated normally but failed to sustain expression from those showing unstable expression. Production varied by emotion: happiness was recognisable on 91% of trials, versus surprise (53%), anger (31%), sadness (18%), disgust (13%) and fear (4%). Recognition showed a related asymmetry (71.9% overall; chance=14.3%), with happiness recognised at 88% and sadness at 50%. Imitation accelerated expression onset by up to 0.68 s in six of seven patients without increasing amplitude. During uninstructed viewing, facial activity did not differentiate emotional from neutral films despite preserved expression on command. Expressive capacity did not predict recognition accuracy (r=.28, p=.54).

Conclusions
Hypomimia may comprise dissociable alterations in facial dynamics, spontaneous emotional responsivity and emotion recognition not captured by a single MDS-UPDRS rating. Their decomposition may provide a socially meaningful characterisation of facial dysfunction in PD.ù

8. Effects of Emotional Auditory Stimuli on Gait Termination and Re-initiation in Parkinson's Disease With and Without Freezing of Gait

Authors
Tiziana Lencioni[1], Francesca Lea Saibene[1*], Vittoria Cigognini[1], Anna Salvatore[1], Ilaria Carpinella[1], Mario Meloni[2], Elisa Pelosin[3]

Affiliations
1 IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy
2 Neurology Unit, Azienda Ospedaliero-Universitaria, Cagliari, Italy.
3 IRCCS Ospedale Policlinico San Martino, Genoa, Italy; Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal, and Child Health, University of Genoa, Genoa, Italy
*presenting author

Abstract
Emotional processing and locomotor control are interconnected through cortico-subcortical networks involving amygdala and basal ganglia. While previous studies have investigated emotional stimuli effects on gait initiation [1], little is known about their influence on gait termination and gait reinitiation in Parkinson's disease (PD), particularly in persons with freezing of gait (FOG). Twenty individuals with PD (10 without FOG, 10 with FOG) and 10 healthy subjects walked while exposed to pleasant, arousing, or neutral everyday-life sounds. Participants were instructed to stop walking immediately after stimulus presentation and restart walking at their preferred speed. Gait kinematics and trunk accelerations (L5) were recorded. Stop reaction time (RT), gait-restart time, and gait dynamics were analyzed using Recurrence-Quantification-Analysis (RQA).
Emotional auditory stimulation primarily affected gait reinitiation. Compared with non-FOG participants, persons with FOG restarted walking earlier across all conditions: 2.39±1.04 vs 3.44±0.93 [s] for arousing stimuli, 2.36±1.02 vs 3.47±1.09 [s] for pleasant stimuli, and 2.27±1.08 vs 3.53±1.16 [s] for neutral stimuli. Stop RT differed significantly during pleasant stimulation (0.87±0.35 vs 1.19±0.29 [s]; p=0.039). RQA revealed lower recurrence and determinism in FOG, indicating less structured locomotor dynamics.
The strongest effect of emotional stimulation emerged during gait re-initiation rather than gait termination. Persons with FOG restarted walking about 1 s earlier than non-FOG participants across all stimulus categories, suggesting altered motor-state regulation. Faster restart behavior combined with less organized gait dynamics indicates a less stable locomotor control strategy in FOG.

Reference
[1] Naugle KM et al. Emotional state affects gait initiation in individuals with Parkinson's disease. 2012; doi:10.3758/s13415-011-0071-9

9. Proactive inhibition and action preparation as a function of impulsivity traits: a TMS study

Presenter: Fabio Giovannelli

Authors
Giovannelli F.,[1] Benedetti V.,[1] Gavazzi G.,[1] Raglione L. M.,[2] Hezayen M.,[2] Chiocchetti B.,[2] Dallagiacoma S.,[2] Piccininni M.,[2] Tramacere L.,[2] Viggiano M.P.,[1] Cincotta M.[2]

Affiliations
[1]Department of Neuroscience, Psychology, Drug Research and Child's Health (NEUROFARBA), University of Florence, Firenze, Italy
[2]Units of Neurology Firenze I, Department of Medical Specialties, Azienda USL Toscana Centro, Florence, Italy

Abstract
TMS studies have shown specific modulations of the corticospinal excitability preceding movement execution. The relationship between action preparation, intentional inhibition processes and impulsive personality traits remains unclear. Our aim was to evaluate the temporal dynamics of corticospinal excitability during action preparation in a proactive inhibition task as a function of impulsivity traits. Thirty-four healthy participants underwent: an assessment of impulsivity traits (BIS-11); a Go-only choice reaction time (CRT) task; and a modified Go/No-go task (GNT), in which they had to respond to 'Go', withhold responses to 'No-go', and decide whether to press or withhold to 'Choose' stimuli. Single-pulse TMS was applied over the left M1 during the readiness period randomly at five time points (-2000, -1500, -1000, -500, or 0 ms before the Go-only, Go/No-go, or Choose cue). In the GNT, in which proactive inhibition was required during the readiness period, the corticospinal excitability was significantly lower compared to the Go-only CRT task. When participants were split into two groups according to the median BIS-11 score, this difference in the excitability between the GNT and the Go-only CRT tasks was lower in subjects with higher impulsivity traits. These data suggest that proactive inhibitory control exerted during action preparation modulates motor cortex excitability as a function of impulsivity traits. We hypothesized that individuals with higher impulsivity traits may require greater proactive control during action preparation in order to exert effective inhibitory control. This paradigm appears as potential tool to investigate the relationship between proactive inhibition and impulsivity traits in Parkinson's disease.

10. Impaired cortical inhibitory control in levodopa-induced dyskinesia

Authors
Giovanni Lombardi[1,2], Luigi Fiorillo[1,3,4], Stefano Scafa[1,3], Felice Di Laudo[9], Anna Castelnovo[6,2,7], Demetra Caroppi[1,10], Ilaria Bertaina[1], Alain Kaelin-Lang[1,2,8] and Salvatore Galati[1,2]

Background
Levodopa-induced dyskinesia (LID) may reflect not only a motor complication of Parkinson's disease (PD), but also impaired corticostriatal inhibitory control. We examined response inhibition, cortical differentiation between action execution and suppression, and diurnal variation in patients with LID.

Methods
Thirty-eight participants were recorded: 9 healthy controls, 10 early-stage PD, 10 advanced PD without dyskinesia, and 9 LID. Participants completed a visual Go/NoGo task in the morning and approximately nine hours later; patients were assessed in the medicated state. Go accuracy, NoGo commission errors, and correct-Go reaction times were measured. Stimulus-locked N2 and P3 amplitude and latency were assessed over a fronto-centro-parietal region, and source reconstruction quantified cortical NoGo–Go differentiation.

Results
Patients with LID showed lower Go accuracy than all other groups at both sessions ($p_{holm} \leq 0.0268$). They made more NoGo errors than controls and early-stage PD in the morning, and than all groups in the evening ($p_{Holm} \leq 0.0425$). Evening Go responses were faster in LID than in controls and early-stage PD, indicating a speed–accuracy trade-off. NoGo stimuli elicited larger P3 responses than Go stimuli in controls and non-dyskinetic PD groups at both sessions, but this differentiation was attenuated and non-significant after correction in LID. Evening NoGo P3 amplitude was lower in LID than in both non-dyskinetic PD groups (p_{Holm}=0.0058 and 0.0105). In the morning P3 interval, LID showed reduced NoGo–Go differentiation in left superior frontal cortex versus controls (p=0.044) and in frontal, cingulate, insular, orbitofrontal, and motor regions versus early-stage PD (p=0.022-0.049).
Conclusions: LID is associated with impaired behavioural inhibition, attenuated late NoGo-related cortical differentiation, and reduced frontal control-network recruitment, supporting a broader disinhibitory phenotype.

Affiliations
1 Neurology Department, Neurocenter of Southern Switzerland, Ente Ospedaliero Cantonale, 6903, Switzerland
2 Faculty of Biomedical Sciences, Università Della Svizzera Italiana, 6962, Switzerland
3 Institute of Digital Technologies for Personalized Healthcare, University of Applied Sciences and Arts of Southern Switzerland, 6962, Switzerland
4 Sleep Research Institute, Madrid, Spain
5 Faculty of Informatics, Università della Svizzera Italiana, 6962, Switzerland
6 Sleep Medicine Unit, Neurocenter of Italian Switzerland, Ente Ospedaliero Cantonale, 6903, Switzerland
7 Department of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, 3008, Switzerland
8 Department of Neurology, Inselspital, Bern University Hospital, 3010, Switzerland
9 Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy
10Department of Biology and Biotechnology Lazzaro Spallanzani, University of Pavia

11. The Shape of Sequence Effect in Parkinson's Disease

Authors
Martina De Riggi, MD1, Anna Sofia Grandolfo MD1, L. Angelini, MD2, D. Birreci, MD1, S. Aloisio, MD1, G. Paparella MD, PhD3, A. Cannavacciuolo, MD, PhD2, and M. Bologna, MD, PhD1,2

Affiliations
1Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy;
2IRCCS Neuromed Pozzilli (IS), Italy;
3Department of Neurology, University of Bari Aldo Moro, Bari, Italy

Introduction
Bradykinesia, the hallmark motor symptom of Parkinson's disease (PD), is commonly assessed through repetitive finger tapping (FT). Kinematic analysis identifies movement amplitude decrement (sequence effect) as a key but variable feature of bradykinesia [1–3]. To date, the temporal pattern ("shape") of amplitude decrement has not been characterized.

Objective
Objectively characterize and compare the temporal patterns of FT amplitude decrement in patients with PD and healthy controls (HC).

Methods
We enrolled 109 patients with PD (mean age 66.6 ± 8.9) and 84 HC (mean age 66.9 ± 9.9). Participants performed three 15-second FT trials (dominant hand in HC; most affected side in PD OFF medication) recorded using optoelectronic motion capture. Amplitude decrement (sequence effect) was assessed across three 5-second segments (0–5, 5–10, 10–15 sec), with slopes averaged across trials. Segments with slopes higher than -0.05 were classified as decremental. Based on the "shape" of the sequence effect, participants were categorized into six patterns: very early, early, stable, late, very late decrement, or no decrement. Group differences were assessed using chi- squared tests.

Results
The pattern distribution of sequence-effect "shapes" differed significantly between PD and HC ($\chi2 = 19.7$, $p = 0.001$). Patients more frequently exhibited a stable decrement pattern ($\chi2 = 8.264$, $p = 0.004$), whereas HC typically displayed no-decrement ($\chi2 = 14.1$, $p = 0.0002$). Beyond these patterns, patients showed earlier amplitude reduction compared to HC.

Conclusions
The sequence effect in PD shows variable temporal patterns that may relate to distinct clinical features, potentially improving patient stratification and targeted interventions.

Bibliography
[1] Bologna M, Espay AJ, Fasano A, Paparella G, Hallett M, Berardelli A. Redefining Bradykinesia. Mov Disord. 2023 Apr;38(4):551-557. doi: 10.1002/mds.29362.
[2] Paparella G, Cannavacciuolo A, Angelini L, Costa D, Birreci D, Alunni Fegatelli D, Guerra A, Berardelli A, Bologna M. May Bradykinesia Features Aid in Distinguishing Parkinson's Disease, Essential Tremor, And Healthy Elderly Individuals? J Parkinsons Dis. 2023;13(6):1047-1060. doi: 10.3233/JPD-230119. PMID: 37522221; PMCID: PMC10578222.

[3] Panyakaew P, Duangjino K, Kerddonfag A, Ploensin T, Piromsopa K, Kongkamol C, Bhidayasiri R. Exploring the Complex Phenotypes of Impaired Finger Dexterity in Mild-to-moderate Stage Parkinson's Disease: A Time-Series Analysis. J Parkinsons Dis. 2023;13(6):975-988. doi: 10.3233/JPD-230029. PMID: 37574743; PMCID: PMC10578277.

12. Dissociated Corticospinal and Corticobulbar Responses to Levodopa in Parkinson's Disease

Authors
F. Ferraioli[1], F. Tomaiuolo[2], C. Karakoc[1], A. Labate[3], S. Massimino[1], V. Rizzo[4], C. Terranova[4], S. M., Cardali[5], A. Germanò[2], A. Falzone[1], A. Avenanti[6], A. Quartarone[7], M. Oliveri[8], F. Esposito[9], M.A., Nitsche[10], L. Trojano[11], and C. M. Vicario[1]

Affiliations
[1] Laboratory of Cognitive Neuroscience, Department of Cognitive Science (COSPECS), University of Messina, Messina, Italy
[2] Department of Clinical and Experimental Sciences, Biomedical, Dental and Morphological and Functional Imaging, University of Messina, Messina, Italy
[3] Neurophysiopatology and Movement Disorders Clinic, University of Messina, Messina, Italy; Neurology Clinic, University of Palermo, Palermo, Italy and Department of Biomedicine, Neuroscience, and Advanced Diagnostic (BIND), University of Palermo, Palermo, Italy. Electronic
[4]Neurophysiology and Movement Disorders Unit, University of Messina, Messina, Italy
[5]Department of Neurosurgery, Azienda Ospedaliera Papardo, University of Messina, Messina, Italy
[6]Center for Studies and Research in Cognitive Neuroscience, Department of Psychology 'Renzo Canestrari', University of Bologna, Cesena Campus, Cesena, Italy; Center for Research in Neuropsychology and Cognitive Neurosciences, Universidad Católica del Maule, Talca, Chile
[7]IRCCS Centro Neurolesi Bonino-Pulejo, S.S. 113 Via Palermo, C.da Casazza, Messina 98124, Italy.
[8]Department of Biomedicine, Neurosciences and Advanced Diagnostics (BiND), University of Palermo, Palermo, Italy
[9]Department of Advanced Medical and Surgical Sciences, MRI Research Center, University of Campania Luigi Vanvitelli, Naples, Italy
[10]Department of Psychology and Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, Dortmund, Germany.
[11]Department of Psychology, University of Campania Luigi Vanvitelli, Caserta, Italy

Abstract
Levodopa improves limb motor function in Parkinson's disease (PD), whereas its effects on bulbar motor control remain less predictable. We investigated whether dopaminergic treatment differentially modulates corticospinal and corticobulbar motor outputs.
Patients with PD were assessed after dopaminergic withdrawal and following levodopa intake, while age-matched healthy controls completed a baseline session. Single-pulse transcranial magnetic stimulation was delivered while motor-evoked potentials were recorded from the extensor carpi radialis (ECR), representing corticospinal output, and the submental muscle (SbM), representing corticobulbar output. Mixed-effects models examined response amplitude, onset latency, and elicitation. Levodopa produced a clear dissociation between the two motor systems. ECR amplitude increased following treatment, consistent with corticospinal facilitation, whereas SbM amplitude remained unchanged. Response timing was also differentially modulated: ECR and SbM onset latencies changed in opposite directions, with ECR latency decreasing and SbM latency increasing. Critically, the Session × Muscle interaction was confirmed in a sensitivity analysis accounting for individual variability in the OFF-to-ON change.
These findings indicate that levodopa does not uniformly facilitate motor output across corticospinal and corticobulbar systems. The divergence in response timing suggests circuit-specific dopaminergic modulation and supports further investigation of submental corticobulbar physiology as a marker of state-dependent motor-network organization in PD.

13. Beyond Tremor Control: Multidimensional Functional and Emotional Recovery after MRgFUS VIM Thalamotomy in Tremor-Dominant Parkinson's Disease

Authors
Viviana Lo Buono, Giovanni Restuccia, Simona Cammaroto, Silvia Marino, Chiara Sorbera, Angelo Quartarone, Lilla Bonanno and Giuseppe Di Lorenzo

Abstract
MRgFUS VIM thalamotomy is an established treatment for medically refractory tremor in PD[1,2]. Its benefits may extend beyond motor symptom control to everyday functioning and emotional well-being, although longitudinal trajectories across these domains remain insufficiently understood.
To characterize the longitudinal effects of unilateral MRgFUS VIM thalamotomy in patients with tremor-dominant PD, focusing on individual patterns of response.
Nineteen patients with tremor-dominant PD underwent unilateral MRgFUS VIM thalamotomy. Assessments were performed at baseline (T0), 3 months (T1), and 6 months (T2). Functional and quality-of-life outcomes were assessed using the Parkinson's Disease Questionnaire-39 (PDQ-39), depressive and anxiety symptoms using the Hamilton Depression and Anxiety Rating Scales (HAM-D, HAM-A), and cognition using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Longitudinal changes were analyzed using repeated-measures non-parametric tests.
PDQ-39 Mobility scores progressively improved from 57.96 at T0 to 37.22 at T1 and 29.03 at T2 ($p<0.001$), while Activities of Daily Living scores improved from 57.17 to 20.60 at T1 and remained stable at T2 ($p<0.001$). HAM-D scores decreased from 20.17 to 17.22 and 15.39, and HAM-A scores from 20.11 to 17.06 and 14.61 at T0, T1, and T2, respectively (both $p<0.001$). At 6 months, 14/19 patients (73.7%) showed concurrent functional and emotional improvement. Global cognition remained stable (RBANS Total, $p=0.078$), with selective improvement in Language ($p=0.010$).
Unilateral MRgFUS VIM thalamotomy was associated with multidimensional improvement beyond tremor-related disability. Functional and emotional benefits evolved over time, while global cognition remained preserved, supporting a broader patient-centered perspective on MRgFUS outcomes.

References
1. Bhatia KP, Bain P, Bajaj N et al (2018) Consensus statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society: IPMDS task force on tremor consensus statement. Mov Disord 33:75–87.
2. Bond AE, Shah BB, Huss DS, et al. Safety and efficacy of focused ultrasound Thalamotomy for patients with medication-refractory, tremor-dominant Parkinson disease: a randomized clinical trial. *JAMA Neurol* 2017; 74(12): 1412.

14. Post-hypoxic myoclonus and Deep Brain Stimulation. Experience from a small patient cohort and literature review highlighting variable outcomes

Authors
De Santis T1,2, Mogilner AY3, Pourfar M3

Affiliations
1Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, NYU Langone Health, New York, USA.
2Department of Neurology, IRCCS Humanitas Research Hospital, Rozzano, Milano, Italy.
3Department of Neurosurgery, NYU Langone Health, New York, USA.

Abstract
Lance Adams Syndrome (LAS), or chronic post-hypoxic myoclonus (PHM), is a rare and disabling condition which occurs in the aftermath of a diffuse hypoxic brain injury, usually when patient regains consciousness. Due to its refractoriness to antiepileptics, deep brain stimulation (DBS) has been attempted over the past fifteen years.
We reviewed data on patients diagnosed with LAS who underwent DBS at NYU Langone Medical Center. Clinical history, myoclonus phenomenology, surgical details, and medications at each follow-up visit along with subjective reports of patient/caregiver and neurologist and Unified Myoclonus Rating Scale (UMRS) scores, were documented.
Despite varying stimulation parameters and contact combinations, none achieved substantial improvement of action and negative myoclonus or regained the ability to ambulate unassisted.
We additionally reviewed the Pubmed database for previous publications of similar cases and compared our results with previous reports.
We identified ten cases of LAS treated with DBS since 2010. The target was GPi in 8/10 patients, the ventralis intermedius nucleus in one, and the subtalamic nucleus in
one. Varying degrees of improvement were reported, with some evidence suggesting that long pulse width and lower frequency might be more effective.
This study highlights the marked variability in reported results and underscores the need to develop a standardized pre-surgical evaluation protocols.
Due to the paucity of prior reports and the limited generalizability of existing evidence, the efficacy of DBS in LAS has yet to be demonstrated. Further case reports, both positive and negative, supported by neurophysiological measures, may help bridge this knowledge gap.

15. Thalamic Lesion Topography and Clinical Outcomes after MRgFUS in Tremor-Predominant Parkinson's Disease

Authors
Boccia V.D, Maheshwary A., Bellini G, Cipriano E, Avanzino L, Inglese M, Mogilner A., Pourfar M.
Presenter: Boccia Vincenzo Daniele

Background
Magnetic Resonance-guided Focused Ultrasound (MRgFUS) is an established treatment for tremor-predominant Parkinson's disease (TP-PD), but factors influencing long-term efficacy and side effects remain unclear.

Methods
We retrospectively analyzed 27 TP-PD patients (median age 73 years [42–88], disease duration 5 years [1–12], UPDRS 19 [10–80], SDR 0.51 [0.26–0.68]) undergoing unilateral MRgFUS thalamotomy. Tremor recurrence was defined as <50% sustained improvement. Lesions were segmented on T2-MRI at the day of surgery (DOS) and at 6 weeks, co-registered to an average T1 space. Thalamic nuclei were segmented using the THOMAS pipeline. Lesion volumes and overlap with thalamic subnuclei were computed.

Results
All patients achieved >50% tremor improvement after the procedure. After 1 year follow up (range 6 weeks–4 years), tremor recurrence occurred in 9 patients (33%). Side effects were observed in 21 patients, resolving in 13 cases. Median lesion volume decreased from 284 mm^3 (91.25–462.26) at DOS to 143 mm^3 (0–578) at 6 weeks. The ventral posterolateral ventral nucleus (VLPv) showed the highest lesion overlap (DOS: 20.5% [5.30–50.89]; 6 weeks: 11.15% [0–25.91]). A higher number of therapeutic sonications correlated with larger lesion volumes (p=0.04). Patients with tremor recurrence showed lower VLPv involvement at 6 weeks (6.59% vs 13.86%, p=0.05). Side effects were associated with greater dorsal VLP (VLPd) involvement (p=0.04) and larger lesion volumes (U=18.5, p=0.03).

Conclusions
Our findings suggest that more ventral lesion placement may optimize therapeutic efficacy while minimizing adverse effects, supporting the role of advanced imaging in refining targeting strategies.

16. A Novel XPR1 In-Frame Deletion in Primary Brain Calcification: Clinical and Systems Neuroscience Insights

Authors
Vincenzo Daniele Boccia, Giulietta Riboldi, Xavier Guell
Presenter: Vincenzo Daniele Boccia

Background
Primary Brain Calcification (PBC) is a genetically heterogeneous disorder characterized by bilateral intracranial calcifications and variable clinical manifestations. Mutations in *XPR1*, a phosphate exporter, account for a minority of cases and show incomplete genotype–phenotype correlations.

Methods
We report a 43-year-old woman presenting with basal ganglia and cerebellar calcifications identified on CT imaging. Clinical evaluation included detailed motor, cognitive, and neuropsychiatric assessments. Genetic testing was performed using a targeted dystonia panel. Imaging findings were interpreted in the context of current knowledge in systems neuroscience of basal ganglia and cerebellar function.

Results
The patient exhibited extensive bilateral calcifications (Total Calcification Score: 21) involving basal ganglia and cerebellum, with only mild motor abnormalities on examination, including subtle cerebellar and basal ganglia signs. Cognitive testing revealed mild deficits, while history was notable for longstanding neuropsychiatric symptoms, including anxiety, mood disturbances, compulsive behaviors, and sensory hypersensitivity. Genetic analysis identified a novel heterozygous in-frame deletion in *XPR1* (c.166_168del; p.Glu56del), located within the functionally critical SPX domain. This variant, absent from population databases and predicted to be deleterious, represents the first in-frame deletion reported in *XPR1* associated with PBC. Family history suggested autosomal dominant inheritance.

Conclusions
This case expands the mutational spectrum of *XPR1*-related PBC and highlights the dissociation between extensive calcifications and relatively mild motor impairment. The prominent neuropsychiatric profile may reflect disruption of cerebellar–basal ganglia networks involved in affective and cognitive processing. These findings underscore the importance of integrating genetic, imaging, and systems-level neurological frameworks to better understand symptom expression in PBC.

17. Prevalence and Clinical Correlates of Fatigue in Parkinson's Disease: A Multicenter Case-Control Study

Authors
Ilaria A. Di Vico[1], Mattia Siciliano[2], Angela Sandri[1], Gabriele Imbalzano[3], Carlo Alberto Artusi[1,3], Rosa De Micco[2], Giovanni Palermo[6], Alessandra Govoni[7], Giulia Pedrotti[1], Pietro Valsecchi[1], Daniele Volpe[4,5], Silvia Ramat[7], Roberto Ceravolo[6], Maurizio Zibetti[3], Monica Norcini [4,8], Alessandro Tessitore[2], Michele Tinazzi[1]

Affiliations
[1] Neurology Unit, University Hospital of Verona; Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy
[2] I Division of Neurology and Neurophysiopathology, Department of Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy
[3] Department of Neurosciences Rita Levi Montalcini, University of Turin, Turin, Italy;
SC Neurologia 2U, AOU Città della Salute e della Scienza, Turin, Italy
[4] Fresco Parkinson Institute Italia Onlus, Fiesole, Italy
[5] Department of Neurorehabilitation, Parkinson's Disease Excellence Center, Fresco Institute Italy, Casa di Cura Villa Margherita, Vicenza, Italy
[6] Unit of Neurology, Fresco Institute; Department of Clinical and Experimental Medicine, Center for Neurodegenerative Diseases – Parkinson's Disease and Movement Disorders, University of Pisa, Pisa, Italy
[7] Department of Neurosciences, Psychology, Pharmacology and Child Health, University of Florence, Florence, Italy
[8] NYU Langone Health, Department of Neurology, New York, NY, USA

Background
Fatigue is a common and disabling symptom of Parkinson's disease (PD), yet it remains under-recognized, and robust case-control data on its prevalence and clinical correlates are lacking **(1,2).**

Objective
To investigate the prevalence, severity and clinical correlates of fatigue in a large multicenter cohort of PD patients compared with healthy controls (HC).

Methods
We recruited 292 PD patients and 161 HC from six Italian PD centers. Fatigue was assessed using the Fatigue Severity Scale (FSS) and the Multidimensional Fatigue Inventory (MFI-20). The association between PD and fatigue was evaluated using multivariable logistic regression adjusted for age and gender, with sensitivity analyses including interaction testing and propensity score matching. Non-motor symptoms (NMS) were accounted for using an extended multivariable model.

Results
PD patients differed from HC in age and gender distribution (both $p < 0.01$) and exhibited significantly higher FSS and MFI-20 scores across all subdomains (all $p < 0.001$). Prevalence of fatigue (FSS ≥ 4) was 35.2% in PD and 20.1% in HC. PD diagnosis was independently associated with fatigue (OR = 2.26, $p < 0.001$), while female gender was associated with increased fatigue risk (OR = 1.58, $p = 0.027$), with no significant PD-gender interaction. Propensity score matching yielded a balanced 1:1 sample (160 PD, 160 HC) and confirmed the association between PD and fatigue (OR = 2.30, $p < 0.001$). In the fully adjusted model accounting for NMS, PD remained independently associated with fatigue (OR = 1.88, $p = 0.014$), together with depression and poor sleep quality, while apathy showed an inverse association.

Conclusions

Fatigue is more prevalent and severe in PD than in HC. Its association with PD persists after adjustment for demographic factors and NMS, supporting fatigue as a core non-motor feature of PD. These findings highlight the need for systematic assessment and targeted management of fatigue in routine PD care.

References

1. Di Vico IA, Cirillo G, Tessitore A, Siciliano M, Venturelli M, Falup-Pecurariu C, Tedeschi G, Morgante F, Tinazzi M. Fatigue in hypokinetic, hyperkinetic, and functional movement disorders. Parkinsonism Relat Disord. 2021 May;86:114-123. doi: 10.1016/j.parkreldis.2021.03.018. Epub 2021 Mar 29. PMID: 33839028.

2. Siciliano M, Trojano L, Santangelo G, De Micco R, Tedeschi G, Tessitore A. Fatigue in Parkinson's disease: A systematic review and meta-analysis. Mov Disord. 2018 Nov;33(11):1712-1723. doi: 10.1002/mds.27461. Epub 2018 Sep 28. PMID: 30264539.

18. Resting-State High-Density EEG Biomarkers of Cognitive Dysfunction and Fatigue in Multiple Sclerosis: A Preliminary Study

Authors
Caterina Formica, Simona De Salvo, Elvira Gjonaj, Fabiana Maria Bonasera, Serena Dattola, Angelo Quartarone, Edoardo Sessa, Carmela Rifici, Silvia Marino

Affiliation
IRCCS Centro Neurolesi Bonino Pulejo

Abstract
Fatigue and cognitive impairment affect patients' daily functioning and quality of life in Multiple Sclerosis (MS). High-density EEG was used to investigate the presence of hallmarks neural alterations associated with cognitive functioning and central fatigue of SM. Thirty patients with MS underwent resting-state HD-EEG recording (256 ch) during eyes-open (EO) and eyes-closed (EC) conditions and cognitive and fatigue evaluations. Clinical assessment revealed significant moderate fatigue (mean FSS = 4.9 ± 1.4; FSMC 59.6 ± 18.3) with a predominance of motor over cognitive fatigue. Spectral power in the theta, alpha, and beta bands was computed for bilateral frontal, central, temporal, parietal, and occipital regions. EO and EC conditions were compared using paired Wilcoxon signed-rank tests with false discovery rate (FDR) correction. Alpha power was significantly higher during EC than EO across all cortical regions (FDR-corrected p = 0.00010–0.00334). Significant correlations emerged during the EO condition. Increased theta power in central, temporal, parietal, and occipital regions was associated with poorer verbal learning and memory performance (SRT-LTS and SRT-CLTR; ρ = −0.57 to −0.73), higher alpha power in bilateral frontal, central, and parietal regions, as well as the left temporal and occipital regions, correlated with lower SRT-CLTR scores (ρ = −0.57 to −0.68). Resting-state HD-EEG revealed alterations of cortical patterns associated with cognitive dysfunction in MS. However, significant associations with fatigue were not observed in this preliminary cohort. The observed trends support further investigation into larger samples. HD-EEG may represent a promising biomarker for monitoring disease-related functional brain changes in MS.

Results
EEG spectral power in the theta, alpha, and beta bands was calculated from 120 seconds of EEG recorded under eyes-open (EO) and eyes-closed (EC) conditions for bilateral frontal, central, temporal, parietal, and occipital regions. Conditions were compared using paired Wilcoxon signed-rank tests with false discovery rate (FDR) correction. Alpha power was significantly higher during EC across all bilateral frontal, central, temporal, parietal, and occipital regions (p_{FDR} = 0.00010 - 0.00334). Beta power was significantly higher during EC only in the left occipital region (p_{FDR} = 0.0268). No significant differences were found in theta power.
Spearman correlations were calculated between regional theta, alpha, and beta power and clinical/ neuropsychological measures, with FDR correction. After correction, significant correlations were identified exclusively in the EO condition. Higher theta power across central, temporal, parietal, and occipital regions was associated with poorer verbal learning and memory performance (SRT-LTS and SRT-CLTR; ρ = - 0.57 to - 0.73, p_{FDR} = 0.004 - 0.044). Higher alpha power in the bilateral frontal, central, and parietal regions, as well as the left temporal and occipital regions, was negatively correlated with SRT-CLTR (ρ = - 0.57 to - 0.68, p_{FDR} = 0.017 - 0.044). No significant correlations were found for EC power.

19. Short-latency Afferent Inhibition as a Potential Neurophysiological Biomarker of Fatigue in Parkinson's Disease

Authors
Rachele Simeon[1], Gaia Bonassi[1], Carla Ogliastro[1], Martina Putzolu[1,2], Sara Terranova[3], Alessandro Botta[3], Anna Marra[1], Giovanna Lagravinese[2], Francesca Di Biasio[2], Roberta Marchese[2], Laura Avanzino[2,3] & Elisa Pelosin[1,2]

Affiliations
[1] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Child Health, University of Genoa, Genoa, Italy
[2] AOM - IRCCS Ospedale Policlinico San Martino
[3] Department of Experimental Medicine, Section of Human Physiology, University of Genoa, Genoa, Italy.

Background
Fatigue is one of the most disabling non-motor symptoms of Parkinson's disease (PD), but its neurophysiological basis remains poorly understood. Cholinergic dysfunction and abnormalities in attentional networks may contribute to its pathophysiology. This study investigated whether short-latency afferent inhibition (SAI), a marker of central cholinergic function, together with behavioural measures of attention, could characterize fatigue in PD.

Methods
In this cross-sectional study we recruited individual with PD and Healthy controls (HC). Participants with PD were classifying using the Parkinson Fatigue Scale-16 (PFS-16) as having clinically relevant fatigue (PD-F: PFS-16 >3.09) or no clinically relevant fatigue (PD-nF: PFS-16 ≤3.09). Participants underwent SAI assessment and completed the Attention Network Task (ANT), which evaluates alerting, orienting, and executive control. Associations among neurophysiological, behavioural, and clinical measures were examined.

Results
Fifty-eight participants (PD-F, n=19; PD-nF, n=19; HC, n=20) completed the experimental protocol. Results for SAI revealed that PD-F showed significant less inhibition compared with both PD-nF and HC participants, consistent with greater central cholinergic dysfunction.
PD-F participants also exhibited slower reaction times, reduced alerting efficiency and altered orienting performance compared to the other two groups.
Finally, reduced SAI was associated with greater fatigue severity, poorer quality of life, and greater motor disability and attentional performance significantly correlated with both fatigue and cognitive function.

Conclusions
SAI may represent a neurophysiological biomarker of fatigue in PD. Together, these findings suggest that cholinergic dysfunction and attentional impairment may contribute to fatigue in PD, identifying potential targets for future therapeutic interventions.

20. Brain fingerprinting as a predictive biomarker of art therapy outcomes in Parkinson's disease

Authors
Augusto Ielo*1, Danilo Genovese2,3, Joan Falcó-Roget4, Enrico Amico5,6, Alessandro Di Rocco7, Monica Norcini8, Angelo Quartarone1, Maria Felice Ghilardi9, Alberto Cacciola10,11

Affiliations
[1] IRCCS Centro Neurolesi "Bonino Pulejo", Messina, Italy
[2] Institute of Neurology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[3] Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy
[4] Computational Neuroscience Group, Sano Centre for Computational Medicine, Kraków, Poland
[5] School of Mathematics, University of Birmingham, Birmingham, United Kingdom
[6] Centre for Human Brain Health, University of Birmingham, Birmingham, United Kingdom
[7] Department of Neurology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Lenox Hill Hospital, New York, United States
[8] NYU Langone Health, Department of Neurology, New York, United States
[9] Department of Molecular, Cellular & Biomedical Sciences, CUNY School of Medicine, New York, United States
[10] Department of Biomedical Sciences, Humanitas University, Milan, Italy
[11] IRCCS Humanitas Research Hospital, Milan, Italy
* Presenting author: Augusto Ielo

Background
Pharmacological therapy improves motor symptoms in Parkinson's disease (PD) but does not halt progression, supporting complementary non-pharmacological approaches. Brain fingerprints represent stable, individual-specific functional connectivity patterns which may provide biomarkers of treatment responsiveness.[1] We tested whether baseline connectivity fingerprints predict response to art therapy in PD.

Methods
Twenty-three patients with PD underwent resting-state fMRI before a 20-session, 10-week art therapy program[2], while 23 age-matched healthy controls underwent fMRI without intervention. Motor response was defined as a ≥15% reduction in UPDRS-III.[3] fMRI data were processed with fMRIPrep/XCP-D and parcellated into 400 cortical regions.[4] Whole-brain identifiability and edgewise intraclass correlation coefficients quantified fingerprint stability.[2,5] Group differences in reliability were assessed with permutation testing and FDR correction. Graph measures derived from fingerprint-informed edges were used to classify responders versus non-responders with supervised learning and leave-one-out cross-validation.

Results
UPDRS-III improved from 37.8 ± 11.7 to 32.5 ± 11.8 (p=0.002); 10 patients (43%) were responders. Identification success was 100% in both groups, although normalized discriminability was lower in PD. Controls showed greater stability in default-mode and control-attention networks, whereas PD showed greater visual-network stability. Random forest classification based on edges with reduced stability in PD achieved
0.83 accuracy and 0.80 ROC-AUC; eigenvector centrality, assortativity, and rich-club organization were key predictors.

Conclusions

PD preserves overall connectome fingerprint identifiability but shows disease-related redistribution of fingerprint reliability. Baseline fingerprint-informed network features predicted individual response to art therapy, supporting brain fingerprinting as a potential biomarker for personalized non-pharmacological rehabilitation.

References

1. Amico E, Goñi J. The quest for identifiability in human functional connectomes. Scientific Reports. 2018;8(1).
2. Cucca A, Di Rocco A, Acosta I, et al. Art therapy for Parkinson's disease. Parkinsonism & Related Disorders. 2021;84:148–154.
3. Navratil P, Abbas G, Abdullah Elmas, et al. Probabilistic mapping of the antiparkinsonian effects of pallidal deep brain stimulation. Brain Communications. 2025;7(5):fcaf374.
4. Thomas Yeo BT, Krienen FM, Sepulcre J, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. Journal of Neurophysiology. 2011;106(3):1125–1165.
5. Stampacchia S, Asadi S, Tomczyk S, et al. Fingerprints of brain disease: connectome identifiability in Alzheimer's disease.
Communications Biology. 2024;7(1).

Acknowledgements

We thank the art therapy team at NYU Steinhardt and the team at the Fresco Parkinson Institute (NYU Langone Health) for data collection.

21. In-Depth Insight into Young-Onset Parkinson's Disease: Demographic, Clinical, and Genetic Features

Authors
Giulia Di Rauso[1,2], Alyssa Boye[1], Kamelia Drenkova[1], Mark Belio[1], Giulietta Riboldi[1]

Affiliations
1 Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, NYU Langone Health, New York, New York, USA
2 Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy.

Background
Young onset Parkinson disease (YOPD) is defined as PD with onset between ages 21 and 50 years[1]. The clinical presentation, disease severity and genetic background may differ across YOPD subtypes and compared with late-onset Parkinson's disease (LOPD)[2].

Objective
This study aims to characterize the demographic, clinical, and genetic features of a YOPD cohort followed at NYULH's Fresco Institute for Parkinson's and Movement Disorders, and compare them with LOPD patients and healthy controls (HC).

Methods
A cohort of YOPD, LOPD and HC were included. Demographic and clinical features were collected. All subjects underwent a clinical assessment, including MDS-UPDRS and MoCA scales. STAI, SCOPA-AUT, RBDSQ, GDS and environmental exposure questionnaire were administered. All subjects underwent Whole Genome Sequencing (WGS).

Results
89 YOPD (55% male, age at onset: 43±7, age at evaluation: 51±8, disease duration: 9±6), 41 LOPD (56% male, aao: 61±7, aae: 66±7, dd: 5±4) and 37 HC (38% male, aae: 59±12 yo) were included. The majority of PD and HC were Caucasian. 23% of YOPD were Ashkenazi Jews (AJ), compared with 32% of LOPD and HC. A positive family history of PD was reported in 38% of HC, 52% of YOPD and 41% of LOPD. YOPD had a higher mean MoCA score than LOPD, while the MDS-UPDRS Part III score was higher, likely reflecting their longer disease duration. Finally, genetic variants in PD-associated genes were evaluated across all three groups.

Conclusion
This study characterizes the demographic, clinical, and genetic features of YOPD, in comparison with LOPD and HC.

References
1. Mehanna R, Marras C, Fleisher J, Post B, Kumar KR, Noyce A, Alcalay R, Morris HR, Hatano T, Salari M, Smilowska K, Wu YR, Zhang B, Tan EK, Savica R; EOPD study group. Diagnostic work up when suspecting early onset Parkinson disease (EOPD). Recommendations from the MDS EOPD study group. Parkinsonism Relat Disord. 2025 Jun;135:107852. doi: 10.1016/j.parkreldis.2025.107852.
2. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. Lancet Neurol. 2021 May;20(5):385-397. doi: 10.1016/S1474-4422(21)00030-2. PMID: 33894193; PMCID: PMC8185633.

22. Implementing genotype-guided Parkinson's disease care in clinical practice: the NEXT-GEN-PRATO ongoing multicenter targeted NGS study

Authors
C. Del Gamba[1], E. Monfrini[2], E. Grassi[1], P. Palumbo[1], M. Norcini[3-4], A. Di Fonzo[2], C. Bianchini[5], M. Bonechi[5], S. Bessi[5]

Affiliations
[1] Unit of Neurology, Department of Medical Specialties, Azienda USL Toscana Centro, Prato, Italy.
[2] Neurology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
[3] Department of Neurology, NYU Grossman School of Medicine, New York, NY, USA.
[4] Fondazione Fresco Parkinson Institute Italia Onlus, Fiesole, Italy.
[5] Unit of Oncological Molecular Pathology, Department of Oncology, Azienda USL Toscana Centro, Prato, Italy

Background
Precision medicine is becoming increasingly relevant in Parkinson's disease (PD), but genetic testing is still not consistently integrated into routine clinical care. This may limit access to molecular diagnoses, prognostic stratification, and genotype-informed therapeutic opportunities. The NEXT-GEN-PRATO study was established to implement a dedicated clinical-molecular workflow in a real-world public hospital setting.

Objective
To estimate the prevalence of monogenic PD in clinically selected adults with PD and to implement a multidisciplinary local workflow for sample processing, molecular analysis, and genotype-phenotype interpretation.

Methods
NEXT-GEN-PRATO is an ongoing, multicenter, non-profit initiative enrolling adult PD patients with features suggestive of a genetic basis, including early-onset disease (≤50 years), family history, specific ethnic backgrounds, or atypical phenotypes. The protocol includes deep phenotyping, targeted NGS using a customized 35-gene panel, bioinformatic analysis, and multidisciplinary genotype-phenotype correlation to guide variants interpretation. Approximately 80 patients are planned for enrolment. Results and Current Status The initial inter-laboratory validation phase of the customized 35-gene panel has been completed on a set of anonymized DNA samples with known genotypes provided by the Milan biobank. Patients' recruitment is now ongoing. No outcome data are available yet.

Conclusions
NEXT-GEN-PRATO aims to bring genetic testing closer to routine PD care, showing that earlier molecular characterization is achievable in a public healthcare framework. This may improve patient stratification and support more individualized therapeutic decisions in the future.

Funding
This study is supported by Fondazione Fresco Parkinson Institute Italia ETS.

23. Botulinum Toxin for Musician's Dystonia: Clinical Findings and Treatment Patterns from a Single-Center Retrospective Cohort

Authors
P. Santurelli, MD,[1] P. Drummond, MD,[1] C. Del Gamba, MD,[2] Dr. G. Riboldi, MD,[1] PhD, A. Castagna, MD,[3] S. J. Frucht, MD[1]

Affiliations
1. The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, Department of Neurology, NYU Langone Health, New York, NY, USA.
2. Unit of Neurology, Department of Medical Specialties, Azienda USL Toscana Centro, Prato, Italy
3. Movement Disorders Center I.R.C.C.S. Fondazione Don Carlo Gnocchi Onlus, via Alfonso Capecelatro 66, 20148, Milan, Italy

Background
Musician's dystonia (MD) is a focal task-specific dystonia characterized by impaired motor control during instrument performance, often leading to professional disability.(1) Botulinum toxin (BoNT) is widely used as symptomatic treatment;(2) clinical phenotypes, treatment strategies, and long-term outcomes remain heterogeneous across centers. Comparative multicenter data are limited.

Objectives
To describe demographic, clinical, and treatment-associated characteristics of patients with MD treated with BoNT across two tertiary centers, and to compare inter-center differences. A secondary objective is to evaluate longitudinal treatment trajectories in patients receiving long-term therapy (≥2 years).

Methods
We will conduct a multicenter retrospective observational study at Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders (NYULH, USA) and IRCCS Fondazione Don Gnocchi (Milan, Italy). Data were collected and analyzed for patients with MD treated between January 2015 and April 2026. Collected variables include demographic and epidemiological characteristics, clinical phenomenology and detailed treatment parameters (BoNT formulation, dosing, injected muscles, injection intervals, guidance technique, adverse effects, and treatment duration). Descriptive analyses will summarize cohort characteristics. Inter-center comparisons will be performed using appropriate statistical tests after assessment of distributional assumptions. Long-term treatments will be analyzed to evaluate dose stability over time, injection interval trajectories and changes in injected muscles. Treatment retention will be assessed using Kaplan–Meier analysis.

Results
Data collection has been completed, and data curation and statistical analyses are currently ongoing on a cohort of 98 patients from two international referral centers.

Conclusions
This multicenter study is expected to provide robust real-world evidence on the clinical and therapeutic heterogeneity of MD and to inform future standardization of MD assessment and BoNT treatment strategies.

References
1. Stahl CM, Frucht SJ. Focal task specific dystonia: a review and update. J Neurol 2017;264(7):1536–1541. https://doi.org/10.1007/s00415-016-8373-z

2. Frucht SJ, George MC, Pantelyat A, et al. Incobotulinum Toxin-A in Professional Musicians with Focal Task-Specific Dystonia: A Double Blind, Placebo Controlled, Cross-Over Study. Tremor Hyperkinetic Mov 2024;14:32. https://doi.org/10.5334/tohm.903

24. Is Raman Spectroscopy salivary test useful in differentiating isolated cervical dystonia patients from healthy controls? Results from a preliminary pilot study

Authors
A. Castagna[1], M. Lus[1,2], L. De Iaco[1], A. Gualerzi[1], V. Mangolini[1], M. Bedoni[1]

Affiliations
[1] IRCCS Fondazione Don Carlo Gnocchi, Via Capecelatro 66 Milano, Italy, 20122
[2] Università degli Studi di Milano

Objective
Isolated cervical dystonia (iCD) is a cortical-subcortical network disorder characterized by abnormal postures and movements due to involuntary cervical muscle contractions [1]. Until now there are not objective biomarkers related to biological fluids that can contribute to the diagnosis. Raman spectroscopy can generate a molecular fingerprint of complex biofluids well suited for chemometric discrimination of disease-related biochemical profiles also profiling subjects with movement disorders [2, 3]. This study has the aim of building a CTRL / Dystonia classification model based on the differential analysis of saliva.

Methods
Saliva was collected with Salivette (SARSTEDT) from a cohort of iCD patients and a control group in Fondazione Don Gnocchi Dystonia Center, Milan. Raman spectra were acquired after swab centrifugation, saliva deposition on aluminium coated slides, and drop air drying. [3].

Results
Raman spectra were acquired from 11 iCD patients (6M/5F -55.9±7.8 age) and 11 healthy controls (6M / 5F 60.1±4.2 age). Spectral differences were observed in multiple ranges between the two groups, with main variations involving bands attributed to lipids, nucleic acids, and amino acids (Figure 1).

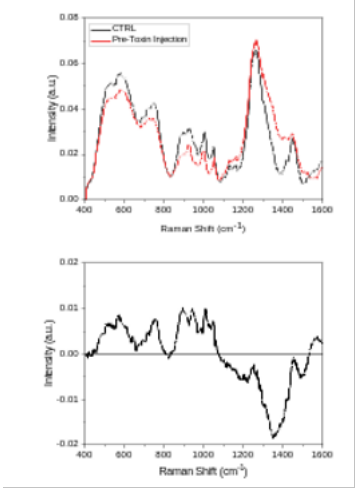


Figure 1 – Averaged Raman spectra of saliva from CTRL and dystonic patients (top) and their difference spectrum (bottom), highlighting protein-, lipid- and nucleic acid-related bands.

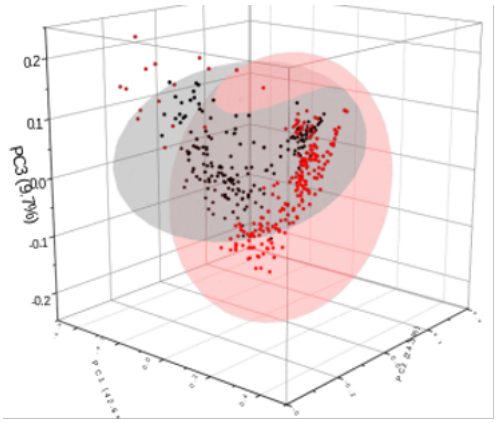


Figure 2 – PCA scatter plot (PC1–PC3) with 95% confidence ellipses showing the separation between CTRL (black) and dystonic patients (red).

Principal Component Analysis (PCA) tested the possibility to discriminate iCD from CTRL subjects by their salivary Raman signature showing that the discriminating spectral regions were related mainly to nucleic acids, protein amino acid composition, protein secondary structure, and lipids (Figure 2).

Conclusion

Although larger longitudinal cohorts are needed, these preliminary findings indicate that Raman spectroscopy can detect disease-related salivary biochemical changes, showing molecular alterations already described in dystonia, including genetic alterations and a reduction of protein S–S bridges in proteins [4].

Bibliography

[1] Albanese A, Bhatia KP, Cardoso F, Comella C, Defazio G, Fung VSC, Hallett M, Jankovic J, Jinnah HA, Kaji R, Krauss JK, Lang A, Tan EK, Tijssen MAJ, Vidailhet M. Isolated Cervical Dystonia: Diagnosis and Classification. Mov Disord. 2023 Aug;38(8):1367-1378. doi: 10.1002/mds.29387. Epub 2023 Mar 29. PMID: 36989390; PMCID: PMC10528915.

[2] Gualerzi A, Picciolini S, Carlomagno C, Terenzi F, Ramat S, Sorbi S, Bedoni M. Raman profiling of circulating extracellular vesicles for the stratification of Parkinson's patients. Nanomedicine. 2019 Nov;22:102097. doi: 10.1016/j.nano.2019.102097. Epub 2019 Oct 21. PMID: 31648040.

[3] Carlomagno C, Bertazioli D, Gualerzi A, Picciolini S, Andrico M, Rodà F, Meloni M, Banfi PI, Verde F, Ticozzi N, Silani V, Messina E, Bedoni M. Identification of the Raman Salivary Fingerprint of Parkinson's Disease Through the Spectroscopic- Computational Combinatory Approach. Front Neurosci. 2021 Oct 26;15:704963. doi: 10.3389/fnins.2021.704963. PMID: 34764849; PMCID: PMC8576466.

[4] Rostasy, K., Augood, S. J., Hewett, J. W., Leung, J. C. O., Sasaki, H., Ozelius, L. J., Ramesh, V., Standaert, D. G., Breakefield, X. O., & Hedreen, J. C. (2003). TorsinA protein and neuropathology in early onset generalized dystonia with GAG deletion. Neurobiology of Disease, 12(1), 11-24. https://doi.org/10.1016/S0969-9961(02)00010-4

25. Goal Attainment Scaling in Isolated Cervical Dystonia Treated with Botulinum Neurotoxin: A Patient-Centred Group-Level Analysis

Authors

M. Lus[1*] ,M. Di Maira[1], L. De Iaco[1], M. Ramella[1], A. Castagna[1]

** presenter*

Affiliations

[1] IRCCS Fondazione Don Carlo Gnocchi Onlus, Via Capecelatro 66 Milano, Italy, 20122

[2] Università degli Studi di Milano

Background

The Goal Attainment Scale (GAS) is a patient-centred tool designed to quantify achievement of individualized goals often used in neurorehabilitation to implement a patient-centred approach[1]. Few studies have applied GAS in isolated Cervical Dystonia (iCD)[2,3]

Methods

We administered GAS to a cohort of iCD patients, regularly treated with botulinum neurotoxin (BoNT) in Don Gnocchi Research Hospital. For each patient, a GAS T-score was calculated for each individual goal at baseline (T0), one month (T1), and three months (T2) after BoNT treatment. Individual goals were sorted in macro-categories, and T-scores of goals in each macro-category were summarized as mean±SD at each timepoint. The most numerous macro-categories were included in the longitudinal analysis. Changes between T0 and T1 and between T1 and T2 were assessed using paired-samples t-tests, including only patients with complete data for each comparison.

Results

We recruited 16 consecutive iCD patients and identified 16 macro-categories, 6 of which were reported more than 5 times and included in the longitudinal analysis (fig.1). The mean T-score of “pain” macro-category improved significantly between T0-T1, all other mean T-scores showed a positive trend from T0 to T1 and remained stable from T1 to T2.

Conclusions

Our preliminary findings suggest that the GAS may be a valuable complementary outcome measure in patients with iCD treated with BoNT by directly reflecting patients’ priorities on aspects that may not be fully captured by other commonly used scales. This approach may widen the assessment of BoNT effects in iCD helping clinicians identify new categories of analysis

Goals	n baseline	T0	T1	Δ T1-T0	p (T0-T1)	T2	Δ T2-T1	p (T1-T2)
Reading	6	35 ± 5.48	40 ± 0 (n 5)	+ 5	0,178	40 ± 7.07 (n 5)	0	1
Pain	8	35 ± 5.35	48.75 ± 5.35 (n 8)	+ 13.75	0,01	41.43 ± 14.64 (n 7)	- 7.32	0,111
Motor Control	8	35 ± 5.34	43.33 ± 12.11 (n 6)	+ 8.33	0,11	40 ± 8.94 (n 6)	-3.33	0,363
Walking	10	33 ± 4.83	42.5 ± 12.81 (n 8)	+ 9.5	0,084	41.42 ± 14.63 (n 7)	-1.08	0,172
Driving	13	35 ± 5.22	43 ± 12.52 (n 11)	+ 8	0,193	42 ± 13.77 (n 11)	-1	1
Social Discomfort	6	31.67 ± 4.08	45 ± 13.78 (n 6)	+ 14	0,08	42 ± 17.89 (n 5)	-3	0,178

Fig 1: Inferential analysis of the most frequent goals categories (n >5).

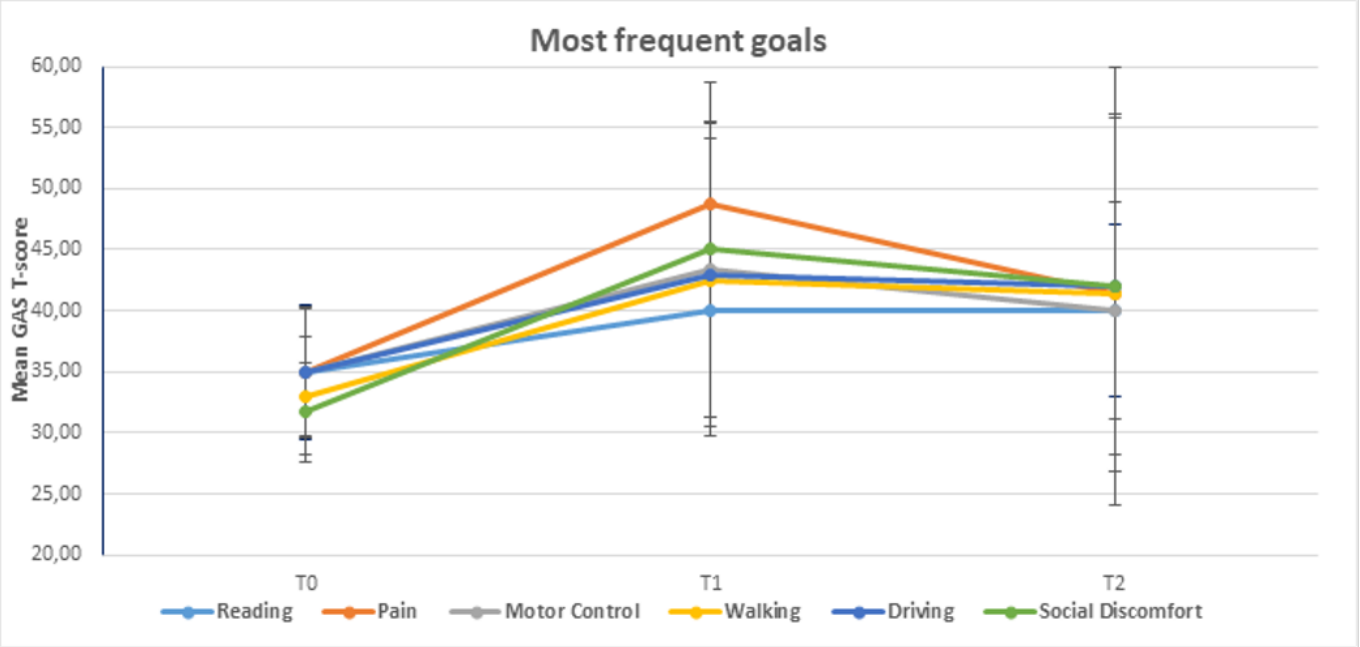


Fig 2: Improvement of the most frequent goal categories during T0-T1 and T1-T2.

Bibliography

1: Krasny-Pacini A, Hiebel J, Pauly F, Godon S, Chevignard M. Goal attainment scaling in rehabilitation: a literature-based update. Ann Phys Rehabil Med. 2013 Apr;56(3):212-30. doi: 10.1016/j.rehab.2013.02.002. Epub 2013 Feb 28. PMID: 23562111

2: Szabó M, Gárdián G, Szpisjak L, Salamon A, Gábor T, Klivényi P, Zádori D. The Application of Goal Attainment Scaling in Cervical Dystonia - An Exploratory Observational Pilot Study. Mov Disord Clin Pract. 2024 Aug;11(8):1013-1017. doi: 10.1002/mdc3.14118. Epub 2024 Jun 3. PMID: 38828630; PMCID: PMC11329570.

3: Panyakaew P, Wongwan P, Bhidayasiri R. The Goal Attainment Scale Refines Patient-Centered Expectations in Botulinum Toxin Treatment of Cervical Dystonia. J Mov Disord. 2024 Oct;17(4):462-465. doi: 10.14802/jmd.24150. Epub 2024 Sep 23. PMID: 39313237; PMCID: PMC11540539.

26. Long-Term Effect of Repeated Botulinum Toxin-A injections performed with Ultrasound and EMG guides in Professional Musicians: A Case Series

Authors
Luca De Iaco[1], Pierpaolo Santurelli[2], Marina Ramella[1], Rosa Maria Converti[1], Anna Castagna[1]

Affiliations
[1] IRCCS Fondazione Don Carlo Gnocchi, Via Capecelatro 66 Milano, Italy, 20122
[2] Movement Disorders Division, Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, Department of Neurology, University of New York, New York, NY, USA

Introduction
Musicians' dystonia is a task-specific movement disorder characterized by loss of voluntary motor control in extensively trained movements. It impacts heavily and often ends the career of the affected musician.
Botulinum toxin A (BoNTA) injection is considered an effective treatment [1] and ultrasound (US) guide is of utmost importance in muscle targeting [2].

Methods
We present a case series of very high-level musicians affected by focal hand-dystonia, treated on a regular basis in Don Gnocchi Research Hospital in Milano, with US+EMG-guided BoNTA injections. The subjects provided overall satisfaction of treatment during the latest interval using a 0-10 Numeric Rating Scale (NRS).

Results
Six musicians were included: 2 violin orchestra players, 2 soloists (guitar, harpsichord), 2 chamber players (piano, flute). Mean disease duration was 23,7±10,7 years, subjects underwent a mean of 17,2±7,4 BONT-A injections in 9±2,4 years. Mean doses for each injected muscle were 15±0U Abo, 9,5±1,4U Inco and 11±2,7U Ona.
Single flexor digitorum fascicles were targeted: 3rd superficialis and profundus in 3 subjects; 4th superficialis in 3; 4th profundus in 2 and 5th superficialis in 1 subject. Injection sites were highly consistent in time.
The mean interval between treatments was 184,7±52,5 days.
Overall mean treatment satisfaction was 7,9±1,3.

Conclusions
In high-performing musicians, with an established career, affected by focal dystonia involving fingers' flexors muscles, we observed high inter- and intra-subject consistency, in terms of dosage and targeted muscle. This can also be influenced by the solid experience of the musicians and their compensating strategies during the wearing-off periods.

Reference from a journal article
[1] Schuele S et al. Botulinum toxin injections in the treatment of musician's dystonia. Neurology 2005 .
[2] Dressler D et al. Botulinum toxin therapy of dystonia. J Neural Transm (Vienna). 2021 Apr;128(4):531-537. doi: 10.1007/s00702-020-02266-z. Epub 2020 Oct 30. PMID: 33125571;

27. Expanding the Motor and Molecular Spectrum of *NAA15*-Related Disorder: A Clinically Recognizable Pediatric Gait Dystonia

Authors
Martino Montomoli, MD[1,2], Kathryn Yang, MD, FRCPC[3], Josh Rong, BSc[1], Amy Tam, BSc[1], Monica Ferrer Socorro, MD[3], Jennifer Friedman, MD, PhD[4], Claire Miller, MD, PhD[1], Darius Ebrahimi-Fakhari, MD, PhD[3]

Affiliations
[1]The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, Department of Neurology, NYU Langone Health, New York, NY, USA
[2] Neuroscience and Human Genetics Department, Meyer Children's Hospital IRCCS, Florence, Italy
[3] Movement Disorders Program, Department of Neurology, Boston Children's Hospital, Boston, MA, USA
[4] Departments of Neurosciences and Pediatrics, Rady Children's Hospital, San Diego, CA, USA

Background
NAA15 encodes the auxiliary subunit of the N-terminal acetyltransferase A (NatA) complex[1]. Heterozygous truncating variants cause a neurodevelopmental disorder characterized by developmental delay and intellectual disability[2]. While a spectrum of movement disorders is emerging, including childhood-onset lower-limb dystonia, the causative variants reported to date have been exclusively truncating[3,4]. Whether non-truncating variants produce a comparable phenotype remains to be established[4].

Objective
To describe two unrelated children with novel, non-truncating *de novo NAA15* variants presenting with isolated gait dystonia.

Methods
We performed detailed clinical phenotyping, longitudinal gait analysis, and trio whole-exome sequencing.

Results
Both patients presented between 4 and 5 years of age with isolated, action-induced, paroxysmal dystonia of the lower limbs.

- **Clinical Signature:** Gait examination demonstrated a characteristic and concordant pattern in both cases, featuring thigh internal rotation, knee flexion, and intermittent equinovarus posturing.
- **Molecular Findings:** Patient 1 harbored a *de novo* in-frame deletion (p.Lys95del) and Patient 2 a *de novo* missense variant (p.Lys101Glu). Both variants cluster within exon 4 in the N-terminal NAA10-binding region.
- **Treatment:** In contrast to prior pediatric cases where trihexyphenidyl was often beneficial **(3, 4)**, this medication was ineffective or poorly tolerated in our patients.

Video Presentation
Core to this work is the longitudinal video documentation illustrating the evolution of gait dystonia over 12–14 months. These videos define a "phenotypic signature" to aid clinicians in suspecting *NAA15* in children with isolated gait dystonia, even in the absence of major neurodevelopmental delays or MRI abnormalities.

Conclusion

hese findings identify isolated childhood-onset gait dystonia as a recognizable motor presentation of *NAA15*-related disorders (proposed designation: **DYT-*NAA15***)[5]. Non-truncating variants at the NAA10-binding interface expand the mutational spectrum and suggest mechanisms beyond haploinsufficiency.

References

1. Arnesen T, et al. Proc Natl Acad Sci USA. 2009;106(20):8157-62.
2. Cheng H, et al. Am J Hum Genet. 2018;102(5):985-94.
3. Yubero D, et al. Mov Disord. 2022;37(11):2320-1.
4. Danti FR, et al. Mov Disord. 2024;39(4):747-9.
5. Albanese A, et al. Mov Disord. 2013;28(7):863-73.

28. Nanomedicine-based cholesterol delivery approach to counteract cortico-striatal disconnection in a prodromal Huntington's disease model

Authors
Canonichesi J[1,2], Campanelli F[1,3], Marino G[4], Natale G[1,3], Caggiati C[5], Zerbini E[5], Vitali M[5], Deligios M[5], Calabresi P[3,4], Tosi G[6], Valenza M[5], Ghiglieri V[1,3]

Affiliations
1. Università Telematica San Raffaele Roma, Roma, Italia.
2. San Raffaele Sulmona, Sulmona (AQ), Italia
3. Neurologia, Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Roma, Italia
4. Neurologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italia
5. Dipartimento di Bioscienze, Università degli Studi di Milano, Milano, Italia
6. Nanotech Lab, Te.Far.T.I., Dipartimento di Scienze della Vita, Università degli Studi di Modena e Reggio Emilia, Modena, Italia

Abstract
Huntington's disease (HD) is a rare autosomal dominant neurological disorder caused by CAG repeat expansion within the HTT gene. Cortico-striatal degeneration, a main feature of HD, is preceded by defective cholesterol synthesis and trafficking in the central nervous system (CNS). Thus, cholesterol replacement has been envisioned as a possible therapeutic strategy, leveraging nanotherapeutic tools designed to cross the blood-brain barrier.
We used a slowly progressive murine model of HD (zQ175DN knock-in mice) to test a nanoparticle-based strategy to deliver cholesterol to the brain, and to assess whether this approach could prevent the onset of early synaptic manifestations of disease.
After chronic systemic treatment with brain-permeable nanoparticles loaded with cholesterol, zQ175DN mice at prodromal disease stage were tested through ex vivo patch-clamp recordings and optogenetic stimulation to assess cortico-striatal excitatory neurotransmission and synaptic plasticity. Immunofluorescence and molecular analysis of striatal synaptosomes allowed structural characterization of cortico-striatal synapses.
Prodromal HD mice presented impaired excitatory tone and reduced cortico-striatal projection density. Moreover, long-term synaptic plasticity was impaired in both striatal spiny projection neurons (SPNs) and cholinergic interneurons (ChInts). Cholesterol-based treatment restored cortico-striatal connectivity and partially rescued synaptic plasticity in SPNs. Western blot analysis of striatal synaptosomes revealed possible molecular links between cholesterol dysfunction and synaptopathy in early HD.
Our findings highlight cortico-striatal disconnection as a prodromal feature of HD, which can be assessed before the onset of overt motor manifestations. Moreover, we showed that cholesterol dyshomeostasis can play a role in cortico-striatal synaptopathy, representing a potential therapeutic target in HD.

29. Seasonal Variations and Air Pollutant Associations in Ischemic and Hemorrhagic Stroke: A Retrospective Analysis

Authors
H. Çağlar, Kadir Çağlar, Ş. Öztürk, M.K. Körez.

Aim/Objectives
To assess the relationship between clinical parameters of ischemic and hemorrhagic stroke and atmospheric quality factors, identify seasonal patterns of stroke incidence, and determine which pollutants independently predict stroke severity. (1,2).

Methods
A retrospective review included 729 patients (671 ischemic, 58 hemorrhagic) admitted between 1 January 2022 and 31 December 2023. Data from hospital electronic records provided demographics, laboratory values, imaging findings, and NIHSS scores. Daily mean SO_2, NO_2, $PM_{2.5}$, PM_{10}, O_3, and CO levels were obtained from the Southern Central Anatolia Clean Air Directorate. Spearman rank correlation assessed associations between pollutants and clinical variables, and chi-square tests compared seasonal frequencies. Analyses were performed with SPSS, with significance set at $p < 0.05$. Ethical approval was granted, and all patient data were anonymized.

Results
The cohort comprised 391 males and 338 females (mean age 70.0 ± 13.44 years). Seasonal distribution of stroke subtypes is shown in Table 1.

Season	Ischemic Stroke n (%)	Hemorrhagic Stroke n (%)	p-value
Winter	182 (27.1)	14 (24.1)	623
Spring	189 (28.2)	15 (25.9)	707
Summer	168 (25.0)	12 (20.7)	461
Autumn	132 (19.7)	17 (29.3)	81

Ischemic stroke incidence was significantly higher in winter and spring than in autumn ($p < 0.05$), while hemorrhagic stroke showed no seasonal variation. In September, male hemorrhagic strokes (19.35%) exceeded ischemic strokes (7.20%) ($p = 0.018$). Among hemorrhagic cases, PM_{10} correlated negatively with hemoglobin ($\rho = -0.259$, $p = 0.049$). In ischemic cases, SO_2 correlated positively with NIHSS scores ($\rho = 0.086$, $p = 0.025$), O_3 correlated negatively with systolic blood pressure ($\rho = -0.085$, $p = 0.027$), and SO_2 correlated negatively with triglyceride levels ($\rho = -0.120$, $p = 0.024$). Multivariate analysis identified age, diabetes mellitus, and low hemoglobin as independent ischemic stroke risk factors, while elevated systolic and diastolic pressures predicted hemorrhagic stroke ($p < 0.001$).

Conclusions
Ischemic stroke peaks in colder months, and specific pollutants such as PM_{10}, SO_2, and O_3 are linked to stroke severity and laboratory abnormalities. Incorporating air-quality monitoring into public-health strategies may reduce stroke burden and guide targeted prevention policies.
Environmental interventions could therefore lessen stroke incidence.

Reference
(1) Shen S, Li X, Yuan C, et al. Association of short-term exposure to sulfur dioxide and hospitalization for ischemic and hemorrhagic stroke in Guangzhou, China. BMC Public Health. 2020;20:1–7.
Toubasi A, Al-Sayegh TN. Short-term exposure to air pollution and ischemic stroke: a systematic review and meta-analysis. Neurology. 2023;101:e1922-e32.

30. Modeling Multiple System Atrophy pathology in striatum organoids

Authors
Manuela Magni1, Elena Vezzoli2, Gaia Faustini3, Gianluca Lopez4, Letizia Bertolasi5, Marco Brevi4, Valentina Vaira4, Arianna Bellucci3, Alessio Di Fonzo5, Emanuele Frattini5

Affiliations
1 University of Milan, Milan, Italy; 2 Advanced Light and Electron Microscopy BioImaging Centre (ALEMBIC), IRCCS San Raffaele Scientific Institute, Milan, Italy; 3 Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy; 4 Division of Pathology, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; 5 Neurology Unit, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Objective
To generate advanced three-dimensional models of Multiple System Atrophy (MSA) derived from patients by developing brain region-specific organoids with striatum identity.

Background
MSA is a progressive neurodegenerative disorder characterized by complex parkinsonian and cerebellar phenotypes and reduced life-span with a median survival of 6-9 years after symptom onset. The neuropathological hallmarks of MSA consist of glial cytoplasmic inclusions (GCIs) enriched in alpha-synuclein within oligodendrocytes and of degeneration of various neuronal populations, primarily of the GABAergic medium spiny neurons (MSNs) in the striatum. No disease-modifying therapy is available for MSA, largely due to the lack of reliable human models capable of reproducing key features of the disease and that could be tested for drug-development applications.

Methods
Induced pluripotent stem cells (iPSCs) of n=2 MSA-P, n=2 MSA-C, and n=2 healthy control were generated from skin fibroblasts and differentiated into striatum organoids (SOs) with a novel GABAergic patterning protocol. SOs were cultured for 150 days *in vitro* (DIV) and analyzed at various time points by means of qPCR, single-nucleus RNA sequencing, immunohistochemistry, Western blot, and transmission electron microscopy (TEM).

Results
SOs were characterized to demonstrate the expression of transcripts and proteins of striatal MSN markers (DARPP32, GSX2, GABA, NeuN, MAP2). In addition to neurons, SOs also contain glial cells expressing astrocyte (GFAP, S100B), oligodendrocyte (MPB, O4, OLIG2), and microglia (IBA1) markers, holding potential to mimic neuron-glia interactions. Analysis of alpha-synuclein in MSA SOs showed increased expression and protein content and the presence of pathological insoluble fractions. Membrane-bound inclusions within oligodendrocytes resembling authentic GCIs were detected in MSA SOs by TEM analysis.

Conclusions
Long-term culture of SOs showed a correct spatial and temporal progression in the expression of genes involved in the development of a striatal identity, mimicking the embryogenesis of the human brain. MSA SOs reproduced key features of alpha-synuclein pathology, most importantly GCI-like inclusions, therefore showing potential to reproduce aspects of the typical human neuropathology.

31. A Novel 2D Synthesis of Cerebellar Anatomy

Author
Xavier Guell [a]

Affiliation
a. Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, Department of Neurology, New York University Grossman School of Medicine, New York

Abstract
Basic knowledge of brain organization is necessary for progress in diagnosis and treatment of brain diseases, including parkinsonian disorders. Here I present a novel synthesis of cerebellar anatomy that reconciles human and animal literature of cerebellar connections. This synthesis is based on two axes: (i) an anterior-posterior and (ii) a medial-lateral axis. (i) An anterior-posterior axis in cerebellar cortex captures motor versus cognitive topography, and relates to cerebellar connections with cerebellar pontine nuclei, thalamus, and cerebral cortex. This anterior-posterior axis is highlighted in human imaging literature, and confirmed in rodent and primate tracing studies. More specifically, two motor representations in cerebellar lobules I-VI and VIII, and three nonmotor representations in VI-Crus I, Crus II-VIIB, and IX-X each relate to motor versus associative areas in pontine nuclei, thalamic nuclei, and cerebral cortex. (ii) A medial-lateral axis in cerebellar cortex captures vestibular versus motor and cognitive topography, and relates to cerebellar cortical connections with deep cerebellar nuclei, vestibular brainstem nuclei, red nucleus, and inferior olive. This medial-lateral axis is highlighted in animal literature. More specifically, lateral cerebellar cortex relates to dentate nucleus, principal olivary nucleus, and parvocellularis aspects of red nucleus. Paravermal cerebellar cortex relates to emboliform nucleus, dorsal accessory olive, and magnocellularis aspects of red nucleus. Vermal cerebellar cortex relates to fastigial nucleus, medial accessory olive, and brainstem vestibular nuclei. This two-dimensional view reconciles findings in human imaging with animal literature, offers a useful novel synthesis of cerebellar anatomy, and unmasks novel questions for future research.

References:
1. Guell, X. How the cerebellum relates to the rest of the brain: from clinical questions to anatomical answers. Editorial article in preparation for special issue of *Cerebellum*, 2026.
2. Guell, X. and Schmahmann, J.D., Phenoconsonance: a new form of neurological analysis that complements anatomical localization and disease pattern recognition. J Neuropsychiatry Clin Neurosci, 2026. 38(2): p. 107-119.
3. Schmahmann, J.D., Guell, X., Stoodley, C.J., and Halko, M.A., The Theory and Neuroscience of Cerebellar Cognition. Annu Rev Neurosci, 2019. 42: p. 337-364.
4. Guell, X., Schmahmann, J.D., Gabrieli, J.D.E., and Ghosh, S.S., Functional gradients of the cerebellum. eLife, 2018. 7: p. e36652-e36652.
5. Guell, X., Gabrieli, J.D.E., and Schmahmann, J.D., Triple representation of language, working memory, social and emotion processing in the cerebellum: Convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort. NeuroImage, 2018. 172: p. 437-449.
6. Guell, X., D'Mello, A.M., Hubbard, N.A., Romeo, R.R., Gabrieli, J.D.E., Whitfield-Gabrieli, S., Schmahmann, J.D., and Anteraper, S.A., Functional Territories of Human Dentate Nucleus. Cerebral Cortex, 2019. 30(4): p. 2401-2417.

32. Alpha-synuclein effects in GBA Parkinson's model: early striatal circuit remodeling

Authors
Maria Mancini[1,2], Deborah Di Martino[1,2], Michela Salvadé[3], Alessandra Stanchina[4], Hien Ferrari[1,2], Natalie Polverino[1,2], Marco Peviani[4], Fabrizio Gardoni[3], Alessandro Fraldi[5,6], Antonio Pisani[1,2]

Affiliations
[1] University of Pavia, Department of Brain and Behavioral Sciences, Pavia, Italy
[2]IRCCS Mondino Foundation, Pavia, Italy
[3] University of Milan, Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Milan, Italy
[4] University of Pavia, Department of Biology and Biotechnology "Lazzaro Spallanzani', Pavia, Italy
[5] University of Naples "Federico II", Department of Clinical Medicine and Surgery, Naples, Italy
[6] CEINGE Advanced Biotechnology, Naples, Italy

Abstract
Mutations in the *GBA* gene are the most common genetic risk factor for Parkinson's disease (PD) and are associated with reduced glucocerebrosidase (GCase) activity and enhanced vulnerability to alpha-synuclein (Syn) pathology. Syn is a lipid-binding protein physiologically enriched at presynaptic terminals, where it regulates vesicle trafficking and membrane organization through interactions with phospolipids. Whether this role translates into circuit dysfunction when Syn aggregates in the context of pre-existing lysosomal impairment remains unclear.
We combined behavioral, electrophysiological, biochemical, and lipidomic approaches to investigate basal ganglia circuit function in wild-type (WT) and *GBA* heterozygous (Het; *GBA1* L444P/+) mice at an early stage of pathology following bilateral striatal injection of Syn preformed fibrils (Syn-PFFs).
At baseline, Het mice showed a reduction of GCase activity across multiple brain regions. Striatal spiny projection neurons exhibited preserved intrinsic excitability but reduced spontaneous excitatory transmission and altered paired-pulse ratio, while long-term potentiation (LTP) remained intact. Behaviorally, Het mice displayed mild motor impairment without cognitive deficits.
Following Syn-PFF injection, WT mice developed increased neuronal excitability and loss of striatal LTP. In contrast, in Het mice, Syn pathology further reduced GCase activity selectively in the midbrain but restored spontaneous synaptic activity, preserved LTP, and rescued motor performance. Preliminary lipidomic analyses reveal genotype-dependent alterations that were similarly normalized in Het mice after Syn injection. In Het neurons, Syn functionally remodels lipid-altered membranes, transiently restoring synaptic performance while its detrimental effects remain restricted to lysosomal vulnerability in selective regions.
These findings reveal a non-linear interaction between *GBA* deficiency and Syn pathology.

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

Authors
Danilo Genovese, MD[1,2] *; Francesco Bove, MD, PhD[1,2]; Alessandro De Biase, MD[1,2]; Alberto Albanese, MD[3]; Angelo Antonini, MD, PhD[4,5]; Carlo Alberto Artusi, MD, PhD[6,7]; Laura Avanzino, MD, PhD[8,9]; Micol Avenali, MD, PhD[10,11]; Luca Baldelli, MD[12,13]; Giovanna Calandra-Buonaura MD, PhD[12,13]; Ilaria Cani, MD[12,13]; Niccolò Casasoli, MD[2,14]; Francesco Cavallieri, MD, PhD[15]; Roberto Cilia, MD[16]; Antoniangela Cocco, MD[3]; Fabiana Colucci, MD[16]; Francesca Di Biasio, MD, PhD[9]; Valentina D'Onofrio, MD[4]; Roberto Eleopra, MD[16]; Valentina Fioravanti, MD, PhD[15]; Giulia Giannini, MD, PhD[12,13]; Nico Golfre' Andreasi, MD[16]; Andrea Guerra, MD, PhD[4,5]; Gabriele Imbalzano, MD[6,7]; Alessandro Izzo, MD[17]; Claudia Ledda, MD[6,7]; Marco Liccari, MD[18]; Leonardo Lopiano, MD, PhD[6,7]; Maria Chiara Malaguti, MD[19]; Raffaella Minardi, PhD[13]; Pierfrancesco Mitrotti, MD[10]; Luigi Michele Romito, MD, PhD[16]; Enza Maria Valente, MD, PhD[20,11]; Roberta Zangaglia, MD[11]; Franco Valzania, MD, PhD[15]; Paolo Calabresi, MD[1,2]; Anna Rita Bentivoglio, MD, PhD[1,2 #]; Carla Piano, MD, PhD[1,2 #]; on behalf of the Italian PARKNET Study.

Background
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 Parkinson Disease (PD) who underwent bilateral subthalamic deep brain stimulation (STN-DBS).

Methods
This retrospective cohort study involved 9 Italian tertiary-level Movement Disorder Centres contributing to the Italian PARKNET project. Demographic and clinical data were collected at baseline and one, three and five years after surgery.

Results
We analyzed a cohort of 353 PD patients who underwent DBS surgery (75 GBA+ and 253 GBA-). 5-year follow-up data were available for 233 patients, including 43 GBA1-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 did not exert a detrimental effect on axial motor signs up to five years after STN-DBS. A careful patients' selection prior to DBS allows the exclusion of patients with levodopa-resistant axial signs or cognitive decline, resulting in a cohort of GBA1 carriers with motor outcomes comparable to the non GBA1-PD population. In this population, with a proper pre-operative selection, STN-DBS may be considered as a valid therapeutic option.

Affiliations
[1] Neurology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy;[2] Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy;[3] Department of Neurology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy;[4] Padova Neuroscience Center, University of Padua, Padua, Italy;[5] Parkinson and Movement Disorders Unit, Study Centre on Neurodegeneration (CESNE), Department of Neuroscience, University of Padua, Padua, Italy;[6] Department of Neuroscience 'Rita Levi

Montalcini', University of Torino, Turin, Italy;[7] Neurology 2 Unit, Department of Neuroscience, A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy;[8] Department of Experimental Medicine (DIMES), Section of Human Physiology, University of Genoa, Genoa, Italy;[9] IRCCS Policlinico San Martino, Genoa, Italy;[10] Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy;[11] IRCCS Mondino Foundation, Pavia Italy;[12] Department of Biomedical and NeuroMotor Sciences (DIBINEM), Alma Mater Studiorum - University of Bologna, Bologna, Italy;[13] IRCCS Istituto delle Scienze Neurologiche di Bologna, Via Altura, 3, 40139, Bologna, Italy;[14] Unit of Neurology, Neurophysiology, Neurobiology and Psichiatry, Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Rome, Italy;[15] Neurology Unit, Neuromotor and Rehabilitation Department, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy;[16] Parkinson and Movement Disorders Unit, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy;[17] Neurosurgery Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy;[18] Clinical Unit of Neurology, Department of Medical, Surgical and Health Sciences, Cattinara University Hospital, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), Trieste, Italy;[19] Department of Neurology, Santa Chiara Hospital, Trento, Italy;[20] Department of Molecular Medicine, University of Pavia, Pavia, Italy

34. Distinct roles of α-synuclein aggregates in synaptic dysfunction and therapeutic potential of novel anti-aggregating compounds

Authors
Laura Bellingacci[1], Anna Aurora Taddei[2], Miriam Sciaccaluga[3], Michela Salvadè[4,5], Giovanni Bellomo[3,6], Cinzia Costa[2], Massimiliano Di Filippo[2], Fabrizio Gardoni[5], Paolo Calabresi[7,8], Alessandro Tozzi[1].

Affiliations
1 Section of Biochemistry and Physiology, Department of Medicine and Surgery, University of Perugia, Italy.
2 Section of Neurology, Department of Medicine and Surgery, University of Perugia, Italy.
3 Department of Life Science, Health, and Health Professions, Link Campus University, Rome, Italy
4 School of Advanced Studies, Center for Neuroscience, University of Camerino, Italy.
5 Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", University of Milan, Italy.
6 Laboratory of Clinical Neurochemistry, Department of Medicine and Surgery, University of Perugia, Italy.
7 Neurology Section, Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy
8 Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy.

Abstract
Aggregation of α-synuclein (α-syn) is a central pathogenic event in synucleinopathies, including Parkinson's disease (PD), and occurs through structurally and functionally distinct species. Among these, soluble α-syn oligomers (OSyn) are increasingly recognized as early, highly neurotoxic forms that trigger synaptic dysfunction, neuroinflammation, and behavioral alterations even at low concentrations, preceding overt neurodegeneration. In contrast, fibrillar α-syn species, such as preformed fibrils (PFFs), are associated with later stages of pathology, including aggregate propagation, dopaminergic dysfunction, and widespread impairment of basal ganglia circuitry.
Using complementary rodent models based on intrastriatal administration of OSyn or PFFs, we delineated the temporal and mechanistic differences between these aggregation states. OSyn exposure induced early deficits characterized by impaired bidirectional striatal synaptic plasticity, reduced spontaneous excitatory neurotransmission, decreased VGluT1 expression at corticostriatal terminals, and the emergence of anxiety-like behavior, in the absence of nigral degeneration[1]. Conversely, PFFs primarily disrupted nigrostriatal function, altering the firing activity of dopaminergic neurons in the substantia nigra pars compacta, enhancing glutamatergic transmission, and impairing both long-term potentiation (LTP) and long-term depression (LTD), preceding neuronal loss and leading to progressive motor dysfunction[2].
Given that oligomeric species are thought to act upstream of fibril formation, the prevention of the transition from oligomers to fibrillar α-syn aggregation represents a promising disease-modifying strategy. In this context, we identified the small molecule SCF2 as a potent inhibitor of α-syn aggregation. SCF2 significantly delayed fibril formation in slice preparations, reduced aggregate burden, and blocked seeded fibril growth. Functionally, SCF2 fully rescued PFF-induced impairment of synaptic plasticity in striatal neurons and prevented pathological alterations in NMDA receptor subunit contribution.
Overall, these findings support a model in which OSyn and fibrillar α-syn exert distinct, yet sequential, pathogenic effects and demonstrate that targeting early aggregation processes with anti-aggregant compounds such as SCF2 can effectively prevent the transition between toxic species and protect against early synaptic dysfunction. This highlights SCF2 as a promising therapeutic candidate for disease modification in PD.

References
1 Bellingacci et al., 2025
2 Tozzi et al., 2021

35. APOE ε4 carriage is associated with basal ganglia microstructural alterations in early Parkinson's disease

Authors
Giovanni Restuccia, Augusto Ielo, Ambra Faraci, Alessia Venuto, Alessandro Grimaldi, Viviana Lo Buono, Angelo Quartarone and Lilla Bonanno

Affiliation
IRCCS Centro Neurolesi Bonino-Pulejo, Messina

Background
Apolipoprotein E (APOE) ε4 is a genetic risk factor for Alzheimer's disease and has been associated with structural and microstructural brain vulnerability in cognitively healthy older adults. However, its role in early Parkinson's disease (PD) remains poorly understood. We investigated whether APOE ε4 carriage is associated with basal ganglia microstructural alterations in early PD and whether similar effects occur in healthy controls (HC).

Methods
Diffusion MRI data from 121 PPMI participants were analyzed: 75 PD (25 ε4 carriers; 50 non-carriers) and 46 HC (16 ε4 carriers; 30 non-carriers). Preprocessed diffusion-weighted images were tensor-fitted to derive fractional anisotropy (FA), mean (MD), axial (AD), and radial (RD) diffusivity. Subcortical segmentations of the caudate, pallidum, putamen, nucleus accumbens and thalamus were used for ROI-based analyses and also combined into a group mask for voxel-wise testing with family-wise error (FWE) correction. Carriers and non-carriers were compared separately within PD and HC.

Results
Within PD, ε4 carriers showed bilateral pallidal and putaminal microstructural alterations. Voxel-wise analyses localized higher MD and RD and lower FA predominantly to the left pallido-putaminal region (p-FWE < 0.05). FA extracted from significant clusters was also associated with CSF α-syn levels with an APOE-specific effect. No comparable APOE-related imaging pattern was detected in HC.
Conclusions: APOE ε4 carriage is associated with a focal basal-ganglia microstructural signature detectable in early PD, without evidence of clinical or cognitive involvement. This suggest that APOE-related microstructural vulnerability may become detectable in the context of early PD pathology, warranting longitudinal validation.

36. Levodopa-responsive parkinsonism with early cognitive impairment in a carrier of the PSEN1 p.Tyr154Cys variant.

Authors
Pio Crolla[1], Pasquale Nigro[2], Edoardo Monfrini[3], Antonio Tufo[1], Gianmarco Susca[1], Alessio Di Fonzo[3], Nicola Tambasco[2,*]

Affiliations
[1] Neurology Department, Perugia General Hospital and University Hospital of Perugia, Perugia, Italy
[2] Movement Disorder Center, Neurology Department, Perugia General Hospital and University Hospital of Perugia, Perugia, Italy
[3] Neurology Unit, Department of Neuroscience and Mental Health, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan , Italy
* Corresponding author at: Movement Disorders Center, Neurology Department, University Hospital of Perugia, Italy

Background and purpose
PSEN1 mutations are the most common genetic cause of autosomal dominant Alzheimer's disease but rarely present with parkinsonism. We describe the clinical phenotype associated with the PSEN1 p.Tyr154Cys variant in a patient presenting with levodopa-responsive parkinsonism and a suggestive family history.

Methods
The proband underwent neurological and neuropsychological assessment, olfactory testing with the Italian Olfactory Identification Test (IOIT), brain MRI, cerebrospinal fluid (CSF) biomarker analysis, and genetic testing. A four-generation pedigree was reconstructed based on the proband's report.

Results
A 53-year-old woman with a one-year history of progressive right upper-limb bradykinesia spreading to the ipsilateral lower limb. Neurological examination showed right-predominant bradykinesia and rigidity without tremor (MDS-UPDRS-III 35, Hoehn and Yahr stage 2). Her MDS-UPDRS part III score improved by 38% following a levodopa challenge test. Marked hyposmia was also documented (IOIT: 22/33 errors). Neuropsychological assessment, atypical for early Parkinson's disease, revealed a cortico-subcortical profile with predominant impairment of memory and executive domains (MMSE 24/30, MoCA 17/30). Brain MRI showed minimal nonspecific white matter changes, which remained unchanged three years later. CSF analysis showed isolated cerebral amyloidosis (Aβ42/40 0.039; ptau181 48 pg/mL; t-tau 262 pg/mL; A+T−N−) with mildly elevated neurofilament light chain (1097 pg/mL). Genetic testing identified the PSEN1 p.Tyr154Cys variant, classified as likely pathogenic. Despite levodopa and rivastigmine treatment, the clinical course was unusually rapid, with motor fluctuations developing within one year. By 2026, continuous subcutaneous foslevodopa/foscarbidopa infusion was required for motor control. According to the proband, relatives of both sexes in successive generations had similar symptoms. In particular, her mother reportedly developed progressive cognitive impairment, including memory loss, at approximately 55 years of age and died at 69.

Conclusion
The PSEN1 p.Tyr154Cys variant may be associated with a clinical phenotype characterized by early levodopa-responsive parkinsonism, prominent cognitive impairment, hyposmia, and rapid motor progression. This observation expands the phenotypic spectrum potentially associated with this variant

and highlights the importance of considering PSEN1-related disease in patients presenting with parkinsonism and early cognitive impairment.

Reference:

Janssen JC, Beck JA, Campbell TA, et al. Early onset familial Alzheimer's disease: mutation frequency in 31 families. Neurology 2003; 60:235-239.

37. Integrated Gene-Expression and Alternative-Splicing Analysis Reveals Molecular Dysregulation Associated with P301L Tau

Authors
Aurelio Minuti[1], Serena Silvestro[1], Salvatore Oddo[2], Luigi Chiricosta[1], Osvaldo Artimagnella[1], Maria Lui[1]

Affiliations
[1] IRCCS Centro Neurolesi "Bonino-Pulejo", Via Provinciale Palermo, Contrada Casazza, 98124 Messina, Italy.
[2] Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Viale F. Stagno D' Alcontres 31, 98166, Messina, Italy.

Presenter: Aurelio Minuti

Abstract
Tau, a microtubule-associated protein, can assemble into insoluble filamentous aggregates that constitute neurofibrillary tangles, a pathological hallmark of Alzheimer's disease and other tauopathies. Notably, gene-expression and alternative splicing alterations associated with pathological tau remain less characterized, particularly through integrated analyses.
Here, we investigated gene-expression and alternative-splicing alterations in a neuronal in vitro model based on differentiated SH-SY5Y cells overexpressing the P301L mutant form of tau, compared with differentiated wild-type SH-SY5Y cells. RNA sequencing followed by differential gene- expression analysis identified 5969 differentially expressed genes (DEGs), including 3108 upregulated and 2861 downregulated genes. Functional enrichment analysis highlighted biological processes related to synapse differentiation and axon/neuron projection guidance.
Using a dedicated RNA-seq-based splicing analysis pipeline, we further identified 220 differential alternative splicing events, including 27 intron-retention events. Genes affected by alternative splicing were significantly enriched in axo-dendritic transport. Notably, RNA-binding proteins involved in neuronal RNA regulation, including *QKI* and *CELF* family members, were also differentially expressed, suggesting a potential link with the altered alternative-splicing landscape.
Overall, our integrated transcriptomic and alternative-splicing analyses indicate that P301L tau overexpression is associated with coordinated gene-expression and alternative-splicing alterations affecting key neuronal processes, including protein translation, neuronal guidance, and intracellular transport. Interestingly, the identification of widespread alternative-splicing changes highlights an additional and still underexplored layer of tau-associated molecular dysregulation.
Further investigation of these alterations and their underlying regulatory mechanisms may provide new insights into tauopathy pathogenesis, potentially contributing to the identification of novel molecular and therapeutic targets.

38. Synergistic neurotoxicity and transcriptomic profiling of PCB co-exposure with MPP^+ in SH-SY5Y and SH-TAU Parkinson's disease models

Authors
Serena Silvestro[1], Simone D'Angiolini[1], Michele Scuruchi[2] and Minuti Aurelio[1]

Affiliations
[1] IRCCS Centro Neurolesi "Bonino-Pulejo", Via Provinciale Palermo, Contrada Casazza, 98124 Messina, Italy.
[2] Department of Clinical and Experimental Medicine, University of Messina, 98125 Messina, Italy.

Presenter: Serena Silvestro

Abstract
Parkinson's Disease (PD) is a multifactorial neurodegenerative disorder driven by gene-environment interactions. Polychlorinated biphenyls (PCBs), notably the non-dioxin-like congener PCB153 and the dioxin-like congener PCB118, are persistent environmental contaminants with documented neurotoxic potential. Although 1-methyl-4-phenylpyridinium (MPP^+) is widely used to model dopaminergic degeneration, the potential synergistic toxicity resulting from co-exposure with specific PCBs, as well as the modulating role of Tau protein pathology in these toxic insults, remains largely uncharacterized, particularly at the transcriptomic level.
This study aims to systematically evaluate the differential cellular susceptibility and synergistic molecular mechanisms induced by co-exposure to PCB153 or PCB118 with MPP^+, utilizing both human neuroblastoma SH-SY5Y cells and Tau-overexpressing SH-TAU cells.
Viability assays determined cytotoxicity thresholds for single and combined treatments. High-throughput transcriptomic profiling was subsequently performed to map dysregulated gene networks and signaling cascades under single and co-exposure regimes across both lines.

Both cell lines exhibited concentration-dependent toxicity following MPP^+ treatment, demonstrating comparable initial susceptibility. However, co-administration of PCB153 or PCB118 significantly amplified MPP^+-induced cytotoxicity, pointing to synergistic neurotoxic interactions. Transcriptomic analyses revealed substantial gene expression shifts, highlighting marked dysregulation in mitochondrial bioenergetics, oxidative stress management, neuroinflammatory pathways, and ubiquitin-proteasome protein clearance mechanisms, with distinct profiles emerging between wild-type and Tau-overexpressing cells.
Our findings validate SH-SY5Y and SH-TAU models for environmental neurotoxicity screening. Transcriptomic profiling elucidates how Tau overexpression modulates vulnerability while uncovering synergistic pathways triggered by PCB co-exposure. Notably, this study underscores the translational importance of integrating gene-environment models to identify prospective biomarkers and therapeutic targets in PD etiology.

39. Investigation of Early Synaptic Dysfunction in *PrknR275W* Mouse Model: Effects of Pharmacological Kainate Receptor Blockade

Authors
Guendalina Bastioli, Maria Regoni, Elena Monzani, Letizia Zanetti, Cecilia Mini, Diana Chierichetti, Martina Moro, Stefano Taverna, Martina Gausa, Flavia Valtorta, Jenny Sassone.

Abstract
Mutations in the *PARK2* gene are are associated with early-onset Parkinson's disease, yet the initial synaptic and circuit-level alterations preceding neurodegeneration remain poorly understood. We investigate intrinsic and synaptic properties of dopaminergic (DA) neurons in the *substantia nigra* (SNc), and of striatal spiny projection neurons (SPNs) in the *PrknR275W* mutation mouse model, focusing on kainate receptor (KAR) involvement. In the SNc the DA neurons from *PrknR275W* displayed a marked increase in spontaneous firing. This hyperactivity was accompanied by an upregulation of KAR and was significantly reduced by pharmacological blockade with UBP310, supporting a functional contribution of these receptors. In the striatum, SPNs exhibited altered glutamatergic transmission, with increased sEPSC amplitude and reduced frequency. Notably, KAR blockade, UBP310, reduced sEPSC amplitude without affecting frequency, suggesting a postsynaptic contribution. These findings identify early, region-specific synaptic dysfunction in *PrknR275W* and implicate KAR overactivity as a key driver of dopaminergic and striatal alterations, highlighting a potential target for early intervention.

40. Opicapone in advanced Parkinson's disease: a real-world longitudinal retrospective study

Authors
G. Susca[1], P. Nigro[1], P. Crolla[1], A. Chiappiniello[2], N.Tambasco[1], L. Parnetti[3]

Affiliations
1. Parkinson's Disease and Movement Disorders Center, Department of Neurology, University of Perugia
2. Medical Physics, University of Perugia
3.Department of Neurology, University of Perugia

Introduction
Oral opicapone is a third-generation peripheral catechol-O-methyltransferase inhibitor approved as add-on therapy to levodopa/dopa decarboxylase inhibitors in adults with Parkinson's disease (PD) experiencing end-of-dose motor fluctuations. In the pivotal phase III trials BIPARK-1 and BIPARK-2, as well as in short-term real-world studies (OPTIPARK, 3–6 months), opicapone demonstrated efficacy and good tolerability. However, long-term real-world data are still needed to better identify patients most likely to benefit from opicapone therapy**.**

Objective
To characterize patients with Parkinson's disease at the time of opicapone initiation and to evaluate the rate and main reasons for treatment discontinuation in routine clinical practice.
Methods:
Patients with idiopathic Parkinson's disease attending the Center for Parkinson's Disease and Movement Disorders of Perugia and treated with opicapone between 2018 and 2025 were included. Data on demographics, disease duration, and onset of motor complications were collected. Motor severity and levodopa equivalent daily dose (LEDD) were assessed at baseline (opicapone initiation) and at the last follow-up visit or treatment discontinuation.

Results
A total of 100 patients were enrolled (60 males and 40 females), with a mean age of 71.6 ± 9.0 years. At the time of opicapone initiation, the mean disease duration was 10.5 ± 5.7 years, and motor complications had begun 2.5 ± 3.2 years earlier. Longitudinal analyses were available for 66 patients. Overall, 28.8% of patients discontinued opicapone after a mean follow-up of 17.3 ± 16.5 months. The most frequent reason for treatment discontinuation was the occurrence of hallucinations. Patients who continued opicapone therapy underwent the last follow-up visit (T1) after a mean of 25.4 ± 20.8 months and were younger and had a lower LEDD at baseline.
Conclusions:
Real-world longitudinal studies provide valuable insights into patient selection and treatment persistence, supporting the safer and more effective use of opicapone in routine clinical practice.

Bibliography
[1] Ferreira JJ, Lees A, Rocha JF, Poewe W, Rascol O, Soares-da-Silva P; Bi-Park 1 investigators. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. Lancet Neurol. 2016
[2] Lees AJ, Ferreira J, Rascol O, Poewe W, Rocha JF, McCrory M, Soares-da-Silva P; BIPARK-2 Study Investigators. Opicapone as Adjunct to Levodopa Therapy in Patients With Parkinson Disease and Motor Fluctuations: A Randomized Clinical Trial. JAMA Neurol. 2017

[3] Reichmann H, Lees A, Rocha JF, Magalhães D, Soares-da-Silva P; OPTIPARK investigators. Effectiveness and safety of opicapone in Parkinson's disease patients with motor fluctuations: the OPTIPARK open-label study. Transl Neurodegener. 2020

41. Physical activity and rTMS modulate inflammatory pathways and improve clinical outcomes in Parkinson's disease

Authors
Jasmine Gambelli1,2, Giulia di Lazzaro2, Alessandro De Biase1,2, Riccardo Di Iorio2, Gloria Modica2, Serena Fragapane2,5, Deborah di Martino3, Emanuela Cardile4, Vincenzo Rizzo4, Andrea Pisani3, Veronica Ghiglieri1,5, Anna Rita Bentivoglio1,2, Paolo Calabresi1,2.

Affiliations
1. Università Cattolica del Sacro Cuore, Roma
2. Fondazione Policlinico Agostino Gemelli, U.O.C. Neurologia, Roma
3. IRCCS Fondazione Mondino, Pavia,
4. Azienda Ospedaliera Universitaria Policlinico Gaetano Martino, U.O.C. Neurologia, Messina
5. Dipartimento di Promozione delle Scienze Umane e della Qualità della Vita, Università Telematica San Raffaele, Roma

Background
Non-pharmacological treatments are emerging as important adjuvant therapies for Parkinson's disease (PD). Regular physical activity (PA) improves motor and non-motor symptoms and promotes cytokine release, influencing brain plasticity and neurochemistry. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive neuromodulation technique, has been shown to improve PD symptoms and modulate inflammatory pathways. However, the mechanisms underlying the beneficial effects of both approaches remain incompletely understood. Here, we present two parallel studies investigating the effects of PA and rTMS in a total of 240 PD patients.

Methods
In the PA study, patients were randomized into a sedentary group (n=60) and an active group (n=60) undergoing high-frequency treadmill training for 3 months. In the rTMS study patients were randomized into two groups: an rTMS treatment group (n = 60) and a sham stimulation group (n=60), serving as a placebo control. Every patient received 10 sessions of bilateral motor cortex rTMS for 5 consecutive days for 2 weeks. In both studies clinical assessments included MDS-UPDRS, NMSS, and MoCA. Blood samples were collected to evaluate peripheral inflammatory markers and markers of neurodegeneration.

Results
PA showed significant improvements in both motor and non-motor symptoms and increased IL-4 and IL-17A levels, suggesting a shift towards an anti-inflammatory th2/th17 profile. rTMS similarly improved motor symptoms and reduced non-motor symptoms, while decreasing neurofilament light chain levels, a biomarker of neuroaxonal injury.
Conclusions
Our findings suggest that PA and rTMS may represent promising adjuvant treatments for PD, potentially acting through modulation of inflammatory pathways and neuroprotective mechanisms.

42. High-Density EEG markers of neuroplasticity following intensive rehabilitation in Parkinson's disease

Authors
Gjonaj E., Ghilardi MF., De Salvo S., Muscarà N., Dattola S., Marino S., Di Lorenzo G., Sorbera C., Quercia A., Quartarone A.

Affiliation
IRCCS Centro Neurolesi Bonino Pulejo, Messina

Evidence from the literature indicates that alterations in neuroplasticity mechanisms are present from the early stages of Parkinson's disease (PD), potentially contributing to motor and non-motor symptoms. Physical exercise may promote neuroplastic adaptations through changes in brain function, structure, and neurotrophic signaling. We investigated changes in resting-state electroencefalografic (EEG) activity following intensive rehabilitation. Ten patients with PD underwent 256-channels EEG recordings during 6-minutes resting-state sessions, with eyes closed (EC) and eyes open (EO), before and after intensive rehabilitation. Spectral power and analysis of current density were analyzed across all frequency bands. Findings in the EC condition showed a significant reduction in alpha power (8–13 Hz) over frontal, central, and left parietal regions following intensive rehabilitation. A smaller reduction in beta power (13–30 Hz) was observed over the left parietal region, while gamma power (30–45 Hz) decreased over the left prefrontal and bilateral temporal regions ($p < 0.05$). In the EO condition, beta power decreased over centro-parietal and right temporal regions, whereas gamma power decreased over central and bilateral temporal regions. Current source density analysis confirmed significant post-rehabilitation changes, mainly in frontal and motor regions. These findings indicate that intensive rehabilitation is associated with changes in resting-state cortical oscillatory activity across multiple frequency bands and distributed cortical regions. Beta power is relevant to sensorimotor processing and motor plasticity. However, evidence of rehabilitation-related changes was also observed in cortical areas involved in motivational, visual, and motor processes, suggesting that EEG may provide potential markers of rehabilitation-induced neuroplasticity.

Reference
Hirsch MA, Iyer SS, Sanjak M. Exercise-induced neuroplasticity in human Parkinson's disease: What is the evidence telling us? Parkinsonism & Related Disorders. 2016;22(Suppl 1):S78–S81. doi:10.1016/j.parkreldis.2015.09.030.
Ghilardi MF, Tatti E, Quartarone A. Beta power and movement-related beta modulation as hallmarks of energy for plasticity induction: Implications for Parkinson's disease. Parkinsonism Relat Disord. 2021;88:136-139. doi: 10.1016/j.parkreldis.2021.05.018.

43. 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.

Authors
F. L. Saibene[1], A. Salvatore[1], M.G. Turinelli[1], S. Feroldi[1], A. Castagna[1], E. Farina[1], M. Alberoni[1], E. Calabrese[1], M. F. Gattoni[1,4], T. Bowman[1], D. Anastasi[1], D. Cattaneo[1], C. Agliardi[1], C. Arienti[5], F. R. Guerini[1], M. Saresella[1], M. Clerici[1], J. Navarro[1], P. Arcuri[1], and M. Meloni[6]

Affiliations
[1] Neurorehabilitation Unit, IRCCS Fondazione Don Carlo Gnocchi ETS, Milan, Italy
[2] Department of Psychology, University of Milano-Bicocca, Milan, Italy
[3] Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy
[4] Department of Statistics, Computer Science, Applications "Giuseppe Parenti", University of Florence, Florence, Italy
[5] Department of Biomedical Sciences, Clinical Epidemiology Research Center (CERC), Humanitas University, Milan, Italy
[6] Unit of Neurology, University Hospital of Cagliari, Cagliari, Italy

Abstract
Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by motor and non-motor symptoms, with significant implications for both quality of life (QoL), and caregiver burden. Although rehabilitation is essential for managing motor symptoms [1,2], evidence on the broader effects of multidisciplinary programmes remains limited [3]. This study evaluated the effects of intensive multidisciplinary rehabilitation compared with home-based self-treatment.
Seventy-three PwPD were randomly allocated to an experimental group (EXP; *n* = 38) or control group (CTRL; *n* = 35). Participants had a mean age of 69.5 ± 6.4 years and modified Hoehn and Yahr stages of 1.5–3. Outcomes included MDS-UPDRS Part III, PDQ-39, Functional Activities Questionnaire (FAQ), and Caregiver Burden Inventory (CBI).
Participants were assessed at baseline (T0), after six weeks (T1), and at three-month follow-up (T2). The

EXP group received daily intensive multidisciplinary outpatient rehabilitation, while the CTRL group followed a home-based programme of stretching and active mobilisation.
At T1, PDQ-39 scores improved in both groups. FAQ scores indicated a decline in functional activities in the CTRL group, whereas the EXP group remained stable. A significant effect of time on CBI scores was observed at T2. Caregiver burden appeared temporarily stabilised in the EXP group during treatment but increased at follow-up.
Functional abilities remained stable in the EXP group but declined in the CTRL group, suggesting that intensive multidisciplinary rehabilitation may help preserve everyday functioning. QoL improved in both groups, while caregiver burden temporarily stabilised during treatment but increased at follow-up, highlighting the need for continued support for caregivers after treatment.

References
[1] Meloni, M., Saibene, F. L., Di Tella, S., Di Cesare, M., Borgnis, F., Nemni, R., & Baglio, (2021). Functional and Cognitive Improvement After an Intensive Inpatient Multidisciplinary Rehabilitation Program in Mild to Severe Parkinson's Disease: A Retrospective and Observational Study. Frontiers in Neurology, 12, 626041.
[2] Ferrazzoli, D., Ortelli, P., Zivi, I., Cian, V., Urso, E., Ghilardi, M. F., ... & Frazzitta,

(2018). Efficacy of intensive multidisciplinary rehabilitation in Parkinson's disease: a randomized controlled study. Journal of Neurology, Neurosurgery & Psychiatry, 89(8), 828- 835.
[3] Saibene FL, Agliardi C, Salvatore A, Arcuri P, Castagna A, Gobbo S, et al. (2024) Investigating the effects of a daily multidisciplinary intensive outpatient rehabilitation program on innovative biomarkers in people with Parkinson's disease: Study protocol for a phase III randomized controlled clinical trial. PLoS ONE 19(10): e0309405. https://doi.org/10.1371/journal.pone.0309405.

44. Casa Parkinson: An Integrated Multidisciplinary Territorial Model of Spe-cialized Care for Parkinson's Disease and Parkinsonisms

Authors
Carlotta Tenerini (1), Monica Norcini (2), Beatrice Melli (2), Pasquale Palumbo (1), Paola Vanni (1) and the Casa Parkinson Multidisciplinary Team (*).

Affiliations
(1) Azienda USL Toscana Centro, Florence, Italy
(2) Fresco Parkinson Institute Italia ETS, Florence, Italy

Introduction
Parkinson's disease (PD) is one of the major neurodegenerative disorders and represents a growing health and social care challenge due to its substantial impact on patients, caregivers, and their health and social care systems. It is also a highly disabling condition. Epidemiological projections indicate that the global prevalence of PD is expected to double by 2030.

Objective
To present preliminary data on the activities of Casa Parkinson, an integrated, multidisciplinary, highly specialized community-based care model in Florence (Q4-Canova), and to assess its potential clinical, care-related and socioeconomic impact.

Materials and Methods
Over recent years, models of care for people with PD have increasingly incorporated integrated multi-disciplinary assessment, personalized treatment plans, regular follow-up, telemedicine, and digital technologies. Casa Parkinson was established in Florence at the Q4 - Canova within the territory of Azienda USL Toscana Centro (AUSL TC). The initiative was developed through a public–private partnership between AUSL Toscana Centro and the Fresco Parkinson Institute Italia ETS Foundation, more recently joined by Fondazione Cassa di Risparmio di Firenze, the Società della Salute and Florence Municipality has also been involved since the project inception. The model provides an integrated, highly specialized community-based care pathway, ranging from diagnostic assessment and treatment planning to the management of advanced stages of the disease. Care is delivered by a multidisciplinary team comprising neurologists and professionals from nursing, neurorehabilitation (physiotherapy, speech and language therapy, and occupational therapy), neuropsychology, and social care, in close collaboration with the hospital network.
The model also incorporates several innovative components, including a dedicated administrative service, specialized nursing intake and coordination, the integration of specialized hospital physicians with community-based professionals, and the involvement of general practitioners and patient associations.
The care pathway also covers home-based care and palliative services for patients with advanced disease, and complementary interventions aimed at supporting motor, cognitive, communicative, and psychosocial functioning. These activities include dance well, art’s laboratory, choir, boxing, archery,

karate, tango, AFA-C. A further structural component of the model is the continuing professional development of healthcare providers through the Fresco Academy.

Results

As of June 2026, 670 patients had completed their first visit at Casa Parkinson. A total of 2,145 neurological consultations, 159 geriatric consultations, 1,600 nursing assessments, 440 physiatric visits, 778 psychological consultations and 332 neuropsychological test assessments had been performed.
A total of 448 patients went thought a Physiotherapy pathway, accounting 2,469 sessions. In addition, 105 occupational-therapy pathways and 477 speech and language therapy sessions were delivered.
During 2025, a total of 4,276 attendances were recorded across Casa Parkinson's complementary interventions. These interventions involved 228 participants, including 32 patients participating in art laboratory, 133 participants in Dance Well classes involving people with PD and caregivers, 27 participants in the choir, and 36 patients participating in boxing activities.

Conclusions

Casa Parkinson represents an innovative model for transferring specialized multidisciplinary expertise from hospital to community, ensuring continuity of care and integrated management of Parkinson's disease (PD).
Preliminary data show high service utilization and the feasibility of combining clinical, rehabilitative, and complementary interventions within a coordinated care pathway. A retrospective/prospective study is underway to assess the model's impact on patients, caregivers, and the wider health and social care system.
Based on the results to date, AUSL TC and the Fresco Parkinson Institute are working to expand the Casa Parkinson model within and beyond Florence, supporting its dissemination and replicability.

(*) Casa Parkinson Multidisciplinary Team: A. Begeja, G. Cerini, G. Cinelli, M. Dainelli, C. Del Gamba, D. Durano, A. S. V. Flores, L. Fontanelli, S. Gherardini, S. Giannoni, L. Kiferle, C. Mannelli, A. Maselli, C. Menichetti, C. Quartetti, L. Raglione, S. Taddeo, A. Tamburini, S. Tamburini, L. Terzuoli, N. Trainotti, A. Trere, C. Varone, M. Winzeler.

45. Cognitive training with a bio-cooperative robotic platform in Parkinson's Disease with Mild Cognitive Impairment: pilot findings from the OPERA project

Authors
Giulia Martinelli 1, Mattia Agresti 1, Sara Della Bella 1, Eleonora Pavan 1, Ylenia Crocetto 1, Simona Abagnale 1, Cristiana Rondoni 2, Alfonso Voscarelli 3, Tommaso Ciapetti 1, Cecchi Francesca 1,4, Giulio Ciccarelli 5, Marco Pirini 3, Francesco Scotto di Luzio 2, Loredana Zollo 2, Anna Estraneo 1 and Cristina Polito 1

Affiliations
1 IRCCS Fondazione Don Carlo Gnocchi, 50143 Florence, Italy.
2 Research Unit of Advanced Robotics and Human-Centred Technologies, Università Campus Bio-Medico di Roma, 00128 Rome, Italy.
3 Khymeia Group, 35129 Padua, Italy.
4 Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze.
5 UOC Neurologia, AORN S.G. Moscati, 83100 Avellino, Italy.

Background
The OPERA project developed PRoBio, a bio-cooperative platform integrating virtual reality, robotic assistance and physiological monitoring for personalized cognitive training in people with Parkinson's Disease and Mild Cognitive Impairment (pwPD-MCI) [1]. This exploratory analysis of the pilot study's secondary outcomes examined pre/post changes in clinical and neuropsychological measures and cognitive performance during training.

Methods
Eleven pwPD-MCI (age: 67.9±5.6 years; MDS-UPDRS III: 28.8±9.5; adjusted MoCA: 23.2±1.6; median Hoehn–Yahr stage: 2) completed twelve 45-minute PRoBio cognitive training sessions over four weeks. Two protocols targeting attention, executive functions, memory and visuospatial abilities alternated weekly, with adaptive difficulty. Pre/post clinical assessments were compared using Wilcoxon signed-rank tests. As for PRoBio cognitive training, percentages of correct responses for each exercise and session were difficulty-adjusted, standardized within exercises and pooled across protocols to derive domain-specific and global composite scores. Trends across six administrations were assessed using regression with patient-specific intercepts and complementary non-parametric tests, with multiple-comparison corrections.

Results
Global and attention-task performance improved (Bonferroni-adjusted $p=0.001$ and $p<0.001$, respectively), with attention gains in 10/11 participants. Executive-task performance improved modestly (FDR-adjusted $p=0.011$); memory and visuospatial tasks showed no significant trends. Performance on attention tasks using the robotic arm improved (Bonferroni-adjusted $p<0.001$). PD-CRS total and subcortical scores decreased (Bonferroni-adjusted $p=0.035$ and $p=0.012$, respectively).

Discussion
These pilot findings suggest improved attention and executive-task performance following PRoBio cognitive training. Lower PD-CRS scores contrasted with trained-task gains. Treatment-related fatigue might contribute to this discrepancy. Larger controlled studies evaluating longer interventions should monitor fatigue to optimize session frequency while limiting burden.

References

[1] Polito, C., Martinelli, G., Della Bella, S., Pavan, E., Crocetto, Y., Abagnale, S., Rondoni, C., Voscarelli, A., Pirini, M., Scotto di Luzio, F., Zollo, L., & Estraneo, A. (2026). Integrated bio-cooperative robotic platform for virtual cognitive training in Parkinson's disease: design and methodology of the OPERA project. Frontiers in neurology, 16, 1680215. https://doi.org/10.3389/fneur.2025.1680215

46. Camptocormia in Parkinson's disease: An integrated rehabilitation approach and instrumental monitoring

Authors
MT. Di Leo, A. Amico Medico Fisiatra

Affiliation
CENTRO EUMEDICA, Caltanissetta

Introduction
Camptocormia represents a significant postural alteration in Parkinson's disease, characterized by marked trunk flexion, with repercussions on postural control, gait, and functional independence. Instrumental movement assessment can allow for objective quantification of postural alterations and contribute to the personalization of rehabilitation treatment.

Case Report
A patient with Parkinson's disease and camptocormia underwent instrumental posture and movement assessment. The initial assessment documented a significant alteration in trunk alignment, based on which an individualized rehabilitation program was developed.

Treatment
The patient underwent postural re-education combined with neuromotor treatment, aimed at improving trunk control and postural alignment. A dynamic back brace was also used, worn for approximately 10 hours a day, to support maintaining postural alignment.

Results
After four months, the patient was reevaluated using the same instrumental method. The comparative analysis showed an improvement in postural alignment compared to the initial assessment. This improvement was also observed without wearing the brace during the reevaluation.

Conclusions
This case highlights the usefulness of an integrated approach including instrumental assessment, orthotic support, and personalized rehabilitation treatment in the management of camptocormia in Parkinson's patients.

Instrumental assessment can be a useful tool for objectively documenting the evolution of postural alignment and monitoring the response to treatment.

47. Intense multimodal outpatient training camp in Parkinson disease (PD): Preliminary results from a pilot study

Authors
Elisa Tatti, Giulia Stramucci, Marina Ioannou, Afifa Zahid, Eirzaad Hussain, Xu Li, Dinh Truong Nguyen, M. Felice Ghilardi, Jose C. Cabassa

Affiliation
CUNY School of Medicine, New York, NY, USA

Abstract
Increasing evidence show that intense inpatient multimodal rehabilitation is highly beneficial in PD. Aerobic exercise, which is part of the most effective inpatient programs, promotes overall health, including cardiovascular function.

We designed a six-week outpatient program for nine PD patients (three weekly sessions, two-hour boxing-based and two-hour various training (yoga, tai chi, functional training, tap dance, jazz dance) per day. We measured systolic and diastolic blood pressure (Sbp, Dbp) in sitting and standing position on each training day before each session. Before and after the program we assessed: visuospatial memory (Rey Complex Figure), attention/processing speed (Digit Span, Trail Making Test [TMT-A & B]), functional mobility, activities of daily living, quality of life (PDQ39) and sleep (PDSS), depression and fatigue.

During training, all subjects reached at least 60% of max heart rate (range:60.3-72.3%) measured with fit-bit watches. In the first week, mean sitting Sbp decreased by 12 (±3.1 SE) mmHg when standing. In the last week, the mean decrement was 5.3±2.3 ($p=0.057$). Mean sitting-to-standing Dbp decreases from 4.1±0.9 to 1.1±0.96 ($p=0.017$). Following training, all subjects improved TMT-A completion time ($p=0.005$) and Rey Complex Figure delayed recall ($p=0.034$). No significant changes were observed for the other tests.

These preliminary results provide the first evidence that outpatients intense activities within aerobic range may promote orthostatic tolerance in PD, with improvements in processing speed and visual memory. These preliminary findings need to be replicated in larger cohorts.

48. Inpatient Rehabilitation programs' impact on motor and non-motor signs of Parkinson's Disease

Authors
Noureddin Elayan, Isabella Henderson, Natalie Hissong, Alessandro Di Rocco, Angelo Quartarone, M. Felice Ghilardi

Affiliations
Northwell Health, New York, NY, USA
IRCSS Bonino-Pulejo, Messina, Italy
CUNY School of Medicine, New York, NY, USA

Abstract
Inpatient rehabilitation programs are relatively new interventions for PD, offering combinations of physical (PT), occupational (OT), speech (ST) therapies, balance and cognitive training coupled with pharmacology optimization. This approach seems to produce better motor and non-motor performance than traditional outpatient care.
Here we examine the short- and long-terms effects of inpatient programs on motor and non-motor signs in terms of clinically meaningful improvement (CMI) using a search of PubMed and Embase from 1992 to 2025. Selection criteria included: at least two rehabilitation modalities (PT, OT, ST, CT, music therapy, balance and gait training, aerobic exercise, recreational therapy); report of pre- and post-treatment for at least one of these measures: UPDRSIII, PDQ39, Berg balance scale (BBS), Time-up-&-go (TUG), Beck Depression Index (BDI), cognitive function tests.
We identified 1,012 studies; 23 complied with inclusion criteria totalizing 2,262 patients (median H&Y: 3; age: 70.6; disease duration: 8.55 years). Interventions' duration varied from 12 to 136 hours; 14 to 60 days, one to five hours daily.
Average UPDRSIII scores were reported in 15 studies: 31.6% achieved average minimal CMI, 36.8% medium CMI, 26.3% large CMI. TUG scores achieved CMI decreases in only 41.7% of eleven studies; BBS in 63.6% of eight studies; PDQ-39 scores in 91% of ten studies (either minimal or large CMI); BDI in all five studies reporting it. Further analyses found strong correlation with program duration only for BBS changes (rho:-0.786; p=0.007). UPDRSIII (four studies) improvement was either maintained (between six week and one year later) or did not worsen compared both to pre-intervention levels; it was better than that of controls tested at the same time points. Similar results were found for TUG (three studies), BBS (one study), PDQ-39 (three studies), BDI scores (two studies).
We conclude that inpatient programs are effective as they produce short- and long-term CMI in multiple PD domains. However, a large patient registry would be helpful to identify treatment predictors, develop evidence-based guidelines and guide tailored care for both inpatient and outpatient programs.

49. Subjective-objective cognitive mismatch in Parkinson's disease: relationships with cognitive reserve and subjective cognitive complaints during home-based cognitive telerehabilitation.

Authors
Maria Grazia Maggio[1], Raffaela Maione[1]*, Lilla Bonanno[1], Fabio Mauro Giambò[1], Emanuela Presti[2], Giuseppe Di Lorenzo[1], Amelia Rizzo[3], Angelo Quartarone[1], Rocco Salvatore Calabrò[1].

Affiliations
[1] IRCCS Centro Neurolesi Bonino-Pulejo, S.S. 113 Via Palermo, C. da Casazza, 98124, Messina, Italy.
[2] Università di Parma, Corso di laurea magistrale in Psicobiologia e Neuroscienze cognitive, Dipartimento di Medicina e Chirurgia, Via Gramsci, 14, 43126, Parma, Italy.
[3] National Institute of Social Welfare, Medical Legal Centre of Messina, Italy.
Presenter/Corresponding author: Raffaela Maione

Background
In Parkinson's disease (PD), subjective cognitive complaints do not always correspond to objective neuropsychological performance, suggesting that perceived and measured cognition may reflect complementary dimensions. Subjective-objective cognitive mismatch may capture aspects of daily cognitive experience not fully detected by standard testing.

Objective
To investigate subjective-objective cognitive mismatch, its association with cognitive reserve, and its changes after home-based telerehabilitation in PD.

Methods
This exploratory longitudinal study included 34 patients with PD, Hoehn & Yahr <2.5, enrolled at the IRCCS Centro Neurolesi Bonino-Pulejo, Messina. Participants completed a 6-week home-based cognitive telerehabilitation program using NeuroNation, with telephone monitoring. Assessments were performed at baseline and post-treatment. Objective cognition was assessed with the MMSE, Raven's Colored Progressive Matrices, and Trail Making Test A-B. Subjective complaints were evaluated using the MAC-Q and PDQ-39 Cognition subscale. Cognitive reserve was measured with the Cognitive Reserve Index Questionnaire. Composite objective, subjective, and mismatch indices were calculated.

Results
All participants completed the program without adverse events. Objective cognitive measures remained stable. Conversely, subjective complaints significantly decreased, as shown by MAC-Q scores, 23.71±6.11 vs 20.74±4.14; p=0.001; pFDR=0.01, and the subjective composite index, p=0.004; pFDR=0.02. The mismatch index did not significantly change, and cognitive reserve was not significantly associated with mismatch or cognitive changes.

Conclusions
In PD, subjective cognitive complaints and objective cognitive performance appear to represent distinct but complementary dimensions. Integrating both may support a more ecological, person-centered cognitive assessment in PD rehabilitation.

50. CREC (Creativity in Everyday Life Challenges): A Pilot Study of a Divergent Thinking-Based Cognitive Intervention in Patients with PD-MCI

Authors
C. Siri[1], A. Ranghetti[2], I. Donato[2], A. Carollo[1], E. Vanni[1], G. Fusi[3], L. Colautti[4], F. Antonietti[4], M. Canesi[1], I. U. Isaias[2], M. L. Rusconi[3]

Affiliations
[1]U.O.C. Rehabilitation of Parkinson's Disease and Movement Disorders, Moriggia Pelascini Hospital, Gravedona ed Uniti, Italy; [2]Parkinson Institute, ASST "G.Pini-CTO", Milan, Italy; [3]Department of Human and Social Sciences, University of Bergamo, Bergamo, Italy; [4]Department of Psychology, Università Cattolica del Sacro Cuore, Milan, Italy

Background
Creativity is a complex cognitive process arising from the interaction of higher-order functions such as cognitive flexibility, working memory, and inhibitory control. Creative thinking may represent a valuable resource for cognitive stimulation in neurodegenerative disease.

Objective
To evaluate the feasibility and preliminary efficacy of a structured cognitive intervention (CREC) designed to enhance flexible, alternative problem-solving strategies in individuals with Parkinson's disease and mild cognitive impairment (PD-MCI).

Methods
Thirty-one PD-MCI patients were recruited across two centers, comprising both inpatients (intensive rehabilitation) and outpatients (home-based). Participants were allocated to Active-CREC (CREC plus rehabilitation), Passive-CREC (CREC at home), or control conditions (with or without rehabilitation). The CREC intervention consisted of 10 remote group sessions (3–4 participants) over four weeks. Assessments were conducted at baseline (T0) and post-intervention (T1).

Results
Repeated-measures ANOVA showed improvements in the CREC group compared to controls, with a trend toward significance ($p<0.06$) on the SDMT and the Stroop Time subtest. Change-delta analysis revealed significant improvement ($p<0.05$) in Alternate Fluency, SDMT, and Stroop Time in the Active-CREC group. Caregivers reported improvements in mood, awareness, communication, and daily functioning, with positive effects on quality of life for both patients and caregivers.

Conclusions
This pilot study indicates that CREC training is feasible and represents a promising approach for supporting cognitive and emotional functioning in individuals with PD-MCI. Although larger samples are needed to confirm these findings, benefits extend beyond cognition to daily functioning, supporting the role of creative thinking in cognitive rehabilitation for Parkinson's disease and its potential for broader clinical applications.

51. When Movement Becomes Music: Investigating Motor Agency Through Interactive Musical Feedback in Parkinson's Disease

Authors
Federica Impellizzeri[1], Maria Grazia Maggio[1], Mirjam Bonanno[1], Michael Thaut[2], Angelo Quartarone[1], Rocco Salvatore Calabrò[1]

Affiliations
[1] IRCCS Neurolesi Bonino-Pulejo Messina
[2] University of Toronto, Canada

Background
Music-based rehabilitation in Parkinson's disease (PD) commonly uses externally generated auditory cues [1], while altered awareness of voluntary action has also been reported in PD [2]. We investigated whether reversing this relationship and allowing movement itself to generate musical consequences, could enhance motor performance and action–outcome agency.

Methods
Twenty individuals with PD were randomized to receive movement-generated musical feedback via Soundbeam (n=10) or active control (n=10). Soundbeam is a touch-free system using ultrasonic sensors to translate body movement into musical events in real-time [3]. Both groups received the same Neurologic Music Therapy (NMT)-based motor training, centered on Therapeutic Instrumental Music Performance (TIMP), for 12 sessions over 4 weeks; only the Soundbeam group received movement-generated musical feedback while auditory events in the control group were matched but independent of movement. Outcomes included Mini-BESTest, MDS-UPDRS III, TUG, 10MWT, Italian SoAS, and an experimental ASAT. The Agency Discrimination Index (ADI) quantified discrimination between self-generated and external sounds.

Results
Both groups improved, with greater changes following Soundbeam. Baseline-adjusted ANCOVA showed adjusted between-group differences of 1.39 points for Mini-BESTest, 1.79 points for MDS-UPDRS III reduction, 0.54 s for TUG reduction, and 0.060 m/s for 10MWT (all $p<0.001$). Contingent agency increased by 10.0 versus 2.3 points, while ADI increased by 13.65 versus 2.65 points; the baseline-adjusted between-group difference for ADI was 11.03 points (95% CI 9.21–12.85; $p<0.001$).

Conclusions
Movement-generated musical feedback may extend conventional auditory cueing by strengthening action-effect coupling while improving motor performance, supporting motor agency as a potential rehabilitation target in PD.

References
1. Ghai S, Ghai I, Schmitz G, Effenberg AO. Effect of rhythmic auditory cueing on parkinsonian gait: a systematic review and meta-analysis. Sci Rep. 2018;8:506. doi:10.1038/s41598-017-16232-5.
2. Saito N, Takahata K, Yamakado H, et al. Altered awareness of action in Parkinson's disease: evaluations by explicit and implicit measures. Sci Rep. 2017;7:8019. doi:10.1038/s41598-017-08482-0.
3. Williams E. "Obsolescence and Renewal": musical heritage, electronic technology, education and the future. Int J Music Educ. 2001;os-37(1):13–31. doi:10.1177/025576140103700103.

52. A Technology-Assisted Upper-Limb Rehabilitation Pathway in Parkinson's Disease: A Pilot Randomised Controlled Study Integrating Robotic Devices and Virtual Reality

Authors
Mirjam Bonanno[1,*], Desireè Latella[1], Lilla Bonanno[1], Caterina Formica[1], Giacomo Mascaro[1], Mauro Botindari[1], Roberta Cellini[1], Giuseppe Di Lorenzo[1], Angelo Quartarone[1], Rocco Salvatore Calabrò[1]

Affiliation
1 IRCCS Centro Neurolesi Bonino-Pulejo
**Poster Presenter*

Background
Upper-limb impairment in Parkinson's disease (PD) limits functional autonomy and activities of daily living. Technology-assisted rehabilitation may support intensive, task-oriented, through robotic devices and virtual-reality feedback.

Objective
To evaluate the motor effects of a progressive proximal-to-distal upper-limb rehabilitation pathway in individuals with moderate PD.

Methods
Twenty-four individuals with idiopathic PD were randomised to an experimental group (EG) or control group (CG; n=12 each). Outcomes included the Fugl-Meyer Assessment for the Upper Extremity (FMA-UE) and 9-Hole Peg Test (9HPT). The EG completed thirty 45-minute sessions using a rotating protocol with PABLO, Hand Tutor, and AMADEO, targeting upper-limb coordination, wrist-hand movements, and selective finger flexion-extension. T1-T0 changes were compared using Mann-Whitney U tests, rank-biserial correlations, and false-discovery-rate (FDR) correction; exploratory linear mixed-effects models (LMMs) assessed Group x Time interactions.

Results
Groups were comparable at baseline for education, Hoehn and Yahr stage, cognition, sex, and handedness. The EG was older ($p = 0.021$; pFDR = 0.080), although this difference did not survive FDR correction, and differed significantly in most-affected-side distribution. FMA-UE improvement was greater in the EG for the right ($p=0.003$; pFDR=0.007; $r=0.61$) and left upper limbs ($p=0.002$; pFDR=0.006; $r=0.65$). Large effects emerged in FMA-A and FMA-D, strongest for left FMA-D ($p<0.001$; pFDR=0.001; $r=0.84$). Improvement on the most affected side also favoured the EG ($p=0.013$; pFDR=0.026; $r=0.51$). Exploratory LMMs confirmed significant Group x Time interactions for bilateral and most-affected-side FMA-UE scores (estimate=6.50; $p=0.003$; pFDR=0.005). No between-group differences emerged for 9HPT completion time.

Conclusion
This pathway may improve global upper-limb motor impairment in moderate PD, but it did not yield a significant between-group advantage in fine manual dexterity.
Larger controlled studies are needed.

53. IL-1β Signaling Drives Early Hippocampal Dysfunction and Social Cognitive Deficits in Experimental Parkinson's Disease

Authors
Federica Campanelli[1,2], Giuseppina Natale[1,2], Federica Servillo[2], Gioia Marino[3], Maria De Carluccio[2], Claudio Grassi[2], Paolo Calabresi[2,3], Veronica Ghiglieri[1,2]

Affiliations
1. Dipartimento di Promozione delle Scienze Umane e della Qualità della Vita, Università Telematica San Raffaele, Rome, Italy, 00166;
2. Neurologia, Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy, 00168;
3. Neurologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, 00168;

Abstract
Parkinson's disease (PD), characterized by dopaminergic neuron loss in the substantia nigra pars compacta and the accumulation of misfolded alpha-synuclein (α-syn), is also associated with early neuroinflammation and cognitive deficits linked to mesocorticolimbic dysfunction.
In an experimental early PD model, male and female mice received unilateral intrastriatal injections of human α-syn pre-formed fibrils (PFFs). Three months after injection, both sexes displayed significant impairments in social cognition and a complete loss of long-term potentiation (LTP) in the hippocampal CA1 region, indicating severe synaptic dysfunction. Quantitative analysis of glial reactivity in CA1 subregions showed no significant changes in microglial density. In contrast, confocal 3D reconstruction demonstrated marked morpho-functional remodeling of microglial somata in male PFF-injected mice, whereas females showed no significant structural changes, suggesting sex-dependent microglial reactivity in the absence of overt microgliosis. Consistently, PFF-injected mice exhibited increased expression of CD68 and the inflammasome-related markers NLRP3 and IL-1β, supporting the hypothesis that IL-1β pathway, which is implicated in the regulation of synaptic plasticity, might be overactivated. We therefore investigated the effects of chronic treatment with Anakinra, an interleukin-1 receptor antagonist. Anakinra significantly improved social behavior, restored hippocampal LTP, and reduced the neuroinflammatory markers in PD mice.
These findings identify IL-1β signaling as a key contributor to early hippocampal dysfunction in experimental PD and suggest that pharmacological inhibition of this pathway may represent a promising strategy to prevent cognitive and social deficits and preserve mesolimbic circuit function.

54. Aerobic exercise reshapes inflammatory responses in Parkinson's disease: emerging role of perivascular macrophage-microglia crosstalk

Authors
Maria De Carluccio1, Federica Servillo1, Jasmine Gambelli1,2, Sofia Nutarelli3,4, Marika Guerra5, Marco Pieraccioli2,3, Francesca Rech4, Giuseppina Natale2,6, Federica Campanelli2,6, Gioia Marino3, Jacopo Canonichesi7,8, Veronica Ghiglieri2,6, Claudio Sette2,3, Paolo Calabresi1,2, Maria Teresa Viscomi 3,4.

Affiliations
1. Neurologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italia;
2. Neurologia, Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Roma, Italia;
3. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italia;
4. Dipartimento Scienze della Vita e della Salute Pubblica, Sezione di Istologia e Embriologia, Università Cattolica del Sacro Cuore, Roma, Italia;
5. Dipartimento di Scienze della Vita, Salute e Professioni Sanitarie, Università Link Campus, Roma, Italia;
6. Dipartimento di Promozione delle Scienze Umane e della Qualità della Vita, Università Telematica San Raffaele, Roma, Italia;
7. Università Telematica San Raffaele, Roma, Italia;
8. San Raffaele Sulmona, Sulmona, Aquila, Italia;

Abstract
Parkinson's disease (PD) progression involves complex interactions between neuronal dysfunction, α-synuclein pathology, and immune-mediated mechanisms. Although aerobic exercise improves motor and non-motor symptoms in PD, the cellular mechanisms underlying responsiveness to structured physical activity remain largely unknown.
Using a progressive α-synucleinopathy model, we investigated whether aerobic exercise could induce adaptive neuroimmune responses during early disease stages. Rats received human α-synuclein preformed fibrils (PFFs) into the dorsomedial striatum, and intensive aerobic exercise was administered 4 weeks after the injection, corresponding to the time of emergence of reactive glial responses in PD-relevant regions, including the dorsolateral striatum and primary motor cortex.
Building on our previous findings showing that exercise restores synaptic plasticity through BDNF-dependent dendritic spine remodeling (Marino Campanelli et al., 2023 *Science Advances*), we applied an integrated morphological, transcriptomic, and biochemical approach to characterize exercise-induced immune adaptations.
Aerobic exercise profoundly remodeled the neurovascular unit, promoting functional interaction between $MHCII^+$ perivascular macrophages (PVMs) and microglial populations. Exercise induced a distinct neuroimmune signature characterized by increased *Spp1* (osteopontin) expression and activation of C1q-associated molecular tagging pathways, suggesting enhanced phagocytic and tissue-remodeling functions. These changes were accompanied by the acquisition of an adaptive microglial phenotype associated with improved neuroimmune communication.
Our findings identify PVM–microglia crosstalk as a novel mediator of exercise-induced brain adaptation and suggest that aerobic exercise promotes macrophagic and microglial immunosurevillant phenotypes against α-synuclein-driven pathology. Thus, this study provides new insights into the mechanisms underlying exercise-mediated beneficial effects in PD and highlights neurovascular immune pathways as potential targets for disease-modifying strategies.

55. Long-lasting and neuroprotective effects of intensive treadmill exercise on synaptic and behavioral outcomes in an α-synuclein model of Parkinson's disease

Authors
Federica Servillo, Gioia Marino, Federica Campanelli, Giuseppina Natale, Maria De Carluccio, Veronica Ghiglieri, Paolo Calabresi

Abstract
Intensive physical exercise improves motor control and reduces cognitive deficits in Parkinson's disease (PD), yet the durability of its neuroprotective effects after training ends remains insufficiently defined. Here, we investigated whether time-limited treadmill training induces persistent neurofunctional recovery in an animal PD model. Rats receiving intrastriatal injections of phosphate-buffered-saline (PBS) or α-syn-preformed fibrils (PFF) underwent 4-weeks of intensive treadmill exercise followed by 4-weeks of rest (PBS/PFF 4-week post-exercise). Outcomes were evaluated and compared with PFF-injected sedentary animals (PFF sedentary) and with animals after 4-weeks of training (PFF active).
PFF rats 4-weeks post-exercise exhibited full restoration of motor coordination and recovered visuo-spatial memory performance, reaching levels comparable to controls. Notably, no differences were observed between PFF active and PFF 4-weeks post-exercise groups, indicating that the beneficial effects of exercise persisted beyond a prolonged washout period.
At the neurobiological level, treadmill training significantly reduced p129-α-syn spreading from the striatum to the substantia nigra pars compacta and preserved tyrosine hydroxylase-positive nigrostriatal terminals compared with PFF sedentary animals. Electrophysiological recordings demonstrated persistence of corticostriatal long-term potentiation in PFF 4-week post-exercise rats. This synaptic recovery was accompanied by a trend toward increased striatal BDNF levels, suggesting a role for neurotrophic signaling in the long-term maintenance of synaptic plasticity.
Overall, these findings demonstrate that a limited period of intensive physical exercise induces durable neuroprotection, maintenance of voluntary movemement control, effectiveness of synaptic plasticity, and dopaminergic integrity while limiting α-syn pathology progression. These results support the concept that physical activity is a sustained disease-modifying strategy in PD.

56. Bioactivated Glucoraphanin exerted neuroprotective effects in an In Vitro Model of Parkinson's Disease

Authors
Alessia Floramo [1], Agnese Gugliandolo [1], Claudia Muscarà [1], Veronica Argento [1], Luca Tagliavento [2], Francesco Meneguzzo [3], Daniele Perenzoni [4], Fulvio Mattivi [5], Emanuela Mazzon [6,*] and Luigi Chiricosta [1]

Affiliations
[1] IRCCS Centro Neurolesi "Bonino-Pulejo", Via Provinciale Palermo, Contrada Casazza, 98124 Messina, Italy;
[2] HyRes srl, Via Salvator Rosa 18, 82100 Benevento, Italy;
[3] CNR-IBE, Via Madonna del Piano 10, 50019 Sesto Fiorentino, Italy;
[4] Department of Food Quality and Nutrition, Research and Innovation Centre, Fondazione Edmund Mach (FEM), Via E. Mach 1, 38098 San Michele all'Adige, Italy; daniele.perenzoni@fmach.it
[5] Center for Food Metabolomics and Bioactives Development (CSMETAB), Trento, Italy;
[6] Department of Innovative Technologies in Medicine & Dentistry, University "G. d'Annunzio" Chieti-Pescara, Via Dei Vestini, 31, 66100, Chieti, Italy;

Presenter: Alessia Floramo

Abstract
Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by a combination of motor and non-motor symptoms. The disease is primarily associated with the loss of dopaminergic neurons in the *substantia nigra*, a process closely related to mitochondrial dysfunction and oxidative stress, which can lead to oxidative damage to nuclear DNA. In this context, interest in phytocompounds has grown significantly in recent years. In particular, glucosinolates (GLs) and their derivatives isothiocyanates (ITCs), produced through the myrosinase (MYR)-mediated hydrolysis of GLs, have attracted substantial attention due to their antioxidant and anti-inflammatory properties, which may contribute to their potential neuroprotective effects. In our study, we evaluated the effects of pre- and post-treatment with the bioactivated GL glucoraphanin (GRA) in an *in vitro* model of PD consisting of differentiated SH-SY5Y cells exposed to the neurotoxin MPP+. Both pre- and post- treatment with bioactivated GRA counteracted MPP+ cytotoxicity. To characterize the molecular effects associated with the treatment, transcriptomic analysis was performed using Next Generation Sequencing (NGS). The results evidenced that the pre-treatment modulated pathways associated with DNA repair, whereas post-treatment modulated pathways and genes associated to a response against oxidative stress, including *SOD1*. Overall, the results indicated that bioactivated GRA exerted neuroprotective effects against MPP+-induced cytotoxicity with different mechanisms that depend on treatment timing.

57. The autoimmune hypothesis: understanding neurodegeneration across idiopathic and genetic models of Parkinson's Disease

Authors
Letizia Zanetti, Stavros Fanourakis, Laura Ducret, Connor Monahan, Kathy Schaefer, Zachary Wright, Jenny Sassone, Philipp Keller, *David L. Sulzer

Abstract
Growing evidence suggests that there is an autoimmune component to Parkinson's disease (PD) pathology, yet the mechanisms by which immune responses contribute to dopaminergic (DA) neuron degeneration remain unknown. Postmortem studies reveal marked T cell infiltration in the substantia nigra (SN) of PD patients (Jakubiak et al., 2024), and circulating autoreactive T cells recognize epitopes from PD-associated proteins, including α-synuclein (Sulzer et al., 2017), and PINK1 (Johansson et al., 2025). These observations raise a fundamental question: how do adaptive immune responses drive neurodegeneration in PD?
To address this, we are investigating potential mechanism of immune-mediated neurodegeneration across three mouse models of idiopathic (1) and genetic PD (2 and 3) that we have developed in parallel. So far:
1) We created a novel adoptive transfer model in which α-synuclein–reactive $CD4^+$ T cells are transferred into α-synuclein–overexpressing mice. Such donor T cells infiltrate the enteric and central nervous systems, trigger robust neuroinflammation in the ventral midbrain, and induce early DA neuron degeneration in the SN pars compacta; this supports a direct pathogenic role for antigen-specific T cells (*unpublished data*).
2) We generated and characterized a novel mouse of PARK2-linked parkinsonism, *Prkn*R275W, which expresses the most common missense mutation (R275W) found in autosomal recessive juvenile parkinsonism patients. This mouse model recapitulates the major pathological hallmarks of PD (Regoni et al., 2024), as well as pronounced neuroinflammation, with $CD4^+$ and $CD8^+$ T cell infiltration (*unpublished data*). These findings support a toxic gain-of-function immune phenotype driven by mutant parkin.
3) We generated and characterized a novel mouse model of PARK9-linked parkinsonism (also known as Kufor-Rakeb syndrome), by constitutively introducing a ATP13A2 V990M knock-in mutation recently identified in a living patient. Unlike previously generated knockout models, our model shows progressive nigrostriatal degeneration, widespread neuroinflammation, and adaptive immune cell recruitment, which is consistent with a toxic gain-of-function mechanism driven by mutant ATP13A2 (*unpublished data*).
Together, these models support a unifying hypothesis in which adaptive immune responses actively drive PD pathogenesis; understanding such mechanisms shared between idiopathic and genetic PD may reveal new therapeutic targets to halt disease progression.

58. Gut epithelial-vascular barrier impairments and NLRP3 inflammasome activation across early Parkinson's disease and isolated REM sleep behavior disorder subjects

Authors
Gabriele Bellini, MD PhD[1-2], Francesco Rettura, MD PhD[3], Clarissa Pierucci[4], Giovanni Palermo, MD PhD[1], Domeniko Hoxhaj MD[1], Michelangelo Maestri Tassoni MD[1], Cristina Segnani, PhD[4], Lorenzo Fontanelli, MD[1], Emanuele Marciano MD[6], Christian Lambiase MD[3], Daniela Frosini, MD[5], Pascal Derkinderen, MD, PhD[7], Enrica Bonanni, MD, PhD[1], Massimo Bellini MD, PhD[3], Nunzia Bernardini, MD[4], Carolina Pellegrini, PhD[4], Roberto Ceravolo, MD[1-8].

Affiliations
1. Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
2. Department of Neurology, The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, NYU Langone Health, New York City, New York, USA.
3. Gastrointestinal Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy
4. Unit of Histology and Embryology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
5. Neurology Unit, Department of Medical Specialties, AOUP, Pisa, Italy
6. Digestive Endoscopy Unit, University Hospital of Pisa, Pisa, Italy.
7. Department of Neurology, Nantes Université, CHU Nantes, INSERM, Nantes, France
8. Center for Neurodegenerative Diseases, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Background
Parkinson's disease (PD) is increasingly recognized as a disorder involving the gut–brain axis, with growing evidence that intestinal barrier dysfunction and enteric inflammation may precede or accompany central neurodegeneration. Isolated/idiopathic REM sleep behavior disorder (iRBD) represents a prodromal stage of synucleinopathies and frequently precedes PD.

Objectives
To investigate epithelial and vascular intestinal barrier integrity and inflammasome-related inflammatory pathways in early PD and iRBD.

Methods
Colonic mucosal biopsies were analyzed for inflammasome-related proteins (NLRP3, ASC, caspase-1, and interleukin-1β) by immunoblotting, and for epithelial, vascular, macrophage, and synucleinopathy markers (claudin-1, PV-1, CD68, and total α-synuclein) by immunofluorescence. PD patients were stratified into body-first and brain-first subtypes based on the presence or absence of REM sleep behavior disorder before the onset of motor symptoms.

Results
Seventeen patients with early PD, eight with iRBD, and ten healthy controls (HC) were included. PD patients exhibited inflammasome activation, with increased ASC, caspase-1, and interleukin-1β compared with HC. iRBD showed increased active caspase-1. NLRP3 levels were reduced in iRBD but not in PD. Total α-synuclein accumulation was increased in PD. Both PD and iRBD displayed decreased claudin-1 and increased PV-1. Stratified analyses revealed elevated active caspase-1 and interleukin-1β in both PD subtypes; ASC predominated in brain-first PD, whereas α-synuclein accumulation was greater in body-first PD.

Conclusions

PD is characterized by impaired intestinal epithelial and vascular barriers and activation of NLRP3-dependent inflammatory pathways. Similar but milder alterations in iRBD suggest early prodromal involvement, but these changes do not clearly distinguish between body-first and brain-first PD.

59. Ex vivo Alpha-Synuclein Effects Mimic Pesticides, Inducing Alterations in Glutamate AMPA Receptor Subunits

Authors
Gioia Marino[1], Federica Campanelli[2], Giuseppina Natale[2], Federica Servillo[3], Jacopo Canonichesi[2], Veronica Ghiglieri[1,2], Paolo Calabresi[1,3]

Affiliations
1. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, UOC Neurologia, Rome, Italy
2. Dipartimento di Promozione delle Scienze Umane e della Qualità della Vita, Università Telematica San Raffaele, Rome, Italy.
3. Neurologia, Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Neurologia, Rome, Italy

Abstract
Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons. In addition to the accumulation of misfolded alpha-synuclein (α-syn) aggregates, environmental factors such as exposure to pesticides have been implicated in PD pathogenesis by promoting neuronal dysfunction and synaptic impairment. In this study, we investigated the synaptic alterations induced by Rotenone exposure and intrastriatal injection of α-syn pre-formed fibrils (α-syn-PFFs) to identify common mechanisms involved in PD.
Our results show that both in vitro Rotenone treatment of corticostriatal slices and in vivo α-syn-PFF injection induce similar changes in excitatory synaptic transmission, evidenced by an increased rectification index. This effect is mainly associated with the synaptic recruitment of Ca^{2+}-permeable AMPA receptors lacking the GluA2 subunit, resulting in altered glutamatergic transmission and ionic conductance. In the α-syn-PFF model, these changes were detected 12 weeks after the injection, and similar alterations were observed in Rotenone-exposed slices. Both models exhibited a reduced NMDAR/AMPAR ratio and prolonged excitatory postsynaptic current (EPSC) decay, indicating a common impairment of excitatory synaptic function. Consistently, pharmacological blockade of GluA2-lacking AMPARs with NASPM significantly reduced abnormal EPSC amplitude in parkinsonian rats 12 weeks after α-syn-PFF injection. Overall, these findings identify Ca^{2+}-permeable AMPARs as key contributors to PD-related synaptic dysfunction and support their potential as therapeutic targets.

60. Physical exercise modulates plasma irisin levels in endurance athletes: implications for Parkinson's Disease

Authors
Piergiorgio Grillo,[1,2,3], Deborah Di Martino[1,2], Alessandra Calculli[1,2], Roberto De Icco[1,2], Luca Martinis[2], Roberto Bottinelli[2,4], Simone Porcelli[4], Carlo Fazio[1,2], Davide Comolli[1,2], Federico Bighiani[1,2], Giulia Di Lazzaro[5,6], Jasmine Gambelli[6], Veronica Ghiglieri[6,7], Silvia Cerri[1,2], Paolo Calabresi[5,6], Michele Terzaghi[1,2], Antonio Pisani[1,2]

Affiliations
[1]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
[2]IRCCS Mondino Foundation, Pavia, Italy
[3]The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, Department of Neurology, NYU Langone Health, NY, United States
[4]Department of Molecular Medicine, University of Pavia, Pavia, Italy.
[5]Neurology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.
[6]Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy
[7]Department of Human Sciences and Quality of Life Promotion, Università Telematica San Raffaele Roma, Rome, Italy

Funding Sources for study: This work was supported by a grant from the Italian Ministry of Health in the Next Generation EU Program - Piano Nazionale di Ripresa e Resilienza (PNRR) – Mission 6C2 - 2.1 ''Valorizzazione e potenziamento della ricerca biomedica del SSN''- PNRR-MAD-2022- 12375804, *"Clinical, molecular and electrophysiological profiling of Parkinson's Disease: the role* of non-pharmacological therapies" – CUP: F23C22001130007.

Introduction
Physical exercise (PE) improves clinical outcomes in individuals with Parkinson's disease (PD) through unclear mechanisms [1]. Irisin, a neuroprotective protein released by myocytes during PE, may play a role, but *in vivo* data in PD are limited [2, 3].

Objective
To investigate plasma irisin in a unique PD population engaged in chronic, intense PE.

Methods
Ninety-three participants were classified based on both disease status (PD versus healthy controls, HC), and PE level (sedentary versus endurance athletes). Endurance athletes included subjects regularly participating in endurance sports (triathlon/long-distance marathon/cycling) for at least 5 years, with an average training duration of 1.5 hours/day, 6 days/week. Four groups were generated: PD-Sedentary (PD-SD, n=30), PD-Endurance Athletes (PD-EA, n=15), HC-Sedentary (HC-SD, n=30), and HC-Endurance Athletes (HC-EA, n=18). Clinical and demographic features were collected. Plasma irisin was dosed in all groups.

Results
PD-EA had a longer disease duration compared to PD-SD (p=0.005) but scored better on both MDS-UPDRS-part III (p=0.029) and MMSE (p=0.016). Plasma irisin was lower in endurance athletes versus sedentary participants regardless of disease status (PD-EA vs PD-SD, p=0.002; PD-EA vs HC-SD, p=0.003; HC-EA vs HC-SD, p=0.046; HC-EA vs PD-SD, p=0.029). In PD-SD plasma irisin positively correlated with

MDS-UPDRS-part III (r=0.395, p=0.034), HY (*r*=0.386, *p*=0.042), and LEDD (*r*=0.385, *p*=0.043). Lower plasma irisin levels were associated with male sex (p<0.001).

Conclusions

Our findings suggest that chronic, intense PE ameliorates the neurological symptoms in individuals with PD, while differently modulating plasma irisin in a sex-dependent fashion. Irisin might mediate the beneficial clinical effects of PE, though further investigation is warranted.

Bibliography

1) Langeskov-Christensen M, Franzén E, Hvid LG, Dalgas U. Exercise as medicine in Parkinson's disease. J Neurol Neurosurg Psychiatry [Internet]. 2024 Oct 16 [cited 2025 Jul 19];95(11):1077–88. Available from: https://pubmed.ncbi.nlm.nih.gov/38418216/

2) Kam TI, Park H, Chou SC, Van Vranken JG, Mittenbühler MJ, Kim H, A M, Choi YR, Biswas D, Wang J, Shin Y, Loder A, Karuppagounder SS, Wrann CD, Dawson VL, Spiegelman BM, Dawson TM. Amelioration of pathologic α-synuclein-induced Parkinson's disease by irisin. Proc Natl Acad Sci U S A. 2022 Sep 6;119(36):e2204835119. doi: 10.1073/pnas.2204835119. Epub 2022 Aug 31. PMID: 36044549; PMCID: PMC9457183.

3) Zhang X, Xu S, Hu Y, Liu Q, Liu C, Chai H, Luo Y, Jin L, Li S. Irisin exhibits neuroprotection by preventing mitochondrial damage in Parkinson's disease. NPJ Parkinsons Dis. 2023 Jan 31;9(1):13. doi: 10.1038/s41531-023-00453-9. PMID: 36720890; PMCID: PMC9889817.

61. Data-Driven Biological Subtypes of Parkinson's Disease

Authors
Piergiorgio Grillo[1,2], C. Wang[3], A. Pisani[2,4], U.J. Kang[1,5], S.M. Fereshtehnejad[,6,7,8], G.M. Riboldi[1]

Affiliations
[1]The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, Department of Neurology, NYU Langone Health, NY, United States
[2]IRCCS Mondino Foundation, Pavia, Italy
[3]Department of Population Health, NYU Langone Health, NY, United States.
[4]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
[5]Department of Neuroscience, Institute for Translational Neuroscience, Parekh Center for Interdisciplinary Neurology, NYU Grossman School of Medicine, New York, NY, United States
[6]Pacific Parkinson's Research Centre (PPRC), Djavad Mowafaghian Centre for Brain Health (DMCBH), University of British Columbia, Vancouver, BC, Canada
[7]Division of Neurology, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[8]Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet, Stockholm, Sweden

Objective
The pathophysiology of Parkinson's disease (PD) is complex and likely heterogeneous among individuals. Using data from PPMI cohort, we aimed to identify distinct biological subtypes of PD through data-driven cluster analysis leveraging currently available biomarker dataset.

Materials and Methods
225 individuals with *de novo* PD were included. A total of 22 biomarkers reflecting different biological pathways (including neurodegeneration, neuroinflammation, mitochondrial impairment, and lipid metabolism/autophagy/-lysosomal dysfunction) and measured in cerebrospinal fluid (CSF), whole blood, serum, plasma, or urine, were selected. Hierarchical clustering was performed using ward.D2 method and Gower dissimilarity, with missing data handled through pairwise comparisons of available values. Clinical-demographic characteristics of the identified clusters were compared. Longitudinal progression of clinical features was evaluated over a 5-year follow-up period.

Results
Three clusters were identified: Cluster I, referred to as the "Mitochondrial-Predominant" subtype; Cluster II, referred to as the "Cryptic" subtype; and Cluster III, referred to as the "Mixed Pathology" subtype. The "Mixed Pathology" subtype was characterized by higher levels of CSF p-tau, S100B, GFAP, YKL-40, and serum NfL, and lower levels of plasma glucosylceramide, plasma ceramide and sphingomyelin compared to the "Mitochondrial-Predominant" and "Cryptic" subtype. The "Mitochondrial-Predominant" and "Mixed Pathology" subtypes showed higher levels of CSF mitochondrial DNA deletions and mitochondrial DNA ND1 compared to the "Cryptic" subtype. In the "Cryptic" subtype no clear dominant biological profiles were detected. From a clinical perspective, subjects belonging to the "Mixed Pathology" subtype were characterized by older age and higher proportion of males. No differences of 5-year clinical progression were found between the clusters.

Discussion
We identified three biological subtypes in a large cohort of de novo PD. The "Mixed Pathology" subtype was characterized by alterations across all the pathological pathways explored (i.e., neurodegeneration, neuroinflammation, mitochondrial impairment, and lipid metabolism/autophagy-lysosomal dysfunction). The "Mitochondrial-Predominant" subtype, in contrast, was characterized by alterations exclusively

involving markers of oxidative stress and mitochondrial dysfunction. Finally, the “Cryptic” subtype included subjects whose biomarker signature did not indicate predominant alterations in any of the aforementioned pathways. The clusters did not show clinical and demographic differences at baseline, except for age and sex, where subjects in the “Mixed Pathology” subtype were indeed older and predominantly males. No difference in mid-term clinical progression was observed between subtypes.

Conclusions
Our study contributes to the understanding of the heterogeneity of PD pathophysiology through the identification of biological subtypes. Further studies with more comprehensive biomarker panels are needed to confirm and expand these results.

Bibliography
Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. Brain. 2017 Jul 1;140(7):1959-1976. doi: 10.1093/brain/awx118. PMID: 28549077.
Deng X, Mehta A, Xiao B, Ray Chaudhuri K, Tan EK, Tan LC. Parkinson's disease subtypes: Approaches and clinical implications. Parkinsonism Relat Disord. 2025 Jan;130:107208. doi: 10.1016/j.parkreldis.2024.107208. Epub 2024 Nov 12. PMID: 39567305.
Rigon L, Poplawska-Domaszewicz K, Metta V, Fogliano C, Nasi ML, Sauerbier A, Dafsari H, Leta V, Falup-Pecurariu C, Odin P, Antonini A, Chaudhuri KR. The challenges with the identification of Parkinson's disease subtypes. Expert Rev Neurother. 2026 Feb;26(2):135-151. doi: 10.1080/14737175.2025.2611250. Epub 2026 Jan 21. PMID: 41474600.

62. The Prokineticin System Is Downregulated in Idiopathic Rapid Eye Movement Sleep Behavior Disorder: Evidence from Olfactory Neurons

Authors
Piergiorgio Grillo[1,2,3], D. Maftei[4], A. Calculli[1,2], T. Schirinzi[5,6], S. Mauramati[7], M. Vincenzi[4], M.G. Di Certo[8], F. Gabanella[8], D. Di Martino[1,2], M. Benazzo[7], C. Severini[8], R. Lattanzi[4] , A. Pisani[1,2], M. Terzaghi[1,2]

Affiliations
[1]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
[2]IRCCS Mondino Foundation, Pavia, Italy
[3]The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, Department of Neurology, NYU Langone Health, NY, United States
[4]Department of Physiology and Pharmacology "V. Erspamer", Sapienza University of Rome, Rome, Italy
[5]Unit of Neurology, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy.
[6]Unit of Neurology, Fondazione PTV - Tor Vergata University Hospital, Rome, Italy
[7]Department of Otolaryngology Head Neck Surgery, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Italy
[8]National Research Council (CNR), Institute of Biochemistry and Cell Biology (IBBC), Rome, Italy

Introduction
PROK2 is a peptide expressed in the adult brain mediating neuroprotective functions. Previous studies reported an upregulation of prokineticin system in PD, but evidence in prodromal α-synucleinopathies was lacking [1, 2].

Objective
to investigate the expression of prokineticin-2 (PROK2) and its receptors (PKR1 and PKR2), along with oligomeric α-synuclein (oligo α-syn) as a marker of α-synuclein pathology, in olfactory neurons (ONs) from individuals with idiopathic REM sleep behavior disorder (iRBD) [3].

Methods
ONs, obtained by nasal brush from 28 iRBD subjects (age:71.2±7.4years; males:89.3%; duration:4.9±2.5years) and 28 healthy controls (HCs) (age:67.2±11.5years; males:64.2%), were analyzed using real-time polymerase-chain-reaction (RT-PCR), immunofluorescence (IF), and western blot (WB). In a subgroup of subjects, results were validated in serum.

Results
In the iRBD group, PROK2 protein expression was reduced in both ONs (IF: $F(1,26)=15.289$, $p<0.001$; WB: $F(1,12)=9.073$, $p=0.011$) and serum compared with HCs (WB: $F(1,12)=4.557$, $p=0.050$). iRBD subjects showed lower mRNA expression of prokineticin receptors compared with HCs (RT-PCR for PKR1: $F(1,26)=16.131$, $p<0.001$; RT-PCR for PKR2: $F(1,39)=4.946$, $p=0.032$). Oligo α-syn accumulation in ONs was higher in iRBD than HCs, yet the difference only tended to statistical significance (IF: $F(1,18)=3.169$, $p=0.092$).

Conclusions
In contrast with findings in PD, we found a downregulation of prokineticin system in iRBD. The causes of prokineticin system downregulation in this prodromal stage may be multiple. The absence of clear oligo α-syn accumulation, known trigger of PROK2, may play a role. On the other hand, a lack of activation of this system might act as predisposing factor for the development of iRBD and, subsequently, full-blown neurodegeneration.

Bibliography

1) Schirinzi T, Maftei D, Passali FM, et al. Olfactory Neuron Prokineticin-2 as a Potential Target in Parkinson's Disease. Ann Neurol. 2023;93(1):196-204. doi:10.1002/ANA.26526

2) Dauvilliers Y, Schenck CH, Postuma RB, et al. REM sleep behaviour disorder. Nat Rev Dis Primers. 2018;4(1). doi:10.1038/S41572-018-0016-5

3) Brozzetti L, Sacchetto L, Cecchini MP, et al. Neurodegeneration-Associated Proteins in Human Olfactory Neurons Collected by Nasal Brushing. Front Neurosci. 2020;14. doi:10.3389/FNINS.2020.00145

63. Parameters of the Alpha-Synuclein Seed Amplification Assay on CSF predict the clinical subtype of Parkinson's Disease at 10-year follow-up

Authors
Piergiorgio Grillo [1,2,3], G.M. Riboldi[1], A. Pisani[2,3], U.J. Kang[1,4], S.M. Fereshtehnejad[5,6,7]

Affiliations
[1]The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, Department of Neurology, NYU Langone Health, NY, United States
[2]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
[3]IRCCS Mondino Foundation, Pavia, Italy
[4]Department of Neuroscience, Institute for Translational Neuroscience, Parekh Center for Interdisciplinary Neurology, NYU Grossman School of Medicine, New York, NY, United States
[5]The Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, ON, Canada
[6]Division of Neurology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada
[7]Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet, Stockholm, Sweden

Objective: To assess the association between the parameters of alpha-synuclein seed amplification assay on CSF (CSF-αSyn-SAA) within 2 years from Parkinson's disease (PD) onset and the clinical evolution of clinical subtypes at 10-year follow-up.

Materials and Methods
The PPMI dataset was used (https://www.ppmi-info.org). Sporadic PD subjects were classified as Mild Motor Predominant (MMP), Intermediate (IM) and Diffuse Malignant (DM) at baseline (n=323) and 10-year follow-up (n=146), based on previously published motor summary score and three non-motor features (cognitive impairment, RBD and dysautonomia). 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) using a 150-hrs protocol. CSF Aβ1-42, tTau and pTau181, CSF and serum NfL were also considered at baseline.

Results
Times of reaction (T50 and TTT) and AUC were respectively shorter and larger from the more benign to the more aggressive PD subtype (MMP>IM>DM). The difference in amplification parameters at baseline was more evident when comparing subtypes based on the 10-year clinical features (T50, $\eta 2=0.036$; TTT, $\eta 2=0.031$; AUC, $\eta 2=0.033$; all p values < 0.05) than when comparing subtypes based on the baseline clinical features (T50, $\eta 2=0.012$; TTT, $\eta 2=0.012$; AUC, $\eta 2=0.013$; all $p<0.05$). Shorter T50 and TTT assessed at baseline were associated with a greater risk of being classified as DM versus MMP at 10-year follow-up (T50, OR=3.286; TTT, OR=4.586; all $p<0.05$). CSF Aβ1-42, tTau, pTau181, CSF and Serum NfL did not differ between groups.

Discussion
Faster SAA reactions assessed at baseline - potentially indicating a greater accumulation of alpha-synuclein - were associated with a more malignant subtype (Diffuse Malignant, DM), characterized by severer motor and non-motor impairment. This association was more pronounced with the DM subtype established on the 10-year clinical features, than with the DM subtype based on the baseline clinical features. Notably, faster SAA reaction assessed at baseline increased the risk of being classified as DM after 10 years by more than 3-4 folds. Taken together, our results suggests that CSF-αSyn-SAA

parameters at baseline are predictors of the long-term clinical outcome of PD subjects at 10-year follow-up.

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

References
Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. Brain. 2017 Jul 1;140(7):1959-1976. doi: 10.1093/brain/awx118. PMID: 28549077.

Grillo P, Concha-Marambio L, Pisani A, Riboldi GM, Kang UJ. Association between the Amplification Parameters of the α-Synuclein Seed Amplification Assay and Clinical and Genetic Subtypes of Parkinson's Disease. Mov Disord. 2024 Dec 18. doi: 10.1002/mds.30085. Epub ahead of print. PMID: 39692283.

Mastrangelo A, Mammana A, Hall S, Stomrud E, Zenesini C, Rossi M, Janelidze S, Ticca A, Palmqvist S, Magliocchetti F, Baiardi S, Mattsson-Carlgren N, Hansson O, Parchi P. Alpha-synuclein seed amplification assay longitudinal outcomes in Lewy body disease spectrum. Brain. 2024 Dec 17:awae405. doi: 10.1093/brain/awae405. Epub ahead of print. PMID: 39689039.

64. Effects of voluntary physical activity on nigrostriatal DA release and nigral physiology in a mouse model of Parkinson's Disease

Authors
Riccardo Melani[1,2], Ryan M. Feeley*[1,2], Vanessa Khachaturyan[1,2], Minna McFarland[1,2], Jyoti C. Patel[1,2], Letizia Zanetti[2,3], Jenny Sassone[3], Margaret E. Rice[1,2]

Abstract
Mounting evidence shows that aerobic exercise can be beneficial for improving symptoms in PD patients, but the mechanisms remain largely unknown. We previously examined dopamine (DA) release in individually housed mice allowed free access to a running wheel or to a locked wheel in their home cages, and found that in *ex vivo* striatal slices from young male mice and aging mice of both sexes, 30 days of voluntary wheel-running exercise boosts 1-pulse evoked dopamine (DA) release in dorso-lateral striatum (DLS), nucleus accumbens core (NAc core) and shell (NAc shell) (Bastioli et al. 2022, 2025). Evoked increases in extracellular DA concentration ($[DA]_o$) were quantified using fast-scan cyclic voltammetry (FSCV). Here, we examined possible beneficial effects of exercise in *Park*R275W mice, a novel Parkinson's Disease (PD) model mouse line that expresses the R275W mutation of *PARK2* and exhibits progressive dopamine (DA) neuron degeneration in the substantia nigra pars compacta (SNc) and motor impairments as they age (Regoni, Zanetti et al. 2024). We examined locomotor behavior and performed Catwalk gait analysis, revealing increased locomotor speed in males, though an improvement in stride length and limb swing duration in both sexes. Male *Park*R275W mice showed increased evoked $[DA]_o$ in DLS, NAc core, and NAc shell, while females did not. Additionally, we used voltage- and current-clamp recordings in SNc DA neurons in midbrain slices from these same *Park*R275W mice to investigate the influence of exercise on somatodendritic DA release, indicated by D2 DA receptor-mediated inhibitory currents (D2ICs), and on SNc DA neuron membrane properties and excitability. We found no difference in evoked D2ICs in the SNc in either sex, and no difference in firing rate or other membrane properties of SNc DA neurons that survived neurodegeneration.

65. A Multisite ULTrasound Investigation of Vagus nerve Echostructure, Regional Substantia nigra, and Extra-neural markers in Parkinson's Disease: the MULTIVERSE-PD project.

Authors
Gabriele Sergi [1], Edoardo Bianchini [1,2], Gaia Anzini [1], Stefano Toro [1], Niccolò Casasoli [1], Giorgio Vivacqua [3], Massimo Marano [1]

Affiliations
1 Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy
2 Univ. Grenoble Alpes, CNRS, Grenoble INP, LIG Sangria, Grenoble, France
3 Department of Microscopic and Ultrastructural Anatomy, Campus Biomedico University of Roma, Rome, Italy

Background
Ultrasonography (US) is a cost-effective tool to investigate brain and nerve tissue. Substantia Nigra (SN) US has been extensively studied in Parkinson's Disease (PD) [1], whereas vagus nerve (VN) US findings are conflicting [2]. The MULTIVERSE-PD study aims to implement US biomarkers in PD. Here, we assessed SN and VN sonography in a well-characterized sample.

Methods
VN cross-sectional area (VN-CSA) and SN hyperechogenic area (SN-HA) were collected in mild-to-moderate PD patients. Participants were assessed through MDS-UPDRS, SCOPA, PDSS-2, ESS, PDQ-8 and other scales, and underwent real-world mobility evaluation with IMUs (McRoberts Move Monitor) and plasma inflammatory and neurodegeneration biomarkers.

Results
Sixty-nine patients were enrolled (41 males, 59.4%; median age 68.0 years [60.0–73.0]; disease duration 7.0 years [4.0–10.0]; Hoehn & Yahr 2.0 [2.0–3.0]). Median SN-HA was 0.41 cm^2 (IQR 0.31–0.49) and VN-CSA 1.40 cm^2 (IQR 1.06–1.61), without inter-side differences. Left SN correlated with MDS-UPDRS Total, Part II and PDQ-8; average SN with MDS-UPDRS Total, BDI-II, NMSS and PDQ-8; least affected side SN with MDS-UPDRS Total and Part III. Least affected side VN correlated with PDQ-8 and NMSS, and left VN with PDQ-8 and MDS-UPDRS Part I. Right SN and VN showed no correlations.

Conclusions
SN hyperechogenicity correlated with motor burden, non-motor symptoms and quality of life. Least affected side SN-HA was linked to motor scores, suggesting utility as a progression marker. Left VN-CSA was linked to non-motor features, consistent with its predominant afferent innervation. Findings support SN and VN ultrasonography as complementary PD biomarkers within a feasible, standardized multisite protocol.

References
1. Li et al. Diagnostic Accuracy of Transcranial Sonography of the Substantia Nigra in Parkinson's disease: A Systematic Review and Meta-analysis. Sci Rep. 2016. doi:10.1038/srep20863
2. Höppner et al. Vagus nerve cross-sectional area decreases in Parkinson's disease. Parkinsonism Relat Disord. 2023. doi:10.1016/j.parkreldis.2023

66. Application of a framework for digital analysis in the longitudinal profiling of Muhammad Ali's voice, early Parkinson's disease and matched controls

Authors
Carlo Giacomina[1,2*], Renato Fusco[1,2], Francesca Leo[1,2], Niccolò Casasoli[1,2], Edoardo Bianchini[2,3], Massimo Marano[1,2]

Affiliations
[1]Università Campus Bio-Medico di Roma
[2]Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy
[3]Univ. Grenoble Alpes, CNRS, Grenoble INP, LIG Sangria, Grenoble, France

Background
Parkinson's disease is a progressive neurodegenerative disorder, whose diagnosis is still anchored to motor manifestations. Among digital biomarkers, voice analysis is gaining relevance [1, 2]. In this study, we developed an automated framework for voice analysis in the tracking of the voice from real Muhammad Ali scenarios.

Methods
Selected audio recordings of Muhammad Ali, captured by interview on YouTube and spanning from 1972 to 1984, were divided into biennia. Fourteen patients with early-stage PD (Hoehn & Yahr ≤ 2) and twelve healthy controls served as reference. Temporal (speech rate, articulation rate, pauses), prosodic (F0) and articulatory (F2 variability) features were extracted with Praat software and compared across biennia and groups with non-parametric tests.

Results
Across 153 segments, Ali's speech rate declined over time (rho=−0.24; q=0.024), from 6.66 syllables/s in 1976–1977 to 5.48 in 1980–1981, below patients' interquartile range, with more pauses and reduced F0 variability. F2 variability reached patients' values in 1982–1984.

Conclusions
Voice analysis of real-life recordings detected speech slowing several years before formal Ali's PD diagnosis announcement (1984), supporting speech timing as a candidate early motor to be adopted in such contexts and validated in larger longitudinal cohorts. Nevertheless, he was still able to win a world championship!

References
1. Harel B, Cannizzaro M, Snyder PJ. Variability in fundamental frequency during speech in prodromal and incipient Parkinson's disease: a longitudinal case study. Brain Cogn. 2004;56:24–29.
2. Rusz J, Cmejla R, Ruzickova H, Ruzicka E. Quantitative acoustic measurements for characterization of speech and voice disorders in early untreated Parkinson's disease. J Acoust Soc Am. 2011;129(1):350–367. doi:10.1121/1.3514381

67. VAgus nerve Non-Invasive Stimulation Home trial for Parkinson's disease: the VANISH-PD trial

Authors
Francesca Proietti[1], Giorgio Vivacqua[1], Edoardo Bianchini[2], Giulia Forte[1], Vincenzo Di Lazzaro[1, 2], Massimo Marano*[1, 2]

Affiliations
[1] Università Campus Bio-Medico di Roma
[2]Fondazione Policlinico Universitario Campus Bio-Medico
*Presenter author

Background
Transcutaneous auricular vagus nerve stimulation (taVNS) may improve motor and non-motor symptoms of Parkinson's disease (PD) [1, 2]. We investigated the feasibility and efficacy of active versus sham stimulation using clinical, digital and biochemical outcomes.

Methods
Twenty-eight patients with PD were randomized to active (n=14) or sham (n=14) taVNS using the Nurosym (Parasym) device (up to 2h/day). The primary endpoint was the change in MDS-UPDRS Part III total score from baseline to treatment completion (18 weeks). Exploratory outcomes included non-motor symptoms, sleep, quality of life, and digital Timed Up and Go (TUG) performance. Within-group changes and baseline-adjusted between-group differences were assessed.

Results
MDS-UPDRS III improved by 2.14p with active stimulation versus 1.07 with sham, without significant between-group differences (p=0.749). Single- and dual-task TUG durations decreased by 1.99 and 2.98 seconds, respectively, only in the Real taVNS group ($p<0.05$). Likewise, digital gait assessment suggested improvements in step regularity and temporal variability, particularly during single-task walking ($p<0.05$). Active stimulation was associated with reductions in NMSS Mood/Cognition (-4.07 points; paired p=0.005). However, neither clinical nor instrumented outcomes demonstrated significant treatment-specific effects after adjustment for multiple comparisons. Stimulation was feasible and well tolerated.

Conclusions
Exploratory improvements observed in gait and non-motor outcomes of patients treated with real and not sham taVNS warrant further investigation in larger trials. Biochemical analysis is ongoing. The protocol was feasible and possible effective.

References
1) Proietti F et al. Vagus Nerve Stimulation in Movement Disorders, from Principles to a Systematic Review of Evidence. Mov Disord. 2025 Dec;40(12):2559-2577.
2) Marano M et al. Left Vagus Stimulation Modulates Contralateral Subthalamic β Power Improving the Gait in Parkinson's Disease. Mov Disord. 2024 Feb;39(2):424-428.