

# ABSTRACTS

## The 2024 Fresco International Workshop on Synaptic Plasticity and Advances in Parkinson's Disease

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# 1. A Convolutional Neural Network model for classifying tremor amplitude in Parkinson's Disease

## Authors

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## Background

Resting tremor is a common and debilitating symptom of Parkinson's Disease (PD) characterized by involuntary rhythmic muscle contractions [1]. The Unified Parkinson's Disease Rating Scale (UPDRS) is used to evaluate both non-motor and motor symptoms [2], whereas wearable systems are employed to recognize human motion and analyze data collected by sensors [3]. The present study evaluates the effectiveness of a Convolutional Neural Network (CNN) model for multiclass classification of resting tremor amplitude in PD patients integrating sensors data and UPDRS information.

## Methods

Data from 3-axis accelerometers placed on arms of 13 PD patients and 11 healthy subjects over approximately two days, including in-clinic and daily living activities, were acquired. Resting data recorded during the UPDRS 3.17 assessment were extracted and used to identify additional resting periods within the recordings through an automatic segmentation algorithm, and were labeled according to the score assigned by the neurologist. At the end, a segment of 90,000 data points was created for each score. A CNN structured into 7 layers was developed, and a 5-fold cross-validation method was employed to test the robustness of the model.

## Results

The CNN model achieves an average accuracy of 96.55% across the validation folds. The proposed model outperformed traditional machine learning techniques as Random Forest, Support Vector Machine and Decision Trees, demonstrating superior accuracy in tremor classification.

## Conclusion

Our method exploited the ability of CNNs to process raw data efficiently, aiming to simplify diagnostic processes and enhance the accuracy of the resting tremor assessment in clinical settings.

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3. Huang, X.; Xue, Y.; Ren, S.; Wang, F. Sensor-Based Wearable Systems for Monitoring Human Motion and Posture: A Review. *Sensors* 2023, 23.

## 2. Structural and functional connectivity predicts MRgFUS thalamotomy outcome in Parkinson's disease

### Authors

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### Abstract

Magnetic Resonance-guided Focused Ultrasound (MRgFUS) thalamotomy has shown efficacy in reducing tremor symptoms in Parkinson's disease (PD). This study aimed to determine if the connectivity between the ablation target and other brain areas predicts treatment outcome better than the target site itself. We analyzed structural and functional connectivity related to successful MRgFUS ablation of the Ventral intermediate thalamic nucleus using a tremor-dominant PD dataset and normative human connectome data from diffusion tractography and resting-state functional MRI. Leave-one-patient-out cross-validation was employed to predict clinical outcomes based on connectivity profiles.

Standard ablation features did not significantly correlate with clinical outcomes (all  $p > 0.05$ ). However, connectivity between the ablation area and regions such as the pre-supplementary and supplementary motor areas, superior frontal gyrus, and cerebellum correlated with clinical improvement. Functional connectivity patterns, including anticorrelation with the primary somatosensory and lateral primary motor cortex, also correlated with outcomes. Cross-validation showed that structural ( $R^2 = 0.52$ ,  $p = 0.005$ ) and functional connectivity ( $R^2 = 0.14$ ,  $p = 0.04$ ) profiles predicted clinical improvement.

Furthermore, dopamine uptake positively correlated with both functional ( $R = 0.59$ ,  $p = 0.01$ ) and structural networks ( $R = 0.71$ ,  $p = 0.002$ ) in the basal ganglia, but not in the cerebral cortex or cerebellum (all  $p > 0.05$ ). Our results suggest that both structural and functional connectivity of the target area show overlap molecular markers of dopamine expression and are independent predictors of clinical improvement in tremor-dominant MRgFUS-thalamotomized PD patients.

### **3. Proton Magnetic Resonance Spectroscopy in Parkinson's Disease patients with and without cognitive impairment**

#### **Authors**

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#### **Abstract**

Cognitive impairment is an important non-motor symptom of Parkinson's Disease (PD), with a prevalence of up to 42% at the time of diagnosis [1-2].

The current study was aimed to identify potential biomarker for the early diagnosis of PD patients with cognitive impairment (PD-CI) by analyzing the metabolite changes in globus pallidus (GP) and substantia nigra (SN), which were selected based on their neurochemical correlate with PD.

Twenty-two diagnosed PD patients, including 13 PD patients with normal cognitive (PD-N) and 9 PD-CI, and 10 healthy controls (HC) participated in this study. All subjects underwent single-voxel Proton Magnetic Resonance Spectroscopy ( $^1\text{H}$ -MRS) and olfaction assessment by IOIT. The MMSE was used to measure global cognitive function in PD patients. Disease severity was measured according to Hoehn and Yahr stage, the motor symptoms were evaluated by UPDRS-III and non-motor symptoms by NMSS, RBDSQ, COMPASS-31, HARS, HDRS, and MOCA.

We found significant differences between PD-CI and HC ( $p<0.001$ ) and between PD-N and HC ( $p=0.002$ ) in IOIT. PD-CI and PD-N were significantly different in the UPDRS-III ( $p=0.02$ ) and MOCA ( $p<0.001$ ). We did not observe significant MRS changes in the GP or SN. These findings imply that PD may not yet be able to crumble this neuronal network in the early stages. However, we found a positive correlation between UPDRS-III scores and Glutamate/Glutamine levels in the SN ( $r=0.73$ ;  $p=0.03$ ) and GP ( $r=0.70$ ;  $p=0.04$ ) of PD-CI, suggesting how the increased glutamate neurotransmission may reflect neurodegenerative process in PD.

#### **Reference**

- [1] Yarnall AJ, Breen DP, Duncan GW, et al. Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study. *Neurology* 2014;82:308-316.
- [2] Aarsland D, Andersen K, Larsen JP, et al. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch. Neurol.* 2003;60:387-392.

## **4. Neurophysiological evidences of functional cerebellar impairment unrelated to structural damage in Early Multiple Sclerosis**

### **Authors**

Boccia V.D. Botta A. Terranova S. Cipriano E. Grasselli G. Capello E. Avanzino L. and Inglese M.

Presenter: Boccia Vincenzo Daniele

### **Introduction**

Cerebellar dysfunction contributes to disability in multiple sclerosis (MS), but clinically evident impairment is rare in early stages. Early detection of cerebellar involvement is essential for managing MS.

### **Aims**

This study aimed to assess early functional compromise in cerebellar-brain connectivity and the corticospinal tract (CST) in early MS patients using transcranial magnetic stimulation (TMS) and structural MRI analyses.

### **Methods**

Twenty early MS patients and ten healthy subjects (HS) were evaluated with TMS to measure motor pathway excitability and cerebellar-M1 connectivity. CST excitability was assessed through Recruitment Curve (RC) slopes (80-140%). Cerebellar-brain inhibition (CBI) was measured using a paired-pulse protocol. MRI included FLAIR and Double-Inversion Recovery (DIR) sequences for cerebellar lesion detection, with structural analyses for cerebellar volumetry, thalamus segmentation, and cortical metrics. Tractography diffusion MRI analysis assessed CST and dentate-rubro-thalamic-cortical (DRTC) tracts.

### **Results**

MS patients showed reduced fractional anisotropy (FA) in the CST compared to HS ( $F:5.63$ ,  $p:0.03$ ). TMS RC slope did not differ significantly ( $t:-1.67$ ,  $p:0.11$ ). Both MS patients and those with cerebellar lesions (CL+) had lower CBI compared to HS ( $U:52.0$ ,  $p:0.04$ ;  $F:5.27$ ,  $p:0.01$ ). CBI impairment did not correlate with DRTC-FA or lesioned tract percentage.

### **Discussion**

Early MS patients exhibit compromised cerebellar-M1 connectivity indicated by reduced CBI, though CST excitability remains unchanged. Structural MRI showed altered CST FA but no direct link to CBI impairment. These findings suggest that neurophysiological measures may detect early cerebellar dysfunction in MS, potentially preceding structural damage. Longitudinal studies are needed to further explore these early functional changes.

## **5. The Language of Space: Where is This and Where is that?**

### **Authors**

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### **Introduction and Objective**

The hypothesis that language-cognitive system interactions play a role in understanding domain-specific semantic terms is supported by a few neurophysiological studies, mainly on the motor cortex. Our goal was to assess if visuospatial coding affects the semantic comprehension of space-related words differently for peripersonal and extrapersonal space, and the causal role of the posterior parietal cortex (PPC).

### **Methods**

Utilizing Unity3D and Oculus Rift S, a virtual reality setup displayed 3D words at peripersonal (60 cm) and extrapersonal (120 cm) space. Participants performed a lexical decision task distinguishing between pseudowords and a near ("this") or far ("that") semantically related words, under conditions with and without tool use. The experiment included baseline, cathodal tDCS over the right PPC, and dual tDCS sessions, measuring Vocal Reaction Times (RTs) and analysing them with repeated measures ANOVA to assess semantic distance effects under various conditions.

### **Results**

Baseline conditions showed significantly faster RTs for near-semantically related words in peripersonal space. Tool use decreased RTs for near-semantically related words in extrapersonal space. Cathodal tDCS can revert this latter phenomenon by increasing RTs for near-semantically related words when a tool is used. Dual tDCS globally reduced RTs, regardless for position, semantics, and tool.

### **Discussion and Conclusions**

The findings suggest visuospatial coding influences near and far semantic processing, with or without a virtual tool, and highlight a causal role for right PPC. The overall RT reduction following dual tDCS could be due to enhanced reading performance from increased left-PPC excitability and decreased inter-hemispheric inhibition from right-PPC.

### **References**

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2. Giglia, G., Pia, L., Folegatti, A., Puma, A., Fierro, B., Cosentino, G., et al. (2015). Far space remapping by tool use: A rTMS study over the right posterior parietal cortex. *Brain Stimul.* 8, 795–800. doi:10.1016/j.brs.2015.01.412.
3. Giglia, G., Mattaliano, P., Puma, A., Rizzo, S., Fierro, B., and Brighina, F. (2011). Neglect-like effects induced by tDCS modulation of posterior parietal cortices in healthy subjects. *Brain Stimul.* 4, 294–299. doi:10.1016/j.brs.2011.01.003.

## **6. Can Wii modulate pseudoneglect? Improving visuospatial attention in healthy subjects by active video gaming**

### **Authors**

Fabrizio Di Giovanni <sup>1</sup>, Giuditta Gambino <sup>1</sup>, Lorenzo Pia <sup>2</sup>, Giuseppe Ferraro <sup>1</sup>, Filippo Brighina <sup>1</sup>, Danila Di Majo <sup>1</sup>, Tommaso Ciorli <sup>2</sup>, Pierangelo Sardo <sup>1</sup>, Giuseppe Giglia <sup>1, 3</sup>

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### **Abstract**

Pseudoneglect phenomenon is a visuospatial attentional bias present in the healthy population, leading subjects to slightly overestimate the left hemifield of space. Interestingly, previous data indicate that athletes involved in open-skill sports exhibit a reduced pseudoneglect compared to the general population. This study aims to explore whether a one-week training period with an open-skill sport exergame can similarly diminish pseudoneglect in healthy subjects. Fifteen non-athletes participants underwent a visuospatial attention task and a control memory task in baseline conditions (t0: Pre-game) and after a brief period (one week, one hour per day, t1: Post-game) of tennis exergaming (ExerGame group: EG). Moreover, two additional experimental groups were assessed under the same conditions: one using a non-exergame platform (Non-Exergame group: NEG) and another one without receiving any video game training (Sedentary group: SE). In the Post-game condition, participants from the EG group demonstrated a marked decrease in leftward space overestimation and made significantly fewer leftward errors compared to the Pre-game condition, without any improvement in the control memory task. The other two groups did not show any differences in the visuospatial attention task and in the control memory task. Our results suggest that a daily training with a tennis exergame has the potential to enhance visuospatial attention isotropy by reducing leftward space overestimation, whereas outcomes from non-exergaming and sedentary inactivity do not change participants' performance. The present study demonstrates how exergame platforms can be used to modulate cognitive abilities in the healthy population, paving the way for potential therapeutic and rehabilitative applications.

## 7. MRgFUS and quality of life in subjects with Parkinson's Disease

### Authors

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### Abstract

Tremor represents one of the most common symptoms of Parkinson's disease (PD) having significant implications on patients' quality of life (QoL)<sup>1</sup>. Magnetic resonance imaging-guided focused ultrasound (MRgFUS) is a non-invasive therapeutic approach for this Parkinson's-related symptom.

We reported changes in quality of life and emotional state in 17 participants with PD following unilateral MRgFUS thalamotomy in tremor predominant<sup>2</sup>. Hoehn and Yahr stages 2-3: MOCA score > 24. PD subjects were assessed at baseline (T0), 3 months (T1) and 6 months (T2) after MRgFUS through standardized assessments for motor symptoms (UPDRS-III; IV) emotional state (HAM-D; HAM-A) and quality of life (PDQ-39).

Statistical analysis was performed on averaged traces from each participant by using the R 4.2 software package. A 95% confidence level was set with a 5% alpha error. Statistical significance was set at  $p < 0.05$ .

One-way analysis of variance (ANOVA), followed by Tukey's test for post hoc analysis showed significant differences at three times in MOB ( $p = 0.003$ ), ADL ( $p < 0.001$ ) sub item of PDQ-39 and HAM-A ( $p = 0.003$ ). In particular, MOB decrease between T0 and T1 ( $p = 0.04$ ) and T0 and T2 ( $p = 0.003$ ). ADL decreases between T0 and T1 ( $p < 0.001$ ) and T0 and T2 ( $p < 0.001$ ). HAM-D decrease between T0 and T1 ( $p = 0.02$ ) and HAM-A between T0 and T2 ( $p = 0.002$ ). MRgFUS treatment effectively increased the QoL scores, indicating its efficacy in the well-being of PD population. Following MRgFUS, PD subjects showed a decrease in anxiety and depression symptoms because of tremor cessation and motor symptoms improvement.

### References

1. Abusrair, A. H., Elsekaily, W., & Bohlega, S. (2022). Tremor in Parkinson's disease: from pathophysiology to advanced therapies. *Tremor and Other Hyperkinetic Movements*, 12.
2. Dahmani, L., Bai, Y., Li, M., Ren, J., Shen, L., Ma, J., ... & Wang, M. (2023). Focused ultrasound thalamotomy for tremor treatment impacts the cerebello-thalamo-cortical network. *npj Parkinson's Disease*, 9(1), 90.

## 8. Transcranial magnetic stimulation of primary motor cortex elicits an-immediate transcranial evoked potential

### Authors

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### Abstract

#### Background

Transcranial evoked potentials (TEPs) measured via electroencephalography (EEG) are widely used to study the cortical responses to transcranial magnetic stimulation (TMS). Immediate transcranial evoked potentials (i-TEPs) have been obscured by pulse and muscular artifacts. Thus, the TEP peaks that are commonly reported have latencies that are too long to be caused by direct excitation of cortical neurons.

#### Methods

In 25 healthy individuals, we recorded i-TEPs evoked by a single biphasic TMS pulse targeting the primary motor hand area (M1<sub>HAND</sub>) or parietal or midline control sites. Sampling EEG at 50 kHz enabled us to reduce the duration of the TMS pulse artifact to a few milliseconds, while minor adjustments of the TMS coil tilt or position enabled us to avoid cranial muscular twitches during the experiment.

#### Results

We observed an early positive EEG deflection starting after approx. 2 ms followed by a series of superimposed peaks with an inter-peak interval of ~1.1-1.4 ms in multiple electrodes surrounding the stimulated sensorimotor region. This multi-peak i-TEP response was only evoked by TMS of the M1<sub>HAND</sub> region and was modified by changes in stimulation intensity and current direction.

#### Discussion

Single-pulse TMS of the M1<sub>HAND</sub> evokes an immediate local multi-peak response at the cortical site of stimulation. Our results suggest that the observed i-TEP patterns are genuine cortical responses evoked by TMS caused by synchronized excitation of pyramidal neurons in the targeted precentral cortex. This notion needs to be corroborated in future studies, including further investigations into the potential contribution of instrumental or physiological artifacts.

## **9. EEG Alteration of Practice-Related Spectral Activity and Connectivity Patterns in Depression: Hallmark of Energy Dysregulation?**

### **Authors**

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### **Background**

Depression is a major mental health concern with increasing prevalence mostly in the younger population. EEG is a cost-effective and accessible instrument that can yield insights about neural plasticity and energy regulation, two aspects that are altered in depression. Previous EEG studies showed that practice increases power in beta range (13-30 Hz) in healthy subjects but not in disorders associated with impaired plasticity and energy dysregulation. Here, we ascertain whether depression presents with alterations of spectral activity and connectivity before and after practice.

### **Methods**

We used publicly available resting state EEG (64 electrodes) recorded before and after a learning task in 122 subjects. Based on Beck Depression Inventory (BDI) score, they were assigned to either high BDI (hBDI, BDI>13, N=46) or control (CTL, BDI<7, N=75) group. We analyzed spectral activity, theta-beta and theta-gamma phase-amplitude coupling (PAC) of EEG before and after the learning task.

### **Results**

At baseline, compared to CTL, hBDI group exhibited greater beta power over fronto-parietal regions and gamma over right parieto-occipital area. After practice, increases in all frequency ranges were observed only in CTL. Theta-beta and theta-gamma PAC were greater in hBDI before the task but not after the task.

### **Conclusions**

This is the first demonstration of the lack of practice-related increases of beta power and connectivity in depression. This phenomenon likely reflects power saturation due to high baseline values. Based on the available evidence in the literature, we further speculate that inhibitory/excitatory imbalance, altered plasticity mechanisms, and energy dysregulation may underlie these findings. Indeed, these results can foster the development of novel therapeutical approaches for depression. Most importantly, they can provide a comprehensive framework for addressing dysfunctions underlying depression, also considering that this symptom often precedes neurodegenerative diseases.

## **10. Cerebral Plasticity in post-stroke patients: applications of High-Density EEG and Mirror Therapy**

### **Authors**

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### **Abstract**

Mirror Therapy (MT) is a promising method in stroke patients' (1). The embodiment of reflected healthy limb may influence the inter-hemispheric connections, with an involvement of affected motor cortex after treatment (2,3).

The purpose is to investigate the role of the MT, focusing on neurophysiological changes respect to cortical reorganizations, reducing hemispheric asymmetry, assessed with 256 channels of High-Density EEG recordings. We enrolled 9 subacute strokes (5 ischaemic; 4 haemorrhagic) with hemiplegic upper limb. The settlement provides a box with a mirror placed between the arms, undergoing two conditions: the first one patient observed healthy hand movements in the mirror (MC); in the second with covered mirror (NMC). The conditions provided tactile stimulation (smooth, rough) and motor stimulation (grasping and finger tapping). EEG beta band (13-30 Hz) power spectral analysis revealed significant results. During finger tapping ( $p = 0.0264$ ) and smooth stimulation ( $p = 0.0378$ ), power increased in the right frontal areas in MC, while it increased in the left fronto-central regions in NMC for finger tapping  $p = 0.0416$ ). For smooth ( $p = 0.0281$ ) and rough ( $p = 0.0339$ ), power was higher in the left centro-parietal and prefrontal areas in NMC. Power beta band showed a significant effect in MC in the right side with an interest of M1 and prefrontal areas whereas a significant activation in the left side for NMC. Our preliminary results analyzed the impact of MT on neural plasticity revealed by the magnitude of power beta band as a marker of neurophysiological response.

### **Reference**

1. Zhuang JY, Ding L, Shu BB, Chen D, Jia J. Associated Mirror Therapy Enhances Motor Recovery of the Upper Extremity and Daily Function after Stroke: A Randomized Control Study. *Neural Plast.* 2021 Sep 29;2021:7266263. doi: 10.1155/2021/7266263. PMID: 34630560; PMCID: PMC8494575.
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## **11. Long-duration response to levodopa, motor learning and neuroplasticity in early Parkinson's disease.**

### **Authors**

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### **Background**

The long duration response (LDR) to levodopa and motor learning could be involved in neuroplastic changes of cortical excitability in Parkinson's disease (PD).<sup>1,2</sup> P300, motor evoked potentials (MEPs) and Bereitschaftspotential (BP) are neurophysiological surrogate markers of neuroplasticity. We aimed to define in PD the effects of LDR and motor learning on neurophysiological parameters involved in neuroplasticity.

### **Methods**

Drug-naïve PD patients underwent a 15-day treatment with levodopa/carbidopa 250/25 mg daily. Achievement of LDR was assessed on the 15th day of treatment (T15).<sup>3</sup> Patients were grouped according to the achievement of a sustained LDR (LDR+) or not (LDR-) and to the assignment of a learning motor exercise (LME) or not (NME). Patients underwent clinical and neurophysiological (P300, MEPs and BP) assessments at baseline (T0) and on T15.

### **Results**

Forty-one PD patients and 24 age- and sex-matched normal controls (NC) were enrolled. Neurophysiological parameters differed between untreated PD and NC. Four groups of patients were obtained at the end of treatments: trained patients with a sustained LDR (LDR+LME group), untrained patients with a sustained LDR (LDR+NME group), trained patients without LDR (LDR-LME group) and untrained patients without LDR (LDR-NME group). At baseline, no differences in clinical and neurophysiological parameters were evident among the groups. After the treatments, significant improvements in neurophysiological parameters were observed in the LDR+LME group (Figures.1-2-3). No modifications were found in the groups without LDR.

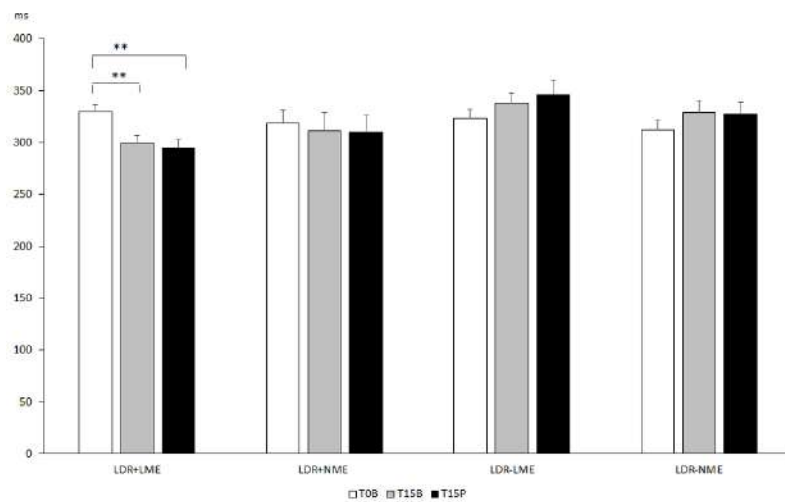
### **Conclusions**

The achievement of a sustained LDR may act synergistically with motor learning to induce adaptive neuroplastic changes in basal ganglia and cortical networks. Our findings support the LDR as the main outcome that should be sought to optimize pharmacological and rehabilitation treatments in early PD.

### **Reference**

1. Zappia M, Colao R, Montesanti R, et al. Long-duration response to levodopa influences the pharmacodynamics of short-duration response in Parkinson's disease. *Ann Neurol*. 1997;42:245-248.
2. Beeler JA, Cao ZF, Kheirbek MA, et al. Dopamine-dependent motor learning: insight into levodopa's long-duration response. *Ann Neurol*. 2010;67:639-647.
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Figure 1. P300 recorded before and after a 15-day treatment period with levodopa. Patients were grouped according to the achievement of a sustained long-duration response (LDR+) or not (LDR-) and to the assigned training, that is, learning motor exercise (LME) or no motor exercise (NME).



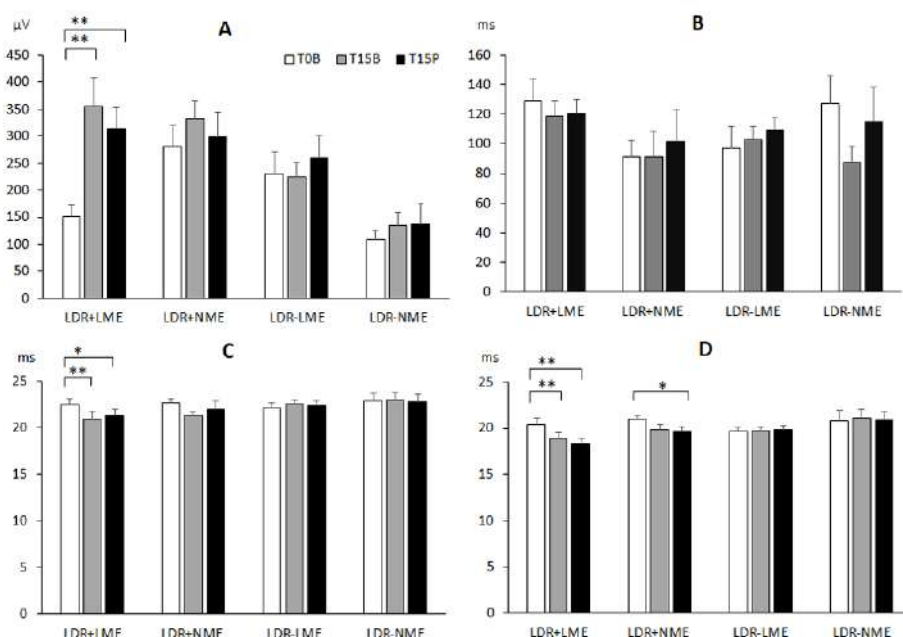
Data are means + standard errors. P300 latency in ms.

T0<sub>B</sub>=base value at T0, that is, the base value in the unmedicated condition (white bars); T15<sub>B</sub>=base value on the 15<sup>th</sup> day of treatment before intake of the morning dose of levodopa (grey bars); T15<sub>P</sub>=peak value after two-hours from intake of levodopa on the 15<sup>th</sup> day of treatment (black bars).

Groups: LDR+LME=long-duration response present and learning motor exercise; LDR+NME=long-duration response present and no motor exercise; LDR-LME=long-duration response absent and learning motor exercise; LDR-NME=long-duration response absent and no motor exercise.

\*\*p<0.01.

Figure 2. Motor evoked potentials by transcranial magnetic stimulation before and after a 15-day treatment period with levodopa. Patients were grouped according to the achievement of a sustained long-duration response (LDR+) or not (LDR-) and to the assigned training, that is, learning motor exercise (LME) or no motor exercise (NME).



Data are means + standard errors. Motor evoked potential (MEP) parameters were recorded on the more affected side.

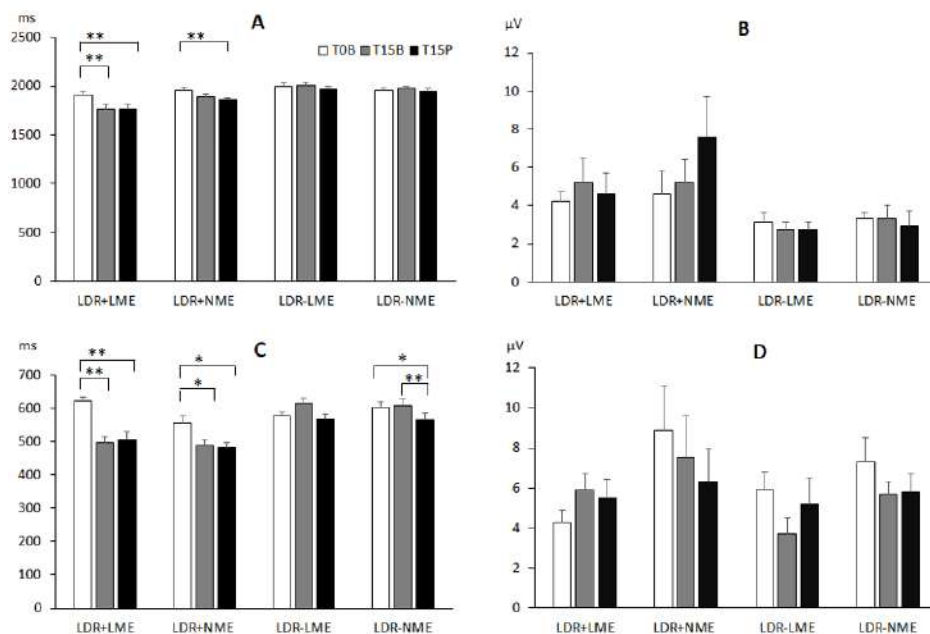
A. MEP amplitudes ( $\mu\text{V}$ ). B. Cortical silent period (CSP) duration. C. MEP latencies at the resting motor threshold. D. MEP latencies at the active motor threshold.

$T0_B$ =base value at  $T0$ , that is, the base value in the unmedicated condition (white bars);  $T15_B$ =base value on the 15<sup>th</sup> day of treatment before intake of the morning dose of levodopa (grey bars);  $T15_p$ =peak value after two-hours from intake of levodopa on the 15<sup>th</sup> day of treatment (black bars).

Groups: LDR+LME=long-duration response present and learning motor exercise; LDR+NME=long-duration response present and no motor exercise; LDR-LME=long-duration response absent and learning motor exercise; LDR-NME=long-duration response absent and no motor exercise.

\* $p<0.05$ ; \*\* $p<0.01$ .

Figure 3. Bereitschaftspotential parameters before and after a 15-day treatment period with levodopa. Patients were grouped according to the achievement of a sustained long-duration response (LDR+) or not (LDR-) and to the assigned training, that is, learning motor exercise (LME) or no motor exercise (NME).



Data are means + standard errors. Bereitschaftspotential (BP) parameters were recorded contralaterally to the more affected side.

A. Early BP latencies. B. Early BP amplitudes. C. Late BP latencies. D. Late BP amplitudes.

$T0_B$ =base value at  $T0$ , that is, the base value in the unmedicated condition (white bars);  $T15_B$ =base value on the 15<sup>th</sup> day of treatment before intake of the morning dose of levodopa (grey bars);  $T15_p$ =peak value after two-hours from intake of levodopa on the 15<sup>th</sup> day of treatment (black bars).

Groups: LDR+LME=long-duration response present and learning motor exercise; LDR+NME=long-duration response present and no motor exercise; LDR-LME=long-duration response absent and learning motor exercise; LDR-NME=long-duration response absent and no motor exercise.

\* $p<0.05$ ; \*\* $p<0.01$ .

## 12. Exploring the Link Between Fatigue and Functional Connectivity in Dopamine and Noradrenaline Circuits in Parkinson's Disease

### Authors

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**Background:** Fatigue is a common and debilitating symptom in Parkinson's disease (PD), negatively impacting patients' quality of life. Despite its prevalence, the underlying mechanisms and effective treatments remain elusive. Previous studies have implicated abnormalities in the Supplementary Motor Area and various neurotransmitter systems in PD-related fatigue.

**Aim:** This study aimed to explore the relationship between fatigue and functional connectivity within dopamine and noradrenaline networks in PD patients.

**Methods:** We recruited 29 PD patients in Hoehn and Yahr stages I-III, excluding those with significant cognitive impairment or severe neuropsychiatric symptoms. Fatigue severity was assessed using the Fatigue Severity Scale (FSS). Resting-state MRI data were analyzed to investigate functional connectivity within dopamine transporter (DAT) and noradrenaline transporter (NET)-defined networks, utilizing the "Receptor-Enriched Analysis of Functional Connectivity by Targets" framework.

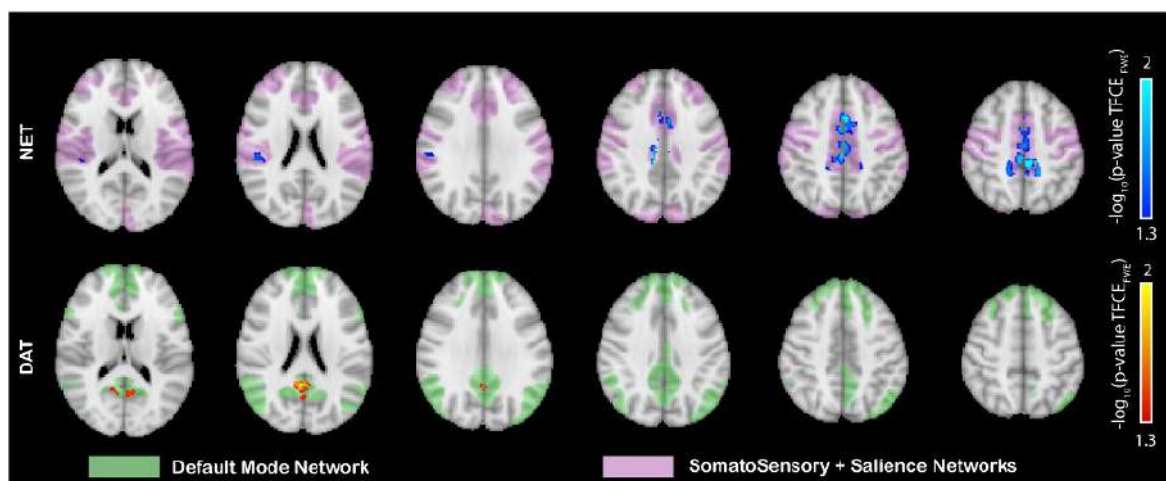
**Results:** We observed a negative linear correlation between fatigue severity and noradrenaline-enriched functional connectivity in regions associated with sensorimotor and salience networks. Conversely, a positive linear trend was noted between fatigue severity and dopamine-enriched functional connectivity within regions of the default mode network. Additionally, FSS scores showed an inverse correlation with NET-enriched functional connectivity (Pearson's  $r=-0.48$ ), while a positive correlation was observed with DAT-enriched functional connectivity (Pearson's  $r=0.33$ ).

**Conclusions:** These preliminary findings suggest that fatigue in PD patients may stem from disruptions in sensorimotor circuits and aberrant monoaminergic connectivity involving both noradrenaline and dopamine systems. Further research is warranted to elucidate the precise mechanisms and potential therapeutic interventions for fatigue in PD.

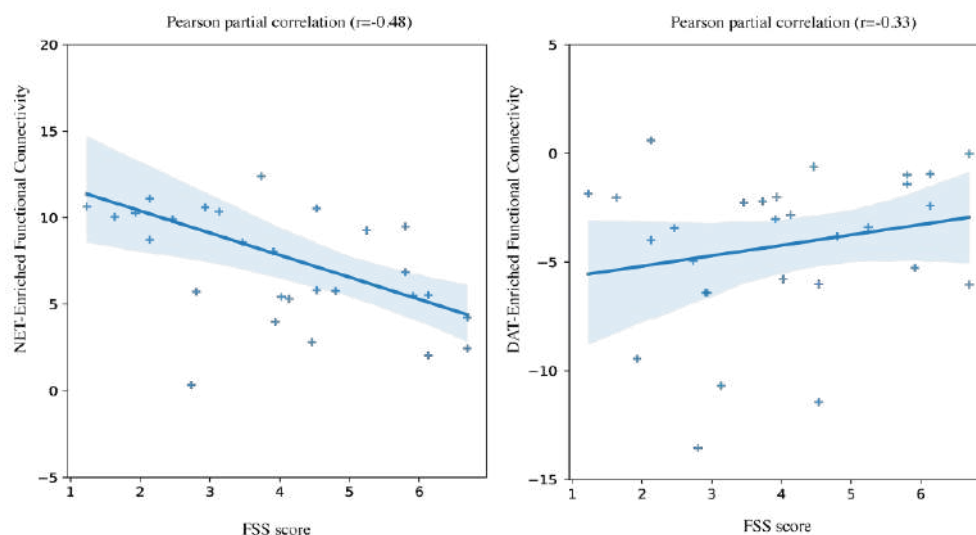
**Keywords:** Parkinson's disease, fatigue, functional connectivity, dopamine, noradrenaline, MRI.

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**Fig. 1:** Clusters of statistically significant NET-enriched FC (top row), overlaid to Schaefer's functional salience and sensorimotor networks in green. In the bottom row, clusters of statistically significant DAT-enriched FC are overlaid to Schaefer's functional default mode network in green. The color scales represent  $-\log(p\text{-value})$ , after correction for multiple comparisons. The statistical maps are overlaid onto the MNI atlas.



### **13. The impact of covid-19 pandemic and vaccination on functional neurological disorders: Insights from a survey study**

#### **Authors**

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#### **Objective**

This study investigates the potential influence of COVID-19 and vaccination on Functional Motor Disorders (FMDs) in an Italian patient cohort. Specifically, we aim to determine whether COVID-19 exacerbated existing FMD symptoms or triggered new ones, and whether these manifestations correlated with beliefs or expectations regarding vaccines and the disease.

Background: FMDs present significant challenges due to their association with heightened susceptibility to stressors and environmental events. Negative expectations may play a pivotal role in FMD pathophysiology. While initial reports suggested no exacerbation of FMD symptoms during COVID-19 lockdowns, subsequent findings documented an increase in de novo FMD cases post-infection and vaccination. Therefore, understanding the COVID-19-FMD relationship is crucial for effective management.

#### **Methods**

A survey was conducted online between January and March 2024, inviting 257 FMD-diagnosed patients from our Specialized Clinic to participate. The survey covered sociodemographic factors, clinical history, COVID-19-related information (including infection and vaccination status), and patients' beliefs and expectations. Data collection is ongoing.

#### **Results**

Preliminary data from 103 surveyed FMD patients (40% completion rate) revealed insightful patterns. Among the 98 participants analyzed (mean age  $43 \pm 12.8$ , 86% female), a substantial proportion contracted COVID-19 during the pandemic (72.4%), with few requiring hospitalization (5%), while most opted for vaccination (88.8%). Following COVID-19, approximately one-third experienced symptom changes, with a similar proportion reporting new symptoms post-vaccination. Notably, 25.5% attributed symptom onset/modification to COVID-19, and 30.6% to vaccination. Varied beliefs and expectations regarding COVID-19 and vaccination were observed, with concerns about neurological complications (22.4%) and worsening FMD symptoms (19.4%) prevalent.

#### **Conclusion**

While the pandemic and vaccination were significant stressors, our data suggest minimal impact on FMD symptoms in most patients. However, negative expectations regarding vaccine side effects and COVID-19 are prevalent. Addressing patient concerns and providing comprehensive medical education on both COVID-19/vaccine and FMD are crucial. The significant impact of post-COVID symptoms on patients' daily lives underscores the need for holistic patient care. Further research is warranted to elucidate correlations and inform clinical practice.

[Keywords: COVID-19, vaccination, Functional Motor Disorders, FMD, neurology, survey study]

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## 14. Pharmacological modulation of Nrf2 pathway in an $\alpha$ -synuclein-based model of Parkinson's disease

### Authors

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### Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder. Multiple mechanisms contribute to PD pathogenesis with a clear involvement of inflammatory events, oxidative stress and mitochondria dysfunctions in disease progression. Misfolded proteins and inclusions containing alpha-synuclein ( $\alpha$ -syn) also contribute to the pathology.

Nrf2 transcription factor, is a master regulator of cell protection, involved in defensive response which embraces key pathogenetic events in PD. Preclinical studies support the centrality of Nrf2 in the pathogenic cascade of PD, specifically highlighting its protective role. However, only few studies are currently available addressing the cellular mechanisms by which Nrf2 regulates neuronal homeostasis and neurodegeneration caused by  $\alpha$ -syn. Of relevance, the role of Nrf2 in modulating  $\alpha$ -syn-driven neuroinflammation and synaptic toxicity is almost unknown. Importantly, since several small molecules modulating Nrf2 activity are available and are already validated *in vivo* at different phases of clinical development, Nrf2 pathway could represent a target for novel disease-modifying treatments.

Here we used state-of-the-art  $\alpha$ -syn mice model allowing for a careful evaluation of the toxic effects induced by  $\alpha$ -syn preformed fibrils ( $\alpha$ -syn-PFFs) from early to late stages of disease. A combination of confocal imaging, biochemistry, molecular biology, and behavioral assays as well as electrophysiological recordings have been used for the analysis of the progression of the disease and to evaluate the efficacy of dimethyl fumarate (DMF), a potent Nrf2 activator, to counteract  $\alpha$ -syn-mediated toxicity.

### Funding

This work has been supported by Fondazione Regionale per la Ricerca Biomedica (FRRB, Regione Lombardia), Linking Park, ID 3433068.

## **15. Association between Parkinson's Disease subtypes and kinetic parameters of alpha-synuclein seed amplification assay in CSF.**

### **Authors**

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### **Objective**

To investigate differences in kinetics parameters of the  $\alpha$ Syn seeding amplification assays in CSF (CSF- $\alpha$ Syn-SAA) in Parkinson's Disease (PD) subtypes based on the presence of RBD and Dysautonomia Symptoms.

### **Background**

RBD and Dysautonomia symptoms mark PD subtypes with peculiar disease course and possibly different pathogenesis<sup>1,2,3</sup>. However, a biomarker able to reinforce the biological relevance of these subtypes lacks. CSF- $\alpha$ Syn-SAA is an accurate biomarker for PD. Kinetic parameters of CSF- $\alpha$ Syn-SAA may reflect variability of alpha-synuclein strains which in turn could explain phenotype heterogeneity of synucleinopathies<sup>4,5</sup>.

### **Methods**

PPMI dataset was used (Datacut 09/2023). PD subjects with RBD (RBDSQ-q6 $\geq$ 1) and/or Dysautonomia (SCOPA-AUT score  $\geq$ 8) were compared to those without (n=308). CSF- $\alpha$ Syn-SAA data come from the assay by Concha<sup>6,7</sup>. Available parameters: Fmax (maximum fluorescence), T50 (time to reach 50% of the Fmax), TTT (time to threshold), Slope and AUC (area under the curve).

### **Results**

Both RBD+ and Dys+ PD patients showed shorter T50 (n=137 RBD+ vs n=171 RBD-, p=0.050; n=167 Dys+ vs n=136 Dys-, p=0.023). Dys+ group also showed shorter TTT (p=0.038) and greater AUC (p=0.043). In subject with PD and both RBD+ and Dys+, T50 was significantly shorter compared to subjects negative for both traits (p = 0.038). SCOPA-AUT and RBDSQ total scores correlated with T50 (r=-0.145, r=-0.148), TTT (r=-0.137, r=-0.130), and AUC (r=0.129, r=0.149).

### **Conclusions**

Kinetics parameters derived from CSF- $\alpha$ Syn-SAA differed between PD subtypes based on RBD and Dysautonomia symptoms. In particular, T50 was shorter in the RBD+ and Dys+ group. This supports the clinical PD subtypes that were previously identified<sup>1</sup>.

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## **16. Theta frequency band analysis to study the relationship between build-up and downscaling process in Parkinson's disease**

### **Authors**

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### **Background**

During slow wave sleep (SWS), slow wave activity (SWA) plays a significant role in downscaling synaptic strength, crucial for the brain's ability to adapt and change. SWA, typically occurring in the early part of the night, serves as a primary electrophysiological marker for the homeostatic process. Conversely, theta activity during wakefulness indicates synaptic potentiation, with SWA decreasing during sleep and theta increasing during wakefulness.

### **Objective**

LID is the major long-term therapy-related complication in Parkinson's disease (PD), characterized by involuntary hyperkinetic movements. A connection between levodopa-induced dyskinesia (LID) in Parkinson's disease (PD) and impairment in sleep-mediated synaptic downscaling has been noted. However, it remains unclear whether this dysfunction is due to impaired SWA-mediated downscaling or a lower build-up process. Therefore, this study focuses on theta activity to investigate the build-up process during wakefulness.

### **Methods**

Three different PD groups—de novo (n = 11), advanced (n = 10), and dyskinetic (n = 10)—were recruited and compared to healthy volunteers (n = 7). All participants underwent physical and neurological examinations and were provided with inertial sensors to monitor their sleep-wake cycle for a week. Two short EEG recordings were conducted, the first in the morning and the second 9 hours later. During the EEG recording, participants also performed a go/no-go task. Preliminary Results: We observed higher theta levels both in the morning and in the evening in patients with LID compared to healthy control patients and to other PD patients without LID. This findings support our initial hypothesis that there are specific differences in this group of PD patients related to cortical synaptic plasticity.

### **Conclusion**

This study sheds light on the relationship between sleep and the onset of LID in PD. Confirmation of these results could lead to innovative therapies aimed at enhancing SWA in PD, potentially offering new treatment avenues for LID.

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## **17. Noninvasive magnetic stimulation reduces side effects of chronic Levodopa in experimental parkinsonism**

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### **Abstract**

Dopaminergic medications are the most used drugs to treat the symptoms of Parkinson's disease (PD). Despite beneficial effects, however, the treatment is associated with motor fluctuations, wearing-off, and the development of dyskinesia. In experimental models, the side effects of dopaminergic medications are associated with impairment in corticostriatal bidirectional synaptic plasticity, alterations of NMDA receptor (NMDAR) subunit ratio, and post-synaptic density composition. In the last decades, repetitive transcranial magnetic stimulation (rTMS) have been suggested as a possible treatment for PD and other movement disorders without providing a clear cellular mechanism.

Here, we explored the therapeutic effects of two-week rTMS in vivo combined with a Levodopa treatment in a symptomatic PD rodent model. Co-treatment prevented NMDAR-dependent plastic abnormalities in the dorsolateral striatum and reduced the incidence and intensity of motor side effects. Immunohistochemical and RNA-scope analyses indicate that renormalization of glial reactivity is observed after rTMS treatment both in PD and dyskinetic condition. ELISA Luminex multiple assay shows that pro-inflammatory cytokines are reduced and anti-inflammatory IL-10 is increased in CerebroSpinal Fluid of animals co-treated with rTMS showing no dyskinetic phenotype.

These findings suggest that inhibitory rTMS protects corticostriatal synapses from the side effects of Levodopa therapy through recovery of glial functions in a PD model, confirming the anti-inflammatory potential of noninvasive magnetic stimulation when appropriate patterns are chosen.

## 18. Role of dopamine denervation, alpha-synuclein and maladaptive plasticity in the development of Levodopa-induced dyskinesia

### Authors

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### Abstract

The use of Levodopa effectively restores striatal dopamine (DA) levels, alleviating Parkinson's disease (PD) symptoms. However, during PD progression, L-dopa-induced dyskinesias (LIDs) complicate symptom management for nearly all patients. Understanding LIDs' mechanisms and developing strategies to manage them are critical for PD care. While previous studies have uncovered a complex molecular and cellular interplay, the primary LIDs' drivers remain elusive. This study employed a translational approach, using four animal models and a large PD patient cohort.

We used 6-hydroxy-dopamine fully- or partially-denervated rats, showing respectively severe or mild DA neuron loss. Two additional models were obtained by intrastriatal-injection of  $\alpha$ -synuclein-preformed-fibrils alone or combined with nigral-injection of adeno-associated-viral vectors overexpressing  $\alpha$ -synuclein. To explore possible translational implications, we measured serum and CSF levels of total (t)- $\alpha$ -synuclein in PD patients, DA denervation with DaTSCAN SPECT and cortical plasticity by transcranial magnetic stimulation (TMS).

Dyskinetic fully-denervated rats lacked striatal synaptic depotentiation, whereas partially denervated rats exhibited no dyskinetic behavior and a reversible long-term potentiation. In  $\alpha$ -synuclein-based models, mild denervation occurred, and even with L-Dopa treatment, dyskinetic behavior did not manifest.

PD patients, with and without LID, did not show differences in t- $\alpha$ -syn levels in serum and CSF. Putaminal DA denervation in PD patients correlated with LID development. Dyskinetic patients exhibited cortical plasticity loss, detected via TMS. Our study highlights striatal dopamine denervation as the main LIDs' driver, while misfolding- $\alpha$ -synuclein contributes indirectly, promoting neurodegeneration. The absence of homeostatic plasticity in striatal and cortical regions represents a consistent LIDs characteristic, observed in experimental models and PD patients.

## **19. Movement disorders following mechanical thrombectomy resulting in ischemic lesions of the basal ganglia: an emerging clinical entity?**

### **Authors**

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### **Background and purpose**

Movement disorders following acute ischemic lesions of the basal ganglia (BG) is a well-known entity and maladaptive plasticity is a possible pathophysiological mechanism. Ischemic strokes due to proximal middle cerebral artery (MCA) occlusion, treated with thrombectomy, can represent a model of selective damage of the BG. Data regarding the incidence of movement disorders in this population are missing. This study aimed to assess the prevalence and features of movement disorders after selective BG ischemic lesions.

### **Methods**

We enrolled consecutive patients with acute ischemic stroke (AIS) due to proximal MCA occlusion, treated with mechanical thrombectomy (MT) and reporting a selective lesion of the BG, at Fondazione Policlinico Universitario Agostino Gemelli IRCCS. Patients were clinically evaluated by a movement disorders specialist for PMDs onset at baseline, and after 6 and 12 months, using Movement Disorders Society (MDS)-recommended rating scales

### **Results**

Sixty-four patients were enrolled, 25 and 13 patients already completed the 6-month and 12-month follow-up respectively. None of them presented with a movement disorder in the subacute phase of the stroke, while 7/25 patients at 6 months and 7/13 patients at 12 months presented with an identifiable movement disorder. The clinical spectrum of PMDs encompassed dystonia, parkinsonism and chorea, either alone or combined. Symptoms were mostly contralateral to the lesion, although a subset of patients presented with bilateral and prominent axial involvement.

### **Conclusion**

Post-stroke movement disorders are not uncommon in long-term follow-up after successfully reperfused AISs. Follow-up in a multidisciplinary team is strongly advisable in patients reporting selective lesions of the BG after AIS, even if asymptomatic at discharge.

## **20. A novel *NAA15* variant in a child with isolated gait dystonia: new insights and phenotypic expansion of an early-onset movement disorder**

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### **Abstract**

Dystonia is among the most prevalent and disabling movement disorders in childhood. The diagnostic evaluation of childhood dystonia is often challenging, given the clinical and etiological heterogeneity of this condition.

We present a 5-year-old female with a recent history of persistent gait abnormality. She was born at full term, and her development was normal. At the age of four, she began dragging her right leg, resulting in frequent falls. Gait was notable for dystonic right leg internal rotation and knee flexion that worsened the longer she walked or ran.

Her initial symptoms started about 6 weeks after Covid infection. An extensive rheumatological workup was negative. MRI Brain and Spine and LP were also unrevealing. For suspicion of a paroxysmal dyskinesia, she was treated with trileptal, which didn't help. Carbidopa/levodopa, and clonazepam were not effective. The gait disturbance worsened over time, especially when concomitant with fever and fatigue, but persistently affecting her right leg.

Whole-exome sequencing analysis identified a heterozygous pathogenic de novo *NAA15* variant (c.283\_285del; p.K95del). *NAA15* gene encodes a component of the NatA N-acetyltransferase complex, which is involved in posttranslational protein modifications. Different variants of this gene have been associated with phenotypes of pediatric neurodevelopmental conditions and also with parkinsonism/dystonia-parkinsonism later in life, but the variant in our patient has not previously been reported.

We report the second pediatric patient with a novel *NAA15* variant with isolated lower limb focal dystonia and normal development. This case further expands the phenotype spectrum of a new group of movement disorders that should be considered in the diagnostic workup of childhood onset focal dystonia.

## 21. Intermediate expansion of *MARCHF6* causes FAME3 without epilepsy

### Authors

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### Background

Familial adult myoclonic epilepsy (FAME) is an autosomal dominant syndrome characterized by adult-onset cortical myoclonus with or without epilepsy, due to intronic repeat expansions reported in 6 distinct genes (FAME1- 4, 6-7).<sup>1</sup> Expansion of noncoding TTTCA/TTTCA repeats in intron1 of *MARCHF6* was identified as the causative mutation of FAME3.<sup>2-3</sup>

### Methods

Proband was seen at Fresco Institute at NYU Langone Health. History, video recording and blood sample were collected. Sample of proband's sister were collected at the University-Hospital Center of Toulouse. Samples were tested for FAME1 (proband) and 3 (both) using long-range PCR amplification, RP-PCR and long-read sequencing with Oxford Nanopore (MinION flow cell R9.4.1) at the University Hospital Essen to describe size, composition and configuration of the expansions.

### Results

Proband was a 63-year-old Caucasian man with 8-year history of cortical myoclonus of the upper limbs, action-induced, anxiety and obsessive-compulsive features (OCD). His father and sister, originally from France, presented similar symptoms, but more severe. There was no history of seizures. Genomic analysis showed an intermediate pathogenic, intronic expansion TTTTA/TTTCA in *MARCHF6*, confirmed with RP-PCR and Nanopore sequencing. Intermediate expansion was confirmed also in the sister but not found in samples from negative control subjects.

### Conclusions

FAME represents a novel non-coding repeat expansion disease model. Here we describe the first family with an intermediate expansion in the *MARCHF6* gene, associated with a milder phenotype characterized by cortical myoclonus of varying severity, anxiety, OCD but no seizures. Our results contribute to the understanding of the phenotypic spectrum of FAME disorders without epilepsy.

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## **22. Personalized rTMS of the pre-SMA to alleviate levodopa-induced dyskinesia in Parkinson's disease: a randomized controlled cross-over trial**

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### **Background**

Most patients with Parkinson's disease (PD) develop levodopa-induced dyskinesia (LID) during long-term levodopa treatment [1]. Our own research has implicated the pre-supplementary motor area (pre-SMA) in the pathophysiology of LID [2]. We also showed that a single session of “inhibitory” 1-Hz repetitive transcranial magnetic stimulation (rTMS) of preSMA reduces the magnitude and delays the onset of LID provoked by subsequent levodopa intake [3]. This acute beneficial effect scaled positively with the rTMS-induced electrical field in the pre-SMA [3].

### **Aim**

This randomized clinical trial (RCT) will employ personalized dosing of rTMS and a novel quadruple pulse version of 1Hz rTMS, contrasting the acute anti-dyskinetic effects of 1Hz quadri-pulse stimulation (QPS) at inter-pulse intervals of 7.7 msec (130 Hz “gamma” bursts) and 50 msec (“beta” bursts).

### **Methods**

Patients will be randomized to 1Hz beta or gamma burst QPS of pre-SMA. On separate days, patients will receive a real or sham QPS session in counter-balanced order before they receive a single dose of levodopa. The intensity of QPS will be individually defined to induce the same mean electrical field in the pre-SMA. Primary outcomes include time between levodopa intake and LID onset, and LID severity assessed using the MDS-Unified Dyskinesia Rating Scale (UDysRS) based on blinded video assessments.

### **Discussion**

The study will shed new light on the acute anti-dyskinetic effects of 1 Hz QPS targeting the pre-SMA. Results will help to optimize therapeutic outcomes and inform neurostimulation strategies for more effective LID treatment.

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## Conflict of Interest

Hartwig R. Siebner has received honoraria as speaker and consultant from Lundbeck AS, Denmark, and as editor (Neuroimage Clinical) from Elsevier Publishers, Amsterdam, The Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany, Oxford University Press, Oxford, UK, and from Gyldendal Publishers, Copenhagen, Denmark.

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## **23. DAT-imaging and clinical phenotypes of Parkinson's disease: findings and follow up at 5 years.**

### **Authors**

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### **Introduction**

An accurate diagnostic and therapeutic approach to Parkinson's disease (PD) requires understanding of the risk to develop nonmotor symptoms (i.e. cognitive and psychiatric disorders).

### **Objective**

To evaluate: 1. the relationship of motor and nonmotor symptoms with specific patterns of striatal dopaminergic denervation in a cohort of symptomatic PD. 2. The prognostic value of specific dopaminergic denervation pattern on cognitive impairment.

### **Methods**

Twenty-eight PD patients with dopaminergic denervation at DAT-SPECT were studied. Patients were divided into two groups based on the evidence of dopaminergic denervation in putamina alone (PD-p) or in putamina and caudates (PD-pc). The two groups were compared as per demographics, motor phenotypes, disease severity according to MDS-UPDRS III, psychiatric symptoms as per NPI and cognitive symptoms as per MoCA score at baseline. Cognitive assessment was repeated at 5 years follow up. Premotor symptoms were also assessed.

### **Results**

twelve patients were classified as PD-p (M/F=5/7; mean age=64,31±8,5years; mean disease duration 3±2.68 mean UPDRS III 20.44±5.96); 16 patients were classified as PD-pc (M/F=10/6; mean±Standard deviation (SD) age 62.33± 8.65 years; disease duration 1.76±1.09 years; UPDRS III 31.29±8.16). The two groups did not differ in terms of age, gender and disease duration. At baseline PD-pc group showed worse UPDRS scores (p<0.0001). Rigid phenotype was found in 66,7% of PD-pc vs. 12,5% in PD-p (p<0.0001); tremulous phenotype was found in 4,8% of PD-pc vs. 56,3% of PD-p (p<0.0001); mixed phenotype was equally found in the two groups (28.6% of PD-pc vs. 31.3% of PD-p, p>0.05. Premotor (present for at least 3 years before the motor onset) mood disorders (depression and anxiety) were found in 47.5% of PD-pc, and 12.5% in PD-p (P=0.001). 71.4% of PD-pc patients had psychiatric symptoms at baseline (generalized anxiety, panic attacks, phobia, obsessive-compulsive disorder, moderate to severe depression). In the PD-p group 31.3% had psychiatric symptoms at baseline (mild depression and/or anxiety). MoCA equivalent score was <17.32 (cut-off) in 32% of PD-pc group and in none of the PD-p patients at baseline. At 5 years follow up MoCA score was below cut off in 83% of PD-pc group and 9% of PD-p.

### **Conclusion**

The evidence of early dopaminergic denervation in the caudates correlates with a more complex phenotype of PD.

## **24. Mind and Movement in Parkinson's disease: what we learned from yoga practice.**

### **Authors**

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### **Introduction**

In one of the best-known Indian scripture (The Bhagavad Gita) yoga practice is referred as "skill in action".

### **Objective**

To report the experience of specifically designed Sivananda hatha yoga in Parkinson's Disease (PD) patients from Abruzzo Region, central Italy.

### **Methods**

24 patients followed by the movement disorder center of Vasto Hospital, Abruzzo, were enrolled in a three months yoga 80 minutes class once a week, structured as: meditation with breathing training (10 minutes), asana practice(60 minutes), deep relaxation through guided meditation (10 minutes). At enrollement (T0) and end of the program (T1) patients were evaluated with Unified Parkinson's Disease Rating Scale (UPDRS) I, II,III, IV, Freezing of Gate (FOG), PDQ39 and subitems. Dopaminergic treatments here reported as levodopa equivalent dose (LED) remained stable, but patients were allowed to take 1 extra L-dopa dose (ELD) per day .Thirteen patients matched for age, disease duration and Hoeh and Yahr stage (HY) not involved in any yoga practice were followed as control group.

### **Results**

The yoga group was composed by 10 males and 14 females, mean  $\pm$ SD age 65,5 $\pm$ 6,78 years (range 52-78 years); mean disease duration 6,8 $\pm$ 3,67 (range2-18years); HY I-IV.

At T0 the group showed: mean UPDRS I 12 $\pm$ 4,59; mean UPDRS II 12,1 $\pm$ 4,79; mean UPDRS III 27,5 $\pm$ 7,66; mean UPDRS IV 1,8 $\pm$ 3,7; mean FOG score 9,4 $\pm$ 6,2; mean PDQ39 total score 57 $\pm$ 17,6; PDQ-mobility score 16,5 $\pm$ 7.4; PDQ-ADL score 7,8 $\pm$ 3,0; PDQ-emotional score 15,9 $\pm$ 3,5; PDQ stigma score 10,9 $\pm$ 1,02; PDQ-cognition score 0,9 $\pm$ 0,99; PDQ-communication score 2 $\pm$ 2,7; PDQ-body score 3,8 $\pm$ 1,4.

At T1 the following scores improved: UPDRS I (p=0.025), FOG (p=0.013), PDQ39 (p=0.023), PDQ-emotional (p<0.001) and PDQ-stigma (p=0.005).

LED remained unchanged between T0 and T1; in the16 patients used to take ELD these decreased at T1 (mean ELD at T0=7,33 $\pm$ 2,8; mean ELD at T1=1,33 $\pm$ 0,98; p=0.043).

All patients reported decreased OFF time at T1 (p=0.053).

No difference were found in the control group, but 6 patients needed pharmacological adjustment due to worsening of rigidity and OFF time.

### **Conclusion**

Yoga practice trains the mind to be alert, aware and focused on physical sensations and movements and this may be a key strategy for patients to cope with the disease.

## **25A. Art therapy as an add on activity to intensive rehabilitation treatment in Parkinson's disease: a booster to patient's well being?**

### **Authors**

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### **Introduction**

Art therapy (AT) lowers depressive symptoms and enhances the benefit of exercise on QoL in elderly [1]. Research on AT in people with Parkinson's disease (PWPd) is still poor and mostly focused on its effects cognition [2].

### **Objective**

We explored the effect of group AT sessions on emotional wellbeing in PWPd.

### **Methods**

We consecutively enrolled 39 non-demented PWPd (AT\_group: age:  $66.7 \pm 7.7$ ; disease duration:  $10.6 \pm 5.6$ ; UPDRS III:  $35 \pm 13.7$ ; M=19) attending the multidisciplinary aerobic motor-cognitive rehabilitation 4 weeks training and participating in AT weekly sessions as add-on activity. AT was performed in small groups but tailored on each patient.

We enrolled 39 PWPd (CNTR) matched by demographic and clinical variables to the AT\_group who attended one session of occupational therapy instead of AT.

Profile of Mood Scale (POMS) was administered to all participants at admission (T0) and discharge (T1) and the changes in the subscales (depression/dejection, tension/anxiety, anger/hostility, fatigue/indolence, confusion, and vigour) were compared within and between groups. The relation between POMS, clinical features, neuropsychological and motor assessments were explored.

### **Results**

POMS scores of the two groups were comparable at baseline; in AT\_group, POMS subscales scores significantly improved between T0 and T1 and delta of change was significantly higher compared to CNTR; POMS subscales correlated with UPDRSIII and 6MWT but the improvement in the motor scales was independent from the change in POMS subscales.

### **Conclusion**

AT activity associated to intensive rehabilitative treatment significantly enhances patient's emotional wellbeing. Noteworthy, this improvement is not related to the improvement in motor symptoms.

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## 25B. Can Art Therapy Improve Emotion Recognition in Parkinson's Disease? A Pilot Study

### Authors

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### Introduction

Facial emotion recognition (FER), especially for negative emotion, is compromised in people with Parkinson's disease (PwPD). Research on AT in PwPD is poor and mostly focused on its effects cognition [2].

### Objective

We explored the effect of group thematic AT sessions on emotion recognition.

Methods: we consecutively enrolled 11 non-demented PwPD (AT\_group: age: 65.4±6.8; disease duration: 14.2±6.9; UPDRS III: 26.3±3.9; M=8) attending the motor-cognitive rehabilitation 4 weeks training and participating in AT weekly sessions as add-on activity. AT was tailored on each patient and focused on the theme of fear.

We enrolled 10 PwPD (CNTR) matched by demographic and clinical variables to the AT\_group who attended one session of occupational therapy instead of AT.

All patients underwent a neuropsychological screening and motor assessments at baseline.

Ekman Face Recognition (EFR), Profile of Mood Scale (POMS), Story Based Empathy test (SET) tests were administered to all participants at admission (T0) and discharge (T1) and the changes in the scores were compared within and between groups.

### Results

At T0, the ability to recognise fear and disgust at EFR was compromised in both groups; at T1, only the AT\_group had a significant ( $p<0.05$ ) improvement in fear, sadness and disgust recognition and in EFR total score. Scores in the other test remained stable.

Conclusion: in our sample, AT activity focused on fear theme, significantly improved the ability to recognize negative emotions. Studies on larger samples are needed to confirm our findings and further explore the impact of these improvement on patient's quality of life.

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## **26. A Wearable Device (Q-Walk) for Rehabilitation of Gait Impairment and for Monitoring and Fostering Motor Activity in Parkinson's Disease**

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### **Introduction**

Gait disturbances in particular FOG occur frequently in mid-advanced Parkinson's disease (PD). In addition, people with PD seems to do not practice sufficiently physical activity during daily living at home. Many devices have been proposed for the rehabilitative treatment of gait impairment in particular for Freezing of Gait (FOG) showing that they are well validated and are promising application of objective measurements. The field of wearable sensor would benefit from more research efforts, increased collaboration among researches, aligned data-collection protocols and shared data sets. Furthermore, it could contribute to provide to clinician's important information on motor activity of PD patients during daily live.

### **Objective**

to test the feasibility, safety and effectiveness of the use of a wearable device (Q-Walk) on gait impairment especially on FOG and to test Q-Walk as a reliable device for monitoring motor performances during daily activities in a preliminary cohort of the first 30 PD patients.

### **Methods**

The pilot Q-Walk protocol was conducted in Villa Margherita and enrolled the first PD patients. PD patients were randomized in two groups: G1 (Q-Walk active) and G2 (Q-Walk inactive device). All subjects were submitted to a gait training at preferred walk for two hour per session. There were two testing moments: T0 at baseline and T1 after 4 weeks. All the PD subjects were submitted to clinical outcomes measures and to recording of 2D S/T parameters of gait from the device and 3D gait analysis.

### **Results**

The preliminary results showed that one active PD subject improved more than one inactive PD subject in the clinical outcomes measures (UPDRS III, 6mWT, ?).

The records from the device provided interesting information on motor activity at home confirming that PD subjects performed much less than reported in literature.

### **Conclusions**

The preliminary study showed that Q-Walk device seems to be a promising device for improving gait disturbances and also for monitoring and fostering motor activities in daily living in people with PD.

## **27. Benefits of archery in PD patients: preliminary results**

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### **Background**

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

### **Methods**

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

### **Results**

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

### **Conclusions**

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

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## **28. Preserved neuroplasticity in patients affected by Parkinson's disease responders to external cueing strategies**

### **Authors**

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### **Abstract**

<sup>1</sup>Neural plasticity in the primary motor cortex (M1) has been shown to be impaired in Parkinson's disease (PD)

Among the contributors to the enhancement of plasticity it has been highlighted the cerebellum, which is able to prime M1 plasticity by processing external sensory information<sup>2</sup>. One of the most used compensatory strategy in PD rehabilitation is external rhythmic auditory cueing (RAC), which showed the ability to improve gait by integrating external sensory information<sup>3</sup>. Anyway, the characteristics of PD patients that can benefit from such compensation strategy are still not clear<sup>4</sup>. The main aim of this study is to explore whether PD patients which showed an improvement of gait in response to RAC (i.e., responders) exhibit intact neuroplastic mechanisms compared to non-responders. We recruited 8 responders and 8 non-responders, all affected by PD, that were tested for corticospinal excitability (CSE) via an I/O curve before and after an intermittent theta burst (iTBS) TMS protocol, used to enhance M1 plasticity mechanisms. Our results showed that responders to RAC exhibited an increased corticospinal excitability post iTBS in terms of increased I/O curve slope ( $p = 0.03$ ) and area under the curve ( $p = 0.04$ ) compared to non-responders, while no differences were found between the two groups at baseline. These preliminary results suggest that PD responders to RAC might have intact neuroplastic mechanisms, possibly related to an increased within-network connectivity between the executive control network and the cerebellar and auditory circuits in response to external stimuli<sup>5</sup>.

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## **29. Coupling Neurologic Music Therapy with Immersive Virtual Reality to Improve Executive Functions in Individuals with Parkinson's Disease: A Quasi-Randomized Clinical Trial.**

### **Authors**

Federica Impellizzeri<sup>1</sup>, Maria Grazia Maggio<sup>1\*</sup>, Paolo De Pasquale<sup>1</sup>, Mirjam Bonanno<sup>1</sup>, Lilla Bonanno<sup>1</sup>, Rosaria De Luca<sup>1</sup>, Giuseppe Paladina<sup>1</sup>, Angela Alibrandi<sup>2</sup>, Demetrio Milardi<sup>3</sup>, Michael Thaut<sup>4</sup>, Corene Hurt<sup>4</sup>, Angelo Quartarone<sup>1</sup>, and Rocco Salvatore Calabrò<sup>1</sup>

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### **Introduction**

Parkinson's disease (PD) is one of the most common neurodegenerative movement disorders, leading to motor and non-motor symptoms, including deficits in executive functions (EF). Neurologic Music Therapy (NMT) has gained recognition for its effectiveness in neurorehabilitation of PD patients, improving motor and cognitive domains<sup>(1,2)</sup>. Moreover, the potential of the virtual reality (VR) platform Computer-Assisted Rehabilitation Environment (CAREN) system in improving motor and behavioural performance in PD has been widely highlighted<sup>(3,4)</sup>. This pilot study combines NMT with the CAREN system in PD patients for the first time.

### **Methods**

In our single-blind quasi-randomized controlled trial, forty patients were assigned to experimental group (EG=20) or control group (CG=20). Both groups underwent two months of training with CAREN scenarios (three times a week for 24 sessions). The EG additionally received NMT applied to the selected scenarios. Participants were evaluated by a neuropsychologist at baseline and immediately after training.

### **Results**

Intra-group analysis showed significant improvements in the EG for MOCA ( $p=0.007$ ), FAB ( $p=0.008$ ), Stroop Time ( $p<0.001$ ), and Visual Search ( $p<0.001$ ). The CG showed a significant difference only in Stroop Error ( $p=0.02$ ).

### **Discussions**

Improvements in EG could be attributed to the integration of rhythmic/music stimulation and the VR component. This combination helps compensate for timing deficits associated with basal ganglia disorders, synchronizes neural activity, enhances motor and cognitive learning, improves communication between brain networks, and consequently boosts EF<sup>(5,6)</sup>.

## Conclusions

Our findings suggest that music structured within NMT techniques, coupled with advanced audio-visual feedback from VR, offers an innovative and potentially more effective approach for managing cognitive and executive deficits associated with PD.

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

#### **Authors**

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#### **Background**

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

#### **Objective**

To assess the effect of DW in patients with PD

#### **Methods**

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

#### **Results**

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

#### **Conclusion**

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

### 31. In-patient multimodal intensive neurorehabilitation and care and pharmacological Optimization in Patients with Moderately Advanced Parkinson's Disease

#### Authors

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#### Abstract

We have previously shown that patients with Parkinson's Disease (PD) benefit from a two-week in-patient multimodal intensive neurorehabilitation and care (i-MINC). Specifically, i-MINC includes up to 5 hours per day, 5 days a week, of PT/OT/SLP/RT/neuro-cognitive therapy. This treatment also encompasses pharmacological optimization with adjustments based upon the patients' observation during their hospital stay. Some reports suggest that treatments that are similar to i-MINC yielded better results when levodopa dosage is changed. Here we review the effects of pharmacological adjustments on outcome measures in terms of levodopa equivalent dosages (LED) in 60 patients (H&Y Stage 3-4) completing a two-week i-MINC. For each patient, we calculated LED of their pharmacological treatments before and at the end of i-MINC. We then divided the patients into three groups according to the type of LED change occurring during i-MINC: Increased (26 patients), Decreased (19 patients), and No Change (15 patients). We then compared the scores of UPDRS Part III, Beck's Depression Inventory-II (BDI), PDQ-39, and Parkinson's Disease Sleep Scale (PDSS) before and after i-MINC in the three patient groups with mixed model ANOVAs (within subject: i-MINC -before, after; between subject: LED Group -Increase, Decrease, No change). The results reported in Table 1 show that, after i-MINC, the scores of all the outcome measures improved independently of LED group.

Table 1. Outcome measures of the three groups before and after i-MINC and results of ANOVA

| Test                                   | Increased<br>(mean±SD)  | Decreased<br>(mean±SD)  | No Change<br>(mean±SD)   | i-MINC                                        | LED Group                                  | i-MINC x Group               |
|----------------------------------------|-------------------------|-------------------------|--------------------------|-----------------------------------------------|--------------------------------------------|------------------------------|
| UPDRS III<br><i>Pre</i><br><i>Post</i> | 60.5±15.9<br>38.9±13.3  | 59.3±9.9<br>40.5±12.6   | 56.4±12.4<br>40.0±11.0   | <b>F=101, p&lt;0.001</b><br><b>ηp2=0.64</b>   | F=0.12, p=0.89<br>ηp2=0.004                | F=0.66, p=0.520<br>ηp2=0.023 |
| BDI<br><i>Pre</i><br><i>Post</i>       | 15.5±10.8<br>10.3±8.6   | 15.4±7.3<br>8.2±4.6     | 11.7±6.8<br>8.8±5.4      | <b>F=36.8, p&lt;0.001</b><br><b>ηp2=0.40</b>  | F=0.598, p=0.55<br>ηp2=0.02                | F=1.88, p=0.162<br>ηp2=0.06  |
| PDQ-39<br><i>Pre</i><br><i>Post</i>    | 46.8±19.9<br>41.5±21.6  | 47.4±13.4<br>43.6±15.0  | 40.4±15.4<br>33.5±14.1   | <b>F=7.18, p=0.010</b><br><b>ηp2=0.114</b>    | F=1.405, p=0.25<br>ηp2=0.048               | F=0.17, p=0.846<br>ηp2=0.006 |
| PDSS<br><i>Pre</i><br><i>Post</i>      | 87.8±29.9<br>111.3±21.7 | 89.3±21.7<br>106.9±21.2 | 108.1±16.5<br>119.9±19.1 | <b>F=25.9, p&lt;0.001</b><br><b>ηp2=0.312</b> | <b>F=3.67, p=0.032</b><br><b>ηp2=0.114</b> | F=0.97, p=0.383<br>ηp2=0.033 |

We conclude that the direction of pharmacological adjustments in terms of LED or no therapy change do not influence the outcome of i-MINC. The present findings also suggest that drug optimization based on direct and continuous patient observation during different situations and conditions may enhance the positive effects of i-MINC.

## **32. In-patient multimodal intensive neurorehabilitation and care improve motor and non-motor functions in the moderately advanced stages of Parkinson's disease: A retrospective study in a US facility.**

### **Authors**

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### **Abstract**

#### **Background**

Previous studies, mostly performed in European centers, have now shown that in-patient multimodal intensive rehabilitation treatments lasting for two to four weeks improve both motor and non-motor symptoms of Parkinson disease (PD) with long lasting effects. Here we ascertain the effects of a similar in-patient program in a US center with a retrospective study in a cohort of 153 patients in the moderately advanced stage of PD.

#### **Methods**

We compared indices of motor and non-motor functions before and immediately after such treatment and also investigated possible difference between men and women. We used available records of: Beck Depression Inventory, PDQ39, PD Sleep Scale, time up and go, Vocal Volume, Voice Handicap and total UPDRS scores.

#### **Results**

We found that at the end of treatment, which lasted an average of 14 days, all outcome measures significantly improved independently of sex.

#### **Conclusions**

These results confirm for the first time in the US previous findings with similar in-patient approach in European centers. They further suggest that this in-patient treatment is a care model that is feasible in US and can provide immediate benefit on motor function and quality of life in patients with moderately advanced PD, future studies with longer follow up periods will ascertain the sustainability of these benefits.

### **33. Biomechanical patterns and clinical correlations of gait in Parkinson's disease patients: an Observational study**

#### **Authors**

Paolo De Pasquale<sup>1</sup>, Mirjam Bonanno<sup>1</sup>, Cristiano De Marchis<sup>2</sup>, Luca Pergolizzi<sup>1</sup>, Emanuele Lo Voi<sup>1</sup>, Antonino Lombardo Facciale<sup>1</sup>, Giuseppe Paladina<sup>1</sup>, Federica Impellizzeri<sup>1</sup>, Angelo Quartarone<sup>1</sup>, Rocco Salvatore Calabrò<sup>1</sup>

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#### **Abstract**

Parkinson's disease (PD) is one of the most common neurodegenerative disorders affecting motor functions. PD patients often exhibit gait patterns, characterized by altered kinematic, kinetic and electrophysiological parameters [1]. This observational study aims to instrumentally identify and quantify gait dysfunction in PD patients compared to healthy controls and to determine demographic and clinical factors influencing gait patterns.

Sixty-nine PD patients underwent clinical and instrumental evaluations to assess gait functionality. Demographic and clinical data were collected prior to motor assessment. Clinical scales assessed gait, balance and risk of falls. Instrumental evaluations were conducted in a motion analysis laboratory using optoelectronic, force plates and electromyographic (EMG) systems. Statistical significance was tested using a T-test for comparison with normal data, and a linear mixed model (LMM) [2] assessed the effect of demographic and clinical factors, including age, disease duration, body side and disease stage (Hoen & Yahr, HY), on each gait parameter.

Results indicated that PD patients exhibited increased temporal and shortened spatial kinematic gait parameters compared to healthy subjects. While demographic and clinical factors did not affect spatial parameters, temporal parameters were influenced by all variables in the LMM. Hip kinetics were affected by all the variables except HY. In EMG data, only tibialis anterior was influenced by all variables.

Identifying and quantifying biomechanical gait parameters are crucial for developing effective rehabilitation therapy. Understanding which gait parameters are influenced by demographic and clinical factors can facilitate the creation of subject specific rehabilitation protocols potentially slowing down progression of disease in PD patients.

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## 34. Simulating spacewalking: The role of anti-gravity treadmill in Parkinson's disease patients

### Authors

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### Abstract

Patients with Parkinson's disease (PD) often manifest gait and balance impairments, including reduced walking speed, shorter step length, and postural instability<sup>1</sup>. Advanced neurorehabilitation technologies, like robotic systems, have shown promise in promoting motor recovery. Alternatively, anti-gravity treadmills like AlterG, originally developed by NASA, facilitate early mobilization and walking with less effort, reducing energy expenditure and fatigue<sup>2</sup>. These treadmills adjust the user's weight and provide customizable body weight support, sustaining up to 80% of the user's body weight. In our pilot study, 20 PD patients were randomly assigned to an experimental group (n=10) using AlterG (A-GT group) or a control group (CG) (n=10) undergoing conventional physiotherapy. Both groups were evaluated before and after treatment using clinical scales, like the Timed Up and Go (TUG), Berg Balance Scale (BBS), Falls Evaluation Scale-International (FES-I), and 6-minute walking test (6MWT). Additionally, the A-GT group underwent gait analysis with an optoelectronic system. The A-GT group showed significant improvements in all clinical outcomes, including the 6MWT, TUG, BBS, and fall risk, with all results showing  $p < 0.01$ . The CG improved in the 6MWT ( $p = 0.02$ ) and BBS ( $p < 0.01$ ). The A-GT group also exhibited changes in spatial-temporal gait features, including step length, cadence, and gait speed (all  $p < 0.01$ ). These findings align with existing evidence<sup>2,3</sup>, highlighting the benefits of AlterG in improving global motor functions and reducing fall risk in PD patients. The integration of AlterG as an adjunctive neurorehabilitation treatment promotes sustained aerobic training with reduced energy effort, facilitated by the microgravity environment that could mitigate pathological gait compensations.

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### **35. Strength Training to Promote Neural Plasticity in Early Onset Parkinson's Disease.**

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#### **Abstract**

People with early onset Parkinson's disease (PwEOPD, < 50 years) typically experience bradykinesia, weakness, dystonia and fatigue, yet few studies have examined gym-based progressive strength training in this cohort. We conducted a phase 1 community trial on the feasibility and outcomes of gym training for EOPD. We hypothesised that modified power lifting, performed twice weekly, supervised 1:1 by trained exercise trainers and/or physiotherapists would be safe, feasible and have a positive influence on the UPDRS, 3RM strength and EueoQOL. Exercise trainers were educated by experienced PD physiotherapists / exercise physiologists to modify gym programs to the individual needs of PwEOPD. The trial is still in progress. Early findings show some positive benefits. Trainers stated that "...there was value in me being there... making sure everything was done with the correct technique." PwEOPD advised "It makes me feel better about myself and the fact that I'm going to be able to keep fitter and stronger for longer," and "the gradual way it was taught really did build up my strength." Barriers to implementation included scheduling sessions given peoples busy work and family commitments, the need for initial comprehensive education of trainers, and fluctuating accessibility to shared equipment in the community gym.

### 36A. Effects of an exoskeleton-assisted rehabilitation program on gait and posture in individuals with Parkinson's disease.

#### Authors

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This work was supported by Fresco Clinical Research Grant 2019 - *Quantitative assessment of training effects using a wearable exoskeleton in Parkinson's disease patients*

#### Abstract

Gait and postural alterations severely impact the quality of life of Parkinson's disease (PD) individuals (Morris et al., 2005). Functional Kinesiotherapy (FKT) allows to enhance mobility and sensorimotor function, while overground robotic gait training (ORGT) might restore functional gait through repetitive locomotion (Gassert et al., 2018).

This study aims to assess the impact of an ORGT program on PD individuals. To this extent, 40 PD individuals were enrolled (Romanato et al., 2022) (ClinicalTrials.gov NCT04778852) and randomly assigned to FKT (age=73.9±6.8years) and ORGT (age=68.5±8.4years) for four weeks of therapy. Gait analysis was performed before (T0) and after (T1) therapy through an 8-camera optoelectronic system, 2 force plates, and an 8-channel surface electromyography system; the electrical activity of 4 muscles was recorded bilaterally (Biceps Femoris, Rectus Femoris, Gastrocnemius Lateralis, Tibialis Anterior). 3D joint kinematics, joint moments, ground reaction forces and muscle activity were determined.

The data of 13 healthy subjects (age=57.8±5.6years) were used as normative bands (Sawacha et al 2009). Statistical analysis was performed (parametric or not parametric testing where appropriate,  $p<0.05$ ) with statistical parametric mapping (Pataky, 2012).

Results showed a comparable improvement (Figure 1) for both populations at the level of joint angles and moments and ground reaction forces. UPDRS III clinical scale showed a better improvement in the ORGT group.

Results seem to suggest that longer treatment periods or longer follow up might be required to obtain better improvements at the level of gait analysis variables.

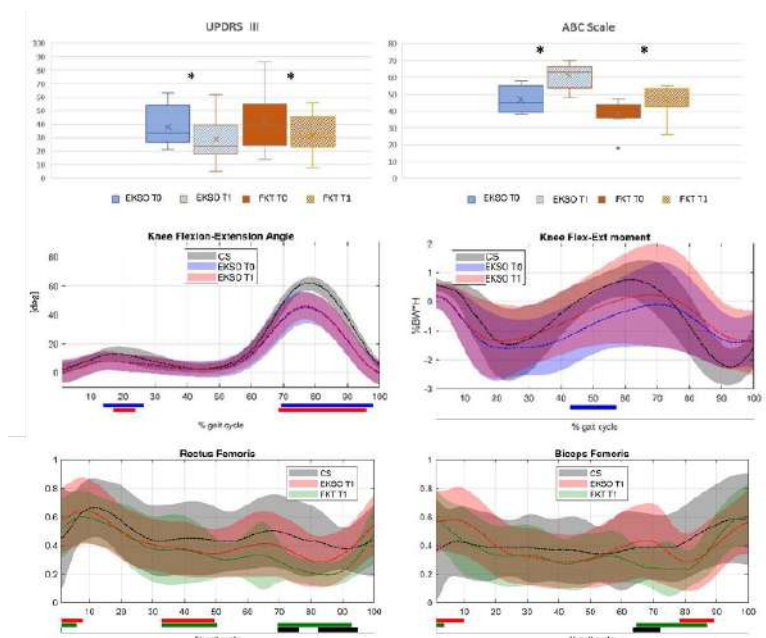


Figure 1.

### 36B. Neuro-musculoskeletal modelling informed rehabilitation in Parkinson's disease: comparison between overground robotic training and Functional Kinesiotherapy.

#### Authors

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*This work was supported by Fresco Clinical Research Grant 2019 - Quantitative assessment of training effects using a wearable exoskeleton in Parkinson's disease patients*

Physical therapy has become a key complementary intervention for managing motor symptoms in Parkinson's Disease (PD) (Deschamps et al., 2022). Approaches range from conventional Functional Kinetic Therapy (FKT) to newer Overground Robotic Gait Training (ORGT) aiming to promote neuroplasticity and restore functional gait.

This study aims to provide new metrics to assess the outcome of FKT and ORGT: muscle forces. These parameters are determined during dynamic tasks such as gait through the application of musculoskeletal modelling informed by surface electromyography signals..

Forty PD individuals were enrolled (ClinicalTrials.gov NCT04778852), randomly assigned to 2 intervention groups (FKT-age=73.3±7.7 years, EKSO-age=68.6±7.9 years). 7 drop out were recorded in the EKSO group. Each subject underwent a gait analysis before and after 4-weeks of therapy at Villa Margherita (Vicenza, Italy) through an 8-camera optoelectronic system (120Hz, Vicon), 2 force plates (960Hz, AMTI) and an 8-channel EMG system (2000 Hz, Cometa). The IORGait protocol (Leardini et al., 2017) was adopted.

Musculoskeletal modelling simulations were performed as in Romanato et al 2022 and trunk. A cohort of 13 healthy controls (age=57.8±5.6 years, BMI=27.3±3.9 kg/m<sup>2</sup>) was used as reference (Sawacha et al 2009). Statistical Parametric Mapping was applied (Pataky, 2012).

Muscle forces results showed larger improvements in the gait of ORGT group (Figure 1). Future studies are needed to explore the link between the observed improvements at the level of muscle forces during gait and their impact on the upright stability in the ORGT group.

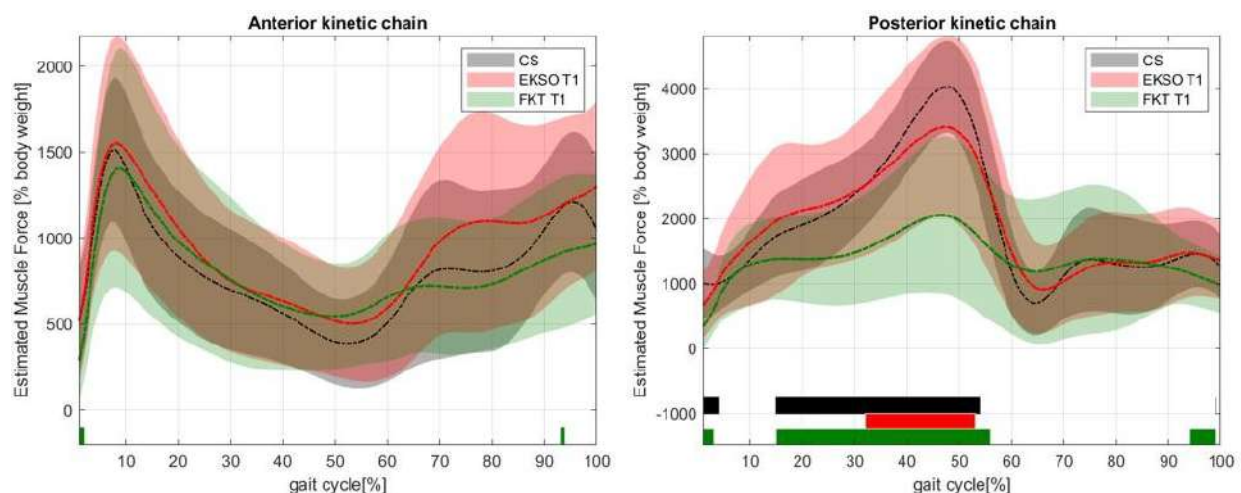


Figure 1.

### **37. Modifications of Muscle Synergies after MIRT in Parkinson's Disease patients: a preliminary study**

#### **Authors**

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#### **Objective**

Parkinson's disease (PD) patients exhibit specific impairments in the spinal circuitry and gait<sup>1</sup>. Deviated gait patterns in PD patients are often associated with an altered coordination of muscles. Multidisciplinary Intensive Rehabilitation Treatment (MIRT), an intensive exercise program, induces changes in neuroplasticity-related phenomena at both functional and structural levels in the spinal cord of PD patients<sup>2</sup>. Muscle Synergy Analysis (MSA) is a promising tool for quantitatively characterizing locomotion impairments in neurological patients<sup>3</sup>. This preliminary study aims to quantitatively assess the effect of MIRT on the muscle coordination patterns of PD patients during gait through MSA.

#### **Material and methods**

6PCS-pt (age mean  $\pm$  SD: 58.83  $\pm$  9.08), underwent MIRT. Clinical scales, assessing gait, balance, risk of falls (10MWT, 6MWT, TUG, BBS, FESi), and instrumental gait analysis were performed PRE and POST treatment. Each patient performed 10 repetitions of walking over a 12m-long walkway at a self-selected speed. Surface EMG signals were collected bilaterally from 8 muscles acting on the ankle, knee, and hip joints. Muscle synergies were extracted separately from the participants' right and left sides through Nonnegative Matrix Factorization.

#### **Results**

MIRT induced an increased gait symmetry in muscle coordination patterns, as indicated by an increased left/right similarity between muscle synergies and an increased similarity with physiological muscle synergy patterns extracted from three healthy control subjects.

#### **Discussion/Conclusion**

MIRT protocol induces improvements within the neural control of PD locomotion, and MSA proves to be a quantitative tool sensitive to and related to improvements in clinical scales.

Key points: Parkinson's disease (PD), Multidisciplinary Intensive Rehabilitation Treatment (MIRT), Gait, Muscle Synergy Analysis (MSA), Neuroplasticity

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### **38. The Longitudinal Effects of MIRT on Motor Learning in Parkinson's patients: a preliminary study.**

#### **Authors**

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#### **Objective**

Parkinson's disease patients (PD-pt) exhibit deficits in motor learning<sup>1</sup>. A recent study has shown a positive effect of Multidisciplinary Intensive Rehabilitation Treatment (MIRT)<sup>2</sup> in PD-pt on the retention of a motor adaptation task<sup>3</sup>. This preliminary study investigates the longitudinal performance of PD-pt on a visuomotor adaptation task before and after 4 weeks of MIRT.

#### **Material and methods**

7 PD-pt (age mean  $\pm$  SD: 57.71  $\pm$  8.73; Hoehn-Yahr Stage from 2 to 3; all right-handed) were tested in a reaching task with visuomotor adaptation, gradually and implicitly applied to reaching movements in steps of 10° for a total of 60° (ROT set). At the initiation and conclusion of the task, participants executed a non-rotated task (0°), referred to as the MOT, and the Aftereffect set, respectively. The task was repeated for two consecutive days (test and retest phase), before and after 4 weeks of MIRT. Non-parametric longitudinal analysis was applied to the percentage of corrected responses for each set across each day, pre- and post- MIRT.

#### **Results**

Longitudinal statistics revealed that the percentage of corrected responses within the MOT set of the post- MIRT retest was higher than ones observed in the Aftereffect of the test phase ( $p < 0.001$ ), pre-and post- MIRT, as well as of ROT test and retest phases of pre-MIRT ( $p < 0.001$ ).

#### **Discussion/Conclusion**

While no direct impact on motor adaptation was observed, post-MIRT patients exhibited enhanced performance on the last motor set compared to the previous aftereffect sets, which serve as a baseline for subsequent motor tasks and indices of motor adaptation, suggesting that MIRT may also indirectly influence visuomotor adaptation.

Key points: Parkinson's disease (PD), Multidisciplinary Intensive Rehabilitation Treatment (MIRT), Motor Adaptation Task, Neuroplasticity

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### **39. Exploring the impact of prismatic adaptation on alexithymia in Parkinson's disease: a pilot study**

#### **Authors**

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#### **Abstract**

Alexithymia, characterized by difficulty in identifying and describing feelings, is a non-motor symptom in Parkinson's disease (PD)<sup>1</sup>. It is linked to dopamine dysfunction in brain areas involved in emotional regulation. Prismatic adaptation (PA) is a neuromodulation technique that induces neural plasticity, impacting visuospatial abilities as well as emotion recognition <sup>2</sup>. The aim of our work is to investigate if PA could also modulate alexithymia.

We recruited five PD patients and randomly assigned them to three groups: two patients each in right PA and left PA groups, and one in the neutral PA group. Alexithymia was assessed using the Perth Alexithymia Questionnaire (PAQ) and the Toronto Alexithymia Scale (TAS-20), administered in a counterbalanced order before and after a PA session. The instructions for the pointing tasks were given by a paradigm constructed with E-prime, which interfaced with the high-density EEG (HD-EEG). Neurophysiological changes were assessed by 256 channels of HD-EEG recordings before and after the PA sessions.

After treatment, alexithymia test scores showed a decrease of 10% in patients undergoing left PA, an average increase of 37% in patients undergoing right PA, and an increase of 22% in the patient with no deviation. HD-EEG data were analyzed using eLORETA to identify active brain areas. The comparison between pre- and post-PA conditions revealed increased frontal activation after PA, with longer-lasting effects for left PA.

These preliminary findings suggest that left PA may reduce alexithymia symptoms in PD patients, potentially offering new avenues for clinical intervention and management of emotional regulation deficits.

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- <sup>2</sup>Mańkowska, A., Harciarek, M., Williamson, J. B., & Heilman, K. M. (2018). The influence of rightward and leftward spatial deviations of spatial attention on emotional picture recognition. *Journal of Clinical and Experimental Neuropsychology*, 40(9), 951-962.

## **40. What is the correlation between Empathy and Alexithymia in Parkinson's Disease and Essential Tremors.**

### **Authors**

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### **Introduction**

Empathy involves complex neural networks that can be affected by degenerative pathologies like movement disorders (MD).<sup>1,2</sup> However, social deficits in Parkinson's disease (PD) are underexplored, studies on social deficits in essential tremor (ET) are also limited.<sup>3,4</sup> This study evaluates empathy and alexithymia in patients with PD and ET.

### **Materials and Methods**

PD and ET patients were enrolled in this cross-sectional study. Each patient underwent Montreal Cognitive Assessment (MoCA), Empathy Quotient (EQ) and Toronto Alexithymia Scale (TAS-20).

### **Results**

40 PD (66.7 ± 6.58 years; 65% men; disease duration 4.5 ± 2.4) and 40 ET (71.0 ± 4.9 years; 60% men; disease duration 5.6 ± 1.6) were enrolled. Results showed low empathy and difficulty identifying feelings across the sample. In PD patients, EQ Social Support (SS) was positively correlated with MoCA ( $r=0.42$ ;  $p=0.007$ ) and negatively correlated with TAS-20 DIF ( $r=-0.35$ ;  $p=0.02$ ). In ET, EQ SS was negatively correlated with TAS-20 DIF ( $r=-0.33$ ;  $p=0.04$ ) and TAS-20 total score ( $r=-0.32$ ;  $p=0.04$ ).

### **Discussion**

In both PD and ET patients, low empathy and difficulty identifying feelings were prevalent, with PD showing a clear link between better social support, cognitive function, and a negative correlation with emotional difficulties, whereas ET showed correlations between emotional problems and reduced social skills.

### **Conclusion**

These preliminary findings support the functional role of subcortical structures (i.e. the basal ganglia and cerebellum), which are primarily responsible for MD, on the deficits related to the ability to understand and share emotions (empathy) and the difficulty in identifying one's feelings (alexithymia).

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## **41. Gender Differences in Cognitive Outcomes in Parkinson's Disease: A Neuropsychological Analysis.**

### **Authors**

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### **Background**

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms (bradykinesia, tremor, stiffness, and postural instability), due to dopamine deficiency in the basal ganglia. PD is associated with a broad spectrum of non-motor symptoms (such as hyposmia, sleep disorders, autonomic dysfunction, cognitive impairment, psychosis, depression, anxiety, and apathy) caused by nigrostriatal degeneration.<sup>1</sup> More than 24% of patients with PD have one or more cognitive symptoms. The most impaired cognitive functions in this neurodegenerative process are executive functions, working memory, visual-spatial abilities, and verbal fluency, while the main behavioral symptoms are depression and anxiety.<sup>2</sup> Emerging evidence suggests that biological sex is an important factor in PD's development and phenotypical expression, yet comprehensive analyses remain limited.<sup>3</sup>

### **Objective**

This study investigates gender differences in cognitive outcomes among patients with PD using a detailed neuropsychological assessment.

### **Methods**

A cohort of 184 PD patients (97 males, 87 females) was evaluated using a comprehensive battery of neuropsychological tests, including measures of attention/orientation, memory, verbal fluency, and visuospatial skills. Statistical analysis was performed to identify gender differences in cognitive performance using the Mann-Whitney U test.

### **Results**

Significant gender differences in memory ( $p < 0.01$ ), language ( $p < 0.01$ ) and visuospatial ability ( $p < 0.05$ ) scores were found.

### **Conclusions**

These findings highlight the importance of considering gender-specific cognitive profiles in the management and treatment of Parkinson's disease.

Understanding these distinctions can lead to more personalized therapeutic approaches, optimizing cognitive rehabilitation strategies to address the unique strengths and weaknesses of each gender.

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## **42. A permissive role for dopamine in the production of vigorous movements**

### **Authors**

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### **Abstract**

Dopamine is essential for the production of vigorous movements, but how dopamine modifies the gain of motor commands remains unclear. Here, we developed a dexterous motor task in which head-restrained mice self-initiate fast and large-amplitude lever pushes with their left forelimb to earn rewards. We show that this task is goal-directed and depends on cortico-striatal circuits in the hemisphere contralateral to the limb used to push the lever. We find that unilateral loss of midbrain dopamine neurons reduces the speed and amplitude of lever pushes, and that levodopa treatment rapidly restores motor vigor, consistent with parkinsonian bradykinesia. Photometry recordings of striatal dopamine levels indicate that the therapeutic efficacy of levodopa does not require phasic dopamine release. In dopamine-intact mice, optogenetic stimulation of midbrain dopamine neurons calibrated to mimic transients evoked by rewards is also insufficient to increase the speed and amplitude of forelimb movements. Together, our data show that phasic dopamine transients are unlikely to specify the vigor of forelimb movements online as they are being executed, and suggest instead that dopamine plays a permissive role in the selection and production of vigorous movements. Our findings have important implications for our understanding of how the basal ganglia contribute to motor control under physiological conditions and in Parkinson's disease.

### **43. Exercise boosts dopamine release in the new ParkinR275W mouse model of autosomal recessive juvenile Parkinsonism**

#### **Authors**

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#### **Abstract**

Mutations in *PARK2* gene cause Autosomal recessive juvenile parkinsonism (ARJP), an early onset familial form of Parkinson's disease characterized by early and severe dopamine (DA) neurons loss in substantia nigra pars compacta (SNc). At the moment, no neuroprotective approach exists, and a symptomatic therapy only is available. Complementing drug treatments, physical exercise has been shown to improve motor performance in individuals living with PD. However, underlying mechanisms are not yet understood. Our previous study showed that voluntary exercise for 30 days leads to an increase in evoked DA release throughout the striatum in WT mice. Based on this observation, we wanted to test the effects of exercise on DA release in pathological conditions. To fulfill this aim, we used our new, innovative mechanistic mouse model of *PARK2*-related ARJP. This model was created by taking advantage of CRISPR/Cas9 genome editing to insert the *PARKIN* R275W missense mutation, found with highest allelic frequency in *PARK2* patients. Characterization of this model showed it recapitulates major Parkinson's disease hallmarks, such as age-dependent loss of DA neurons in the SNc, progressive motor impairment, and decrease of DA content. Using the method of fast-scan cyclic voltammetry (FSCV), we further characterized the mouse model assessing the electrically-evoked DA release in striata slices before and after an exercise protocol. Data suggested a DA release impairment in non-runner, 6-months-old R275W mice, which worsened in aged (12-months-old) mice. Subsequently, we analyzed the effect of 30-days voluntary running protocol in 12-months old mice: we observed an increase in stimulus-evoked DA release in the striatum as well as a trend of amelioration of motor phenotype. These findings suggest a role of exercise in treatment of PD by boosting DA release in the brain, shedding light on the importance for research to learn underlying mechanistic insights.

## 44. Exploring the synergy between microbial factors and glucocerebrosidase dysfunction in human iPSC-derived macrophages and microglia

### Authors

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### Abstract

The gut-brain axis is increasingly implicated in the pathophysiology of Parkinson's disease (PD). *In vitro*, *in vivo* and clinical data indicate that short chain fatty acids (SCFAs) are associated with inflammation and  $\alpha$ -synuclein accumulation in the gut that could ultimately be propagated to the brain. Despite tremendous efforts, the exact role of SCFAs and other microbial factors in the disease pathogenesis remains controversial. In this study, we aim at dissecting the role of microbial factors and potential interaction with glucocerebrosidase (*GBA1*)- related genetic risk to impact inflammation and  $\alpha$ -synuclein pathology. To this end, we employed induced pluripotent stem cell-derived macrophages, microglia and intestinal organoids from control and *GBA1*-PD cases (L444P, E326K) to characterise the effects of microbial factors and  $\alpha$ -synuclein pre-formed fibrils. Cytokine secretion, lipid metabolism, migration and phagocytosis were altered in response to LPS or SCFAs in macrophages and microglia from control and *GBA1*-PD cases. Cytokine secretion and  $\alpha$ -synuclein clearance in response to pre-formed fibrils were decreased in immune cells with *GBA1* variants. These results suggest that impaired glucocerebrosidase activity alters key functions of peripheral and brain-resident immune cells. Intestinal organoids with *GBA1* variants and corresponding controls resembled the cell type composition of the human intestine. Reduced glucocerebrosidase function was associated with increased  $\alpha$ -synuclein expression in intestinal organoids with *GBA1* variants. Given the known link between glucocerebrosidase and  $\alpha$ -synuclein in the gut-brain axis, ongoing work is addressing the interaction between genetic vulnerability and SCFAs on neuro-immune interactions and PD pathology using complex organoids with immune cells.

#### **45. Different vulnerability of striatal neurons and functional impairments temporal onset in a preclinical model of Huntington's disease during the progression of the pathology**

##### **Authors**

Trucco A., Spaiardi P., Castagno A.N., Raffin F., Mancini M., Cazzola J., Faravelli G., Talpo F., Biella G.

##### **Abstract**

Huntington's disease (HD) is a rare genetic neurodegenerative disorder characterized by a triad of psychiatric, cognitive, and motor symptoms. Cortex and striatum are the primary cerebral areas affected by HD. Within the striatum, spiny projection neurons (SPNs) represent about 95% of striatal neurons and they transmit information to downstream nuclei of the basal ganglia. However, less represented GABAergic fast-spiking and low-threshold interneurons (FS-INs, LTS-INs) along with cholinergic tonically active neurons (TANs) contribute to a fine modulation of striatal microcircuitry. While numerous studies have delved into the dysfunction of striatal SPNs in HD, the morphological and functional alterations among other striatal cell types need to be investigated. To address this gap, we performed whole-cell patch clamp recordings on mouse brain slices from wild-type and R6/2 mice – a transgenic mouse model of HD, by studying the electrophysiological changes within SPNs, FS-INs, LTS-INs, TANs at two distinct timepoints: early (6-8 wk) and late stages (11-13 wk) of HD. By analyzing action potential shape (current-clamp) and spontaneous excitatory postsynaptic currents parameters (voltage-clamp), we underscore the existence of a different vulnerability of striatal neurons to HD. Specifically, LTS-INs and TANs are preserved from HD-related damage. In contrast, significant functional impairments were observed in FS-INs during the early stage of HD while, as HD progresses to its late stages, alterations become apparent also in SPNs. In conclusion, our findings indicate a specific temporal pattern of cell damage, with FS-INs playing a pivotal role in driving changes in striatal circuit dynamics during HD progression.

## **46. Temporal evolution of glial cell phenotype in A53T $\alpha$ -synuclein transgenic mice: new Disease related Mechanisms?**

### **Authors**

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### **Abstract**

Neuroinflammation is a hallmark of Parkinson's disease (PD) pathophysiology, with evidence suggesting that neurotoxic glial cells might contribute to symptoms and progression; however, it is still unclear whether glia activation is a primary event or a result of neurodegeneration. Therefore, the aims of this project are:

- 1) To study the temporal evolution of the glial phenotype in the midbrain and striatum during the PD progression.
- 2) To identify the genes involved in the transition from a neuroprotective to a neurotoxic glial phenotype.

To address these issues, we performed Western blot analysis in the midbrain and striatum of 4-6-12-16-month-old mice expressing the human A53T- $\alpha$ -synuclein to characterize pro- and anti-inflammatory glia subtypes. We found that at 12 months, glial cells shift to a detrimental phenotype, with neurotoxic astrogliosis in the midbrain and detrimental microgliosis in the striatum. To study the molecular determinants of glial phenotype transition in brain regions related to PD, we analyzed a pre-existing single-nucleus RNA-Seq database on the same animal model. We found that the GNAO1 gene is selectively dysfunctional in mesencephalic but not in striatal astrocytes. GNAO1 encodes a G $\alpha$ o protein that controls the synthesis of cAMP-modulating inhibitory and stimulatory inputs to the adenylyl-cyclase-5. GNAO1 mutations are linked to neurological disorders such as developmental delay, hypotonia, epilepsy, and hyperkinetic movement disorder, suggesting a relationship with PD. Molecular and functional analysis of post-natal astrocytes from wild-type and A53T mouse pups confirmed these findings, prompting further inquiry into GNAO1's role in the astrocytes phenotypic transition in A53T mice.

## 47. Nrf2 and neuroinflammation in Parkinson's Disease patients at different clinical stages

### Authors

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### Abstract

Multiple evidence suggest that neuroinflammation plays a role in the pathogenesis of Parkinson's disease (PD) and has been considered a potential target for therapies.

Here, we explored the role of the transcription factor Nrf2, a master regulator of protection against inflammation and oxidative stress, as potential index of PD pathophysiology and prognostic biomarker.

Therefore, we evaluated the expression of Nrf2 and Nrf2-related antioxidant enzymes in peripheral blood mononuclear cells (PBMCs) from PD patients at different disease stages (early, moderate and advanced, according to Hoen & Yahr scale) and healthy controls (HC). Changes in the expression of these proteins were correlated with alpha-synuclein levels in PBMCs and plasmatic levels of inflammatory (i.e., IL-6, IL-1 $\beta$ , TNF $\alpha$ , IFN $\gamma$ , CX3CL1) and neurodegenerative (neurofilament light chain, Nfl) biomarkers.

Nrf2 and antioxidant protein levels were assessed by Western Blot, while alpha-synuclein levels were evaluated by ELISA. ELLA<sup>TM</sup> technology was used to quantify plasma levels of inflammatory and neurodegenerative markers.

Preliminary results show a slight increase in Nrf2 and Superoxide Dismutase levels with advancing disease, accompanied by a decrease in pro-inflammatory TNF $\alpha$  in plasma. Nfl levels are higher in PD compared to HC, supporting the ongoing neurodegenerative process. Inflammatory cytokines and alpha-synuclein levels showed no differences between groups.

The recruitment of patients is still ongoing; thus we expect that the increase in sample size will allow us to better define Nrf2's role in PD progression. Moreover, correlations with gender will potentially allow us to understand the contribution of sex hormones in PD, which predominantly affects men.

This work has been supported by Fondazione Regionale per la Ricerca Biomedica (Regione Lombardia), project ID 3433068 - Acronym: LINKING PARK

## 48. Prokineticin-2 expression in colonic mucosa of Parkinson's disease patients

### Authors

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### Background

Elevated levels of prokineticin-2 (PK2), regarded as a protein involved in modulating immune/inflammatory responses, have been detected in the *substantia nigra*, serum and olfactory neurons from PD patients. Of note, emerging evidence suggests that gut alterations, including dysbiosis and enteric inflammation, play a role in PD via the gut-brain axis.

### Objectives

To investigate the expression of PK2 in colonic biopsies of PD patients.

#### Methods

Mucosal biopsies from the descending colon were obtained in eleven PD patients and five asymptomatic subjects. Biopsy samples were processed for PK2 immunofluorescence.

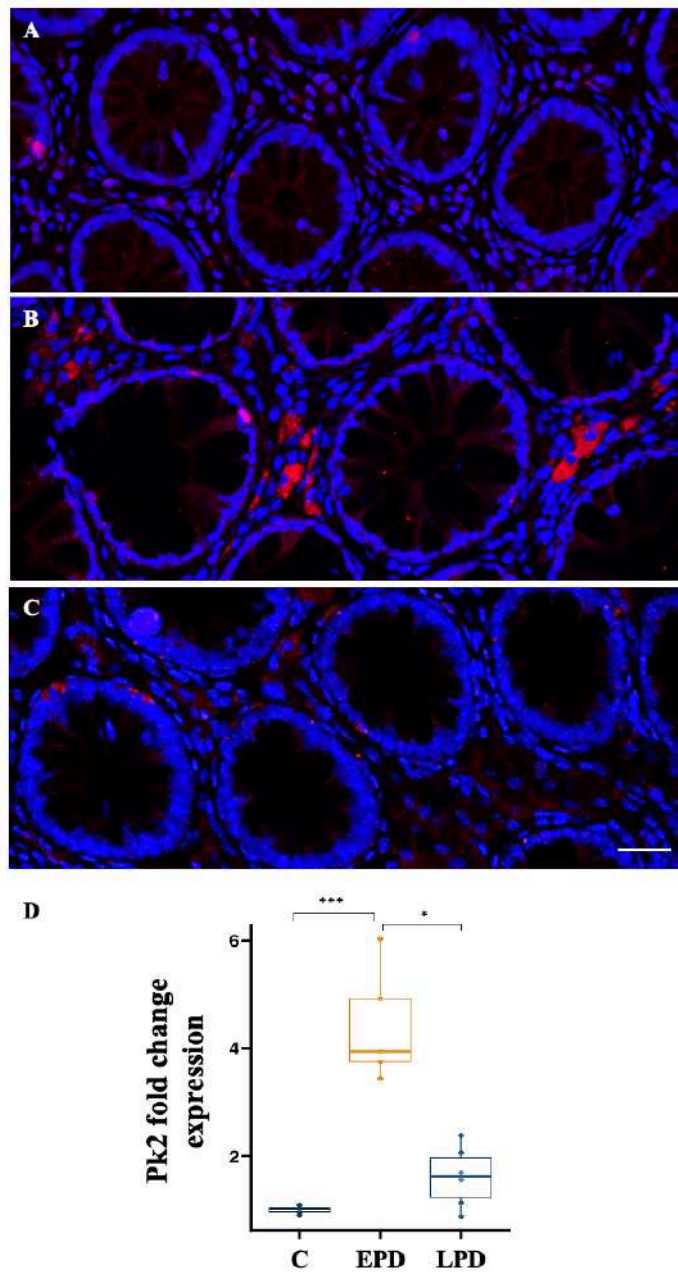
### Results

We revealed an increased PK2 expression in colonic mucosa from PD patients in the early stages compared to controls ( $4.42 \pm 1.06$  vs  $1.00 \pm 0.07$ ,  $p = 0.0009$ ) and it was inversely correlated with the disease duration. We also detected a colocalization with microglia cells and activated macrophages.

### Conclusions

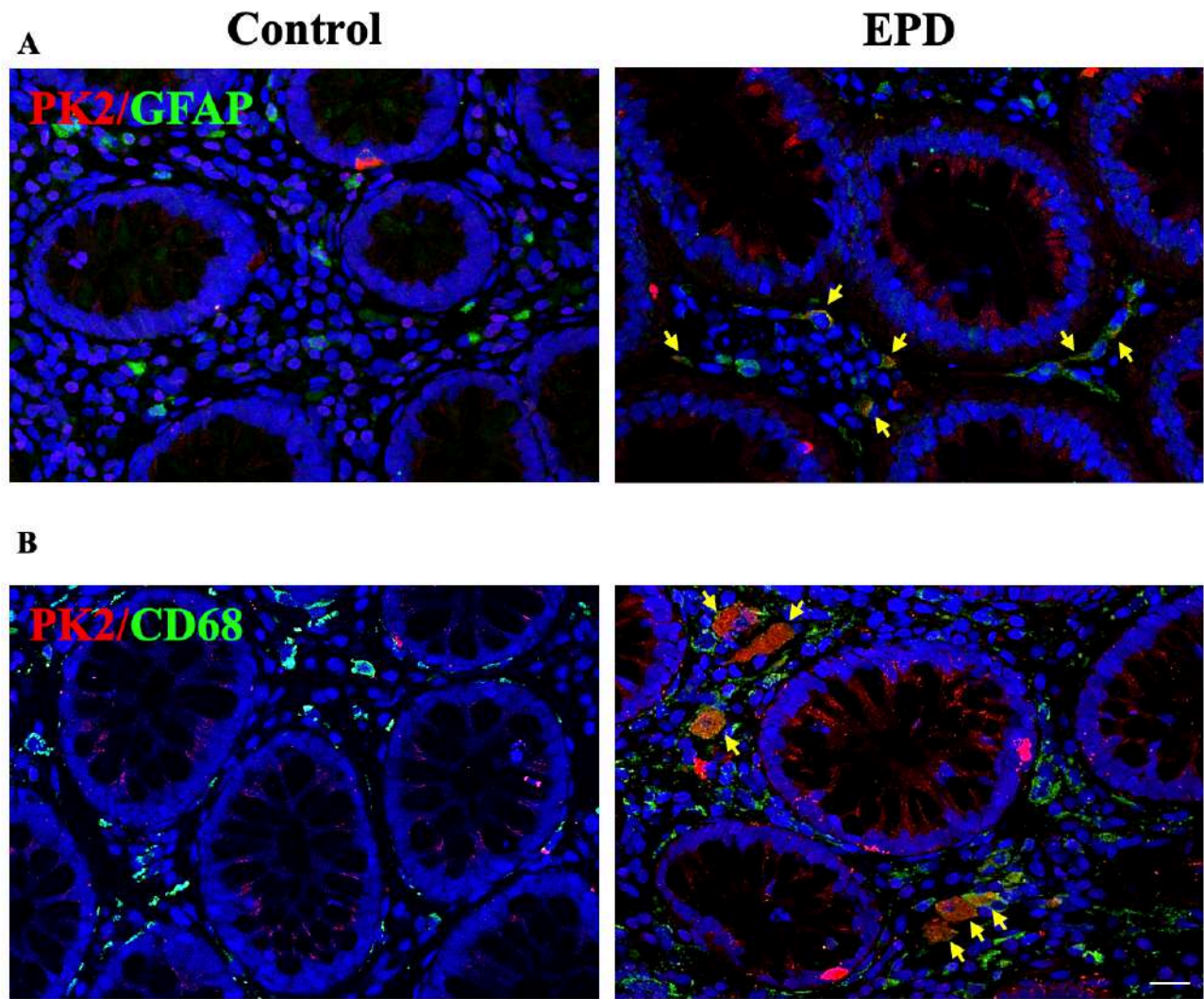
PK2 is highly expressed within the colonic mucosa of early PD patients, suggesting the potential role of PK2 in gut inflammation, especially in early stages of PD.

Fig. 1 - PK2



Graph displays the fold change of the red positive pixels percentage detected in the mucosal area examined. \*\*\*  $p \leq 0.001$  significant difference between EPD versus controls. \*  $p \leq 0.05$  significant difference between EPD versus LPD. Representative confocal microscopy photomicrographs of PK2 immunostaining (red) in colonic mucosal biopsy sample from (A) healthy subjects, (B) EPD and (C) LPD patients. Scale bar: 25 mm. Abbreviations: EPD = Parkinson's disease patients with disease duration less than 5 years; LPD = Parkinson's disease patients with disease duration more than 5 years.

Fig. 2 - PK2/Gfap and PK2/CD68



Representative confocal microscopy images of PK2 (red) and GFAP or CD68 (green) double immunostainings in colonic mucosal biopsy sample from healthy subjects and EPD patients. Scale bar: 20 mm.

## **49. Oligomeric alpha-synuclein causes early striatal synaptic dysfunction associated with non-motor symptoms**

### **Authors**

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### **Abstract**

In synucleinopathies,  $\alpha$ -syn is thought to exist within a dynamic equilibrium, comprising both  $\alpha$ -syn oligomers (OSyn) and more aggregated forms. OSyn has been associated with neurodegeneration, neurotoxicity, and proinflammatory responses, even at low concentrations, and is thought to be involved in Parkinson's disease (PD) pathogenesis. To date, it is not clear whether the neurotoxicity exerted by  $\alpha$ -syn aggregates is due to the presence of scattered oligomeric species, anticipating the formation of proper fibrillary  $\alpha$ -syn, or whether it is sustained by  $\alpha$ -syn species that are already in balance with more aggregated  $\alpha$ -syn seedings. To define the events occurring during the initial stages of  $\alpha$ -syn spreading, as well as to assess the in vivo relevance of OSyn for the development of motor and non-motor symptoms, we performed electrophysiological and behavioral tests in a rat model of synucleinopathy obtained by intrastriatal injection of OSyn, envisioning a scenario that precedes the formation of fibrillary  $\alpha$ -syn aggregates. OSyn rats were found to display early abnormalities of motor activity and increased anxiety-like behavior, together with bidirectional impairment of striatal long-term synaptic plasticity. Novel pharmacological strategies will be evaluated to reverse these changes. Overall, this research will help further elucidate the events in the earliest stages of PD and the pathophysiological phenomena that lead to the onset of early non-motor symptoms. Moreover, our work will unravel the initial mechanisms underlying the synaptic dysfunction produced by the oligomeric form of alpha-synuclein that accumulates in the striatum.

## **50. Working memory deficits triggered by A53T alpha-synuclein pathology in prefrontal cortex is regulated by astrocyte glucocorticoid receptors**

### **Authors**

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### **Abstract**

Cognitive deficits, ranging from mild impairment to dementia, are common in Parkinson's disease (PD) and related synucleinopathies. Mood disorders such as depression, anxiety, or apathy, which often co-occur with these conditions, can also affect cognition. However, alpha-synuclein ( $\alpha$ Syn) pathology alone does not fully account for the observed variability in cognitive impairment. The role of environmental or genetic factors in cognitive susceptibility remains poorly understood. Glucocorticoid (GC) hormone signaling through the glucocorticoid receptor (GR) is known to significantly influence mood and memory, with astrocytes playing a key role in these processes.

Our research investigates how astrocyte GC-GR actions impact cognitive deficits associated with  $\alpha$ Syn pathology. We used mice with conditional GR gene deletion in astrocytes and induced  $\alpha$ Syn pathology by injecting an A53T-human SNCA viral vector into the prefrontal cortex (PFC). Behavioral analyses revealed that only astrocyte GR knockout mice exhibited working memory deficits in the presence of  $\alpha$ Syn pathology, suggesting that GR signaling in astrocytes mitigates the negative effects of  $\alpha$ Syn on neuronal function. Additionally, GR deletion in astrocytes increased pathological  $\alpha$ Syn levels and triggered glial reactivity.

Using STED microscopy, we observed enhanced synaptic coverage at inhibitory synapses in GR mutant mice with  $\alpha$ Syn pathology. Light-sheet microscopy revealed that the absence of GR in astrocytes altered spontaneous calcium signaling, which is crucial for neuronal activity regulation. Further work is under way to understand how altered astrocytic calcium activity regulates pathological  $\alpha$ Syn actions on neuronal activity. Overall, preliminary findings suggest that astrocyte GR acts to prevent  $\alpha$ Syn-induced cognitive deficits by modulating astrocytic and neuronal functions.

## 51. Differential and regulated actions of microglia to two distinct strains of $\alpha$ -synuclein

### Authors

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### Abstract

Accumulating evidence suggests that misfolding of alpha-synuclein ( $\alpha$ -syn) protein into conformationally distinct strains contributes to the clinical and pathological heterogeneity found in synucleinopathies such as Parkinson's disease. However, our knowledge on microglial responses to distinct strains of  $\alpha$ -syn remains sparse.

We examined microglial responses to two  $\alpha$ -syn strains, fibrils and ribbons previously characterized for their structural properties and neuronal toxicity. Stereotaxic injection of these strains in the striatum showed their retrograde translocation into substantia nigra (SN) accompanied by pathological accumulation of  $\alpha$ -syn detectable as early as 4 weeks. Analysis of dopamine neurodegeneration showed fibrils induced dopamine neuronal loss more rapidly, evident at 3 months compared to 6 months for ribbons, accompanied by microgliosis in the SN and striatum. Expression of inflammatory mediators showed potent activity of fibrils as well as strain-dependency. Remarkably, fibrils and not ribbons triggered inhibition of cathepsin S and B/L enzymatic activities as well as autophagy pathway.

To explore whether the two strains differentially impact transcriptional factors that control microglial responses, we analyzed the role of glucocorticoid receptor (GR), known to regulate diverse microglial functions including lysosomal and inflammatory activities. GR levels in response to fibrils but not ribbons, decreased significantly in SN. Interestingly absence of GR in microglia worsened dopaminergic neuronal loss in response to ribbons, evident at 3 months post-injection. Microglial gene expression analyses in SN revealed strain-dependent target specificity and regulation by GR. Overall our results indicate that microglia responses are  $\alpha$ -syn strain-dependent and microglial regulators e.g. glucocorticoids most likely play a role in determining neurotoxic actions of  $\alpha$ -syn strains.

## 52. Siah2-E3 ligase: A link between $\alpha$ Syn aggregates and mitochondrial dysfunction in Parkinson's Disease?

### Authors

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### Abstract

Nowadays, the role of  $\alpha$ -synuclein ( $\alpha$ Syn) in Parkinson's Disease (PD) has been consolidated as one of the main causes of dopaminergic neurodegeneration. However, the lack of understanding the key molecular events responsible for  $\alpha$ Syn accumulation and dopaminergic neuronal loss in Substantia Nigra pars compacta represents an obstacle for the developing of new neuroprotective therapies able to halt PD progression. Among the different cellular mechanisms hypothesized, mitochondrial dysfunction represents a crucial target in both sporadic and familial forms of PD. Evidence shows that the E3 ligase Seven in absentia Homolog 2 (Siah2) plays a role in modulating  $\alpha$ Syn aggregation, as well as in interacting with mitochondrial proteins. Therefore, it represents an interesting target to explore in the pathogenesis of  $\alpha$ Syn-induced mitochondrial dysfunction in *in vitro* and *in vivo* models of PD. To this aim experiments have been performed *in vivo* in A53T $\alpha$ Syn transgenic mouse, a model reproducing a familial form of PD, and *in vitro* in SH-SY5Y dopaminergic cell treated with neurotoxic agents, a model reproducing a sporadic form of PD. In these models  $\alpha$ Syn protein expression and aggregation and Siah2 expression have been evaluated. Moreover, the activation of LC3-II protein expression, a marker of mitophagy, and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ), a marker of mitochondrial biogenesis was detected. Finally, by using confocal microscopy, these findings have been correlated to mitochondrial morphology, membrane potential and [Ca<sup>2+</sup>]<sub>m</sub>.

## 53. Generation of multifunctional phages for *in vitro* diagnosis

### Authors

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### Abstract

Phage display is a molecular technique that involves the genetic insertion of nucleotide sequences in-frame into one of the genes coding for a capsid protein of a bacteriophage. It is primarily used for discovering biomarkers, developing therapeutic antibodies, and investigating protein-protein interactions. A challenge in using phages for diagnostic and therapeutic monitoring assays is to have a detection system that can reveal and quantify the interaction between the peptide displayed on the phage capsid and the target of interest while avoiding technical complexity and high costs. In this study, we generated new helper phage vectors by inserting genes coding for green fluorescent protein (sfGFP) or Avi-tag peptide in-frame into gene 3 of the M13 helper phage. We then combined these generated helper vectors, M13K-sfGFP or M13K-sBT, with a phagemid vector harboring engineered pVIII with a peptide-probe specific for desired target, creating a “dual-display phage”. This system allows sfGFP or Avi-tag and the peptide probe to be displayed on the same phage particle in a single step. Furthermore, our system facilitates the easy exchange of the displayed peptide probe on pVIII to achieve the desired selectivity while retaining the pIII-engineered gene. To illustrate its effectiveness, we conducted proof-of-concept studies on *P.aeruginosa*, *E.coli*, and SH-SY5Y cells, demonstrating the capability to detect and quantify interactions using a plate reader or fluorescence microscopy without the need for signal amplification. Our multifunctional phages will advance the development of simple detection systems for *in vitro* diagnosis, potentially reducing time and costs compared to current methods.

## 54. Ambroxol improves glucocerebrosidase function and attenuates $\alpha$ -synuclein pathology in patient-derived midbrain organoids of *GBA1*-Parkinson's disease

### Authors

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### Objective:

To test the efficacy of ambroxol on  $\beta$ -glucocerebrosidase (GCase) dysfunction and  $\alpha$ -synuclein ( $\alpha$ -syn) pathology in midbrain organoids (MOs) derived from Parkinson's disease (PD) patients carrying *GBA1* variants.

### Background

Variants in *GBA1*, encoding the lysosomal GCase enzyme, are the most frequent genetic risk factor for PD. In *GBA1*-PD, enzymatic-dependent and non-enzymatic factors likely contribute to  $\alpha$ -syn pathology, as suggested by the similar risk of developing PD in carriers of one *GBA1* variant, showing a residual GCase enzyme activity, and in individuals with biallelic mutations leading to enzymatic function loss and presenting with Gaucher disease (GD).

### Methods

Induced pluripotent stem cell (iPSC) lines of two patients carrying the L444P *GBA1* variant (a *GBA1*-heterozygous PD patient and a *GBA1*-homozygous PD/GD patient) and three healthy controls were differentiated into MOs with a novel dopaminergic-patterning protocol. MOs at 90 days *in vitro* were treated with ambroxol for 10 days. Samples collected in basal conditions and after treatment underwent immunofluorescence, Western blot, electron microscopy imaging, and GCase enzymatic activity assays.

### Results

Generated MOs displayed features of human midbrain post-natal maturation (*e.g.*, key dopaminergic markers, neuromelanin pigmentation). GCase enzymatic activity was reduced in *GBA1* heterozygous MOs and undetectable in *GBA1* homozygous MOs, leading to increased levels of the enzymatic substrate – glucosylceramide. In *GBA1*-mutant MOs, misfolded GCase protein was retained in the endoplasmic reticulum and initiated the unfolded protein response. *GBA1*-mutant MOs displayed detergent-resistant  $\alpha$ -syn and aggregates of insoluble  $\alpha$ -syn with biochemical, immunohistochemical, and ultrastructural features of Lewy body pathology. Upon treatment with ambroxol, GCase enzymatic activity in *GBA1* heterozygous MOs was restored to normal levels and GCase protein was relocated to its physiological lysosomal site. Ambroxol significantly reduced the amount of  $\alpha$ -syn and the load of Lewy-like pathology in treated MOs.

### Conclusions

We report the first demonstration of the efficacy of ambroxol in rescuing  $\alpha$ -syn pathology in MOs derived from PD patients. Our results support the role of ambroxol targeting  $\alpha$ -syn aggregation by mobilizing the sequestered mutant GCase from the endoplasmic reticulum to the lysosome. Additionally, the restoration of GCase activity in *GBA1* heterozygous MOs may contribute to the reduction of  $\alpha$ -syn levels by means of non-specific protein disposal. These observations support a role for ambroxol administration in engaging with the GCase pathway and  $\alpha$ -syn in PD and potentially acting as a promising disease-modifying compound.

## 55. Using a novel engineered phage to prevent A $\beta$ toxicity

### Authors

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### Abstract

Alzheimer's disease (AD) is characterized by progressive synaptic dysfunction, cognitive decline, and memory loss caused by the accumulation of A $\beta$  and tau. Despite extensive research, no definitive cure is available, emphasizing the urgent need for innovative approaches to manage and mitigate the disease. In this study, we tested the efficacy of an engineered bacteriophage as a therapeutic agent against A $\beta$  toxicity in SH-SY5Y neuroblastoma cells. We used a previously identified engineered bacteriophage (herein referred to as 12CIII1) that selectively recognizes circulating conformation-specific A $\beta$  autoantibodies present in the blood of AD patients. Using a computational approach, we provide evidence that 12CIII1 binds to different assembly states of A $\beta$ . Specifically, our data suggest that 12CIII1 has little affinity for A $\beta$  monomers, while most interactions occur with nonamers and dodecamers. This is notable as the oligomeric forms of A $\beta$  are primarily responsible for neurotoxicity. We also found that 12CIII1 protects SH-SY5Y cells from A $\beta$  toxicity, as evidenced by a significant increase in cell viability and neurite number and length. This finding underscores the phage's efficacy in mitigating the detrimental impacts of A $\beta$ . These results highlight the potential of the 12CIII1 phage as a promising candidate for therapeutic intervention in AD, offering a novel strategy to combat cellular toxicity and support neuronal health.

## **56. Cannabinerol restores mRNA splicing defects induced by $\beta$ -amyloid in an in vitro model of Alzheimer's disease.**

### **Authors**

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### **Abstract**

Alzheimer's disease (AD) is the most common form of dementia, characterized by  $\beta$ -amyloid (A $\beta$ ) plaques and neurofibrillary tangles, leading to neuronal loss and cognitive impairments. Recent studies have reported dysregulation of RNA splicing in AD pathogenesis. In a previous transcriptomic study, we demonstrated the neuroprotective effect of the phytocannabinoid cannabinerol (CBNR) against cell viability loss induced by A $\beta$  in differentiated SH-SY5Y cells. We noticed that A $\beta$  exposure or CBNR pre-treatment regulated genes involved in mRNA splicing. Here, we investigated whether CBNR can restore splicing defects induced by A $\beta$  in an AD in vitro model. For this purpose, we took advantage of the rMATS computational tool for detecting five categories of differential alternative splicing events (ASEs) from RNA-Seq data: A3SS (alternative 3' splice site), A5SS (alternative 5' splice site), MXE (mutually exclusive exons), RI (retained intron), and SE (skipped exon). We obtained 456 significant ASEs in A $\beta$  samples compared to controls (65 A3SS, 38 A5SS, 41 MXE, 72 RI, 240 SE). Similarly, 481 ASEs were differentially regulated by CBNR pre-treatment compared to A $\beta$  samples (77 A3SS, 46 A5SS, 44 MXE, 52 RI, 262 SE). These ASEs belonged to genes mainly associated with DNA repair and cell cycle regulation. Interestingly, 85 ASEs were shared between the two comparisons and were restored by CBNR. All these data suggest that CBNR may restore dysregulation of splicing in this AD model. Additionally, investigating RNA-binding protein and miRNA motifs around ASE regions could reveal trans-gene regulation by CBNR, potentially explaining its neuroprotective role.

## 57. Assessing the Molecular Relationship Among miR-125b, A $\beta$ , and Tau

### Authors

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### Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder. Increasing evidence indicates that miRNA dysfunction is involved in AD pathogenesis, although the underlying mechanisms remain unclear. Notably, circulating levels of miR-125b are reduced in the blood of AD patients and correlate with Mini Mental State Examination scores. Conversely, in primary neurons, miR-125b overexpression promotes Tau phosphorylation and affects the activity of proteins related to cell cycle regulation. To investigate the molecular interactions among miR-125b, tau, and A $\beta$ , we employed SH-SY5Y cells, either stably transfected with tau or exposed to A $\beta$  oligomers and assessed changes in miR-125b levels. Additionally, to explore the impact of both tau and A $\beta$  on miR-125b levels, tau-expressing cells were treated with A $\beta$  oligomers. We will present data on cell morphology and vitality, which were assessed using optical microscopy and MTT assays. Furthermore, we used bioinformatic tools such as mirPath and KEGG to identify key targets of miR-125b in AD. Overall, our data provide initial insights into the molecular connections between miR-125b and AD neuropathology.

This work has been funded by the European Union (NextGeneration EU) through the MUR-PNRR project SAMOTHRACE.

## 58. Olfactory function and its relationship with structural brain network topology in Parkinson's disease and prodromal stages

### Authors

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Olfactory dysfunction is a non-motor symptom of Parkinson's Disease (PD) holding significant predictive value for PD development [1]. This study aims to explore the association between structural network and olfactory function among PD patients, prodromal (PR), and healthy (HC) individuals.

Diffusion Magnetic Resonance Imaging (dMRI) data were derived from the Parkinson's Progression Markers Initiative (PPMI), including 97 PD, 65 PR subjects, and 61 HCs. PD and PR subjects were further divided into four subgroups based on University of Pennsylvania Smell Identification Test (UPSIT) score [2]: 14 PR\_AO+, 51 PR\_AO-, 36 PD\_AO+, 61 PD\_AO- (AO+ anosmia; AO- no anosmia). Whole-brain probabilistic tractography was combined with the Schaefer parcellation (n=100) to reconstruct connectivity matrices that underwent topological network analysis [3]. ANOVA (Tukey's HSD post hoc) or Kruskal-Wallis (Dunn's post hoc) was applied and correlation analyses (Pearson or Spearman) were performed.

Intergroup analysis shows significant differences in modularity between HCs and PR\_AO+ ( $p = 0.007$ ), HCs and PR\_AO- ( $p = 0.028$ ), PR\_AO+ and PD\_AO- ( $p = 0.014$ ). Structural consistency analysis reveals significant differences between HCs and PD\_AO+ ( $p = 0.020$ ). Additionally, differences in small-world omega were observed between HCs and PR\_AO+ ( $p = 0.023$ ) and between PR\_AO+ and PD\_AO- ( $p = 0.043$ ). Correlation analysis for PR\_AO+ shows a significant negative correlation between UPSIT scores and assortativity ( $r = -0.558$ ,  $p = 0.038$ ) and a positive correlation with power-law gamma ( $p = 0.622$ ,  $p = 0.018$ ).

The findings suggest network alterations in PR and PD subjects with olfactory dysfunction, highlighting the need of developing potential novel biomarkers for PD diagnosis and monitoring.

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## 59. Exploring pharmaco-dynamic resting-state EEG correlates of Parkinson's disease with and without dyskinesia: a preliminary analysis

### Authors

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### Background

Analyses of electroencephalographic (EEG) oscillations have been used to characterize the cortical neurophysiological signature of Parkinson's disease (PD)[1]. However, only few studies have investigated how EEG signatures change following L-DOPA administration in PD [2, 3].

Furthermore, it has been suggested that common methods used to analyze brain oscillations may conflate contribution from periodic and aperiodic activity, leading to potential misinterpretations of spectral power variations [4]. In this study we investigate differences and changes in periodic and aperiodic activity using parametrized spectra obtained from PD patients with and without L-DOPA-induced dyskinesias (LID) and healthy controls (HC).

### Methods

3-minutes resting-state EEG data from 28 PD patients (15 PD with LID and 13 without) were collected before and three times after an oral dose of L-DOPA. EEG data from 10 age-matched individuals without PD served as healthy controls. At each time point, spectral parameterization [5] was performed to investigate sensorimotor spectral power within canonical frequency bands as well as aperiodic parameters. This allowed us to characterize differences between PD and HC as well as dopamine-related dynamic changes in spontaneous cortical activity in PD.

### Results

A linear mixed effect model revealed significantly lower aperiodic offset in both PD groups compared to HC in electrodes overlying primary sensorimotor cortices. No significant differences were observed in oscillatory power in the alpha (8-12Hz) and beta (15-30Hz) bands. Furthermore, no significant changes in alpha or beta power or aperiodic parameters were observed across timepoints.

### Conclusions

The aperiodic offset of the EEG spectrogram is significantly lower in PD and PD-LID groups than in HC, which may affect the interpretation of oscillatory brain activity in PD due to conflation with the aperiodic component. Further analysis is needed to corroborate these preliminary findings.

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