

Abstracts

Research seminar 6th of May 2025

Non-pharmacological rehabilitation research and
Parkinsons disease

*The Danish Knowledge- and Competence Center for Rehabilitation for People with
Parkinsons disease*

PARKINSON
foreningen



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Session 2 - Parkinson's and everyday living

2.1. Relative Hope, Relative Care - Parkinson's disease carers on hope and evolving care

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Background: Parkinson's disease (PD) is a neurodegenerative condition that profoundly impacts the everyday lives, relationships, and social lives of those affected. As the disease progresses, the need for caregiving increases, leading some to describe PD as a "family disease." While caregiving in PD has often been viewed as a burden, the role of hope in this context remains underexplored. Given that hope has been identified as an important source of strength in serious illness, understanding everyday life as a PD relative across different stages of the disease and relatives' sources of hope is crucial to providing better support for caregivers.

Aim: We aimed to explore the everyday life of PD relatives, examining the nuances of care in different disease stages, and exploring sources of hope.

Methods: Six months of ethnographic fieldwork, including participant observation in PD support groups for relatives, along with in-depth interviews with 15 caregivers.

Preliminary results: We found hope and care relative to the stages of the disease progression, as hope and care evolve in intensity and complexity over time. With the concept of "evolving care," we illustrate how caregiving tasks, roles, and emotions change over time, requiring caregivers to continuously revise, refine, and redefine their care efforts. Hope appeared multiple and dynamic, as hope assumed several modes and dimensions in a person and between persons. Sources of hope included medical treatments, training, healthy living, faith, and shared experiences, as well as interacting with family and other PD relatives. Psychotic episodes and dementia were identified as critical tipping points of care and hope, where relatives find it difficult to mobilize hope for a life together and contemplate caring for their loved one until death.

Conclusion: In conclusion, our study highlights the evolving nature of care and hope in PD caregiving, emphasizing their dynamic, stage-dependent transformation. Hope, deeply rooted in social relationships, serves as a vital source of strength for relatives, though it becomes fragile during critical moments like psychotic episodes and dementia. Support is crucial during these tipping points.

2.2. Non-pharmacological Rehabilitation for People Living with Advanced Parkinson Disease: A Scoping Review of Interventions

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Background: Rehabilitation becomes increasingly important in the more advanced stages of Parkinson's Disease. As the disease reaches its more debilitating stages and pharmacological or surgical treatment becomes less relevant, non-pharmacological interventions including rehabilitation becomes key. Existing systematic interventions typically target patients in early to mid-stages of the disease.

Aim: The objective of this scoping review was to identify and map the available evidence on non-pharmacological rehabilitation interventions for people living with advanced Parkinson's disease.

Methods: This scoping review was conducted in accordance with the methodology for scoping reviews developed by the Joanna Briggs Institute. A systematic search was conducted in PubMed, EMBASE, CINAHL and Cochrane. Studies published in English from 2000 to May 2024 were considered eligible and screened for relevance.

Results: Thirteen studies were included. The majority of the interventions were experimental; one had a focus on feasibility and one a mixed focus of effect and feasibility. Most interventions were referred to as either rehabilitation, training or therapy, with the two feasibility interventions focusing on comprehensive assessment and referrals. The majority used modalities concerned with levels of functioning. Studies focusing on stage 4 (H&Y) Parkinson's disease were prominent.

Conclusions: This scoping review provides a foundational overview of existing non-pharmacological rehabilitation interventions for advanced Parkinson's disease, revealing a small yet diverse range of approaches, from single-disciplinary to multidisciplinary interventions. It offers initial insights that can point to areas where further research can solidify and expand effective, targeted care strategies for people living with advanced Parkinson's disease.

2.3. Non-Pharmacological Interventions for Cognitive Impairments in Parkinson's Disease: An Umbrella Review

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Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by both motor and non-motor symptoms, including cognitive impairments that significantly reduce quality of life. Cognitive difficulties range from mild cognitive impairment (MCI) to Parkinson's disease dementia (PDD), impacting executive function, memory, and other domains. Non-pharmacological interventions, such as cognitive training and physical exercise, have gained attention as potential strategies to address cognitive impairments. However, the fragmented nature of existing evidence complicates the identification of effective interventions.

Objective/Hypothesis: This umbrella review aims to synthesize knowledge from existing literature reviews to map the range and characteristics of non-pharmacological interventions targeting cognitive impairments in home-dwelling individuals with Parkinson's disease.

Method/Study design: Following the Joanna Briggs Institute methodology and PRISMA guidelines, systematic reviews, meta-analyses, and scoping reviews published between 2018 and 2024 were included. Eligible studies addressed non-pharmacological interventions focusing on cognition in individuals with PD, emphasizing home-dwelling populations. Data from six reviews were systematically extracted, charted, and assessed for quality using the JBI Critical Appraisal Tool.

Preliminary Results: Six systematic reviews were included, encompassing interventions such as cognitive training, physical exercise, and combined approaches. While interventions demonstrated modest improvements in specific cognitive domains, outcomes varied depending on the intervention type, participant characteristics, and study quality. Methodological limitations, including small sample sizes and inconsistent cognitive assessments, were common. Most reviews achieved high methodological quality, but the primary studies synthesized often demonstrated significant risks of bias.

Conclusion (Perspectives): Non-pharmacological interventions show promise for mitigating cognitive impairments in PD, but evidence remains inconsistent. Tailored, multidimensional approaches integrating cognitive and physical training may provide the most comprehensive benefits. Future research should focus on high-quality, standardized studies with long-term follow-up to strengthen the evidence base and inform clinical practice. This review underscores the importance of addressing the interplay between motor and cognitive impairments in PD management.

Session 3 – Physical activity and Parkinson's

3.1. The impact of physical activity and exercise participation in early Parkinson's disease

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Background: Exercise is beneficial in managing Parkinson's disease, yet its potential remains less clear in early stages. This cross-sectional study examines the impact of physical activity and exercise participation in early Parkinson's disease.

Objectives: To compare disease-specific, physical function, cognitive performance, and patient-reported outcomes across healthy controls and early-stage Parkinson's disease patients categorized as 'highly active' (moderate to high intensity aerobic exercise \geq twice-weekly) or 'low-active' (exercise \leq twice-weekly).

Methods: 70 low-active patients, 35 highly active patients, and 35 healthy controls were included. Assessments included Timed Up and Go Test, Six Spot Step Test, Six Minute Walk Test, Mini Balance Evaluation Systems Test, Lower Extremity Muscle Peak Power, Aerobic Capacity, Physical Activity, Montreal Cognitive Assessment, Symbol Digit Modalities Test, Parkinson's Disease Questionnaire, Non-Motor Symptoms Questionnaire, Falls Efficacy Scale-International, European Quality of Life Questionnaire, Beck Depression Inventory-II, and the Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale.

Results: High-activity patients outperformed low-activity patients in physical functions, while showing comparable results to healthy controls on several tests. Low-activity patients showed impairments in all physical function and activity outcomes relative to healthy controls. Cognitive scores were similar across patient groups, although healthy controls performed better in processing speed. No significant differences were found between patient groups in quality of life or depressive symptoms.

Conclusions: Regular engagement in aerobic exercise in early Parkinson's disease was associated with preserved physical function, suggesting its potential role in mitigating disease-related decline. These findings advocate for early, high-intensity exercise interventions in Parkinson's disease management strategies.

3.2. Efficacy of aerobic exercise on brain MRI measures in Parkinson's disease

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Background: Physical exercise is a potentially inexpensive and easily accessible disease modifying therapy in Parkinson's disease. Recent studies using magnetic resonance imaging (MRI) point to several promising disease progression markers.

Objectives: To determine whether 24 weeks of moderate to high-intensity progressive aerobic exercise affects brain MRI measures in people with Parkinson's disease.

Methods: We conducted a randomized controlled trial (with a 24-week follow-up) including an exercise group (supervised aerobic exercise followed by self-guided physical activity) and a control group (habitual lifestyle). Mildly to moderately impaired patients aged 42–80 years were randomized (1:1). The primary outcome was R2* (effective transverse relaxation rate) in the substantia nigra pars compacta (SNpc) after 24 weeks, analyzed using the intention-to-treat principle. Additional outcomes included quantitative susceptibility mapping (QSM), free water and neuromelanin levels, brain volumetry, levodopa dose equivalency (LDE), cardiorespiratory fitness, 6-min walk test (6MWT), Symbol Digit Modalities Test (SDMT), and the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

Results: Seventy participants were recruited. SNpc R2* did not change over the intervention period (mean between-group change -1.14, 95% confidence interval [CI] -5.14 to 2.87). Similarly, no effects were seen in cardiorespiratory fitness (+1.64 mL O₂/min/kg, -0.23 to 3.51) and MDS-UPDRS III (-0.67, -5.35 to 4.00). Oppositely, LDE (-78.4, -154.6 to -2.14) and red nucleus QSM (-12.53, -25.95 to 0.89) improved following 24 weeks of exercise. Changes in cardiorespiratory fitness correlated with changes in the 6MWT as well as the SDMT.

Conclusions: These findings do not support a neuroprotective effect of progressive aerobic exercise in terms of R2* and most secondary MRI outcomes in people with Parkinson's disease. However, LDE decreased 18% following exercise and some secondary MRI outcomes improved, while cardiorespiratory fitness correlations suggest potential effects of exercise on walking capacity and cognitive performance. Further investigations are warranted due to the limitations of this study (e.g., control group increasing physical activity and cardiorespiratory fitness).

3.3 Parkinson's disease and voluntary walking – a systematic review and meta-analysis

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Introduction: Despite the common use of walking as a rehabilitation intervention in people with Parkinson's disease (pwPD), no previous review has examined the isolated effect of walking on gait parameters (i.e., velocity, distance, stride length, or step length etc.) in pwPD compared to non-active controls. We therefore aimed to quantify the effect of interventions targeting voluntary walking on gait function in pwPD.

Materials and methods: PubMed and EMBASE were searched for relevant studies. Eligibility criteria were: 1) randomized controlled trials (RCT) or pilot RCT's, 2) participants diagnosed with Parkinson's disease, 3) evaluation of any voluntary structured walking intervention (>3 weeks and/or >6 training sessions), and 4) pre- and post-intervention walking assessments. Post-mean data of short and long walking tests, Timed-Up and Go (TUG) test, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale III (MDS-UPDRS III), and Parkinson's Disease Questionnaire-39 were extracted and analyzed.

Results: Fifteen studies (11 RCT, 4 pilot-RCT) were included covering 590 pwPD (mean age 65.7 (±7.5) years; 208 women). Meta-analyses showed positive effects of voluntary walking interventions on gait speed (i.e., short walking tests, standardized mean difference (SMD) = 0.60 [0.23; 0.96]), gait distance (i.e., long walking tests, SMD = 0.84 [0.56; 1.12]), step length (SMD = 0.71 [0.34; 1.09]), stride length (SMD = 0.58 [0.14; 1.00]), MDS-UPDRS III (SMD = -0.39 [-0.62; -0.16]), and TUG (SMD = -0.38 [-0.73; 0.04]).

Conclusion: Voluntary walking demonstrated improved gait and mobility function, as well as lower disease severity. These results support the use of voluntary walking during rehabilitation, but future large scale and long-term studies are needed to support these results.

3.4. High-intensity aerobic exercise increases brain synaptic SV2A protein density and striatal frontal connectivity in Parkinson disease patients: A PET-MRI study

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Introduction: Physical exercise is a non-pharmacological intervention that has beneficial effects on both the motor and non-motor symptoms of Parkinson's disease (PD). However, the mechanisms underlying these benefits remain unclear. We tested the hypothesis that a high-intensity aerobic exercise protocol can improve brain connectivity and synaptic density in people with Parkinson's (PwP). This study will help determine whether long-term exercise induces synaptic changes and provide a rational basis for using this approach to combat the disease.

Methods: This in vivo study combined functional magnetic resonance imaging (fMRI) with positron emission tomography (PET) data. 40 PwP were recruited and two timepoints were evaluated: (1) a baseline scan prior to exercise protocol; and (2) 24 weeks after regular exercising or remaining sedentary. 20 PwP were assigned to high-intensity aerobic exercise training, and 20 PwP kept their daily life routine. The exercise protocol included supervised training: Five training sessions per 14 days for 24 weeks (1 x continuous + 1-2 x interval training / week). ¹¹C-UCB-J PET, a marker of synaptic SV2A protein, was used to evaluate the brain synaptic density/plasticity.

Preliminary results: Supporting a beneficial effect of exercise, preliminary analysis showed that 6 months of exercise increased the binding of the synaptic density marker [¹¹C]UCB-J in some active cases. Preliminary analysis of substantia nigra (SN) [¹¹C]UCB-J SUVR-1, revealed that 6 months of exercise improved the mean SV2A level in the most affected SN (ca. 18%, p=0.039) which was not observed in PwP who did not performed the high-intensity exercise protocol. There was also an increase in the brain functional connectivity, evaluated by resting state fMRI, between the left putamen and left prefrontal cortex (cluster size of 311 voxels) when we compared PwP before and after exercise. In addition, subjects revealed an improvement in their depressive features and tests to evaluate walking (time to get up and go test, Six-spot step test and 6 minutes of walking test).

Preliminary conclusions: These findings suggest that long-term aerobic exercise may promote synaptic plasticity and improve brain connectivity in PwP, supporting its potential as a therapeutic strategy for PD.

3.5. Mapping the correlation of everyday physical activity with motor and non-motor symptoms in Parkinsons disease

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Background: People with Parkinson (PwP) are generally less physically active compared to individuals of similar age groups, and this physical activity (PA) tends to decrease further as the disease advances. Inactivity is associated with increased symptom burden, reduced functional level and quality of life, as well as a higher incidence of non-motor symptoms. Previous research has primarily been based on self-reported data and snapshots of PA and symptom burden. It is relevant to investigate the relationship between these parameters using objective measurements in everyday life.

Objective: The aim of the study is to evaluate how bradykinesia, dyskinesia and non-motor symptoms, monitored in everyday life, relate to PA offering a more precise understanding of their association.

Method: This study is an add-on study of the self-management project, Empower-PD 5. The participants in this study are the full cross-sectional cohort enrolled in the Empower-PD project. Empower-PD was an 8-week self-management program, with 3- and 6-month follow-ups. Participants received expert presentations, took part in workshops, and set individual goals. The effects were assessed using questionnaires and PKG watches, which monitored symptoms and activity in daily life. Participants were recruited through hospitals, clinics, rehabilitation centers, and self-referrals. Inclusion criteria were a PD diagnosis, age over 18, H/Y stage 1–3, and cognitive function (MoCA ≥ 25). Physical activity was measured by daily step count, motor symptoms by scores for bradykinesia (BKS) and dyskinesia (DKS), and non-motor symptoms were assessed using the Non-Motor Symptoms Questionnaire (NMSQ). Data were analyzed using correlation analyses to evaluate the relationship between physical activity and symptoms.

Results: The study included 80 participants, primarily in the early stages. The participants had an average daily step count of 6,139, moderate BKS, and low DKS, with considerable variation. Correlation analyses showed a moderate to strong negative relationship between step count and BKS, indicating that more steps were associated with less BKS. There was also a moderate to strong positive relationship between steps and DKS, while the relationship between steps and NMS was weak and not statistically significant.

Conclusion: Daily step count was moderately associated with lower BKS and increased DKS, generating a hypothesis about the significance of PA for motor symptoms. However, the study design had its limitations and did not allow for an assessment of causality. Wearables enabled objective measurements of symptoms and activity in daily life, which could contribute to a better understanding of symptoms, treatment effects, and activity levels. Future research should explore how such technologies can be applied in both research and clinical practice.

3.6. Unlocking the pleasurable urge to move to music in people with Parkinson's disease through rhythm and social connection

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Introduction/Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms, significantly impacting quality of life. Music-based therapies, particularly Rhythmic Auditory Stimulation (RAS), have shown promise in improving motor function and emotional well-being by engaging motor and reward networks. However, most RAS studies neglect the prosocial and inclusive nature of music, which may enhance therapeutic outcomes through social interactions. This study investigates how rhythmic complexity and social conditions influence the pleasurable urge to move to music (PLUMM) and motor quality in PD.

Purpose/Hypothesis: This study aims to identify the effects of rhythmic complexity and social interaction on PLUMM and motor quality in PD. We hypothesize that social conditions improve PLUMM and motor quality compared to auditory or audiovisual conditions and that moderate rhythmic complexity will yield the most significant improvements.

Methods: Forty participants with mild-to-moderate PD completed a tapping task under three conditions: auditory, audiovisual, and social (with an experimenter). They tapped along to rhythms of varying complexity (isochronous, low, moderate, and high). Dependent variables included PLUMM ratings, motor quality measured via motion energy analysis from video recordings, and felt synchronicity. Data were analyzed using linear mixed-effects models, with additional correlations to empathy traits, felt synchronicity, and disease severity.

Preliminary Results: Significant main effects of condition ($p < 0.001$) and rhythmic complexity ($p < 0.001$) were observed for PLUMM ratings, with the social condition eliciting higher scores compared to auditory ($p = 0.001$) and audiovisual conditions ($p < 0.001$). Motor quality also showed significant main effects of condition ($p = 0.02$) and rhythmic complexity ($p = 0.01$), especially comparing auditory an social conditions ($p = 0.01$). Empathy ($r = 0.43$, $p = 0.006$) and felt synchronicity ($r = 0.33$, $p = 0.04$) positively correlated with PLUMM ratings, while disease severity showed a non-significant negative association ($r = -0.19$, $p = 0.26$). No significant correlations were found in terms of motor quality.

Conclusion (Perspectives): Including social interactions in RAS enhances PLUMM and motor quality in PD, supporting its clinical application. The findings suggest that social and rhythmically engaging interventions can improve therapeutic outcomes, emphasizing the need for tailored music-based therapies that incorporate social dimensions to maximize their benefits for individuals with PD.

Session 4 – Poster session with coffee and cake

4.1. Supporting family caregivers of people living with Parkinson's disease: Protocol for a complex intervention

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Introduction: Parkinson's disease (PD) represents an urgent healthcare concern due to its rising prevalence and high care costs. This neurodegenerative disease, with its progressively heterogeneous symptoms, requires extensive nursing support of people with PD (PwPD), but also their families. Families take on caregiving roles and provide multifaceted support, which may lead to caregiver burden and affect their own health. Thus, it is pivotal to support family caregivers (FCs) of PwPD. Research shows that interventions aimed at FCs are sparse. However, a compassionate nurse-patient relationship is essential for providing person-centered, high-quality nursing care, tailored to FCs' needs based on PD onset, stage, symptoms and the context of their everyday life.

Aim: To develop, test, and evaluate a nurse-led, person-centered intervention to support FCs of PwPD to manage as caregivers in everyday life, using the Fundamentals of Care (FoC) framework.

Method: Using the MRC-framework for complex interventions, three sub-studies will be conducted:

I) A scoping review: To map the existing evidence on supportive interventions aimed at FCs of individuals with neurodegenerative diseases

II) A development study: To develop a person-centered nurse-led evidence-based intervention aimed at FCs in cocreation with stakeholders, based upon the core dimensions of FoC: A trusting therapeutic relationship; Integrating a person's needs and, The context of care

III) A feasibility study: To qualitatively evaluate the feasibility of the nurse-led person-centered intervention to support FCs of PwPD, using observations and semi-structured interviews

Perspectives: An in-dept rationale for the study will be presented, along with an outline of how FoC will be used as a theoretical framework for developing, delivering, and evaluating the intervention. It is assumed that the study will have the perspective to provide valuable insights on how a nurse-led, evidence-based, and cocreated person-centered intervention may support FCs in managing everyday life. Engaging stakeholders will ensure the development of a high-quality intervention tailored to contextual factors. This is expected to positively influence the subsequent testing phase during the implementation process across a larger population of FCs, including multicenter sites across regions. A detailed description of the intervention will facilitate adaptation, benefiting FCs of individuals with other neurodegenerative diseases.

4.2. Parkinson's Disease and Cognitive Impairments – Everyday Life and Formal and Informal Support in Rural Areas (PARKLAND)

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Background: Cognitive impairments are common non-motor symptoms of Parkinson's disease and contribute substantially to both individual and societal burdens. These impairments can significantly diminish quality of life for individuals with Parkinson's disease and their families, affecting daily functioning, independence, and overall well-being. Patients living in rural areas often face additional challenges. International studies indicate that they experience notably lower quality of life compared to their urban counterparts, largely due to reduced access to treatment, rehabilitation services, and formal support systems.

Aim: This study aims to explore the daily lives, including the formal and informal support, of individuals with Parkinson's disease and cognitive impairments living in rural areas of Southern Denmark.

Method: Semi-structured interviews will be conducted with up to 15 participants. Patient recruitment will take place in collaboration with the Department of Neurology at the Hospital of Southern Jutland.

Inclusion criteria are as follows:

- Diagnosed with idiopathic Parkinson's disease for more than two years
- MoCA cognitive score below 26
- Aged 50 years or older
- Living at home in rural areas within the catchment area of the Hospital of Southern Jutland

The interviews will explore participants' experiences of daily life with Parkinson's disease and cognitive impairments, including activities of daily living (ADLs), physical activity, social relationships, community engagement, and access to both informal and formal support services, treatment, and rehabilitation. Qualitative data will be analyzed using thematic analysis, guided by Everyday Life Theory (1) and the Transactional Model of Occupation (2).

At baseline, the following data will be collected: date of diagnosis, cognitive status, MoCA score, functional ability (MDS-UPDRS, patient-administered part), and quality of life using both the PDQ-39 and EQ-5D-5L instruments.

In parallel with the primary study, a secondary analysis of REHPA's Parkinson's database will be conducted to examine rural-urban disparities in quality of life in Southern Jutland.

A Patient and Public Involvement (PPI)-inspired advisory board will be established to support and inform the project.

Implications for clinical practice: The study will offer in-depth qualitative insights into the daily lives of a vulnerable patient group, providing a valuable foundation for the development of tailored rehabilitative services.

Timeline: Participant inclusion began in March 2025. Interviews are scheduled to commence in May and will be completed by November 2025 at the latest.

Theoretical perspectives: The theoretical perspective will among other theories be inspired by theory of everyday life by Birte Bech-Jørgensen and "The Transactional Model of Occupation (TMO) to illustrate the complexity of activity and theory of everyday life.

4.3. Transcranial magnetic stimulation evoked potentials used to assess pain and gait symptoms in persons with Parkinson's disease: a protocol

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Introduction/background: Parkinson's disease (PD) is the fastest growing neurodegenerative disease and affects about 2% of people older than 65 years. The types and intensity of appendicular motor symptoms such as limb tremor and rigidity, fit clear mechanistic models linking alpha synuclein deposition neurodegenerative changes in dopaminergic nigrostriatal pathways. This mechanistic knowledge allows for the development of effective mechanism-based therapies based on dopamine-replacement medications and neuromodulation. However, non-motor (i.e., chronic pain, constipation, cognitive dysfunction, mood, sleep, and genitourinary) and axial motor (i.e. gait) symptoms are also part of the disease, being equally related to neurodegenerative processes affecting non-dopaminergic projection fibers and systems. However, very little is known about the central abnormalities related to non-motor (specifically pain) and axial (i.e., gait) symptoms despite being the largest daily challenges. Following previous studies showing that non-motor symptoms may present different corticospinal motor excitability profiles depending on the symptom phenotyping, we propose to perform the first comprehensive description of brain connectivity profiles relating to pain and gait in people with PD.

Aim/hypothesis: The main hypothesis is that different clusters of non-motor and axial symptoms will present distinct transcranial magnetic stimulation (TMS) evoked potential (TEPs) characteristics on concomitant electroencephalographic (EEG) recordings, and these differences will be related to symptom intensity.

Methods/study design: People with PD (Hoehn-Yahr 1-3) diagnosed according to the UK brain bank criteria will be included and assessed for non-motor symptoms (Kings non-motor symptom questionnaire), pain (Parkinson Disease Pain Scoring system), quality of life (PDQ8), mood, sleep, motor state (Part III UPDRS), and medication use, along with motor (gait: timed up and go task) symptoms. TEPs will be recorded from all participants during TMS-EEG recordings, with TMS targeting their primary motor cortex. TEPs amplitudes, as well as M1 natural frequency, power in the alpha frequency, and phase-based connectivity measures will be computed and classified according to normative data from healthy individuals.

Perspectives: This will be the first study comprehensively studying non-motor symptoms in people with PD and assess potential cortical neurophysiology markers of these dysfunctions. This effort will pave the way for the development of mechanism-based preventive and therapeutic interventions for non-motor symptoms.