Dutch Parkinson Scientists Conference 2024

“Translational Neuroscience”

Program & Abstract Booklet
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@DPSConference24

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Foreword from the organizing committee

Dear fellow colleagues and researchers,

It is with great pleasure that we welcome you to the 2024 DPS Conference in Utrecht. After the success of last year's gathering in Nijmegen, we are thrilled to bring together another dynamic group of scientists, clinicians, and professionals who share a commitment to advancing our understanding of Parkinson's disease.

The theme of this year's conference, **"Translational Neuroscience,"** embodies the bridge between basic scientific discoveries and their application to patient care. We are especially honoured to have **Prof. Dr. Thomas Perlmann** from Karolinska Institutet as our keynote speaker, sharing his cutting-edge work in the field of Parkinson's disease.

We encourage you to engage deeply with the program, explore new perspectives, and take full advantage of the opportunity to connect with fellow researchers from diverse backgrounds. Whether you are presenting your latest research, attending talks, or participating in the junior pre-conference, your contribution to this vibrant community is invaluable.

Thank you for joining us in Utrecht. We look forward to a day of inspiring discussions, learning, and collaboration that will continue to drive progress in Parkinson's research.

Warmest regards,
The DPS Conference Committee 2024

Sponsors

This conference is kindly supported by:

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Programme DPS conference 2024

Registration open from 8:30

9:00 – 9:15	**Opening statement**: *Jeroen Pasterkamp (UMC Utrecht)*
9:15 – 10:15	**Keynote lecture:** *Thomas Perlmann (Karolinska Institutet)*
10:15 – 10:55	**Dutch Research Tour**
	UMC Utrecht - *Jeroen Pasterkamp & Paul Hop*
	Amsterdam UMC - *Wilma van de Berg & Bram van der Gaag*
10:55 – 11:20	**Coffee break**
11:20 – 12:00	**Dutch Research Tour**
	LUMC - *Dagmar Hepp & Manon Mijnsbergen*
	UMCG - *Sygrid van der Zee & Eugenia Goya*
12:00 – 12:30	**Best Abstracts**
	Jinte Middeldorp (BPRC)
	Gobert Heesink (UTwente)
12:30 – 14:00	**Lunch + Poster presentations**
14:00 – 14:40	**Dutch Research Tour**
	Radboud UMC - *Sirwan Darweesh & Milan Beckers*
	Erasmus MC - *Vincenzo Bonifati & Wim Mandemakers*
14:40 - 15:00	**Patient researchers** – **Parkinson Vereniging:** *Paul Passier*
15:00 – 15:20	**Coffee break**
15:20 – 15:50	**Best Abstracts**
	Sofie Lövdal (UMCG)
	Ehsan Pishva (Maastricht University)
15:50 – 16:20	**Award Ceremony by ParkinsonNL:** *Anneke Mels*
16:20 – 16:50	**Parkinson Alliance research agenda 2025:** *Wilma van de Berg*
16:50 – 17:00	**Closing statement + Poster/presentation Prizes:** *Jeroen Pasterkamp*
17:00 – 18:00	**Social, drinks and bites**

Abstracts

The predictive value of FDG PET-derived biomarkers for neurodegenerative disease progression in isolated REM Sleep Behavior Disorder

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Background:
Isolated REM sleep behavior disorder (iRBD) is the strongest prodromal risk marker for alpha-synucleinopathies. FDG-PET visualizes brain glucose metabolism, revealing functional brain changes related to neurodegeneration. In Parkinson's Disease (PD), these changes are captured in the PD-related pattern (PDRP). Previous small longitudinal studies have shown steeper increases in PDRP z-scores in iRBD patients who later converted to PD or dementia with Lewy bodies (DLB) compared to non-converters. Larger studies are required to validate its predictive utility. The REMPET3 consortium comprises FDG-PET data from seven international centers, primarily collected for previously published or ongoing research. The goal of this study is to assess PDRP progression and its predictive power concerning phenoconversion to PD, DLB or Multiple System Atrophy (MSA).

Methods:
Imaging and clinical assessments were collected at three different timepoints, with 213 scans at baseline, 79 at the first follow-up, and 20 at the second. Participants were classified as converters (PD, DLB, or MSA) or non-converters. PDRP was identified using Principal Component Analysis. Current data is incomplete, final phenoconversion status is expected in October 2024. Predictive analyses will follow once data collection is completed.

Results:
Converters show mean PDRP z-scores of 1,80 ± 1,38 at BL, 2,77 ± 2,34 at FU1, and 6,49 ± 2,18 at FU2. For non-converters mean PDRP z-scores were 1,34 ± 1,41 at BL, 1,14 ± 1,56 at FU1, and 2,33 ± 1,37 at FU2.

Conclusions:
Although final phenoconversion status is incomplete, preliminary results show higher PDRP z-scores in converters versus non-converters across all time points.

Keywords: Parkinson's Disease, FDG-PET, PDRP

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Molecular mechanisms of *Bacillus subtilis*-induced protection against alpha-synuclein aggregation and toxicity in *Caenorhabditis elegans*

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Background:
The accumulation of misfolded alpha-synuclein (αSyn) protein into pathological aggregates plays a central role in the pathogenesis of Parkinson's disease (PD) and other synucleinopathies. Although PD is primarily considered a central nervous system disease, multiple studies have implicated the gut microbiome in its progression and severity. However, how gut bacteria affect PD remains unclear. We have previously shown that *B. subtilis* PXN21, a probiotic strain commercially available, extends lifespan, inhibits αSyn inclusions, and efficiently removes preformed inclusions in a *C. elegans* model with ectopic expression of human αSyn (Goya et al, 2020).

Methods:
To uncover protective bacterial metabolic pathways, we screened a genome-wide *B. subtilis* single-gene deletion library of non-essential genes (Koo et al, 2017). We tested around 4000 mutants from *B. subtilis*, by feeding them one by one to the αSyn-expressing worms and we analysed αSyn-inclusion levels.

Results:
Genes involved in the TCA cycle, ATP synthesis, and purine metabolism from *B. subtilis* are involved in modulating αSyn inclusions in the host. Given that purine metabolism is deregulated in PD at transcriptomic and metabolic levels, but its relevance is not fully understood yet, we decided to focus on this pathway. Among the top hits, we identified *B. subtilis* delta *purB*, encoding for adenylosuccinate lyase, an enzyme involved in two steps within the purine biosynthesis. By genetic and pharmacological complementation assays, we are dissecting the role of specific metabolites from the purine metabolism on αSyn inclusions and their toxicity in the worm.

Conclusions:
Overall, our study has the potential to reveal bacterial compounds with disease-modifying potential for PD.

Keywords: Microbiome, *C. elegans*, Purine biosynthesis

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Motivation Matters: Elucidating factors driving exercise in people with Parkinson's Disease

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Background:
Although exercise interventions are well-established in PD research, most studies have not considered individual preference in exercise interventions. Given that only 27% of persons with Parkinson (PwP) meet the recommended guidelines for physical activity, lack of motivation and other barriers might be the cause of this. Thus, it is crucial to understand determinants of motivation to improve exercise adherence in PwP.

Methods:
In an online survey, 672 PwP answered questions about their practiced and preferred exercises, demographics, depression, self-compassion, disease severity, motivation, and barriers to exercise. A multiple regression analysis with current motivation as an outcome measure and several determinants based on survey data was applied. The study also compared PwP's exercise preferences with those explored in intervention studies, using observational and systematic review data.

Results:
Results indicate that higher current and pre-morbid motivation levels to exercise align as well as greater self-compassion, lower age, lower disease severity, and less depression. Key barriers include fatigue, weather conditions, and reduced energy for other activities post-exercising. PwP's preferred exercises were compatible with their most frequently practiced activities (walking, biking, and swimming), but discrepancies between preferred exercises and those used in studies, notably in walking, biking, swimming, boxing, and tennis, are seen.

Conclusions:
Our findings enrich existing research on motivation and exercise adherence in PwP, confirming that motivation distinctly impacts the drive to exercise in PwP. Understanding these preferences, motivational factors, and barriers can elucidate how to motivate PwP to continuously exercise and help therapists incorporate these insights into their daily practice.

Keywords: Parkinson's disease, exercise adherence, motivation

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Brain morphology correlates of neuropsychiatric symptoms in Parkinson's disease

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Background:
Parkinson's disease, a neurodegenerative disorder defined by its motor symptoms, has increasingly been recognized as a disease involving non-motor features, including neuropsychiatric symptoms. This study aims to overcome limitations of previous, small-size investigations and explore the brain morphology correlates of these neuropsychiatric symptoms in a well-powered dataset from the ENIGMA-PD working group.

Methods:
We collected T1-weighted MRI and clinical data across five cohorts from Amsterdam and Stanford (total n=367, age mean±SD: 62.7±9.94, 40% female). FreeSurfer was applied to obtain cortical thickness and subcortical volumes, followed by quality assessment including visual inspection and outlier detection. Depression and anxiety severity were assessed using the Beck Depression Inventory (range[0,40]; mean±SD: 10.58±7.46) and Beck Anxiety Inventory (range[0,43]; mean±SD: 11.26±7.99), respectively. We applied linear-mixed effects models, corrected for age, sex, ICV, and cohort, and determined significance using the FDR correction (p_{adj}<.05).

Results:
None of the correlations between brain morphology and depression or anxiety measures remained significant after FDR correction. When uncorrected (p<.05), several brain regions were thinner or smaller with increasing depression or anxiety severity (***cortical*:** temporal, frontal, cingulate cortex; ***subcortical:*** amygdala, hippocampus, caudate nucleus, thalamus). Overall, more brain regions correlated with depression severity than with anxiety severity.

Conclusions:
This preliminary analysis shows subtle associations between brain morphology, depression, and anxiety that do not reach statistical significance. These subtle findings await further confirmation using the full dataset of the ENIGMA-PD working group, in which we aim to further explore neuropsychiatry-related brain morphometry in Parkinson's disease.

Keywords: Parkinson's disease, MRI morphology, Neuropsychiatry

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The effects of mindfulness based cognitive therapy on psychological distress in people with Parkinson's disease – a randomized controlled trial

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Background:
Parkinson's disease (PD) is a neurodegenerative disorder with cardinal symptoms like tremor, motor slowness, and muscle stiffness. Beyond the typical motor symptoms, many people with PD experience neuropsychiatric symptoms like depression and anxiety. Presumably, this is due to an increased sensitivity to stress. Mindfulness-based cognitive therapy (MBCT) is a promising way to reduce stress in PD, by training participants to pay attention to the present moment, in a non-judgmental and friendly way. Previous studies suggest that this may lower depression and anxiety in PD, whereas effects on motor symptoms are less clear, and underlying cerebral mechanisms remain fully unclear. The aims of this trial are to test whether MBCT improves psychological distress and clinical symptoms in PD, and to explore the cerebral and biochemical mechanisms underlying stress(-reduction) in PD.

Methods:
The MIND-PD-study is an ongoing randomized controlled trial investigating the impact of stress-reduction through MBCT in PD. 62 patients receive their usual treatment plus MBCT, 62 patients get treatment as usual. The main endpoint is psychological distress post-intervention, as measured by the Hospital Anxiety and Depression scale. Further effects and working mechanisms of MBCT are assessed using questionnaires and biochemical samples at baseline, post-intervention and after a 1-year follow-up period; (f)MRI will be acquired at baseline and follow-up.

Results:
Preliminary results of this trial are expected by November 2024. Network analyses (independent component analysis) on resting-state fMRI will be used to analyze the cerebral response to acute stress in PD. Results will include stress-related functional connectivity maps and their relation to subjective markers of psychological distress.

Conclusions:
MIND-PD aims to determine the effects of stress and stress-reduction (with MBCT) on PD, both in terms of clinical symptoms and its underlying biological mechanisms. This knowledge may pave the way for novel treatment development.

Keywords: Psychological distress, disease progression, mindfulness

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Developing AAV based gene therapy to target the catecholaminergic system in Parkinson's Disease

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Background:
Adeno-Associated Viral (AAV) vectors show promise for gene therapy in Parkinson's disease. We previously demonstrated a Tyrosine Hydroxylase (TH) promoter in combination with AAV.PhP.eB crosses the blood-brain barrier and targets catecholaminergic neurons.

1. **Establish a mouse model**: We utilized AAV-TH-α-synucleinA53T to induce Parkinson's disease in mice.
2. **Develop smaller TH promoters**: The TH promoter (2.5 kb) is challenging to package within the AAV's limited capacity (4.7 kb). We explored smaller promoter fragments to drive transgene expression in catecholaminergic neurons.

Methods:
A pilot study using 3.5 x 10^{11} GC of AAV PhP.eB-TH-α-synucleinA53T in mice assessed alpha-synuclein's impact on catecholaminergic neurons. Subsequently, we evaluated low (1 x 10^{11}) and medium (5 x 10^{11}) doses on functional tests. Small promoters were evaluated *in-vitro in SH-SY5Y* cells. Constructs were packaged into AAV with either luciferase or GFP and studied *in vivo* after systemic administration in mice.

Results:
Histological analysis revealed a significant decline in TH-positive neurons in the substantia nigra. In the motor function tests the medium-dose group exhibited a higher error rate on the narrow beam. All promoters were functional *in vitro*. Bioluminescence confirmed their activity in the cranial area. However, GFP expression was unexpectedly detected only in the olfactory bulb.

Conclusions:
Our findings suggest that this model can be used to study α-synucleinA53T's effects on the catecholaminergic system. To improve the model we are currently evaluating animals injected with a higher dose. We will continue developing smaller TH-promoters. Meanwhile, the large 2.5 kb TH-promoter remains useful for constructs up to 2.2 kb or in dual vector systems.

Keywords: Gene Therapy, A53T alpha-synuclein, PD mouse model

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An intersectional mouse genetics approach for sparse labelling of midbrain dopamine neurons

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Background:
The midbrain dopamine (mDA) system is organized into distinct anatomical regions, including the substantia nigra pars compacta (SNc), ventral tegmental area (VTA) and retro-rubral field (RRF). Individual mDA neurons between and within these regions differ in their molecular makeup, connectivity, function, and vulnerability in disease. mDA neurons project towards the striatum, where SNc neurons project their axons primarily to the dorsolateral striatum, while VTA neurons predominantly project to the ventromedial striatum. In adult mice, mDA neurons form large and complex axonal arbors. Understanding the characteristics of mDA neurons and their axonal arbors will help to better understand the mechanisms underlying disorders such as Parkinson disease.

Methods:
We used an intersectional genetics approach in combination with 3D light sheet microscopy to sparsely label and visualize mDA neurons and their dendritic and axonal projections in healthy adult mice and in the 6-hydroxydopamine (6-OHDA) mouse model of Parkinson disease. Brains from Gucy2c-Cre:Pitx3-Flp:Ai65 (GPA) mice were whole-mount immunostained, cleared using iDISCO, and imaged using a lightsheet microscope. 3D reconstructions of whole brains and manually traced neurons were reconstructed in Imaris software.

Results:
GPA mice successfully label a subset of mDA neurons in each mouse. 74 neurons from 3 representative healthy brains were reconstructed to compare anatomical (37 VTA, 22 SNc, 9 RRF) and molecular (36 Aldh1a1^{+}, 38 Aldh1a1^{-}) subtypes at a morphological level. In addition, 6-OHDA treated GPA mice successfully capture the rapid and drastic degeneration of affected axonal arbors.

Conclusions:
Our work provides new tools and a framework for further understanding mDA neurons and their complex connectivity patterns in health and disease.

Keywords: mouse genetics, dopamine neuron morphology**,** lightsheet microscopy

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Neural mechanisms underlying auditory rhythmic cueing to improve gait in mouse models of Parkinson's disease

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Background:
The sudden inability to walk, named freezing of gait, is one the most debilitating symptoms of Parkinson's disease. Conventional therapies, such as levodopa medication and deep brain stimulation, have shown a limited efficacy of treating this motor symptom. Auditory rhythmic cueing has emerged as a promising non-invasive therapy to improve these gait deficits. This intervention involves presenting rhythmic auditory stimuli, thereby providing an temporal structure which patients can use to synchronize their gait patterns. Regardless of its therapeutic potential, the neural mechanisms underlying the effects of auditory rhythmic cueing on gait improvement are poorly understood.

Methods:
Our approach makes use of two complementary mouse models of Parkinson's disease to investigate the neural mechanisms behind auditory rhythmic cueing. Our methodological approach works at a two levels. First, we will conduct extensive gait analysis to characterize the mouse models and optimize the therapeutical intervention. Second, we will utilize in-vivo electrophysiological recordings to examine brain activity during successful auditory rhythmic cueing.

Results:
At the behavioral level, we expect auditory rhythmic cueing to reduce overall gait variability in mouse models of Parkinson's disease. Furthermore, we hypothesize that gait improvement during auditory rhythmic cueing will be correlated with a reduction of pathological beta oscillatory activity in the basal ganglia.

Conclusions:
We present two complementary mouse models of Parkinson's disease that will allow us to investigate the effect of auditory rhythmic cueing on gait.

Keywords: cueing, freezing of gait, Parkinson's disease

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Acute effect of intermittent hypoxia on BDNF concentration in people with Parkinson's Disease

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Background:
Metabolic and sleep disturbances are common symptoms in people with Parkinson's disease (PD), which are resistant to dopaminergic medication. Animal studies have shown that intermittent hypoxia (IH) increases brain-derived neurotrophic factor (BDNF) levels, which contributes to neuronal survival and plasticity, but few studies have investigated IH in people with PD. We therefore investigate the acute effects of IH on sleep quality and BDNF concentrations in people with PD.

Methods:
Fifteen PD (71±5 years; 19-38 UPDRS; 2-3 H&Y) and 15 healthy individuals (control group; 62±8 years) underwent two different intervention blocks. During IH they alternated between 6 minutes of hypoxia (~10% O2) and 5 minutes of normoxia (~21% O2), while during normoxia, they received normal oxygen concentrations. Blood samples and number of awakenings (normalized to baseline) were assessed immediately and 24 hours after the intervention. A repeated-measures three-way ANOVA was conducted with group, intervention and time as factors.

Results:
A significant group effect showed that the PD group had reduced BDNF concentrations compared to controls ($p=0.004$; $\eta^2=0.20$). The significant group´time interaction effect revealed that this group effect was larger 24 hours ($p=0.01$, $\eta^2=0.34$) than immediately after ($p=0.02$, $\eta^2=0.18$) the interventions. No significant differences in BDNF were found for the type of intervention and no effects on the sleep parameters ($p>0.05$).

Conclusions:
While the intervention was well accepted and feasible, the current study found no evidence for acute effects of IH on BNDF levels in people with PD. Longer-term follow-up may be required to observe the effects of IH treatment.

Keywords: Intermittent hypoxia therapy, non-motor symptoms, neurotrophins.

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A generalisable and open-source algorithm for real-life monitoring of tremor in Parkinson's disease

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** These two authors contributed equally to this work.*

Background:
Wearable sensors allow to objectively and continuously monitor Parkinson's Disease (PD) tremor in daily life. We aimed to develop an open-source algorithm for real-life monitoring of PD tremor which achieves generalisable performance across different sensor devices.

Methods:
To detect tremor episodes, we used cepstral coefficients extracted from wrist gyroscope signals in combination with a logistic classifier. First, we trained and evaluated the classifier based on video-annotated gyroscope data collected during unscripted daily life activities (PD@Home dataset: n=8 PD with tremor, n=16 PD without tremor, n=24 matched controls). Second, we validated the algorithm in an independent dataset using a different sensor device (Personalized Parkinson Project, PPP, n=520 PD and n=50 controls). Performance on this dataset was evaluated by manual annotation of a sample of predicted tremor and non-tremor windows. Third, in the PPP, we derived weekly aggregated measures for tremor time and power, and assessed their test-retest reliability and correlation with MDS-UPDRS tremor scores.

Results:
The average sensitivity of the tremor detection algorithm on PD@Home was 0.70 (±0.18, standard deviation), with a specificity of 0.96 (±0.05). Performance on PPP was comparable, with a sensitivity of 0.50-0.76 and a specificity of 0.97-0.99. Weekly aggregated tremor time and power showed good to excellent test-retest reliability (intra-class correlation coefficient between 0.87-0.98), and a moderate correlation to the MDS-UPDRS rest tremor score (ρ=0.32-0.55).

Conclusions:
The proposed algorithm can reliably quantify Parkinson's tremor in real-life, with generalisable performance across two sensor devices. This opens possibilities to support clinical trials and individual tremor management.

Keywords: Parkinson's disease, real-life tremor detection, wearable sensor

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Parkinson's Care: Digital Updates in Parkinson's Disease Management

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Abstract

Recent technological advancements are revolutionizing the understanding, diagnosis, and management of Parkinson's disease (PD). This presentation highlights pioneering studies leveraging artificial intelligence (AI) and machine learning to enhance early prediction, monitor symptoms, and enable personalized treatments for PD patients. Researchers at Great Ormond Street Hospital for Children NHS Foundation Trust (GOSH) have developed an AI tool capable of predicting Parkinson's disease in individuals up to seven years before clinical symptoms appear. Utilizing a panel of eight blood-based biomarkers, this breakthrough allows for earlier and more effective interventions. Radboud University Medical Centre Nijmegen advocates using smart sensors to measure non-motor symptoms of Parkinson's disease at home. These sensors provide reliable data on sleep disturbances, depressive symptoms, and cognitive performance, facilitating continuous monitoring and personalized treatment strategies. Leidy Guarin et al. introduced a machine learning system that quantifies motor symptoms and predicts disease progression by analyzing video recordings of finger-tapping tests. This system detects subtle changes in motor function, enhancing early diagnosis and treatment planning. Cornell University researchers identified three distinct subtypes of Parkinson's disease using machine learning. These subtypes—Inching Pace (PD-I), Moderate Pace (PD-M), and Rapid Pace (PD-R)—exhibit unique genetic signatures and progression rates, supporting the development of tailored treatment strategies. The diabetes drug metformin shows promise in alleviating cognitive symptoms in PD-R patients, highlighting the potential for precision medicine in Parkinson's disease management. These technological advancements underscore the potential of AI and machine learning to significantly improve the diagnosis, monitoring, and treatment of Parkinson's disease, paving the way for more personalized and effective healthcare solutions

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Cardiorespiratory Fitness in Parkinson's disease: Associations with autonomic dysfunction and physical activity

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Background:
Both autonomic dysfunction, one of the early non-motor signs of Parkinson's disease (PD), and reduced physical activity could contribute to a reduced cardiorespiratory fitness in people with PD. However, the contribution of both pathways is not well understood.

Methods:
We included a subset of individuals with PD (Hoehn and Yahr stage 1-3) from the STEPWISE interventional study who completed a cardiopulmonary exercise test. We examined the association between cardiorespiratory fitness parameters (peak oxygen consumption, VO_{2peak}), maximum heart rate (HR_{max}), and heart rate recovery at 1 and 3 minutes (HR_{rec1}, HR_{rec3})) and autonomic dysfunction (SCales for Outcomes in PArkinson's disease-Autonomic dysfunction, SCOPA-AUT) and physical activity (step counts). Using multivariable regression, we adjusted for age, sex, beta-blocker use, step count (when analyzing SCOPA-AUT) and SCOPA-AUT (when analyzing step count).

Results:
We analyzed the cardiopulmonary exercise tests of 59 people with PD (n=22, 37% females), aged 65.1 (SD: 7.9) years with 4.5 years (SD: 3.5) of disease duration. We found statistically significant associations between HR_{max} and SCOPA-AUT (β=-0.74, 95% CI=[-1.42, -0.06]), HR_{rec3} and step counts (β=3.03, 95% CI=[0.40, 5.65]) and VO_{2peak} and step counts (β=1.14, 95% CI=[0.07, 2.21]). No associations were found for HR_{rec1}.

Conclusions:
More symptoms of autonomic dysfunction were associated with lower maximum heart rate and more physical activity was associated higher lower heart rate recovery at 3 minutes and higher peak oxygen consumption. Future studies are needed to determine the clinical relevance of our findings, for example by studying the effect over interventions or disease progression.

Keywords: Parkinson disease, cardiorespiratory fitness, autonomic dysfunction

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Machine learning-based tracking of disease progression in iRBD using brain FDG PET

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Background: Isolated REM-sleep behaviour disorder (iRBD) is a strong indicator of prodromal alpha-synucleinopathy. The REMPET consortium aims to study FDG PET as a biomarker in REM-sleep behaviour disorder and conversion to Parkinson's disease (PD), dementia with Lewy bodies (DLB) or multiple system atrophy (MSA).

Methods: We consider FDG PET scans of n = 86 iRBD patients, who were followed up and rescanned either one or two times with approximately four years in between. First, we extract feature vectors using principal component analysis, and train a Generalized Matrix Learning Vector Quantization model to classify healthy controls (HC), PD, DLB and MSA. This results in a decision space, which can be visualized in 2D, and prototypes representing typical examples of each class. We project the RBD patients into the trained GMLVQ space and evaluate their trajectory over time.

Results: Preliminary results show that the majority of patients maintained a clear trajectory towards the PD or DLB space over time, moving away from the HC region. Further analysis, e.g. regarding conversion prediction, will be available in November.

Conclusions: FDG PET in combination with machine learning can be used to follow disease progression in REM-sleep behaviour disorder

Keywords: RBD, machine learning, disease progression

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Self-awareness and neurophysiology of loudness changes in the Parkinson voice

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Background:
One of the least explored Parkinson's Disease (PD) motor symptoms are loudness changes in the voice. As we communicate with the voice, ineffective voice modulation can lead to social isolation. We investigated (i) awareness of loudness changes, (ii) sensorimotor feedback in voice production, and (iii) EMG of vocal tract modulation in PD.

Methods:
i. Awareness of loudness changes were explored with the Voice Symptom Scale, often used in general voice disorders.
ii. Sensorimotor feedback was investigated in a playback EEG paradigm, including an auditory-motor, auditory only, and motor condition. We compared expected and actual sensorimotor feedback to one's own voice in early event-related brain potentials (N1/P2).
iii. We recorded vocal tract modulation during EEG sensory feedback processing with an electromyographical, specialized toolbox.

Results:
i. Voice-related questionnaires such as the Voice Symptom Scale are not sensitive enough to measure variability in the PD voice.
ii. N1/P2 ERPs, measuring successful sensory suppression, were altered in PD.
iii. Data analysis and correlations with ERP sensory suppression are ongoing.

Conclusions:
i. Standard voice symptom questionnaires appear not sensitive enough to measure variability in awareness of voice loudness changes; PD tailored questionnaires are needed to inform clinical assessment and intervention.
ii. Modulation of early ERP components show that not only subjective (in-)awareness of voice changes, but also objective neurophysiological measures indicate that PD voice changes might critically affect communication.
iii. Should ERP and EMG measures align, they can serve as objective and quantifiable measures to tailor individualized voice interventions beyond current voice standard treatments.

Keywords: Parkinson voice, EEG, sensory feedback

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Discovery of a highly selective, orally bioavailable, brain-penetrant LRRK2 Inhibitor

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Background:
Leucine-rich repeat kinase 2 (LRRK2) is a signaling protein that is a key therapeutic target in Parkinson's disease (PD). Gain-of-function mutations, e.g. LRRK2[G2019S], that increase LRRK2 kinase activity have been identified in a large number of PD patients. Recently, an increased LRRK2 kinase activity was observed among a population of idiopathic PD patients. Thus, combined genetic and biochemical evidence supports a hypothesis that the LRRK2 kinase function is causally involved in the pathogenesis of sporadic and familial forms of PD. Inhibition of the LRRK2 kinase activity is under clinical investigation and is demonstrating dose-dependent reduction of biomarkers of LRRK2 activity in CSF and urine while showing good tolerability and safety. Complete systemic inhibition of LRRK2 must be avoided. Total suppression of LRRK2 protein is associated with adverse effects in kidney and lung.

Methods:
Various drug discovery approaches, from molecular modeling and high-throughput screening to GLP toxicology studies, were used for the development of the lead series of highly brain-penetrant LRRK2 inhibitors.

Conclusions:
We developed lead molecules with superior kinome selectivity compared to the publicly known best references. The lead molecules exhibit nanomolar potencies against LRRK2[WT] and the [G2019S] mutation. Achieved 1000x selectivity against other kinases and >500x selectivity against other targets from the safety panel. Demonstrated favorable pharmacokinetics, high Brain(unbound)/Plasma(unbound) ratio, as well as a good ADME and in vivo safety profile for oral administration.

Keywords: LRRK2, Parkinson’s Disease, kinase inhibitor

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Validity and reliability of wrist sensor-based measures of the arm swing during free-living gait in Parkinson's disease

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Background:
Previously, we developed a modular pipeline using wrist-worn sensor data to (1) detect free-living gait, (2) filter out gait segments with other arm activities, and (3) quantify the arm swing range of motion (ROM) of individuals with Parkinson's disease (PD). Here, we assessed the construct validity and reliability of the extracted arm swing parameters in a larger, free-living PD cohort.

Methods:
We used the first two weeks of wrist accelerometer and gyroscope data of 415 participants with early-stage PD from the Personalized Parkinson Project. We validated the weekly median and 95th percentile arm swing ROM in three ways: in the first week, (1) the difference between the most and least affected side, and (2) the Spearman correlation with the MDS-UPDRS part III; and between the first and the second week, (3) the test-retest reliability using the Intraclass correlation coefficient (ICC).

Results:
Participants wearing the watch on the most affected side had a smaller median (Δ degrees = -0.65, $p < 0.0001$) and 95th percentile (Δ degrees = -2.67, $p < 0.0001$) ROM. Similarly, participants with a higher MDS-UPDRS part III showed a smaller median (r_s = -0.40, $p < 0.0001$) and 95th percentile (r_s = -0.47, $p < 0.0001$) ROM. The reliability was high for both the median (ICC = 0.86, 95% CI [0.83-0.88]) and the 95th percentile (ICC = 0.91, 95% CI [0.89-0.93]) ROM.

Conclusions:
Both the median and the 95th percentile arm swing ROM demonstrate construct validity and reliability. Future work will assess their sensitivity to disease progression, to inform the use in clinical trials.

Keywords: Digital biomarkers, arm swing, gait

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Navigating life with Parkinson's disease: a focus group study on coping strategies and considerations for self-management support

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Background:
The progressive impact of Parkinson's disease (PD) on one's individual well-being, family, social and professional life, requires ongoing adaptation. A valuable way to address these diverse challenges is through self-management interventions. A tailored version of the blended self-management tool Parkinson Partner in Balance, for partners or relatives of people with PD (PwP), has the potential to enhance coping skills and support PwP themselves in overcoming their challenges. In this study the focus was on identifying relevant factors to create such a self-management tool.

Methods:
Four focus groups were conducted with PwP (n=10). An inductive content analysis using a phenomenological approach was performed independently by two researchers (MD, BB-H).

Results:
We identified 3 main categories. (1) Rational realization vs. emotional experience: transition of coping strategy; 2) factors that influence coping, including mindset and skills, access to support, and social circles and communication, and 3) considerations for successful self-management of PD, highlighting key areas such as maintaining autonomy and sense of identity, psycho-emotional guidance, peer support and lifestyle.

Conclusions:
Coping with and adapting to PD is an individual and dynamic process. The transition between different strategies is influenced by multiple turning points. Tailored self-management support can be helpful in enhancing coping abilities during these transitions and adjusting to a life with PD. We used the results of this study to adapt the already available Parkinson Partner in Balance self-management tool and created a version for people with PD. A pilot-study on its feasibility is being conducted.

Keywords: Parkinson's disease, coping, self-management.

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The role of the subthalamic nucleus in decision-making and reward processing

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Background:
Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a standard treatment method for improving Parkinson's disease (PD) motor symptoms. However, the effects of DBS on cognition and behaviour are less clear. To evaluate and improve this existing treatment option and its potential side effects, such as impulsivity and apathy, it is of high importance to disentangle the neural mechanisms of reward processing in the STN.

Methods:
We record neural activity in the STN using the Medtronic percept while PD patients perform a reward-processing task. Participants play a game of luck, imagine receiving and rate a variety of rewards.

Results:
Preliminary behavioural results show that participants are able to perform the selected task and that different aspects of reward processing (positive, neutral and negative rated outcomes) are captured. By capturing the participants own assessment of the valence of the rewards, instead of using average ratings of larger samples, we ensure a more reliable labelling of neural data. These neural signals can then potentially be used to decode reward valence.

Conclusions:
By analysing the neural correlates of a reward processing tasks, we hope to gain further insights into the decision-making and reward processing as well as potential behavioural and cognitive effects of DBS.

Keywords: STN, decision-making, reward processing

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★ SARS-CoV-2 infected macaques as a model to study the link between COVID-19 and Parkinson

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Background:
COVID-19 induced systemic inflammation and neurological damage could contribute to the development of neurodegenerative diseases, including Parkinson. With more than 700 million reported coronavirus infections worldwide, the impact of such late-onset outcomes is inconceivable.
Viral infections can trigger α-synucleinopathies, and SARS-CoV-2 infection is considered responsible for the development of parkinsonism, however, the mechanism by which COVID-19 triggers neurodegeneration remains to be determined.

Methods:
We study SARS-CoV-2 infected macaques, a model for mild COVID-19, euthanized at different time points after infection; acute (1-2 weeks), post-acute (~7 weeks) and long-term (>3 months). During the studies we collect blood plasma and CSF for proteomics analyses, including a CNS disease panel of ~120 analytes by NULISAseq. In some studies, we also analyze neuroinflammation by longitudinal TSPO-PET imaging. Finally, we collect brain tissues for postmortem molecular and histological analyses. For this study, the substantia nigra was investigated for dopaminergic neuron loss (TH staining), alpha-synuclein accumulation and neuroinflammation.

Results:
By longitudinal TSPO-PET imaging we showed ongoing neuroinflammation throughout the brain. In the substantia nigra we not only found signs of neuroinflammation, but also a decline in the number of dopaminergic neurons, accompanied by aberrant α-synuclein, including phosphorylated α-synuclein aggregates. Moreover, in plasma and CSF we found indications for ongoing neurodegeneration, such as increased NFL, but also altered levels of Parkinson-related proteins.

Conclusions:
This study suggests a direct link between SARS-CoV-2 infection and neuropathology associated with Parkinson's disease, in a model that closely resembles humans.

Keywords: Non-human primate, COVID, Neurodegeneration

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Microglia control dendron bundle connectivity in the dopaminergic substantia nigra

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Background:
Parkinson's disease (PD) is characterized by the progressive loss of dopaminergic (DA) neurons in the ventral substantia nigra pars compacta (vSNc). These neurons are known to exhibit complex neuron morphologies to regulate various behavioral responses. One often overlooked morphological aspect is dendrite morphology. Interestingly, dendrites of vSNc neurons can form so called "dendrons". Dendrons have been proposed to function as integrative units regulating SNc neuron activity, but their functions and contribution to PD remain elusive.

Objective:
To understand their role in health and disease fundamental knowledge on the molecular mechanisms involved in correct formation and connectivity of dendrons is necessary.

Methods:
Immunohistochemistry was performed to assess involvement of glia in dendron development in both human and mice, pointing towards a role for microglia. PLX5622-induced depletion and repopulation of microglia allowed specific investigation of their role in dendron formation and connectivity.

Results:
Removing microglia at crucial developmental timepoints affected glutamatergic synapse formation on dendrons at early developmental timepoints, while ablation at later stages interfered with synapse pruning. This indicates a temporal shift in microglial activity, without disturbing dendron morphology. These effects were shown to be specific for dendrons and long-lasting, and microglial morphology confirmed their shift in activity.

Discussion:
Our results are the first to show microglia-mediated synapse formation and pruning specifically on vSNc DA dendrons. Further molecular analysis will unravel which microglial factors mediate the temporal shift in microglial activity and whether subsequent changes in electrophysiological activity in dendrons could be relevant disease initiators of DA-mediated disorder such as Parkinson's disease.

Keywords: Dendron, microglia, substantia nigra

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Brainstem Structural Connectivity in relation to REM-Sleep Without Atonia in Lewy Body Diseases Using DWI at 7T

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Background:
REM-sleep behavior disorder (RBD), characterized by dream enactments through movements and vocalizations, is closely associated with (prodromal) Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Animal studies suggest that pathological loss of muscle atonia during REM-sleep (RSWA) relates to dysregulated brainstem circuits, with a possible key role of the locus subcoeruleus (SubC), pedunculotegmental nucleus (PTg) and the paramedian nucleus (PMnR). We used ultra-high field diffusion-weighted imaging (DWI) to evaluate RSWA-related brainstem structural connectivity in Lewy body disease in humans.

Methods:
We collected 7T-DWI (1.5mm isotropic voxel size) and polysomnography from 14 male participants (9 PD and 5 DLB), age 70.1±7.0 years, time since diagnosis 3.9±2.7 years. Structural connectivity (bilaterally averaged between-region tract count) between SubC and PTg contralaterally, and SubC and PMnR was assessed using seed-based probabilistic tractography. RSWA percentage was evaluated using SINBAR criteria. A linear model corrected for Age assessed the structural connectivity-RSWA relationship.

Results:
An average of 152 streamlines were found between SubC and PTg, and 25,072 between SubC and PMnR. RSWA varied from 0.01% to 53.8%. Linear regressions showed no significant correlations between RSWA and SubC-PTg (r=0.16, p=0.594) or SubC-PMnR (r=0.06, p=0.843) connectivity. Age also showed no significant correlation with SubC-PTg (r=-0.33, p=0.247) or SubC-PMnR (r=-0.38, p=0.183) connectivity.

Conclusions:
Our findings demonstrate that 7T DWI effectively identifies brainstem tracts involved in RBD's pathophysiology. The lack of correlation with RSWA may be due to severe white matter degeneration in Lewy body disease or the small sample size. Larger samples are needed for further analysis.

Keywords: REM-sleep Behavior Disorder, DWI, Brainstem

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Changes in action tremor in Parkinson's disease over time: clinical and neuroimaging correlates

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Background:
The various symptoms of Parkinson's disease (PD) may change differently over time as the disease progresses. Tremor usually manifests early in the disease, but unlike other motor symptoms, its severity may diminish over time. The cerebral mechanisms underlying these symptom-specific longitudinal trajectories are unclear. Previous MRI studies have shown structural changes in brain regions associated with PD tremor, suggesting that structural longitudinal changes may define clinical trajectories. We aimed to investigate the longitudinal trajectory of PD tremor in relation to bradykinesia and rigidity, and assess whether tremor progression is related to structural changes in tremor-related areas.

Methods:
We used data from the Personalized Parkinson Project: a two-year longitudinal study involving 520 PD patients and 60 healthy controls, who were measured twice clinically and with MRI. Mixed-effects models were used to compare tremor, bradykinesia, and rigidity progression, investigate gray matter changes in tremor-related regions (cerebello-thalamo-cortical circuit and pallidum), and calculate associations between symptom severity and brain structure. Whole-brain gray matter and the lateral occipital gyri were included to address anatomical specificity.

Results:
Bradykinesia and rigidity worsened over two years, whereas tremor behaved differently: resting tremor severity remained stable, whereas postural and kinetic tremor severity decreased. Attenuation of postural and kinetic tremor was associated with, but not restricted to, atrophy in tremor-related areas. Opposite relationships were observed for bradykinesia and rigidity.

Conclusions:
Action tremor (postural and kinetic) is an early symptom of PD, which reduces with disease progression. Longitudinal brain atrophy correlates with tremor and other motor symptoms in opposite ways.

Keywords: Parkinson, tremor, progression

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Blood-based multivariate methylation risk score for cognitive impairment and dementia in Parkinson's disease

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Background:
The established link between DNA methylation and pathophysiology of dementia, along with its potential role as a molecular mediator of lifestyle and environmental influences, positions blood-derived DNA methylation as a promising tool for early dementia risk detection.

Methods:
In conjunction with an extensive array of machine learning techniques, we employed whole blood genome-wide DNA methylation data as a surrogate for 14 modifiable and non-modifiable factors in the assessment of dementia risk in independent dementia cohorts.

Results:
We established a multivariate methylation risk score (MMRS) for identifying mild cognitive impairment cross-sectionally, independent of age and sex ($P = 2.0 \times 10^{-3}$). This score significantly predicted the prospective development of cognitive impairments in independent study Parkinson's disease (hazard ratio for MCI/dementia = 2.59).

Conclusions:
Our work shows the potential of employing blood-derived DNA methylation data in the assessment of dementia risk in PD.

Keywords: Parkinson's disease dementia, Epigenetics, lifestyle

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★ An epigenomic assessment of α-Synucleinopathy and co-pathologies in Lewy body dementias

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Background:
Lewy body diseases (LBD) are a group of neurodegenerative disorders that are characterized by the presence of abnormal protein deposits called α-Synuclein in the brain. α-Synucleinopathies often occur with abnormal accumulation of tau and amyloid-β in the brain. Epigenetic mechanisms—molecular processes that modify gene expression without changing the underlying genetic sequence—represent a potential area of contribution that has been under-researched to date.

Methods:
Genome-wide DNA methylation in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) was profiled for a total sample size of 1,251 in three independent cohorts. The UK Brain Bank Cohort (UKBBN, n = 805; 419 donors; PFC and ACC), the Netherlands Brain Bank Cohort (NBB, n = 322; PFC) and the Brain's for Dementia Research Cohort (BDR, n = 124; PFC).

Results:
Meta analyses identified three differentially methylated positions (DMPs) with genome wide significant association ($P < 9 \times 10\text{-}8$), including sites annotated to the genes UBASH3B and PTAFR and an intergenic loci cg13847853. A further 20 DMPs were associated at a more lenient false discovery rate (corrected $P < 0.05$). Subsetting meta-analysis to samples with LB pathology in the absence of significant Alzheimer's pathology (Braak NFT stage < 3, n = 798) showed attenuated significance, with only cg13847853 passing multiple testing correction.

Conclusions:
We conducted the largest meta-analysis of DNA methylation changes related to LB pathology in brain to date, identifying several DMPs significantly associated with the pathology. We also demonstrated that methylomic signatures associated with LB pathology is independent of the result of co-pathology.

Keywords: Lewy body dementias, Epigenetics, DNA methylation

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Polychlorinated Biphenyl-Induced Neurotoxicity in iPSC-Derived Dopaminergic Neurons and Implications for Parkinson's Disease

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Background:
Parkinson's disease (PD) is a neurodegenerative disorder influenced by environmental exposures and genetic factors. Polychlorinated biphenyls (PCBs) have been linked to an increased risk of PD. We investigated the effects of PCB-180, a PCB congener that accumulates in the brain, using iPSC-derived dopaminergic neurons to better understand PCB-induced neurotoxicity.

Methods:
iPSC-derived dopaminergic neurons were exposed to varying concentrations of PCB-180 (0.01 µM, 0.5 µM, and 10 µM) for 24 h and 74 h. We performed transcriptomic analysis to examine gene expression changes and compared these results with known PD-related neurotoxins like MPP+ and rotenone, as well as PCB-exposed human populations.

Results:
PCB-180 exposure disrupted key cellular functions such as oxidative phosphorylation, synaptic function, and neurotransmitter release. These alterations resembled the molecular changes seen in PD-related compounds and human populations exposed to PCBs. Gene expression patterns observed in iPSC-derived neurons were validated in postmortem PD brain tissues, reinforcing the role of PCB-induced neurotoxicity in PD pathogenesis.

Conclusions:
Our findings provide insight into how PCB-180 affects cellular mechanisms relevant to PD, suggesting that environmental exposure to PCBs may contribute to neurodegenerative diseases. The use of iPSC-derived dopaminergic neurons allowed us to link in vitro findings with human data.

Keywords: PCBs, neurotoxicity, transcriptomics

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Molecular mechanisms of *Bacillus subtilis*-induced protection against alpha-synuclein aggregation and toxicity in *Caenorhabditis elegans*

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Background:
The accumulation of misfolded alpha-synuclein (αSyn) protein into pathological aggregates plays a central role in the pathogenesis of Parkinson's disease (PD) and other synucleinopathies. Although PD is primarily considered a central nervous system disease, multiple studies have implicated the gut microbiome in its progression and severity. However, how gut bacteria affect PD remains unclear. We have previously shown that *B. subtilis* PXN21, a probiotic strain commercially available, extends lifespan, inhibits αSyn inclusions, and efficiently removes preformed inclusions in a *C. elegans* model with ectopic expression of human αSyn (Goya et al, 2020).

Methods:
To uncover protective bacterial metabolic pathways, we screened a genome-wide *B. subtilis* single-gene deletion library of non-essential genes (Koo et al, 2017). We tested around 4000 mutants from *B. subtilis*, by feeding them one by one to the αSyn-expressing worms and we analysed αSyn-inclusion levels.

Results:
Genes involved in the TCA cycle, ATP synthesis, and purine metabolism from *B. subtilis* are involved in modulating αSyn inclusions in the host. Given that purine metabolism is deregulated in PD at transcriptomic and metabolic levels, but its relevance is not fully understood yet, we decided to focus on this pathway. Among the top hits, we identified *B. subtilis* delta *purB*, encoding for adenylosuccinate lyase, an enzyme involved in two steps within the purine biosynthesis. By genetic and pharmacological complementation assays, we are dissecting the role of specific metabolites from the purine metabolism on αSyn inclusions and their toxicity in the worm.

Conclusions:
Overall, our study has the potential to reveal bacterial compounds with disease-modifying potential for PD.

Keywords: Microbiome, *C. elegans*, purine biosynthesis

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Modelling chronic inflammation in the enteric nervous system: Insights into Parkinson's Disease pathophysiology

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Background:
Parkinson's disease (PD) affects 1% of people over 60 and increasing evidence points to the involvement of the gut-brain axis in the pathophysiology of the disease. To explore this, we have generated an *in vitro* human enteric nervous system (ENS) model, composed of enteric neurons and enteric glial cells. With this model, we aim to study the immunometabolism of ENS cells and its connection to PD.

Methods:
ENS cells were generated from human pluripotent stem cells following a protocol developed by Gogolou et al. (2021). The formation of enteric neurons and enteric glial cells was investigated via immunostaining. To model chronic inflammation, ENS cultures were exposed to pro-inflammatory cytokines IL-1β and TNFα (5 ng/mL each) for 14 days, after which, immunometabolic changes and PD-related phosphorylated alpha-synuclein levels were assessed.

Results:
Immunostaining confirmed the presence of neurons (TUJ1) and glial cells (GFAP), with neurons expressing alpha-synuclein. After 14 days of IL-1β/TNFα exposure, IL-6 levels returned to baseline, while IL-8 remained elevated, suggesting that some immune responses adapt to chronic inflammation while others persist. Additionally, several metabolic pathways were significantly altered in enteric glial cells after prolonged inflammation. Finally, our preliminary results showed an increase of phosphorylated alpha-synuclein in enteric neurons after 14 days of IL-1β/TNF-α exposure, novel evidence connecting inflammation in the ENS to pathology mechanisms of Parkinson's disease.

Conclusions:
Our findings demonstrate that our system effectively models chronic inflammation in the human enteric nervous system and serves as a promising tool to study the ENS's role in Parkinson's disease. Future studies will explore how immunometabolic changes from prolonged pro-inflammatory cytokine exposure contribute to the increase of phosphorylated alpha-synuclein, shedding more light on Parkinson's disease mechanisms.

Keywords: phosphorylated alpha-synuclein, chronic inflammation, enteric nervous system

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★ Structural insights on alpha-synuclein oligomers at the single molecule level using smFRET

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Background:
Alpha-synuclein (αS) is an intrinsically disordered protein that structurally behaves similarly to a polymer free in solution. It can, however, self-assemble into oligomeric species that act as key intermediates for fibril formation. Eventually, αS monomers adopt a beta-sheet conformation and end up in amyloid fibrils, this is the case in Parkinson's disease. However, little is known about the structural changes of αS monomers during its aggregation, in particular when αS is incorporated in rare and transient oligomers.

Methods:
To gain insights on the structural changes of αS during aggregation, we perform single-molecule FRET (smFRET) measurements on monomers incorporated in oligomers. With smFRET, we obtain a distribution of FRET efficiencies and associated relative photon arrival times that together describe intramolecular distances and dynamics. We can thus probe the conformational space of different segments within the protein chain.

Results:
By comparing free monomers with oligomers, we detect differences in the conformational space per chain segment and so gain structural insights on monomers that are incorporated in these oligomers. We can thus follow how αS monomers change structurally during aggregation.

Conclusions:
With this technique, we gain structural knowledge that advances our understanding of the different aggregation steps and the potential to elucidate molecular mechanisms of safeguarding chaperone proteins. This may aid the development of therapeutics that modulate αS fibril formation.

Keywords: Oligomers, structure, smFRET

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Neuroprotectivity of Mitochondrial-containing Extracellular Vesicles in Parkinson's Disease

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Background:
Parkinson's Disease (PD) is characterized by the progressive loss of dopaminergic neurons, driven in part by mitochondrial damage from reactive oxygen species (ROS), which accelerates neurodegeneration. Extracellular vesicles (EVs) found in blood are known for carrying essential cellular cargo and have emerged as promising therapeutic vehicles, particularly when loaded with healthy mitochondria. In this study, we explore the neuroprotective role of mitochondrial-containing EVs (mitoEVs) isolated from the blood of participants in the Lifelines cohort. These EVs were characterized and their neuroprotective effects were tested in vitro on HT22 cells neuronal cultures to assess their functional relevance to PD pathology.

Methods:
EVs were characterized using Nanoparticle Tracking Analysis (NTA) for size and concentration, Dot blot assays for surface markers, and mass spectrometry for proteomic profiling. To assess the function of EVs on neuronal-like cells, we conducted MTT assays for cell viability and used Flow Cytometry (FACS) with Propidium Iodide (PI), and MitoSOX, to measure oxidative stress.

Results:
Mitochondrial-containing EVs were successfully isolated, as confirmed by electron microscopy (EM) and the detection of EV markers, including CD9, CD63, and Annexin II, along with the mitochondrial marker Tim23. These EVs demonstrated a protective effect on HT22 cells exposed to ferroptosis-inducing agents such as erastin, glutamate, and RSL3. Additionally, mitoEVs significantly reduced mitochondrial ROS levels in HT22 cells.

Conclusions:
Mitochondrial-containing EVs were successfully isolated and demonstrated neuroprotective effects in vitro, reducing ferroptosis-induced damage and mitochondrial ROS levels, suggesting potential as a therapeutic strategy for Parkinson's Disease.

Keywords: mitoEVs, neuroprotectivity, Parkinson's Disease

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User Experiences and preliminary effects of the Cue2walk smart cueing device for Freezing of Gait in people with Parkinson's Disease

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Background:
Freezing of Gait (FoG) impairs mobility and increases the risk of falls, leading to reduced quality of life in people with Parkinson's Disease (pwPD). While drug treatments offer limited relief, non-pharmacological interventions such as external cueing have shown promise in managing FoG. The Cue2walk, a wearable smart cueing device, was developed to detect FoG episodes and hereupon provide rhythmic external cues in the form of sound and/or vibration to help pwPD manage FoG in daily life. Although the Cue2walk is already on the market, its effectiveness has not been studied.

Methods:
This open-label pilot study evaluated user experiences and preliminary effects of using the Cue2walk on FoG symptoms, quality of life, and overall health among a sample of 17 users. Data were collected through an online questionnaire, which included the EQ-5D-5L scale, additional Parkinson's-specific questions, and a Net Promoter Score (NPS) for customer satisfaction.

Results:
81% of the respondents reported positive effects on FoG duration, 75% on falls, 63% on daily activities and 62% on self-confidence. Overall health (measured with EQ-5D-5L) increased from 5.1/10 to 6.2/10 and responders' average NPS was 7.8/10. No negative effects were reported. A strong correlation ($r=0.64$, $p<0.05$) was observed between longer device usage and greater positive impact on daily activities.

Conclusions:
This study suggests that the Cue2walk is a valuable tool for managing FoG and enhancing the quality of life for pwPD. Further research with larger populations and extended follow-up is recommended to validate these findings and assess the long-term efficacy of the device.

Keywords: Smart cueing; User experience; Quality of Life

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Cue2walk: A wearable device for automated Freezing of Gait detection and provision of cues in Parkinson's Disease - A performance study

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Background:
Freezing of Gait (FoG) severely affects quality of life in Parkinson's Disease (PD) patients. External cueing can be used to overcome FoG. However, manual activation of cueing is often too late, whereas continuous cueing can lead to habituation. Therefore, the Cue2walk, a single-sensor device for automated FoG detection and provision of external cues, was developed. To maximize effectiveness of the device, it is important to maximize detected FoG episodes and minimize undetected FoG episodes. This study investigated the performance of the Cue2walk.

Methods:
A gait circuit of 3-5 minutes at home during daily activities, including FoG-triggering tasks like turning and walking through narrow passages, was completed by 24 PD patients with daily FoG. The measurements were videotaped and annotated for FoG by two experienced raters. Participants wore a Cue2walk, with cueing functionalities turned off, to collect acceleration data. After the measurements, the acceleration data was run through the Cue2walk algorithm, using both pre-determined settings and individually optimized settings. Performance of the Cue2walk was quantified in terms of sensitivity, specificity and latency (time between onset and detection of FoG).

Results:
The individually optimized setting of the Cue2walk showed good sensitivity (82.1±19.7%) and latency (2.0±1.4s) and excellent specificity (95.8±7.9%). Sensitivity was significantly higher than for the standard setting (47.8±38.4%, $p=0.002$), while specificity and latency were similar for both settings (92.9±14.8%, $p>0.999$; 1.7±1.4s, $p>0.999$).

Conclusions:
The Cue2walk shows good FoG detection performance when individually optimized, highlighting the need for a personalized approach. Clinical effectiveness of the device needs to be determined in future research.

Keywords: Freezing of Gait detection; Sensitivity; Specificity

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Towards early disease differentiation and label-free imaging of synucleinopathies with novel infrared spectroscopies and microscopies

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Background:
Two major challenges in the synucleinopathy field are (1) the capability to achieve early differentiation between different synucleinopathies (Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy), and (2) to realize label-free monitoring of alpha-synuclein (aSyn) aggregation in model systems and patient material.

Methods:
Here, I present three new, infrared-based approaches to face these challenges. Recent development in the vibrational spectro-microscopy field allow for (A) fast and sensitive assessment of amyloid strain structure, (B) plasmonically-enhanced detection of the structure of antibody-bound proteins, and (C) high-resolution chemical and structural characterization of biospecimen with label-free vibrational spectro-microscopy. Building on these developments, we are exploring the potential of three implementations of these breakthroughs for the synucleinopathy field, (A) by improving the reproductive and disease-specific sensitivity of seed-amplification assays (SAAs) by recording two-dimensional infrared (2DIR) spectra of SAA endproducts, (B) by detecting and structurally characterizing different aggregating aSyn-species in cerebrospinal fluid by determining their structure after antibody-based capture with 2DIR-spectroscopy, and (C) by recording hyperspectral optical photothermal infrared (OPTIR) microscopy images of biospecimen like brain tissues and model systems.

Results:
The first results show that the strong amyloid-structure sensitivity of 2DIR indeed has the capability to elucidate subtle differences in the amyloid fibril structure. Furthermore, the OPTIR images reveal detailed and specific distributions of different types of aSyn aggregates.

Conclusions:
While further investigation is warranted, the employed infrared-based techniques have demonstrated that early 2DIR-based detection and differentiation of synucleinopathies in biofluids is feasible, and similarly, that the distribution, chemical composition, and protein structure of aSyn in brain tissues with OPTIR can be achieved in a label-free manner, thus allowing the detection and characterization of aggregation in biospecimen and model systems without influencing the aggregation process with fluorescent labels.

Keywords: infrared spectro-microscopy, early synuclein differentiation, label-free alpha-synuclein detection.

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Systematic rare variant analyses identify *RAB32* as a susceptibility gene for familial Parkinson's disease

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Background:
Despite substantial progress, causal variants are identified only for a minority of familial Parkinson's disease (PD) cases, leaving high-risk pathogenic variants unidentified.

Methods:
To identify such variants, we uniformly processed exome sequencing data of 2,184 index familial PD cases and 69,775 controls.

Results:
Exome-wide analyses converged on *RAB32* as a novel PD gene identifying c.213C > G/p.S71R as a high-risk variant presenting in ~0.7% of familial PD cases while observed in only 0.004% of controls (odds ratio of 65.5). This variant was confirmed in all cases via Sanger sequencing and segregated with PD in three families. *RAB32* encodes a small GTPase known to interact with LRRK2. Functional analyses showed that RAB32 S71R increases LRRK2 kinase activity, as indicated by increased autophosphorylation of LRRK2 S1292.

Conclusions:
Here our results implicate mutant RAB32 in a key pathological mechanism in PD — LRRK2 kinase activity — and thus provide novel insights into the mechanistic connections between RAB family biology, LRRK2 and PD risk.

Keywords: Parkinson's disease, genome-wide association studies, genomics

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Preclinical animal models of the gut-brain axis in PD: a systematic review and meta-analysis.

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Background:
The microbiome-gut-brain axis is thought to play an important role in the development and progression of Parkinson's disease (PD). To gain better understanding of how model choice affects measures of gut microbiota diversity and other PD related outcomes, a systematic review of literature was performed. In this review we will examine how potential moderators such as animal species used, PD model type, and geographic location of study influence the motor function in these models as well as gut-brain axis related parameters.

Methods:
The PubMed and Embase databases were searched using terms related to PD, microbiota, and filter terms for animal studies. A random effects meta-analysis was performed and a Bayesian penalized meta-regression was used to examine moderator effects.

Results:
Mice were the most common model species used in 90 studies of the 99 that were included, this was followed by rats (6) and fruit flies (3). Meta-analysis suggests that motor function is decreased to a similar extent regardless of the PD model type, PD model species, or geographical location of the study. The overall risk of bias is unclear for the included studies.

Conclusions:
Preliminary results show that we were able to identify studies that induced an effective PD-like phenotype shown by the development of motor dysfunction. The next steps of our study include the meta-analysis of microbiota composition changes (alpha/beta diversity). Furthermore, the severity of non-motor outcomes in relation to motor symptom severity as well as other gut-brain axis related parameters will also be assessed.

Keywords: Preclinical, Microbiome, Animal models

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Altered endosomal trafficking and metabolism in LRRK2 G2019S hiPSC-derived microglia

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Background:
Microglia - the resident immune cells of the central nervous system - play a crucial role in defending and maintaining homeostasis in the brain. They are key players in the process of neuro-inflammation thus microglial dysfunction may contribute to the onset of Parkinson's Disease (PD) pathology and the characteristic degeneration of dopaminergic neurons.

Methods:
To perform research on CNS brain cells such as microglia, certain limitations have to be overcome since human samples can only be obtained post-mortem, and murine models don't fully recapitulate the human PD pathology. Patient-derived induced pluripotent stem cells (iPSCs) provide a valuable model to obtain human brain cells for in vitro research. Therefore, we established a protocol that allows robust differentiation of patient-derived iPSCs carrying the LRRK2 G2019S mutation into microglia.

Results:
hiPSCs are clustered into embryoid bodies (EBs) and patented towards hematopoietic precursors which under differentiation conditions produce microglia progenitors. The progenitors are collected from the supernatant and further differentiated into mature microglia. Subsequently we analysed the role of LRRK2-G2019S in endosomal trafficking in the differentiated microglia as well as changes in metabolism.

Conclusions:
Together our data show the relevance of LRRK2-G2019S in microglia function.

Keywords: Microglia, autophagy, metabolism

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Can Curli be a driver of α-synuclein aggregation in Parkinson's Disease?

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Background:
A hallmark of Parkinson's disease (PD) is aggregation of α-synuclein in neurons of the central (CNS) and enteric nervous system (ENS). Recent studies suggest that the gut microbiome can trigger this aggregation in the ENS, after which it will spread to the brain in a prion-like manner. A specific bacterial product, named Curli, has shown to accelerate this aggregation *in vivo*. To investigate the molecular mechanisms behind this, we wanted to investigate the role of Curli on the start of α-synuclein aggregation in our established *in vitro* human ENS model.

Methods:
Using the protocol from Gogolou *et al.* (2021), human embryonic stem cells were differentiated into enteric neurons and enteric glial cells. These cells express neuronal (TUJ1) and glial cell (GFAP) markers together with relevant PD proteins, including α-synuclein. Using this model, the role of different concentrations of Curli on α-synuclein aggregation with or without addition of proinflammatory cytokines (IL-1β and TNFα, both 5 ng/mL) was investigated. After 18 days, cells were analyzed for immunometabolic responses and α-synuclein aggregation.

Results:
Blinded scoring of phosphorylated α-synuclein staining showed a slight increase in intensity upon exposure of Curli together with proinflammatory cytokines. In addition, the lower dose of 0.1 µg/mL Curli increased IL-6 secretion in the inflammatory conditions from 9 days of exposure onward.

Conclusions:
Although preliminary, exposure of 0.1 µg/mL Curli with proinflammatory cytokines seems to increase the inflammatory response and phosphorylated α-synuclein in our ENS cells. Future studies are warranted to explore the aggregation of α-synuclein in our model.

Keywords: Parkinson's disease, α-synuclein aggregation, enteric nervous system

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