Early stage neuroimaging and behavioral biomarkers of PD progression and underlying mechanisms

Gábor Perlaki[1], Evgeniya Kirilina[2], Kerrin J Pine[2], Mikhail Zhubkov[3], Puneet Tawlar[3], Pierre-Louis Bazin[4], Norber Kovacs[1]*, Gilles Vandewalle[3]*, Anneke Alkemade[5]*, Nikolaus Weiskopf[3]**

[1]Department of Neurology, University of Pécs, Pécs, Hungary,
[2]Department of Neurophysics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany,
[3]GIGA-CRC Human Imaging, University of Liège, Liège, Belgium,
[4]Full brain picture Analytics, Leiden, Netherlands,
[5]Integrative Model-based Cognitive Neuroscience Research Unit, University of Amsterdam, Amsterdam, Netherlands

* - principle investigator, ** - coordinator

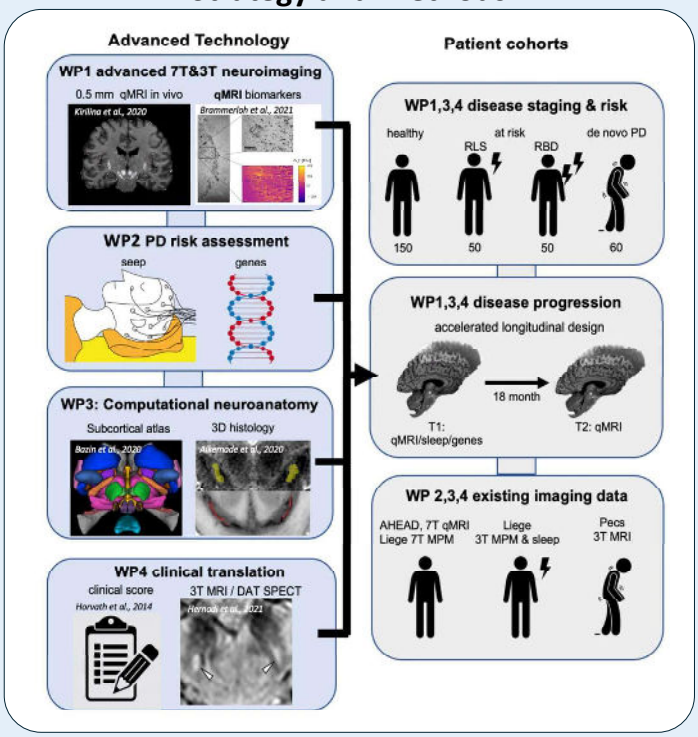
Motivation

The early stages of Parkinson's disease (PD), is characterized by iron accumulation and neurodegeneration of small brain nuclei that are crucial for regulating sleep and wakefulness. Altered sleep patterns are often among the earliest signs of PD, appearing years before diagnosis. However, neuronal loss in brainstem can go undetected for decades, and the spread of PD pathology in preclinical stages, and its connection to early symptoms, remain largely unexplored. The IronSleep project leverages cutting-edge ultra-high-resolution quantitative neuroimaging at 7T, recent advancements in neuroanatomy, and state-of-the-art sleep research and genetics to investigate the degeneration of subcortical nuclei in preclinical PD and their association with sleep disruptions.

Aims and Hypothesis

We aim to detect subtle anatomical changes in the substantia nigra and locus coeruleus, two regions central to PD pathology, and link these changes to sleep patterns in healthy aging, high-risk groups, and early-stage PD patients. Our ultimate goal is to establish multimodal biomarkers for preclinical PD by integrating clinical, behavioural, electrophysiological, genetic, and neuroimaging data to identify individuals at high risk or in the very early stages of PD, paving the way for longitudinal studies to identify prodromal PD. We aim to use this biomarker to understand the mechanisms of PD progression at early disease stages.

Strategy and Methods



Imaging data acquisition: Ultra-high-resolution multi-parametric MRI protocols were implemented at both 7T (600µm) and 3T (800µm) across 3 imaging sites to obtain quantitative parameter maps: proton density (PD), longitudinal relaxation rate (R1), effective transverse relaxation rate (R2*) and quantitative susceptibility mapping (QSM). This multiparametric protocol was combined with T2 mapping, diffusion-weighted imaging and neuromelanin-sensitive MRI as well as T2*-weighted measurements for the visual assessment of nigral hyperintensity (i.e. swallow-tail sign).

Image analysis: Processing steps includes denoising of multi-contrast data with a local complex-valued PCA-based method, calculation of multiparametric maps of quantitative MR parameters by the hMRI toolbox (https://hMRI.info), and automatic parcellation of the subcortical brain regions by Multi-contrast Anatomical Subcortical Structures Parcellation (MASSP) algorithm, enhanced by multimodal 3D histology.

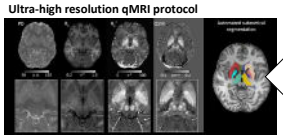
Clinical and sleep phenotyping: As part of the clinical phenotyping detailed motor and non-motor symptom mapping (e.g. MDS-UPDRS, Hoehn-Yahr Scale, non-motor symptoms scale, Epworth Sleepiness Scale, depression, anxiety, apathy, cognitive performance, impulsive-compulsive disorders) are performed, and detailed clinical data (e.g. comorbidities, medication used) are recorded. Sleep is characterized by various measures of sleep macro- (e.g. REM sleep duration) and microstructure (e.g. sleep spindles, cycling alternating pattern in NREM sleep) in addition to EEG frequency bands (e.g. theta EEG band). Sleep features associated with polygenic risk for PD are also examined in an age-dependent manner.

Clinical cohort: Early-stage PD, prodromal PD and healthy controls are examined in an accelerated longitudinal design (*2nd* timepoint at 18 months).

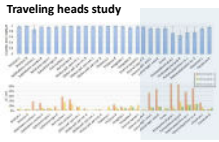
Results

WP1 advanced 7T & 3T neuroimaging

Ultra-high resolution qMRI protocol



Traveling heads study



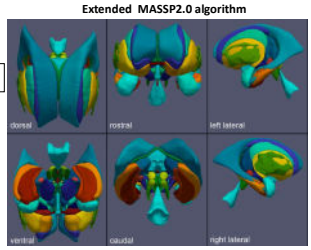
QMRI parameters at submillimeter resolution provide 10% accuracy across sites and repetitions

3D nigral atlas revisiting radiological text books

3D histology based detailed atlas of nigrosomes within the substantia nigra was created revisiting established interpretation of nigral swallow tail sign

WP3: Computational neuroanatomy

Extended MASSP2.0 algorithm

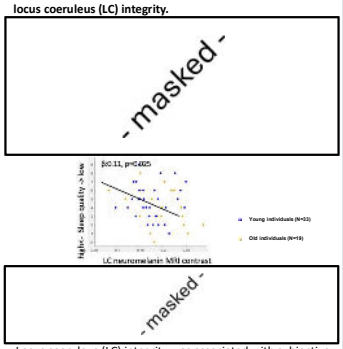


3D representations of the MASSP2.0 subcortex atlas.

The MASSP algorithm was improved by expanding the list of automatically segmented brain structures involved in Parkinson's disease. A new extended version of our atlas, and a new release of the extended automated MASSP algorithm, now including 35 subcortical structures in both hemispheres, have been submitted for publication. MASSP was successfully retrained for data acquired at clinical 3T scanner.

WP2 Sleep and PD risk assessment

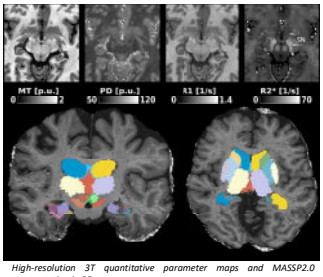
Linking sleep metrics, PD polygenic risk score (PRS) and locus coeruleus (LC) integrity.



Locus coeruleus (LC) integrity was associated with subjective sleep quality.

WP4 Clinical translation

Applying method in patients at clinical field strength



High-resolution 3T quantitative parameter maps and MASSP2.0 segmentation in PD.

Clinical characteristics such as low MDS-UPDRS II and III scores were identified in association with the preservation of nigral hyperintensity on T2*-weighted MR images in PD (n=152; p=0.006 and p=0.013). The 3T data acquisition and analysis pipeline was promising based on test–retest variability (generally <10%).

References:

Alkemade A, Großmann R, Bazin PL, Forstmann BU. Brain Struct Funct. 2023;228(6):1399-1410.
Talwar P, Deantoni M, Van Egroo M, et al. Sci Rep. 2023;13(1):20873.
Hernadi G, Perlaki G, Kovacs M, Pinter D, Orsi G, Janszky J, Kovacs N. Sci Rep. 2023;13(1):10594.
Brammerloh M, Kirilina E, Alkemade A, et al. Radiology. 2022;305(3):674-677.

Significance and Impact

We developed ultra-high-resolution, multimodal quantitative MRI measures with potential to become quantitative diagnostic markers for PD and its progression, promising to outperform conventional markers based on the visual assessment of neuromelanin MR imaging or the nigral hyperintensity sign. The crucial first steps toward clinical translation were performed by adapting our pipeline to 3 T and initiating longitudinal studies in healthy and PD populations at multiple sites.

Outlook

Next steps will include the dissemination of the developed methodology, the extension of our present dataset by including the analysis of a larger cohort of patients, risk groups and healthy controls, as well as the translation of our existing methodology to clinical settings. Future challenges include the acceleration of the MRI acquisition to be applicable in routine diagnostic as well as bridging the gap between advanced ultra-high field high-resolution research methods and clinically applicable time-efficient protocols at lower field strengths (e.g. ≤1.5 Tesla)

Federal Ministry of Education and Research
ZonMw
fnrs LA LIBERTÉ DE CHERCHER
PROGRAM FINANCED FROM THE NRDI FUND