

IronSleep

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

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Aims, research questions and working hypothesis: 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 other symptoms. However, neuronal loss in brainstem can go undetected for decades, and the precise patterns and spread of PD pathology in preclinical stages, as well as their connection to early symptom progression, 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.

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, behavioral, 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.

Means/methods implemented by the consortium

We integrate ultra-high-resolution multi-parametric quantitative MRI at both 7T (600 μ m) and 3T (800 μ m) with automated parcellation of subcortical brain regions using the Multi-contrast Anatomical Subcortical Structures Parcellation (MASSP) algorithm, enhanced by multimodal 3D histology. These advanced imaging tools are deployed across three neuroimaging sites to study genetically characterized cohorts, including healthy participants, individuals with sleep alterations linked to PD risk, and early-stage PD patients in an accelerated longitudinal design. Our approach correlates genetic risk factors and neuroimaging markers with specific sleep features, aiming to deepen our understanding of early PD markers and risks.

What are the outcomes of the project?

We developed an advanced neuroimaging protocol for precise, robust estimation of multiple quantitative MRI (qMRI) parameters at submillimeter resolution, which we validated in a multisite traveling head study. Additionally, we enhanced the MASSP algorithm by incorporating more structures and successfully retrained it for imaging data acquired at a 3T clinical field strength. Using 3D histology, we created a detailed atlas of nigrosomes within the substantia nigra in MNI space. Retrospective analysis of clinical characteristics, such as low MDS-UPDRS scores, identified potential factors that may contribute to the preservation of nigral hyperintensity on T2*-weighted MR images in PD, highlighting the PD subgroups where our new quantitative pipeline is being tested. Our methods have demonstrated the sensitivity needed to detect subtle differences in brain microstructure, such as those associated with healthy aging. We also found correlations between genetic risk scores for PD and sleep features, as well as evidence that locus coeruleus integrity predicts sleep characteristics in healthy aging cohorts.

Significance and impact of the work on the field

Compared to many other neurological conditions (e.g. cerebrovascular diseases, brain tumors, multiple sclerosis, epilepsy), the diagnostic MR imaging is still underdeveloped in PD and the diagnosis is established clinically up until today. Although there are some promising MRI markers for PD, such as absent nigral hyperintensity sign, these are merely qualitative and subjective. Our pipeline provides high-resolution, fully quantitative multi-model MR measures having the potential to become quantitative diagnostic markers for PD and allowing longitudinal monitoring of the disease. 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.

Next steps and future challenges

Next steps should include the dissemination of the methodology developed in IronSleep project, 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).