Visualizing Parkinson's disease brain signatures using advanced MRI techniques

Impact paragraph

Parkinson's disease (PD) is a progressive neurological disorder characterized by slowness of movements (bradykinesia), stiffness (rigidity) and resting tremor. In later stages of the disease, PD patients often suffer from postural instability and gait problems. Also, a broad spectrum of non-motor symptoms, such as cognitive impairment, depression, autonomic failure and sleep disorders can occur. In less than two centuries PD has become a common disorder, affecting 6.2 million people worldwide in 2015 (1). Moreover, in about 20 years the PD population is expected to reach more than 12 million patients globally (2). Due to the progressive character, wide variety of symptoms and the long-lasting disease course PD greatly affect the quality of life of patients and their caregivers. Moreover, non-motor symptoms seem to have an even greater effect on the quality of life than motor manifestations (3). However, the underlying cause of the non-motor symptoms is not very well understood. Although dopaminergic medication is used to improve PD motor symptoms and reduce physical disability, there are currently no treatment options which can cure PD or slow down the disease process. Because of the increasing patient numbers and the great impact on society, patients and caregivers, urgent calls are made to search for ways to prevent and treat PD. Accurate diagnostic markers and monitoring indicators are highly necessary for the development of new therapeutic strategies. This thesis aims to attribute to the elucidation of the PD pathophysiology by investigating structural and functional changes in the PD brain with magnetic resonance imaging (MRI) techniques and to search for radiological biomarkers.

The main findings of these thesis are that disruptions in the default mode network serve an important role in the pathophysiology of cognitive impairment in PD. In line with this, white matter tract alterations are probably more important in the early stages of cognitive decline in PD compared to grey matter alterations. Also, we confirmed that cognitive impairment is more prevalent in PD patients with a postural instability and gait disorder subtype, compared to patients with a tremor-dominant subtype. Furthermore, a comprehensive description of the study protocol of the TRACK-PD study is provided. This is the first and largest longitudinal ultra-high field 7T MRI study in PD patients to date. Based on the data of this study, we confirmed that neuromelanin related signal intensity in the locus coeruleus differs between PD and healthy controls (HC). No differences between PD and HC could be established in diffusion measures of the olfactory tract.

1. Contribution to science

The findings of this thesis provide several interesting insights into the PD pathophysiology of both motor and non-motor symptoms. Acquiring knowledge about the neurodegenerative disease process is essential for the development of new therapeutic strategies. Also, specific functional and structural MRI alterations might be able to serve as radiological biomarkers that can aid in the diagnostic process of PD. Furthermore, the identification of biomarkers which are correlated with clinical symptoms or disease progression is crucial for the development of monitoring biomarkers that can be used in future disease modifying therapy studies.

The TRACK-PD study, of which the study protocol is described in chapter 5 of this thesis and published in BMC Neurology, will provide an unique database consisting of longitudinal clinical, genetic and radiological information of a relatively large group of PD patients and HC. It is the biggest longitudinal 7T MRI study so far and thereby functions as a biobank for ongoing and future research. Within our research group, several other analysis are currently being performed with this data. This for example includes the search for neuroanatomical correlates of anxiety in PD and functional connectivity patterns in relation to cognitive impairment. In addition, the data is available for other researchers on reasonable request and can therefore be used by other research groups globally. In this way it will be possible to answer many more future research questions with data of the TRACK-PD study.

Furthermore, the outcomes in this thesis related to cognitive impairment in PD might have implications for future studies. Based on our results it is indicated that white matter tract alterations are more important in the early phases of cognitive decline compared to grey matter disruptions. This is an important outcome, which may guide future studies investigating the pathophysiology of cognitive impairment in PD. It can also provide guidance for the development of new therapies. For example, other researchers have recently indicated that the white matter disruptions might be induced by a demyelination process (4). This offers a new perspective on the pathophysiology of cognitive decline in PD and creates a novel target for future intervention studies searching for disease modifying therapies.

Lastly, based in the studies described in this thesis several suggestions for future studies are given in the general discussion. This includes the application of multimodal imaging techniques, automated analysis methods and the use of machine-learning approaches. In addition, it seems beneficial to combine different biochemical and imaging techniques for the diagnosis and monitoring of PD, since different techniques are likely to complement each other. Moreover, longitudinal analysis are essential to

determine the temporal relationship between imaging alterations, PD symptoms and disease progression in general. Other research groups may be encouraged to develop new studies and research questions based on these suggestions.

2. Contribution to society

As described above, PD is a highly prevalent disease worldwide with an enormous impact on both society and the life of patients and caregivers. The most important goal of PD research is to develop new disease-modifying strategies which are able to cure the disease or at least slow down disease progression. Understanding the PD pathophysiology enables researches to determine the most promising targets for future medication strategies and is therefore an essential step in the development of new therapies. Furthermore, in order to develop and test new treatment options valid biomarkers are necessary to monitor and evaluate therapy effect. The TRACK-PD study aims to contribute in the search for these new biomarkers, which can potentially be used in intervention studies. For example, the neuromelanin related alterations in PD, which have also been established in the study in chapter 6 of this thesis, has recently led to the development of new therapeutic strategies focusing on neuromelanin accumulation in PD (5). In addition, gene therapies are being researched for monogenetic forms of PD (6). Future analysis incorporating the genetic information collected by the TRACK-PD study can provide insights in the clinical and radiological phenotype of genetic-linked PD, which can be used for the development of new interventions. Studies investigating iron chelation therapy in PD have not yet led to satisfactory results (7). However, future analysis on iron-sensitive sequences of the TRACK-PD study, might provide information that can be useful for the development of novel iron-related treatment strategies.

Moreover, quality of life in PD patients is influenced to a greater extent by non-motor than motor symptoms. In the past, the majority of studies have however focused on motor symptoms. In the first part of this thesis structural and functional cerebral alterations related to cognitive impairment in PD are explored. These studies provide valuable information regarding the neurodegenerative process underlying this important non-motor symptom. From the patient point of view it is essential to improve our knowledge about these and other non-motor symptoms, in order to create more effective management options.

The diagnosis of PD is complicated by the heterogenous nature of the disease and the fact that it is a clinical diagnosis. Patients often experience a delay in diagnosis and have visited multiple healthcare providers, before getting diagnosed with PD. Furthermore, the disease course of different patients is highly variable and at this moment we are

not able to predict this for the individual patient. Studies have shown that a correct explanation about the disease and diagnosis had a long-lasting impact on the quality of life of PD patients (8). This emphasizes the importance of a correct clinical diagnosis and preferably also an accurate prediction of what the patient can expect for the upcoming years. By studying specific PD symptoms in relation to MRI alterations this thesis aims to contribute to an improved diagnostic process. Furthermore, the longitudinal nature of the TRACK-PD study enables us to study symptoms over time and will create the possibility to correlate clinical symptoms with specific MRI changes. It might therefore help to better predict the disease course of an individual patient based on MRI characteristics.

The fact that this kind of biomarker research is important to patients is underlined even further by the overwhelming number of participants which have voluntarily registered themselves for participation in the TRACK-PD study. It was truly inspirational to meet so many PD patients, each with their own story and distinct experience of the disease. Since the study outcomes are relevant to these patients, we attach great importance to communicating the results with the participants by sending them a comprehensible Dutch summary of all study results.

3. References

1. Collaborators GBDN. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(5):459-80.
2. Dorsey ER, Bloem BR. The Parkinson Pandemic-A Call to Action. JAMA Neurol. 2018;75(1):9-10.
3. Santos-Garcia D, de la Fuente-Fernandez R. Impact of non-motor symptoms on the quality of life of patients with Parkinson's disease: some questions beyond research findings. J Neurol Sci. 2013;335(1-2):239.
4. Kan H, Uchida Y, Ueki Y, Arai N, Tsubokura S, Kunitomo H, et al. R2* relaxometry analysis for mapping of white matter alteration in Parkinson's disease with mild cognitive impairment. NeuroImage: Clinical. 2022;33:102938.
5. Gonzalez-Sepulveda M, Compte J, Cuadros T, Nicolau A, Guillard-Sirieix C, Peñuelas N, et al. In vivo reduction of age-dependent neuromelanin accumulation mitigates features of Parkinson's disease. Brain. 2023;146(3):1040-52.
6. McFarthing K, Buff S, Rafaloff G, Fiske B, Mursaleen L, Fuest R, et al. Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2023 Update. J Parkinsons Dis. 2023;13(4):427-39.
7. Levi S, Volonté MA. Iron chelation in early Parkinson's disease. The Lancet Neurology. 2023;22(4):290-1.
8. Global Parkinson's Disease Survey Steering C. Factors impacting on quality of life in Parkinson's disease: results from an international survey. Mov Disord. 2002;17(1):60-7.