Visualizing Parkinson's disease brain signatures using advanced MRI techniques

Summary

The studies presented in this thesis investigated the role of magnetic resonance imaging (MRI) as a biomarker for Parkinson's disease (PD). In part I we focused on cognitive impairment and explored structural and functional alterations related to cognitive decline in PD patients. Part II specifically investigates the use of ultra-high field 7T MRI as an early biomarker for PD.

1. Part I

Chapter 2 is a meta-analysis of resting-state functional MRI (fMRI) studies in PD patients with cognitive impairment. For this meta-analysis an extensive search was performed to select all existing studies focusing on resting-state fMRI characteristics of PD patients with cognitive impairment compared to either cognitively unimpaired PD patients or healthy controls (HC). Seventeen studies were included in the meta-analysis, consisting of 222 PD patients with mild cognitive impairment, 68 patients with PD dementia, 289 cognitively unimpaired PD patients and 353 HC. A voxel-based meta-analysis was performed using the anisotropic effect-size version of the signed differential mapping method. Results showed that PD patients with cognitive impairment predominantly display a reduced connectivity in brain areas that are part of the default mode network. The default mode network is believed to serve an important role in several cognitive functions. Alterations in this network have also been described in other neurodegenerative disorders, such as Alzheimer's disease and frontotemporal dementia. Although results of this meta-analysis might be influenced by methodological heterogeneity and variations in patient characteristics across individual studies, it provides a more definite step in the differentiation of network disruptions associated with cognitive impairment in PD. It suggests an important role for the default mode network in the pathophysiology of cognitive decline and indicates that functional connectivity alterations of the default mode network might be able to serve as a biomarker for cognitive impairment in PD.

In **chapter 3** functional brain network characteristics and cognitive performance is compared between different motor subtypes of PD. For this study, data of a cross-sectional resting-state 3T MRI study was used. Based on a numerical ratio derived from the mean tremor score and mean-postural instability and gait disorder score at the MDS-UPDRS III, two subgroups were defined, namely a tremor-dominant (TD) and postural instability and gait disorder (PIGD) subgroup. Differences in functional connectivity were investigated using dual regression analysis and inter-network connectivity analysis. Also, cognitive performance was investigated between subgroups. The PIGD

subgroup performed worse compared to the TD subgroup across all cognitive domains. Resting-state fMRI network analyses suggested the connection between the visual and sensorimotor network to be a potential differentiator between PIGD and TD subgroups. However, after correcting for dopaminergic medication use these results were not significant anymore. So based on this study, no reliable connectivity differences between PIGD and TD motor subgroups could be established.

Chapter 4 compares grey matter alterations between clusters of PD with mild, moderate and severe stages of cognitive impairment. In this cross-sectional study, 124 PD patients underwent extensive clinical and neuropsychological assessments as well as a 3T MRI scan of the brain. Four groups were identified ranging from cognitively intact patients to patients with severe deficits in all cognitive domains, whilst showing comparable levels of motor disability and disease duration. Each group was compared to the cognitively intact PD group using voxel- and vertex-based morphometry. After correcting for age, significant differences in grey matter volume, cortical thickness and cortical folding were only seen between cognitively unimpaired PD patients and PD patients with severe cognitive deficits. Volume alterations were restricted to the right posterior cingulate and the right precuneus. Reduced cortical thickness was seen in the right inferior temporal gyrus and reduced folding in the right temporal region. As these differences were not associated with age, we assume that they are associated with underlying pathology of the cognitive decline. However, given the limited involvement of grey matter differences between groups, we hypothesize a more important role for white matter tract alterations in early stages of cognitive impairment in PD.

2. Part II

Chapter 5 provides the detailed protocol of the TRACK-PD study, which is the first and largest longitudinal ultra-high field 7T MRI study in PD patients to date. In this study an extensive 7T MRI protocol of the brain is performed at baseline and repeated after 2 and 4 years. Extensive assessment of motor, cognitive, neuropsychiatric and autonomic symptoms are performed at baseline and follow-up visits with wearable sensors, validated questionnaires and rating scales. At baseline a blood DNA sample is also collected. This study will provide a relatively large, longitudinal database of PD with extensive information related to motor and non-motor symptoms. Due to the use of ultra-high field 7T MRI it creates the opportunity to investigate the brain in even more detail than the MRI techniques with lower field strengths (1.5 or 3T) used clinically. Aim of this study is to improve our understanding of PD and its pathophysiology by establishing MRI characteristics that can distinguish between PD patients and healthy control subjects. In addition, we aim to detect new imaging biomarkers for disease

progression that could be valuable for the evaluation of future therapies. Lastly, correlating MRI characteristics to clinical phenotype and genetics might help us to further define PD subtypes.

Chapter 6 describes an ultra-high field imaging study comparing neuromelanin related signal intensity in the substantia nigra (SN) and locus coeruleus (LC) between early-stage PD patients and HC. In addition, the association of neuromelanin related signal intensity in the SN and LC with cognitive performance was explored. The study was conducted using data from the TRACK-PD study described in chapter 5. Masks for the SN and LC were automatically segmented and manually corrected. Mean signal intensity of the SN and LC was calculated and normalized to the mean signal intensity values of pre-selected reference regions. PD participants displayed a lower contrast-to-noise ratio (CNR) in the right SN and left LC. After adding age as a confounder, the CNR of the right SN did not significantly differ anymore between PD and HC. Additionally, a significant positive correlation was found between the SN CNR and the 15 Words Test. These results confirm that neuromelanin related signal intensity of the LC differs between early-stage PD patients and HC. No significant differences were found in the SN. These result are in favour of the theory of bottom-up disease progression in PD. Furthermore, it suggests that loss of SN integrity might influence working memory or learning capabilities in PD patients.

In **chapter 7** we visualized the olfactory tract with DWI techniques on ultra-high field MRI and evaluated if previous findings, showing distinctive diffusion measures of the olfactory tract between PD and HC, could be replicated on 7T MRI. The study was conducted using data from the TRACK-PD study described in chapter 5. Manual seed regions of interest were drawn in the olfactory tract region. Tractography of the olfactory tract was performed using a deterministic streamlines algorithm. Diffusion measures (fractional anisotropy and mean- radial- and axial diffusivity) of the generated streamlines were compared between groups. Diffusion measures did not differ between hyposmic PD patients, anosmic PD patients and normosmic HC. The study showed that fiber tracking of the olfactory tract was feasible in early-stage PD patients using 7T DWI data. However, based on these results 7T diffusion measures of the olfactory tract are not useful as an early clinical biomarker for PD. Using olfactory testing instead of a self-reporting questionnaire might be better suited to objectively identify hyposmic participants and define olfactory subgroups in future studies.

Chapter 8 provides a general discussion in which the most relevant findings of this thesis are discussed and put into perspective. Also, advantages and limitations of MRI biomarkers are highlighted and potential future research directions are described.