Moving along the non-motor spectrum of Parkinson's disease

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SUMMARY OF FINDINGS

The main aim of this thesis was to provide more insight into pain and cognition as non-motor symptoms of Parkinson's disease (PD). This was achieved by studying pain and cognitive functioning of PD patients in clinical practice in (Chapter 2 & Chapter 3), investigating non-motor symptom interactions in (Chapter 4), and exploring underlying neural mechanisms of pain and cognition (Chapter 5 & Chapter 6). A short summary per chapter is provided in this chapter.

PART I: CLINICAL STUDIES
CHAPTER 2: PAIN IS RECOGNIZED AS A SYMPTOM IN PD PATIENTS
Chapter 2 addressed clinical pain assessment in PD. We were interested in how clinician's pain assessments correspond with the pain perception of the patient. Additionally, we aimed to compare clinical evaluations of patients' pain between neurologists. Fifty-seven patients filled out questionnaires including pain-related questions, and their medical statuses were checked for pain-related information. In addition, 23 PD patients with pain underwent pain evaluation by three independent neurologists. First, we found no significant level of agreement on pain between the patient and the clinician, yet patients did receive appropriate analgesics, albeit according to the clinician's evaluation rather than to the patient's evaluation. Second, interrater agreement between three neurologists was strongest for the item on pain related to response fluctuation, agreement on other types of pain was lower.

CHAPTER 3: THERE IS NO DIRECT ASSOCIATION BETWEEN COGNITION AND PAIN
In Chapter 3, we hypothesized an association between clinical pain and neuropsychological functioning, based on the overlap in brain areas involved in both pain and cognition. We tested neuropsychological functioning of 48 patients with PD and 57 healthy controls, and both the affective as well as the sensory aspect of pain were assessed. PD patients experienced more pain than controls, particularly regarding the affective aspect of pain. Linear regression analyses showed that cognition was not related to pain. Instead, clinical pain was primarily related to symptoms of depression

and anxiety. The difference between the affective and the sensory aspect of pain might be due to the neuropathology of PD, which is mainly present in areas processing the affective aspect of pain (e.g. the insula). This study underlines that symptoms of depression and anxiety should be considered when pain is treated.

CHAPTER 4: INVESTIGATING NON-MOTOR SYMPTOMS AS A NETWORK PROVIDES NEW INSIGHT INTO SYMPTOM-INTERACTIONS

When looking at how non-motor symptoms (NMS) impact daily life, most studies investigate NMS by assessing the contribution of *individual* symptoms to quality of life (QoL). However, symptoms could also have an interactive relationship. This interaction might be overlooked when only studying these individual contributions. The aim of Chapter 4 was, first, to assess how NMS impact quality of life, and, second, to investigate NMS by using a network approach. This approach treats symptoms as nodes and associations between symptoms as edges in a network, providing the opportunity to investigate the dimensional spectrum of NMS. Seventy PD patients completed questionnaires on NMS and QoL. The non-motor symptom domains Mood and Pain are significant contributors to QoL. The network analysis suggests that Mood and Sleep play central roles in the NMS-network, and that Mood and Cognition are strongly related. Because of power issues, the generalizability of our results is limited. However, complementary information from the network analysis does suggest that focusing on sleep problems could potentially ameliorate both mood and pain symptoms. Future studies should focus on investigating the presence of causal relationships.

PART II: NEUROIMAGING STUDIES

CHAPTER 5: PAIN IN PD IS RELATED TO THE ARCHITECTURE OF FUNCTIONAL NEURAL CONNECTIONS

Research has shown that functional connectivity during the resting-state is related to persistent pain in PD. Besides measuring the strength of connections, functional topology of the brain (i.e. the architecture of functional neural connections) can also be assessed. Functional topology has been implicated as a correlate of human behavior. In Chapter 5, we aimed to (1) assess the differences between PD patients and controls with respect to pain and resting-state network topology, and (2) investigate how resting-

state network topology is associated with clinical pain in both PD patients and controls. Resting-state activity of 24 PD patients (both on and off medication) and 27 controls was assessed with fMRI. We investigated pain with the colored analogue scale and the McGill pain questionnaire. We calculated the following measures of functional network topology: betweenness centrality (BC) was used to assess hubness, and global efficiency (GE) was used to assess integration of the network. PD patients experienced more pain than controls. GE of the whole brain was higher in PD patients (on as well as off medication) compared to healthy controls. GE of the specialized pain network was also higher in PD patients compared to controls, but only when patients were on dopaminergic medication. BC of the pain network was lower in PD patients off medication compared to controls. We found a positive association between pain and GE of the pain network in PD patients off medication. For healthy controls, a negative association was found between pain and GE of the pain network, as well as between pain and BC of the pain network. Our results suggest that functional network topology differs between PD patients and healthy controls, and that this topology can be used to investigate the underlying neural mechanisms of pain symptoms in PD.

CHAPTER 6: COGNITION IN PD IS RELATED TO THE DYNAMICS OF FUNCTIONAL CONNECTIONS

It has previously been observed that dynamic functional connectivity (dFC) in PD is associated with better attention performance and with motor symptom severity. In Chapter 6, we aimed to investigate dFC of both the default mode network (DMN) and the frontoparietal network (FPN) as neural correlates of cognitive functioning in patients with PD. Additionally, we investigated pain and motor problems as symptoms of PD in relation to dFC. We used the same data as for Chapter 5. Memory and executive functioning were assessed with neuropsychological tests. Pain was assessed with the numeric rating scale; motor symptom severity was assessed with the Unified Parkinson's Disease Rating Scale. Resting-state dFC was defined by calculating the variability of functional connectivity over a number of sliding windows within each scan. dFC of both the DMN and FPN with the rest of the brain was calculated. Patients performed worse on tests of visuospatial memory, verbal memory and working memory. No difference existed between groups regarding dFC of the DMN nor the FPN with the rest of the

brain. A positive correlation existed between dFC of the DMN and visuospatial memory. Our results suggest that higher dynamics of the DMN with the rest of the brain are beneficial in PD patients, particularly for visuospatial memory. Furthermore, we suggest that brain dynamics of the DMN, as measured with dFC, could be a phenomenon specifically linked to cognitive functioning in PD, but not to other symptoms.