

Summary

(Dis)Inhibition - Imaging Neuropsychiatry in Parkinson's disease

The aim of this thesis was to gain a better understanding of the neurobiological factors that contribute to the development of anxiety, depression and impulse control disorders (ICD) in Parkinson's disease (PD) using multiple neuroimaging techniques.

In **Chapter 1** we provide a general introduction on PD, a short description of its pathophysiology and the neuropsychiatric symptoms of depression, anxiety and impulse control disorders (ICD) that occur frequently in the disease.

Chapter 2 describes an investigation on the relation between brain volume and anxiety symptoms in 110 PD patients. We focused on volume of the amygdala and hippocampus, two structures that are important for the processing of emotions. The severity of anxiety symptoms was negatively correlated with volume of the left amygdala. This reduction in left amygdalar volume was independent of the severity of motor symptoms and medication use. These results are consistent with studies in non-PD patients with anxiety disorders. We discuss a number of possible interpretations of these results and tentatively hypothesize that degeneration of the amygdala is caused by the Parkinson pathology and that this subsequently leads to the development of anxiety symptoms. Replication of these results with prospective follow-up studies is, however, necessarily to substantiate this hypothesis.

In **Chapter 3** we present the results of a study on the relationship between striatal dopamine transporter (DaT) availability and the severity of depressive symptoms in 100 PD patients. Using Single Photon Emission Computed Tomography (SPECT) scans we determined DaT availability in the caudate nucleus and putamen. The caudate nucleus is involved in cognitive and motivational processes and the putamen in motor skills. We replicated previously findings on the association between the severity of motor symptoms in PD and decreased DaT availability in the putamen. Furthermore, we showed that DaT availability in the caudate nucleus but not the putamen was negatively associated with the severity of depressive symptoms. We thus showed a double association between depressive and motor symptoms on striatal DaT availability that concurs with our understanding of the cortico-striatal-thalamocortical (CSTC) circuits and their functions and showed a role for dopamine depletion in the pathophysiology of PD-related depression.

In **Chapter 4** we investigate the relation between striatal DaT availability measured with SPECT scans and the development of symptoms of ICD after commencing dopamine replacement therapy. In this study, 31 PD patients underwent a DaT SPECT scan when they were diagnosed and at that time showed no signs of ICD and were naïve for dopamine replacement therapy. Thirty months (on average) after the DaT SPECT scan and after commencing

dopamine replacement therapy, patients were evaluated with questionnaires to determine whether or not they (had) experienced symptoms of ICD. Eleven out of the 31 PD patients (35%) had developed symptoms of ICD after starting dopamine replacement therapy. Our results showed that striatal DaT availability determined at baseline in a medication-naïve state was lower in the 11 patients that had developed ICD symptoms compared with the 20 patients that had not. The severity of ICD symptoms was also negatively correlated with DaT availability in the ventral and antero-dorsal striatum, that are important for motivation & reward and cognition, respectively. These results suggest that a reduced DaT availability in these striatal areas forms a risk factor for the development of ICD after commencing dopamine replacement therapy. It also suggests that a DaT SPECT scan can be used (in the future) for evaluating the risk on developing ICD after patients commence dopaminergic treatment and allow closer monitoring of those that prove to be at increased risk.

Chapter 5 provides an overview of the studies that had been conducted thus far on depression and ICD in PD and animal models. In this chapter we also discuss our own results in **Chapter 3** and **4** on the relation between striatal DaT availability and symptoms of depression and ICD, respectively. In Chapter 5 we concluded based on our own results and those of others that depression in PD is associated with a decreased activation of brain areas involved in emotions and motivation due to dopamine denervation. ICD, on the other hand, are associated with an increased activation of the same brain areas. This increased activation seems to be due to an interaction between dopamine replacement therapy and pathological alterations in the ventral striatum. Our hypothesis is that dopamine receptors in the ventral striatum have become hypersensitive for dopamine (or equivalent agonists) due to the PD-related degeneration of dopamine projections towards this area. Because of this denervation-induced supersensitivity of the dopamine receptors in the ventral striatum, activity within the emotion and motivation CSTC circuit is increased. This increased activity may make patients more vulnerable to reward-related cues and underlie the development of ICD.

Nevertheless, even without a diagnosis of ICD, PD patients already seem to have trouble inhibiting their impulses. The ability to inhibit impulses is operationalized with response inhibition tasks, tasks in which subjects have to inhibit an automatic or no longer applicable response. In **Chapter 6** we investigated impulse control abilities in 21 medication-naïve PD patients using a stop-signal task during functional magnetic resonance imaging (fMRI) scanning and compared them with 37 age, gender and education matched healthy controls. The inclusion of only PD patients that did not (yet) receive dopamine replacement therapy and were without psychiatric complaints allowed us to examine the effects of the PD pathology on impulse control, not obscured by (chronic) medication effects or neuronal alterations related to ICD development. The results showed that our medication-naïve PD patients compared with healthy controls were significantly slower in response initiation. Nevertheless, speed of

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response inhibition, a marker for impulse control, was only marginally reduced. In contrast, previous studies in medicated PD patients did show significant reductions in response inhibition, although admittedly this may also be due to the previously employed and outdated method of calculating the speed of response inhibition. Our neuroimaging results showed that PD patients exhibited reduced inhibition-related activation of the bilateral inferior frontal gyrus and inferior parietal lobule. Furthermore, activation of the inferior frontal gyrus was negatively correlated with disease severity. These results show that PD patients are still reasonably capable of inhibiting their responses early in the disease and prior to commencing dopamine replacement therapy but that they do show alterations in inhibition-related brain activity. These alterations in inhibition-related activity may form a neurobiological substrate for the development of ICD after commencing dopamine replacement therapy. This hypothesis deserves further investigation by means of prospective follow-up studies in PD patients before and after commencing dopamine replacement therapy while monitoring the possible development of ICD symptoms.

Problems with inhibiting impulses and dysfunction of inhibition-related brain areas are not only observed in PD but also in other disorders within the impulsive-compulsive spectrum. Disorders within this spectrum are characterized by impulse control deficits and include disorders such as obsessive-compulsive disorder, attention-deficit hyperactivity disorder and Tourette syndrome. In **Chapter 7** we discuss neuroimaging studies on response inhibition in patients with PD or these other disorders within the impulsive-compulsive spectrum. At the end of this chapter we present a model that tries to explain the results of all these studies by providing a common neurobiological mechanism for impulse control deficits within these disorders. Our model postulates that the functional and behavioral deficits in response inhibition in PD and the other disorders compared with healthy controls can be conceptualized as a left-directed shift in the inverted-U-shape relation between task demands and inhibition-related brain activation that results in patients have to spend additional brain resources to inhibit their impulses. Impulse control deficits ensue when demands become too high and compensatory brain activation fails. What causes this shift is unknown but we tentatively hypothesize a role for dopamine that seems to dysfunction in all of the discussed disorders.

Finally in **Chapter 8** we present a general discussion of the previous chapters in the light of current scientific literature, provide a review on PD-related alterations in neurotransmission and CSTC signaling and what their effects are on the development of anxiety, depression and ICD. At the end of this chapter we also discuss the clinical implications of our findings. Because this thesis focused on the pathophysiology of three neuropsychiatric disorders and not on therapeutic interventions, our results cannot directly be applied to clinical practice but do provide clues for future screening and therapeutic methods. Among others, we advocate a broader application of DaT SPECT scans other than for just the

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differential diagnosis of movement disorders. Our results suggest that these scans may also be used to identify PD patients at risk of developing ICD after commencing dopamine replacement therapy. We also advocate an increased scientific interest in the pathophysiology of anxiety in PD. Surprisingly little research has been devoted to anxiety in PD and until this day there is no evidence-based treatment available. Research on the role of serotonin and noradrenalin in the pathophysiology of PD-related neuropsychiatric disorders is also warranted and should ultimately lead to a better prediction, recognition and treatment of these disorders with high negative impact on the patients' quality of life.

