One

General Introduction
Parkinson’s disease (PD) (Parkinson 2002): it’s the second most common neurodegenerative disorder (after Alzheimer’s disease), affecting 1% of the elderly population above 60 years of age with incidence increasing steeply with age (de Lau and Breteler 2006). The etiology of PD is currently unknown – hence the term idiopathic PD – although different hypothetical models of the proposed pathogenesis include gene mutations (Houlden and Singleton 2012), environmental toxins (Pan-Montojo and Reichmann 2014), neuroinflammation (Tansey and Goldberg 2010), infectious diseases (Takahashi and Yamada 1999), autoimmunity (Monahan et al. 2008) or prions (Olanow and Brundin 2013). It has even been proposed that if we live long enough we will all develop Parkinsonian symptoms and PD is therefore seen by some as a disease of accelerated aging (Collier et al. 2011; Rodriguez et al. 2014). Whatever the cause of PD development, the characteristic all idiopathic PD patients have in common is the accumulation of proteinaceous deposits in the brain, called Lewy neurites and Lewy bodies (Spillantini et al. 1997). In fact, currently the only way to definitively diagnose PD is by the neuropathological demonstration of Lewy bodies at post-mortem examination (first criterion for definitive PD) (Gelb et al. 1999). Lewy bodies and Lewy neurites consist of filaments of alpha-synuclein, a small presynaptic protein whose normal function in the brain is until this day still poorly understood (Bendor et al. 2013). The appearance of Lewy bodies and neuritis inside the brain occurs in stages with a caudal (brainstem) to rostral (neocortex) gradient (Braak et al. 2003). Spreading of this pathology is also associated with neuronal cell loss in brain areas vulnerable to synucleinopathy, such as the olfactory bulbs, dorsal nucleus of the vagus nerve, substantia nigra, ventral tegmental area, amygdala, hippocampus and multiple other brain regions (Braak et al. 2003). When the pathology reaches the substantia nigra and more than 50% of the dopaminergic neurons have degenerated (second criterion for definitive PD), the motor symptoms – for which PD is most commonly known – ensue (Spillantini et al. 1998). The substantia nigra is the origin of dopamine neurons that project towards the dorsolateral part of the striatum, important for motor control (Kish et al. 1988). Not only dopamine gets depleted during the course of the disease. Serotonin, noradrenaline, acetylcholine and multiple other neurotransmitters are also affected by the PD pathology (Dickson et al. 2009). Furthermore, motor symptoms (e.g. rigidity, hypokinesia, bradykinesia and tremor) are not the only ones that may occur in PD. As shown in figure 1.1, PD has many different faces; there is a diverse array of symptoms that can occur in PD, either due to the pathology itself or the treatment of PD. These symptoms can be categorized by domain. Symptoms can be classified as motor symptoms, autonomic symptoms, neuropsychiatric symptoms, sleep disturbances, cognitive problems and sensory symptoms. Figure 1.1 is not meant to give an exhaustive account of the symptoms in PD and not all symptoms necessarily have to occur in any given patient. In fact, the assortment of symptoms varies substantially between PD patients. Two major PD subtypes are differentiated on the basis of motor symptoms: tremor
dominant and non-tremor dominant PD, the latter usually associated with postural instability and gait problems (Thenganatt and Jankovic 2014).

Neuropsychiatry

One class of symptoms that has a particularly high impact on the quality of life of patients and constitutes the subject of this thesis relates to the neuropsychiatric symptoms. More than 60% of PD patients report one or more neuropsychiatric symptom(s) at some point in the course of their illness (Aarsland et al. 1999). This domain includes symptoms of depression, impulse control disorders (ICD), apathy, psychosis and anxiety. Depression, anxiety and ICD have an approximate prevalence of 35%, 40% and 14%, respectively (Richard 2005; Weintraub et al. 2010; Aarsland et al. 2012). These disorders are highly comorbid which suggests a common – or at least overlapping – pathophysiology. Depression and anxiety can also occur prior to the onset of motor symptoms (Aarsland et al. 2009), while ICD almost exclusively develop after PD patients commence dopamine replacement therapy (Weintraub et al. 2013). Despite their high prevalence, these disorders are often underrecognized and consequently undertreated (Shulman et al. 2002). Some symptoms may also prove difficult to treat pharmacologically, as this can lead to exacerbation of other PD-related symptoms, e.g. motor or autonomic symptoms. Alternative treatments are therefore being explored, e.g. bright light therapy (Rutten et al. 2012). Developing new effective treatments starts with understanding the underlying neurobiological mechanisms. The last decade has therefore seen an increased interest in studies trying to elucidate the pathophysiology of neuropsychiatric symptoms in PD.

Readers interested in the pathophysiology of anxiety in PD are referred to reviews of (Dissanayaka et al. 2014) and (Sagna et al. 2014). The literature on the pathophysiological mechanisms of depression and ICD is extensively reviewed in Chapter 5 and is associated with dysfunction of the limbic cortico-striatal-thalamocortical (CSTC) circuit that connects ventral prefrontal cortical areas with the ventral striatum and other structures of the basal ganglia (Groenewegen and Uylings 2010). This circuit also has connections with limbic areas, such as the amygdala, and plays an important role in motivation and reward processes. Figure 1.2 shows the circuitry of the limbic CSTC circuit and the two other CSTC circuits that have functions in motor (motor circuit) and cognitive (associative circuit) processes. More details on these circuits are provided in Chapter 5.

Research in the field of PD-related neuropsychiatry is still fully ongoing. Nevertheless, one overall conclusion that can already be drawn is that neuropsychiatric symptoms are not simply the consequence of adjusting to the diagnosis of a debilitating medical condition like PD. In fact, their development seems intimately linked to the PD-related pathological alterations and the treatment with dopamine replacement therapy. What these alterations are and how to prevent or correct them is still incompletely elucidated. In this thesis we
try to provide a small piece of that intricate puzzle.

Aims and outline of thesis

The main aim of this thesis was to gain a better understanding of the underlying neurobiological mechanisms of PD-related anxiety, depression and ICD (Chapter 2-5) as well as inhibitory control (Chapter 6-7) using multiple neuroimaging modalities and analytical tools. Chapter 2 reports on a cross-sectional study that focuses on the association between brain volume and anxiety symptoms in PD. No prior study has investigated the structural correlates of anxiety in PD, although studies in non-PD patients with anxiety disorders have consistently shown that anxiety symptoms are related to morphometric alterations of the amygdala and hippocampus, two structures that are important for emotional processing.

Depression and ICD were studied in the light of dopaminergic denervation. Dopamine is a major neuromodulator in the three CSTC circuits (Groenewegen and Uylings 2010). Dopamine denervation in PD leads to circuit dysfunction and this may not only underlie the motor symptoms (motor circuit dysfunction) (Pirker 2003) but also neuropsychiatric symptoms (limbic and associative circuit). Degeneration of dopamine neurons projecting towards the striatum can be measured in vivo with Single Photon Emission Computed Tomography (SPECT) imaging and a radiotracer selective for the dopamine transporter. The dopamine transporter (DaT) is located in the presynaptic membrane of dopamine neurons and its function is to reabsorb dopamine after it has been released into the synaptic

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**Figure 1.1** – Symptoms of Parkinson’s disease categorized per domain

<table>
<thead>
<tr>
<th>Motor symptoms</th>
<th>Bradykinesia, Hypokinesia, Tremor, R rigidity, Dyskinesia, Gait Problems, Postural Instability, Freezing, Dysarthria, Stooped posture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic symptoms</td>
<td>Hypersalivation, Sweating, Constipation, Orthostatic Hypotension, Dysphagia, Hot Flushes, Micturition problems, Sexual Dysfunction</td>
</tr>
<tr>
<td>Neuropsychiatric symptoms</td>
<td>Depression, Impulse Control Disorders, Apathy, Anxiety, Psychosis, Dopamine Dysregulation Syndrome, Punding</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>Insomnia, Excessive Daytime Sleepiness, REM-sleep Behavior Disorder, Restless Legs Syndrome, Sleep Apnea</td>
</tr>
<tr>
<td>Cognition</td>
<td>Executive Dysfunction, Cognitive Slowing, Dementia</td>
</tr>
<tr>
<td>Sensory symptoms</td>
<td>Hyposmia, Hypogeusia, Pain</td>
</tr>
</tbody>
</table>
Because of its localization in the presynaptic membrane, reductions in DaT availability provide a measure for striatal dopamine denervation (Booij et al. 1999; Scherfler et al. 2007). In Chapter 3 we investigate the association between striatal dopamine denervation, as measured with DaT SPECT, and symptoms of depression (Vriend et al. 2014c). A link between striatal dopamine and severity of depressive symptoms had already previously been reported (Remy et al. 2005; Weintraub et al. 2005; Hesse et al. 2009), although no study had looked at the differential effects of dopamine denervation in subregions of the striatum (i.e. putamen or caudate nucleus) on the occurrence of depressive or motor symptoms. This allows us to more precisely locate the neurobiological deficits associated with depression and provide clues to its treatment.

In Chapter 4 we looked at the association between striatal DaT availability and the development of ICD symptoms. Previous cross-sectional studies already provided evidence that ICD in PD are associated with reductions in striatal DaT availability (Cilia et al. 2010; Lee et al. 2014; Voon et al. 2014), but these studies were unable to ascertain whether the reductions were a premorbid trait, the consequence of chronic treatment, or a secondary effect of ICD development. Here we describe a follow-up study that looked at whether a DaT SPECT scan in a baseline medication-naïve state could predict the later development of impulse control disorders symptoms after start of dopamine replacement therapy (Vriend et al. 2014a), a major determinant for the development of these symptoms (Weintraub et al. 2010). If correct, this would then suggest that a DaT SPECT scan can be applied as a method to assess the risk on developing ICD after commencing dopaminergic therapy for PD.

Chapter 5 provides a model – in part based on the results of Chapter 2 and 3 – on how PD-related depression and ICD, two disorders that are frequently co-occurring in PD and show overlap in underlying pathophysiology, may develop due to an interaction between dopamine denervation and dopamine medication and concomitant dysfunction of CSTC circuits (Vriend et al. 2014b). Chapter 5 also provides a review of the currently available preclinical and neuroimaging literature on the pathophysiology of these disorders.

We also studied the neural correlates of response inhibition in PD as an experimental operationalization of impulse control. In Chapter 6 we investigated the neural correlates of response inhibition using functional magnetic resonance imaging (fMRI) in medication-naïve PD patients without psychiatric symptoms (Vriend et al. 2015). Studying response inhibition in medication-naïve PD patients allowed us to look at the influence of the PD pathology on (the neural correlates of) impulsivity, unbiased by the possible effects of dopamine replacement therapy. Chapter 7 subsequently reviews the current literature on neuroimaging of response inhibition deficits in PD and disorders that are characterized by impulse control deficits (e.g. obsessive-compulsive disorder and attention deficit hyperactivity disorder) (van Velzen et al. 2014). In the final part of that chapter we try to come to a common model that explains all these findings according
to compensatory capacity, dopamine signaling and dysfunction of CSTC circuits. Finally, this thesis concludes with a general discussion in Chapter 8 that reviews the results of all previous chapters in the light of current scientific knowledge and suggests possible future ventures in the research field of PD-related neuropsychiatry.

Figure 1.2 – The three parallel and partly segregated cortico-striatal-thalamocortical circuits of the brain. Abbreviations: OFC = orbitofrontal cortex, Nacc = nucleus accumbens, ACC = anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex, VTA = ventral tegmental area, SN = substantia nigra
Chapter 1   General Introduction
Chapter 2  The association of amygdalar and hippocampal volume with anxiety symptoms
Chapter 3   The association between striatal dopamine transporter availability and the severity of depressive symptoms
Chapter 4   The association between striatal dopamine transporter availability at baseline and the development of impulse control disorders after commencing dopamine replacement therapy
Chapter 5  Review of the pathophysiology of depression and impulse control disorders in Parkinson’s disease
Chapter 6 | Functional neural correlates of response inhibition in medication-naïve Parkinson’s disease patients
Chapter 7 | Review of the neural correlates of response inhibition deficits in Parkinson’s disease and other disorders characterized by failures in impulse control
Chapter 8 | General Discussion

Study populations

The majority of studies described in this thesis (Chapter 2-4) were conducted in a cohort of patients recruited via the outpatient clinic for movement disorders of the VU University medical center (Amsterdam, The Netherlands). These patients visited the outpatient clinic for diagnosis and underwent clinical evaluation with clinician-rated scales and self-report questionnaires and gave consent for use of their data for research purposes. Additionally they underwent structural magnetic resonance imaging (MRI) and SPECT imaging with the $[^{123}I]$FP-CIT ($[^{123}I]$N-ω-Fluoro-propyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane) radiotracer, that has a high affinity for the striatal DaT. Due to its ability to measure the severity of striatal dopamine denervation it is regularly used in the VU University medical center to support clinically based differential diagnosis for movement disorders.

The study described in Chapter 6 was conducted in medication-naïve PD patients who were recruited through collaborating outpatient clinics for movement disorders. Age, gender and education-matched healthy controls included unaffected relatives of participating PD patients, co-workers and participants recruited through advertisement. All participants underwent functional MRI (fMRI) imaging during performance of a response inhibition task, i.e. the stop signal task. DaT SPECT scans were also acquired in a subset of PD patients. The studies reported in Chapter 2, 3 and 6 were conducted cross-sectionally. In Chapter 4 we used a retrospective longitudinal design.
In this thesis we used multiple imaging modalities and analytical tools to study in vivo markers of neuropsychiatric symptoms in PD. These imaging techniques are discussed below.

**DaT Single Photon Emission Computed Tomography (SPECT)**
SPECT scans make use of a radioactive isotope coupled to a ligand that has affinity for a specific target within the body. This isotope-ligand complex is called a radiotracer. Radiotracers are injected into the bloodstream prior to scanning and allowed to diffuse throughout the body. During scanning, the photons (γ-rays) that are emitted by the radioactive decay of the radiotracer are detected by the γ-cameras of the SPECT scanner. After scanning, a computer analyzes the spatial and temporal information of these emissions and reconstructs a 3D image. [123I]FP-CIT (a cocaine analogue) is a tracer that binds with high affinity to the DaT in the striatum. A binding ratio is calculated to determine the striatal DaT availability. The binding ratio represents the ratio between specific binding of [123I]FP-CIT to the DaT and unbound or nonspecific binding. Tracer binding in the striatal region of interest (ROI) is corrected for nonspecific binding by dividing by the binding in a reference region where the DaT is virtually absent, e.g. the occipital region (Scherfler et al. 2005). The DaT binding ratio is computed with the following formula:

\[
\frac{\text{ROI}_{\text{binding}} - \text{reference}_{\text{binding}}}{\text{reference}_{\text{binding}}}
\]

This DaT binding ratio is used for analyses.

**T1-weighted structural MRI**
We used T1-weighted MRI images to visualize the anatomy of the brain. Using specific software we can automatically calculate brain volumetrics. We specifically looked at the volume of the subcortical structures, the hippocampus and amygdala. For this we used FreeSurfer software (surfer.nmr.mgh.harvard.edu/) that automatically segments subcortical structures by assigning each voxel to a label according to a probabilistic atlas (Fischl et al. 2002). We additionally used voxel-based morphometry (VBM) implemented in Statistical Parametric Mapping (SPM; www.fil.ion.ucl.ac.uk/spm/) to perform voxel-wise statistical analyses on local gray matter concentrations in the hippocampus and amygdala (Ashburner and Friston 2000).
**Functional MRI**
Functional MRI was used to visualize brain activation during performance of the stop-signal task. An MRI sequence is used that is sensitive to the Blood Oxygenation Level Dependent (BOLD) response. The BOLD response refers to the increase in oxygen consumption following the task dependent activation of a certain brain area. This increase in oxygen consumption can be visualized by the MRI scanner because oxygenated and deoxygenated blood have different magnetic properties. The BOLD response therefore provides a measure of brain activation. SPM was used for the statistical analyses.