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To my family

ABSTRACT

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University of Turku, Faculty of Medicine, Institute of Clinical Medicine, Department of Neurology, Doctoral Programme in Clinical Research

Annales Universitatis Turkuensis, Medica-Odontologica, Turku, Finland, 2018

Parkinson's disease (PD) is a common neurodegenerative movement disorder. The motor symptoms of PD are linked to the degeneration of dopaminergic neurons of the substantia nigra, which leads to dopamine depletion in the striatum. Non-motor symptoms (NMSs), such as depression, hallucinations and impulse control disorders (ICDs), are important manifestations of PD. The role of dopamine in the pathophysiology of these symptoms is less clear. This thesis investigated NMSs in PD and their association with brain dopamine function using dopamine transporter (DAT) single-photon emission computed tomography (SPECT) imaging. Furthermore, factors that predict the DAT imaging outcome were investigated.

The results suggest that ICDs of PD are associated with multiple other psychiatric symptoms. Furthermore, an older age, shorter motor symptom duration and asymmetric motor symptoms are associated with an abnormal DAT imaging outcome. The results also demonstrate that lower DAT binding in the limbic striatum is associated with the development of hallucinations in PD. Finally, although PD patients suffer from multiple NMSs, the total burden of these symptoms does not differentiate PD patients from parkinsonism patients with normal DAT binding.

The results demonstrate that the total NMS burden is not a specific manifestation for Parkinson's disease and is unrelated to brain dopamine function. Clinical factors, such as patient age, motor symptom duration and motor symptom asymmetry, may be useful for selecting which patients should undergo DAT SPECT imaging. Moreover, DAT imaging may be useful in predicting subsequent NMS manifestations, such as visual hallucinations; however, further studies are required.

Keywords: Parkinson's disease, dopamine transporter, non-motor symptoms, impulse control disorders, hallucinations, dopamine, brain imaging

TIIVISTELMÄ

Elina Jaakkola

NEUROPSYKIATRISET OIREET JA AIVOJEN DOPAMIINITRANSPORTTERIKUVANTAMINEN PARKINSONIN TAUDISSA

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Parkinsonin tauti on yleinen neurodegeneratiivinen liikehäiriö. Parkinsonin taudin motoristen oireiden ajatellaan johtuvan keskiaivojen mustatumakkeen dopaminergisten hermosolujen tuhoutumisesta. Motoristen oireiden lisäksi ei-motoriset oireet, kuten masennus, hallusinaatiot ja impulssikontrollihäiriöt, ovat tärkeitä Parkinsonin taudin ilmentymiä. Dopamiinin merkitys Parkinsonin taudin ei-motoristen oireiden patofysiologiassa on vielä epäselvä. Tässä väitöskirjassa tutkittiin Parkinsonin taudin ei-motorisia oireita sekä niiden yhteyttä aivojen dopamiinitoimintaan käyttäen aivojen dopamiinitransportterien yksifotoniemissiotomografiakuvausta. Lisäksi tutkittiin kliinisiä tekijöitä, jotka ennustavat dopamiinitransportterikuvauksen tulosta.

Tämän tutkimuksen kohteina olleilla henkilöillä Parkinsonin taudin impulssikontrollihäiriöt esiintyivät usein yhdessä muiden psykiatristen oireiden kanssa. Epänormaaliin löydökseen dopamiinitransportterikuvauksessa liittyivät korkea ikä, lyhyt motoristen oireiden kesto sekä epäsymmetriset oireet. Tulokset osoittavat myös, että aivojen alentunut dopamiinitransportterisitoutuminen limbisessä aivojuoviossa liittyy Parkinsonin tautia sairastavilla hallusinaatioiden kehittymiseen. Lisäksi, vaikka Parkinsonin tautia sairastavat potilaat kärsivät monista ei-motorisista oireista, näiden oireiden kokonaismäärä ei näyttäisi erottavan Parkinsonin tautia sairastavia potilaita niistä potilaista, joilla esiintyy parkinsonismia mutta joiden aivojen dopamiinitransportterisitoutuminen on normaalia.

Tulokset osoittavat, että ei-motoristen oireiden kokonaismäärä ei ole spesifinen ilmentymä Parkinsonin taudille, eikä se liity aivojen dopamiinitoimintaan. Kliiniset tekijät, kuten potilaan ikä, oireiden kesto ja motoristen oireiden epäsymmetria, voivat olla avuksi, kun valitaan tutkittaviksi potilaita, jotka hyötyvät aivojen dopamiinitransportterikuvauksesta. Vaikka aihetta on tutkittava vielä lisää, tulosten perusteella dopamiinitransportterikuvaus voi olla hyödyksi, kun ennustetaan ei-motoristen oireiden, kuten hallusinaatioiden, kehittymisiä Parkinson-potilailla.

Avainsanat: Parkinsonin tauti, dopamiinitransportteri, ei-motoriset oireet, impulssikontrollihäiriöt, hallusinaatiot, dopamiini, aivokuvantaminen

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ABBREVIATIONS

AADC = aromatic L-amino acid decarboxylase

BAI = Beck anxiety inventory

BDI = Beck depression inventory

BIS-11 = Barret impulsiveness scale

CUPS = clinically uncertain parkinsonian syndrome

DAT = dopamine transporter

DDS = dopamine dysregulation syndrome

GP = globus pallidus

ICD = impulse control disorder

LEDD = levodopa equivalent daily dose

UPDRS = Unified Parkinson's disease rating scale

MMSE = Mini-mental state examination

MSA = multiple system atrophy

NMS = non-motor symptom

NMSS = Non-motor symptoms scale

PD = Parkinson's disease

PET = positron emission tomography

PSP = progressive supranuclear palsy

QUIP = the Questionnaire for impulsive-compulsive behaviors in Parkinson's disease

RBD = REM sleep behavior disorder

ROI = region of interest

SBR = specific binding ratio

SCL-90 = Symptom Checklist 90

SN = substantia nigra

SPECT = single-photon emission computed tomography

STN = subthalamic nucleus

SWEDD = scan without evidence of dopaminergic deficit

VMAT2 = vesicular monoamine transporter 2

VTA = ventral tegmental area

LIST OF ORIGINAL PUBLICATIONS

I Jaakkola E, Kaasinen V, Siri C, Martikainen K, Cilia R, Niemelä S, Joutsa J. Impulse control disorders are associated with multiple psychiatric symptoms in Parkinson's disease. *J Parkinsons Dis. 2014;4(3):507-15.*

II Jaakkola E, Joutsa J, Kaasinen V. Predictors of normal and abnormal outcome in clinical brain dopamine transporter imaging. *J Neural Transm. 2016 Mar;123(3):205-9.*

III Jaakkola E, Joutsa J, Mäkinen E, Johansson J, Kaasinen V. Ventral striatal dopaminergic defect is associated with hallucinations in Parkinson's disease. *Eur J Neurol. 2017 Nov;24(11):1341-1347.*

IV Jaakkola E, Joutsa J, Mäkinen E, Noponen T, Pitkonen M, Levo R, Mertsalmi T, Scheperjans F, Kaasinen V. Burden of non-motor symptoms in unclear parkinsonism and tremor. *Submitted.*

1 INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder classically characterized by motor symptoms, mainly bradykinesia, rigidity and rest tremor (parkinsonism). These motor symptoms are thought to arise from the degeneration of dopaminergic cells of the midbrain substantia nigra (SN), which results in dopamine depletion in the striatum (Kalia & Lang, 2015). In addition to motor symptoms, non-motor symptoms (NMSs) have gained substantial interest in recent years. NMSs in PD include a variety of different symptoms, such as depression, hallucinations, impulse control disorders (ICDs), constipation, hyposmia, sleep disorders and many other symptoms. Some NMSs may arise prior to motor manifestations, whereas some NMSs predominantly develop during the later disease stages (Schapira *et al.*, 2017). PD patients suffer from NMSs more often than healthy controls (Bago Rožanković *et al.*, 2017; Marinus *et al.*, 2018). However, the specificity of NMSs in PD is not clear as other patients with parkinsonism also exhibit these symptoms (Taylor *et al.*, 2016). NMSs may affect the quality of life of PD patients more than motor symptoms (Martinez-Martin *et al.*, 2011), and the clinical recognition of these symptoms is often insufficient (Chaudhuri *et al.*, 2006).

Approximately 14 % of PD patients suffer from ICDs, including pathological gambling, hypersexuality, compulsive shopping and binge eating (Weintraub *et al.*, 2010). ICDs are often related to dopaminergic treatment, particularly dopamine agonists (Weintraub *et al.*, 2010). The comorbidity of ICDs with other psychiatric symptoms is only partially understood.

The dopamine transporter (DAT) is a cell membrane protein that transfers dopamine from the synaptic cleft back into the presynaptic neuron. Molecular DAT imaging is widely used in clinical neurology, as well as in research. In PD, DAT levels are decreased; thus, DAT imaging may differentiate degenerative causes of parkinsonism from parkinsonism patients with an intact brain dopamine system (Brooks, 2016). In recent years, there has been a major interest in investigating the relationship between brain dopamine function and NMSs in PD; however, the role of dopamine in the genesis of PD NMSs has been only partially clarified (Qamar *et al.*, 2017). For the development of pharmacotherapies, understanding the neural mechanisms that underlie the NMSs of PD is of high importance.

This thesis focuses on the role and occurrence of NMSs in PD. Several approaches are used to evaluate the associations between brain DAT imaging and clinical factors, mainly NMSs.

2 REVIEW OF LITERATURE

2.1 Parkinson's disease

2.1.1 Epidemiology and risk factors

PD is a common neurodegenerative disorder. PD was first described in 1817 by Dr. James Parkinson, an English physician, who recognized the combination of rest tremor, festination and stooped posture as a distinct disease (Parkinson, 1817). Dr. Parkinson called the condition shaking palsy; however, the disease was subsequently renamed as PD by Dr. Jean-Martin Charcot (Obeso *et al.*, 2017). The incidence of PD is, on average, 8-18 per 100 000 person-years and increases with age (de Lau & Breteler, 2006). Thus, the prevalence also increases by age (41 per 100 000 at age 40-49 years, 107 at age 50-59, 173 at age 55-64, 428 at age 60-69, 425 at age 65-74, 1087 at age 70-79 and 1903 at age >80), which makes the disorder relatively common in the elderly (Pringsheim *et al.*, 2014). The world's population is ageing, and the prevalence and incidence of PD are increasing in parallel, potentially doubling by the year 2040 (Dorsey & Bloem, 2018).

The most important risk factor for PD is age; however, other risk-increasing factors include male sex, family history of PD, earlier head trauma, exposure to pesticides, rural living, drinking well water and the use of beta-blockers (Tanner & Goldman, 1996; Noyce *et al.*, 2012). In addition, depression is a risk factor for Parkinson's disease (Wang *et al.*, 2018). The male-to-female incidence ratio in PD appears to be increasing (Kaasinen *et al.*, 2015b), whereas rural living continues to be a risk factor for PD, despite the changes in agriculture and other changes in society (Isotalo *et al.*, 2017). However, tobacco smoking, alcohol consumption, coffee drinking and the use of non-steroidal anti-inflammatory drugs (NSAIDs) or calcium channel blockers may decrease the risk for PD (Noyce *et al.*, 2012). Approximately 5-10 % of PD cases are explained with monogenic hereditary factors and 15 % of PD patients have family history of PD (Deng *et al.*, 2017).

2.1.2 Clinical features

2.1.2.1 Motor symptoms

The classic motor symptoms of PD include bradykinesia, rigidity, rest tremor and postural instability. Bradykinesia is an essential item in the definition of parkinsonism and refers to the slowness and/or scarcity of movements (Postuma *et al.*, 2015b). PD tremor is typically a rest tremor with unilateral onset and a frequency of 4-6 Hz, albeit postural or kinetic tremor may co-occur (Postuma *et al.*, 2015b; Bhatia *et al.*, 2018). This asymmetry of motor symptoms, which is contralateral to the more severely affected side of the brain, is characteristic of PD in all disease stages (Djaldetti *et al.*, 2006). PD rigidity is typically described as a "lead-pipe" resistance with a potential cogwheel phenomenon (Postuma *et al.*, 2015b). The motor phenotypes of PD may be roughly divided into tremor-dominant and postural instability gait difficulty (PIGD) or akinetic-rigid phenotypes (Fereshtehnejad & Postuma, 2017).

2.1.2.2 Diagnosis

Neuropathological confirmation is required for a definitive diagnosis of PD (Gelb *et al.*, 1999). However, in the clinical context, PD diagnosis is based on typical symptoms and signs in a clinical examination in accordance with the UK Brain Bank Criteria (Hughes *et al.*, 1992). The International Parkinson and Movement Disorder Society (MDS) has recently proposed new diagnostic criteria for PD (Postuma *et al.*, 2015b). The new MDS criteria take into account typical motor characteristics, as well as supportive factors, such as a favourable response to dopaminergic medication, and as to non-motor symptoms, hyposmia has been taken into account in the supportive criteria. Importantly, in the new MDS criteria, there are also items that support an alternative diagnosis or are considered to be absolute exclusion criteria for the diagnosis of PD. The new diagnostic criteria are presented in Table 1.

Table 1. MDS clinical diagnostic criteria for established Parkinson's disease (shortened and modified from (Postuma *et al.*, 2015b)). All four criteria must be fulfilled in clinically established diagnosis of PD.

1. Patient has parkinsonism
• Parkinsonism is defined as bradykinesia that is combined with rest tremor and/or rigidity
2. Patient has two or more supportive criteria
• Clear response to dopaminergic treatment • Dyskinesia induced by levodopa • Documented extremity rest tremor • Hyposmia or cardiac sympathetic denervation
3. Patient does not have any absolute exclusion criteria
• Unequivocal cerebellar abnormalities • Downward vertical supranuclear gaze palsy, or slowing of vertical saccades • Probable behavior variant of frontotemporal dementia or primary progressive aphasia within the first five years • No upper extremity involvement after three years • Treatment with drugs known to cause drug-induced parkinsonism • No response to high levodopa doses in at least moderate severity of the disease • Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia • Normal functional presynaptic dopaminergic imaging outcome • An alternative diagnosis is more likely than PD
4. Patient does not have any red flags
• Rapid gait impairment resulting in wheelchair use within the first five years • No motor disease progression in at least 5 years • Early bulbar dysfunction • Inspiratory respiratory dysfunction • Severe autonomic failure within the first 5 years • More than one fall per year because of impaired balance within the first 3 years • Disproportionate anterocollis or contractures of hand or feet within the first 10 years • Absence of non-motor symptoms within the first 5 years • Pyramidal tract signs, that are otherwise-unexplained • Bilateral symmetric parkinsonism

PD = Parkinson's disease

The diagnostic accuracy of PD is suboptimal, as approximately 25 % of the diagnoses are incorrect in clinic-pathological studies (Joutsa *et al.*, 2014; Rizzo *et al.*, 2016). Therefore, additional diagnostic biomarkers for PD are needed, particularly in the diagnosis of borderline cases with inconclusive symptoms, signs or medication response. Furthermore, as the disease process of PD is considered to begin several years prior to the manifestation of motor symptoms (Postuma *et al.*,

2012a), these diagnostic tools would be valuable for the early identification of patients at the prodromal phase. MDS criteria for prodromal PD for research purposes have been recently proposed (Berg *et al.*, 2015). As disease modifying treatments are under development (Lang & Espay, 2018), early diagnosis may be particularly important in the future.

2.1.2.3 Treatment

To date, the treatment for PD is symptomatic with a primary focus on the motor symptoms. Disease modifying treatments are under intensive investigation but have yet to be discovered. Neuroprotective drugs for PD are under development, such as medication that decreases calcium levels in nigral neurons or serum urate increasing treatment (Lang & Espay, 2018). Neurotrophic factors protect the growth of neurons. The delivery of neurotrophic factors to the brain could promote the function of midbrain dopaminergic neurons in PD, although these treatments have not been proven to be effective to date (Hegarty *et al.*, 2017). However, a good candidate for a trophic factor may be cerebral dopamine neurotrophic factor (CDNF), which appears to be protective for dopamine neurons (Lindholm *et al.*, 2007), and clinical trials with PD patients are ongoing. Immunotherapies for PD that target aggregated alpha-synuclein are also under development, such as a vaccine or monoclonal antibodies (Brundin *et al.*, 2017). Furthermore, glucocerebrosidase (GCase) decreases alpha-synuclein levels; thus, treatments that elevate the activity of GCase are under investigation (Brundin *et al.*, 2017).

Dopaminergic therapies are used to substitute the dopaminergic deficiency in PD. L-3,4-dihydroxyphenylalanine (levodopa or L-dopa) is a precursor of dopamine that passes the blood-brain-barrier and is subsequently decarboxylated by aromatic L-amino acid decarboxylase (AADC) to dopamine. Levodopa remains the most effective drug for the treatment of the motor symptoms of PD; in particular, bradykinesia and rigidity respond well to dopaminergic treatment (LeWitt & Fahn, 2016). The most difficult complications of levodopa treatment include dyskinesia and fluctuations of motor and non-motor symptoms (Olanow & Stocchi, 2017). Motor and non-motor fluctuations reflect improving (on periods) and worsening (off periods) of the symptoms. In addition to oral levodopa, enteral levodopa infusion therapy (levodopa-carbidopa intestinal gel) is used in advanced patients with difficult motor complications (Olanow *et al.*, 2014). Levodopa therapy is always administered together with carbidopa or benserazide (dopa decarboxylase inhibitors) (Gershanik, 2015) and may be complemented with catechol-O-methyltransferase (COMT) inhibitors, such as entacapone (Müller, 2015); these inhibitors are used to prevent the metabolism of dopamine into its non-effective metabolites in

the periphery, which cause unwanted side effects and prevent the medication from reaching the brain. Monoamine oxidase B (MAO-B) degrades dopamine in the brain. MAO-B inhibitors are used in PD to increase brain dopamine levels (Schapira, 2011). Dopamine agonists, such as non-ergot dopamine agonists pramipexole, ropinirole and rotigotine, mimic dopamine in the brain by activating dopamine receptors, mainly the D2 receptor family (D2, D3 and D4 receptors). Presumably while also targeting dopamine D3 receptors in limbic areas, the use of dopamine agonists may lead to neuropsychiatric complications, such as impulse control disorders (ICDs) (Connolly & Lang, 2014). Apomorphine is a non-ergot dopamine agonist that targets both D1 and D2 receptors, and it may be used as a continuous infusion or a rescue medication (injections) in advanced PD with difficult motor fluctuations (Titova & Chaudhuri, 2016).

Furthermore, certain non-dopaminergic drugs are used in the treatment of PD. For example, amantadine, a N-methyl-D-aspartate (NMDA) antagonist, is mainly used for levodopa-induced dyskinesia (Vijayakumar & Jankovic, 2016). Anticholinergic drugs may be used to treat tremor in younger PD patients (Fox *et al.*, 2018).

In advanced PD with motor fluctuations, deep brain stimulation (DBS) may be used to target the subthalamic nucleus (STN) or globus pallidus interna (GPi) (Ramirez-Zamora & Ostrem, 2018). The exact mechanism of action of DBS is unknown; however, DBS seems to deactivate the overactivated indirect basal ganglia pathway.

2.1.3 Pathophysiology

2.1.3.1 Normal physiology of relevant pathways in PD

Basal ganglia circuits. The basal ganglia comprise a group of subcortical nuclei in the forebrain and midbrain that participate in controlling body movement and behaviour. The basal ganglia consist of the striatum, globus pallidus, substantia nigra (SN) and STN. The striatum may be further divided into the caudate nucleus, putamen and nucleus accumbens. The globus pallidus consists of the GPi and globus pallidus externa (GPe) and ventral pallidum and the SN of the pars reticulata (SNr) and pars compacta (SNc) (Wolters & Baumann, 2014).

Together with cortical regions, the basal ganglia form complex circuits that participate in multiple different brain functions. Briefly, the striatum is the main input structure of the basal ganglia; it receives information from multiple cortical areas and relays it to other basal ganglia nuclei (Parent & Hazrati, 1995). The striatum

is often conceptualized to have three functionally distinct parts: sensorimotor (mainly the posterior putamen), associative (the dorsal part of the caudate nucleus and the anterior part of the dorsal putamen) and limbic/ventral striatum (mainly the nucleus accumbens) (Parent & Hazrati, 1995). From the striatum, the information is projected back to the cortex through the output nuclei of the basal ganglia (the GPi, ventral pallidum and SNr) via the thalamus. These basal ganglia – thalamocortical circuits follow a similar functional division as the striatum (Alexander *et al.*, 1986). The sensorimotor striatum receives input from the motor, premotor and somatosensory cortices (sensorimotor circuit). The associative striatum receives input from the prefrontal cortex (associative/cognitive circuit), and the limbic striatum receives input from the limbic areas, such as the orbitomedial, prefrontal and limbic cortices (limbic circuit). The output from these circuits is projected back to the respective cortical areas.

There are three major basal ganglia pathways: the direct, indirect and hyperdirect pathways (figure 1) (Wolters & Baumann, 2014). Output from the basal ganglia is gamma-aminobutyric acid (GABA)-ergic (inhibitory). The direct pathway inhibits this inhibition, thereby stimulating movement, whereas the indirect and hyperdirect pathways stimulate the inhibition, thereby suppressing movement. The direct pathway projects from the striatum to the output structures (GPi or SNr). The indirect pathway projects from the striatum to the GPe, then to the STN and finally to the output structures. The hyperdirect pathway projects from the cortex directly to the STN. The striatum mainly consists of two types of medium spiny neurons (MSNs) that express D1 dopamine receptors or D2 dopamine receptors. Dopamine increases the output from the basal ganglia by two mechanisms; dopamine conversely impacts the direct and indirect basal ganglia pathways, thus activating the direct pathway (D1 receptors) and inhibiting the indirect pathway (D2 receptors) (Gerfen & Surmeier, 2011). Activation of the direct pathway stimulates motor, cognitive and emotional processes, whereas activation of the indirect pathway inhibits these functions. Thus, the basal ganglia control movement and behaviours by stimulating the desired action and inhibiting inappropriate responses.

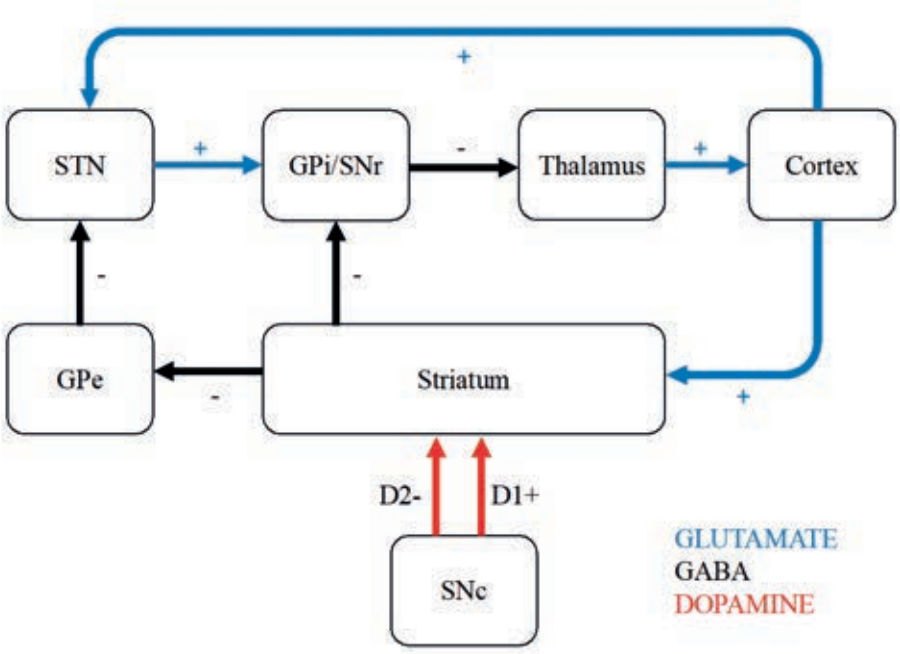

Figure 1. Direct, indirect and hyperdirect basal ganglia pathways. Dopamine activates the direct pathway (D1) and inhibits the indirect pathway (D2) (Wolters & Baumann, 2014). D1 = dopamine receptor D1, D2 = dopamine receptor D2, GABA = gamma-aminobutyric acid, GPe = globus pallidus externa, GPi = globus pallidus interna, SNc = substantia nigra pars compacta SNr = substantia nigra pars reticulata, STN = subthalamic nucleus.

Brain dopaminergic pathways. Dopamine is one of the monoamines in the brain, together with noradrenaline and serotonin. Dopamine is involved in important functions, such as voluntary movement, motivation, reward and attention. There are three major brain dopaminergic pathways (figure 2) (Crocker, 1994). The nigrostriatal dopaminergic pathway projects from the SNc to the dorsal striatum. The mesolimbic dopaminergic pathway projects from the midbrain ventral tegmental area (VTA) to the ventral striatum (mainly the nucleus accumbens). The mesocortical dopaminergic pathway also originates from the VTA, terminating in the prefrontal cortex (Crocker, 1994; Girault & Greengard, 2004).

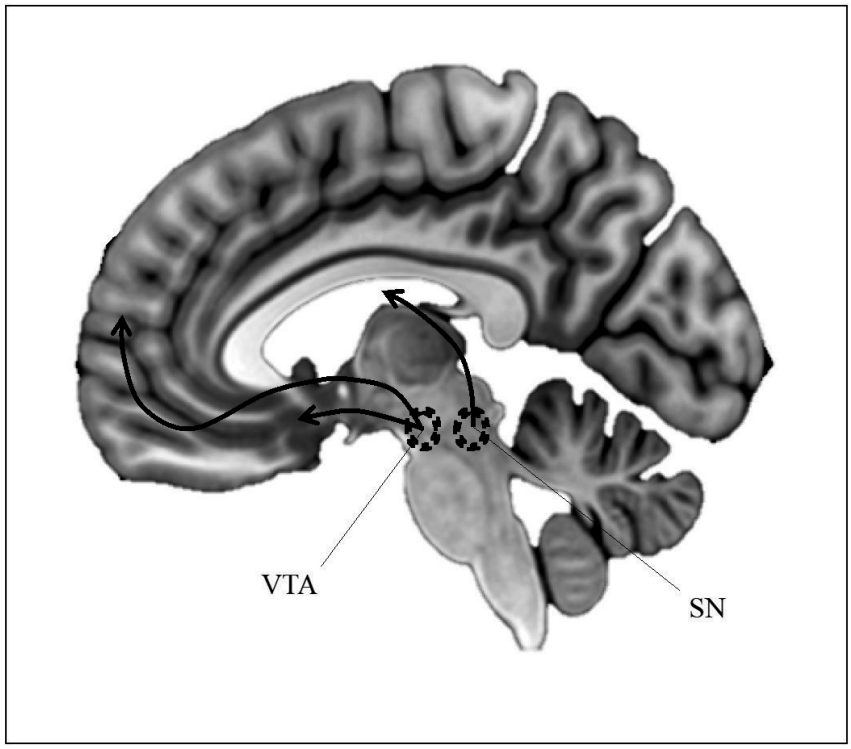

Figure 2. The main human dopaminergic pathways originating from the midbrain. Nigrostriatal pathway projects from the SN pars compacta to the dorsal striatum. Mesolimbic pathway projects from the VTA to the ventral striatum. Mesocortical pathway projects from the VTA to the prefrontal cortex. SN = substantia nigra, VTA = ventral tegmental area.

Brain dopamine receptors and metabolism. Dopamine is synthesized in two steps in the cytosol of dopaminergic neurons. First, tyrosine is hydroxylated to L-DOPA by tyrosine hydroxylase (TH), and L-DOPA is subsequently decarboxylated to dopamine by AADC (Meiser *et al.*, 2013). There are five types of dopaminergic receptors (D1-D5). D1 and D5 receptors are excitatory, whereas D2-D4 receptors are inhibitory (Beaulieu & Gainetdinov, 2011). D1 and D2 receptors are predominately located in the striatum, whereas D3 receptors are dense in mesolimbic areas. After dopamine is released to the synaptic cleft, DAT is the most important factor responsible for clearing dopamine back to the presynaptic neuron, thus regulating dopamine levels (Giros *et al.*, 1996). Vesicular monoamine transporter (VMAT2) transfers dopamine into intracellular vesicles that are mainly located in nerve terminals, thus storing dopamine (Meiser *et al.*, 2013). For dopamine synapse function, refer to figure 3.

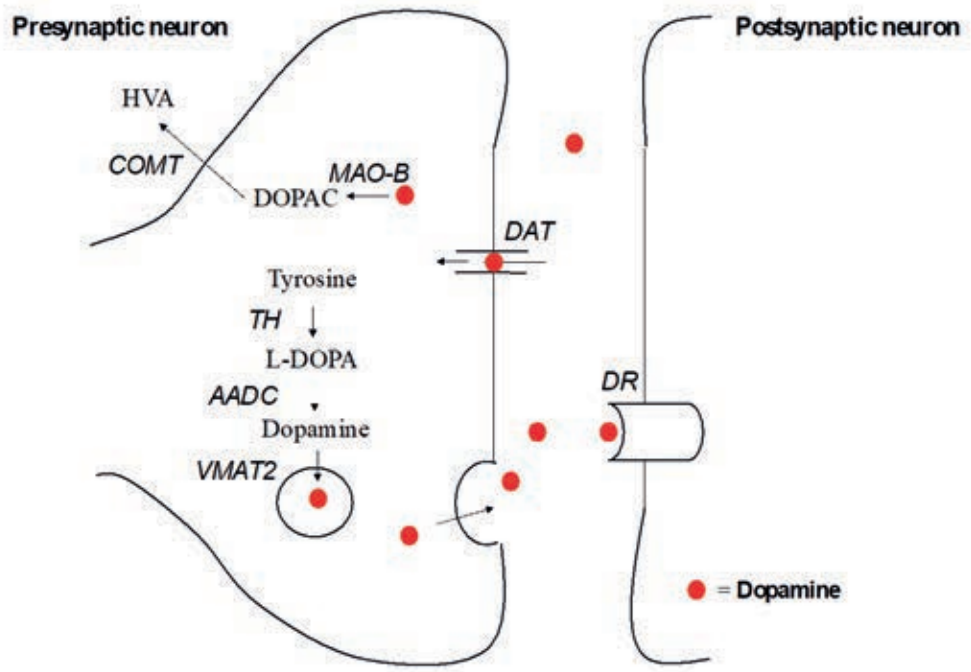

Figure 3. Illustrative figure of the presynaptic terminal of the dopaminergic synapse. AADC = aromatic L-amino acid decarboxylase, COMT = catehcol-O-methyltransferase, DAT = dopamine transporter, DOPAC = 3,4-dihydroxyphenylacetic acid, DR = dopamine receptor, HVA = homovanillic acid, L-DOPA = L-3,4-dihydroxyphenylalanine, MAO-B = monoamine oxidase B, TH = tyrosine hydroxylase, VMAT2 = vesicular monoamine transporter 2.

2.1.3.2 Neuropathology

Degeneration of the substantia nigra. In PD, a progressive loss of dopaminergic neurons in the SNc occurs (Dickson, 2018). These neurons project to the striatum; thus, the degeneration leads to striatal dopaminergic depletion, which results in motor symptoms, particularly bradykinesia and rigidity. Motor symptoms often arise after approximately 50 % of the dopaminergic cells in the SNc have died (Marsden, 1990; Schwarz *et al.*, 2000). The severity of neuronal loss in the SNc seems to correlate with the Unified Parkinson's Disease Rating Scale (UPDRS) motor score (Greffard *et al.*, 2006). The ventrolateral part of the SN is most vulnerable for neurodegeneration (Dickson, 2018). Extranigral dopaminergic neurons in the VTA are somewhat better preserved (Alberico *et al.*, 2015). Degeneration also occurs in non-dopaminergic neurons, albeit often in the later disease stages

(Halliday *et al.*, 1990b). Rest tremor in PD does not seem to originate from SN pathology (Hallett, 2012).

Lewy pathology. PD is defined as an alpha-synucleinopathy (Goedert *et al.*, 2013). Alpha-synuclein is a normal protein in the brain. When misfolded, alpha-synuclein aggregates in the cell body or processes forming Lewy bodies or Lewy neurites, respectively (Dickson, 2018). Braak *et al* have suggested staging the Lewy pathology development as follows: First, the enteric nervous system, olfactory bulb and lower brainstem are affected (stages 1-2). Then, the pathology spreads, ascending to the midbrain, in the SNc and additional midbrain grey matter (stages 3-4; motor symptoms of PD arise at stage 3). Finally, the neocortex is affected (stages 5-6) (Braak *et al.*, 2003). Lewy pathology also extends to extranigral areas, such as the locus coeruleus, nucleus basalis of Meynert, pedunculopontine nucleus, raphe nuclei, autonomic nervous system (such as the dorsal motor nucleus of vagus), amygdala and hypothalamus. The spreading of the Lewy pathology has been reported take place transsynaptically (Hawkes *et al.*, 2009). However, the link between dopamine neuron loss and alpha-synuclein is not clear, as neuronal cell death and Lewy pathology may develop separately (Surmeier *et al.*, 2017).

2.1.3.3 Neurotransmitters in PD pathophysiology

Dopamine. In PD, dopaminergic deficiency in the striatum leads to underactivation of the direct (D1) and overactivation of the indirect (D2) basal ganglia pathways. Dopamine depletion is most severe in the putamen and thus in the sensorimotor basal ganglia – thalamocortical circuit (Parent & Parent, 2010), which results in reduced movement, i.e., bradykinesia, freezing of gait and rigidity (Hamani & Lozano, 2003). Thus, dopamine is the main neurotransmitter involved in PD pathophysiology, and the current symptomatic treatment of PD is mainly targeted to correct the dopamine deficit.

Other neurotransmitters. In addition to dopamine, other neurotransmitter systems are disrupted in PD (Sanjari Moghaddam *et al.*, 2017). Serotonergic dysfunction occurs in PD as a consequence of serotonergic neuronal loss (Halliday *et al.*, 1990a) and Lewy pathology in the Raphe nuclei (Politis & Niccolini, 2015). According to Braak's staging, Lewy pathology spreads to the Raphe nuclei before continuing to the midbrain/SN (Braak *et al.*, 2003). This suggests that serotonergic neurons in the Raphe nuclei are affected prior to the SN (Politis & Niccolini, 2015). Serotonergic dysfunction in PD seems to be involved in many symptoms, such as tremor, dyskinesia, depression and visual hallucinations (Politis & Niccolini, 2015). In addition, noradrenergic deficiency occurs in PD as a consequence of the degeneration of the locus coeruleus (Espay *et al.*, 2014). Moreover, cholinergic

deficiency occurs in PD, which leads to cognitive deficits (Rizzi & Tan, 2017). There is also relative cholinergic overactivity in PD as a result from the dopaminergic depletion. Thus, although blockage of cholinergic receptors in the striatum may alleviate the motor symptoms in PD by decreasing the imbalance between dopamine and acetylcholine, cholinesterase inhibitors may alleviate cognitive decline in PD (Rizzi & Tan, 2017).

2.2 Imaging of the brain dopamine system in Parkinson's disease

2.2.1 In vivo imaging of the brain dopamine system

2.2.1.1 Molecular imaging

In nuclear medicine imaging, radioactive tracers are used to evaluate molecular-level physiological and pathological functions of the body. A radiotracer contains a molecule with certain biological properties and is labelled with a radioactive atomic nucleus (radionuclide) that is unstable. To become stable, the radionuclide decays and emits ionizing radiation. A gamma or positron emission tomography (PET) camera is employed to record the radiation, which is used to form the image reflecting radiotracer tissue uptake. Radiotracers are most commonly injected intravenously and accumulate in the known target tissue via circulation. In single photon emission computed tomography (SPECT), the radionuclide decays in the target tissue and emits a single photon (gamma radiation). SPECT camera detectors circle around the patient and detect the radiation. Gamma quants that hit the camera in a skewed angle are excluded. ^{123}I and ^{99m}Tc are examples of common gamma radiation emitters used in SPECT imaging. In PET imaging, radionuclide decays by emitting a positron (β plus decay). The positron collides with an electron in the tissue, and two photons are emitted in opposite directions (annihilation). The PET camera subsequently recognizes the photon pair (gamma rays) as a coincidence event (two photons hit the camera from opposite sides approximately at the same time). Thus, in contrast to SPECT scanning, PET detectors do not circle around the patient; however, the detector is circle-shaped. Examples of radionuclides used in PET scanning include ^{11}C, ^{18}F and ^{15}O. Both SPECT and PET are often combined with computed tomography (CT) to integrate the anatomical and physiological information. The resolution of SPECT is not as good as that of PET; however, SPECT has better availability and is associated with lower costs. The half-lives (time for a specific nuclide to lose half of its radioactivity) of the radionuclides that are used in PET are often notably shorter than the half-lives of the

radionuclides used in SPECT. Thus, the production of PET radiotracers is more difficult, and the imaging time is limited. For example, the half-life for ^{123}I used in SPECT is 13.22 hours, whereas the half-life is 109.8 minutes for ^{18}F used in PET (Reference to the review; Levin, 2005).

2.2.1.2 Dopamine neurotransmission and PET/SPECT.

The brain dopamine system may be imaged with several approaches using SPECT or PET imaging. SPECT may be used to measure the presynaptic DAT density (Brooks, 2016). The functions of DAT, VMAT2 or AADC may be measured with several PET radioligands (Kaasinen & Vahlberg, 2017). Furthermore, the postsynaptic dopamine receptor availability may be imaged using SPECT or PET scanning to assess synaptic dopamine levels (Laruelle, 2000). For example, [^{11}C]-raclopride is a radiotracer that is commonly used to measure dopamine D2 receptor availability. Raclopride is a dopamine D2/D3 antagonist that binds to D2-like dopamine receptors competitively with endogenous dopamine. The increased levels of synaptic dopamine result in decreased levels of raclopride binding (Liu *et al.*, 2017a).

2.2.2 Presynaptic dopaminergic imaging in Parkinson's disease

Presynaptic dopaminergic molecular imaging is used in PD to visualize and quantify the dopaminergic depletion in the striatum. Postsynaptic dopamine receptor imaging is widely used in PD research to measure changes in dopamine levels after pharmacological or other stimuli; however, it is less useful in the clinical assessment of dopaminergic degeneration in PD. The dopamine receptor capacity may exhibit a compensatory increase in the early PD stages (Rinne *et al.*, 1990), whereas dopamine receptor measures decrease with disease progression and the use of dopaminergic medication (Antonini *et al.*, 1997; Thobois *et al.*, 2004).

AADC converts brain L-dopa into dopamine. ^{18}F labelled 6-fluoro-L-3,4-dihydroxyphenylalanine (fluorodopa) is a commonly used PET radiotracer for measuring brain AADC activity in PD (Liu *et al.*, 2017c). Fluorodopa is converted to fluorodopamine in the presynaptic neuron by AADC and is subsequently transferred into the intracellular vesicles by VMAT2. In PD, the AADC levels are decreased less than the levels of DAT or VMAT2, possibly because of the upregulation of dopamine synthesis by AADC (Kaasinen & Vahlberg, 2017).

VMAT2 packages monoamines into presynaptic vesicles. In the striatum, VMAT2 primarily packages dopamine. Therefore, VMAT2 levels reflect dopaminergic sig-

naling. VMAT2 function may be measured using the radioligand [^{11}C] or [^{18}F]dihydrotetrabenazine (DTBZ). Striatal VMAT2 levels correlate with PD duration but not with the UPDRS motor score (Bohnen *et al.*, 2006).

DAT imaging is the most commonly used imaging method for measuring dopamine function in the striatum. DAT imaging is discussed in chapter 2.2.2.1.

Patients with PD have clearly lower striatal presynaptic dopaminergic tracer binding than healthy controls with practically no overlap (Kaasinen & Vahlberg, 2017). Dopamine depletion in the striatum follows a particular pattern; the posterior putamen is affected first, followed by the anterior putamen and, finally, the caudate nucleus (Kaasinen & Vahlberg, 2017). Furthermore, dopamine depletion seems to develop exponentially in PD (Kaasinen & Vahlberg, 2017). The dopaminergic deficit is worse in the hemisphere contralateral to the extremities with more severe motor symptoms (Brooks, 2016). When PD motor symptoms begin, approximately 29-44 % of normal DAT function remains (Lee *et al.*, 2000). The corresponding numbers for VMAT2 binding and fluorodopa uptake are 38-49 % and 48-62 %, respectively (Lee *et al.*, 2000).

2.2.2.1 DAT imaging in Parkinson's disease

DAT SPECT and to a lesser extent DAT PET imaging is widely used in PD research, as well as clinical practice. After dopamine is released into the synaptic cleft, DAT is the most important factor responsible for transporting dopamine back to the presynaptic neuron, thus regulating dopamine levels (Giros *et al.*, 1996). In PD, there is a dopamine deficiency in the striatum, and DAT availability exhibits a compensatory decrease to increase the synaptic dopamine in the striatum (Niznik *et al.*, 1991; Lee *et al.*, 2000).

Commonly used DAT ligands are presented in table 2. There are certain differences between the ligands. For example, [^{123}I]2β-carbomethoxy-3 β-(4-iodophenyltropane) ([^{123}I]β-CIT) takes 24 hours to spread throughout the brain, whereas [^{123}I]N-3-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane ([^{123}I]FP-CIT) only takes a few hours (Brooks, 2016). The shorter distribution time enables imaging to be performed on the same day that the injection is administered with [^{123}I]FP-CIT. However, the striatal:cerebellar ratio is higher for [^{123}I]β-CIT as a consequence of the lower non-specific signal (Brooks, 2016). DAT is sparse in the cerebellum and cortical areas (Piccini, 2003); thus, the cerebellum and occipital cortex are commonly used as reference regions (Joutsa *et al.*, 2015a; Brooks, 2016).

Table 2. Commonly used ligands in brain dopamine transporter imaging.

	Ligands
PET	[^{18}F]FP-CIT, [^{18}F]FE-PE21, [^{11}C]CFT, [^{11}C]RTI32, [^{11}C]methylphenidate, [^{11}C]nomifensine
SPECT	[^{123}I]altropane, [^{123}I]β-CIT, [^{123}I]FP-CIT, [^{99}MTc]TRODAT

[^{123}I]FP-CIT SPECT was approved by the European Medicines Agency (EMA) in 2000 (DaTSCAN) (EMA, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000266/human_med_000739.jsp&mid=WC0b01ac058001d124). The Food and Drug Administration (FDA) approved the use of FP-CIT SPECT in 2011 (DaTscan) (FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022454Orig1s000Lbl.pdf). EMA-approved indications for FP-CIT SPECT are the differentiation between essential tremor and degenerative parkinsonian syndromes (PD, multiple system atrophy (MSA) or progressive supranuclear palsy (PSP)) and the differentiation between Lewy body dementia (LBD) and Alzheimer's disease. The FDA-approved indication for scanning is the differentiation between essential tremor from tremor caused by parkinsonian syndromes (PD, MSA, or PSP). In clinical practice, indications for DAT SPECT are more diverse (Thiriez *et al.*, 2015). [^{123}I]FP-CIT SPECT is helpful in detecting the degenerative disease in clinically uncertain parkinsonism. [^{123}I]FP-CIT SPECT scans of a PD patient and a patient with normal DAT binding are represented in figure 4. However, DAT imaging is not able to differentiate between different degenerative parkinsonian syndromes. Ultimately, clinical PD diagnosis remains the golden standard (Ba & Martin, 2015).

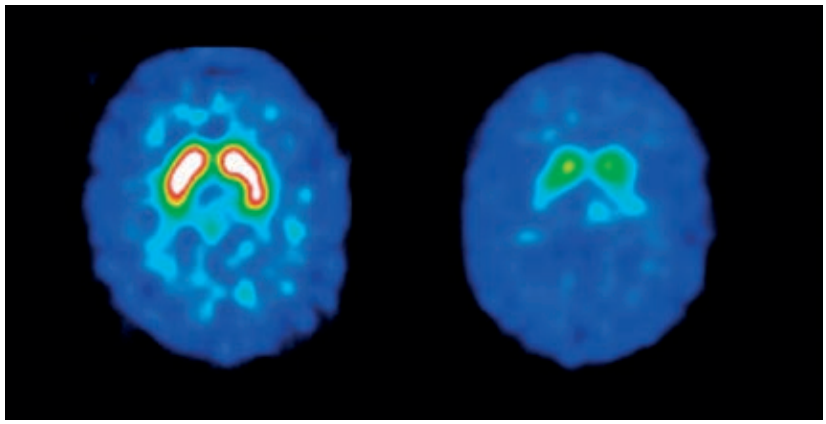

Figure 4. [^{123}I]FP-CIT binding in patient with normal DAT (left) and patient with Parkinson's disease (right).

FP-CIT binds to different molecules depending on the brain region. FP-CIT binds to DAT in the putamen, caudate and ventral striatum where DAT density is highest (Piccini, 2003). In extrastriatal regions, FP-CIT binding reflects the levels of serotonin transporter (SERT) in the raphe nuclei, which are rich in SERT (Qamhawi *et al.*, 2015), or noradrenaline transporter (NET) in the locus coeruleus, which is rich in NET (Isaias *et al.*, 2011). FP-CIT has a high affinity for DAT, moderate affinity for SERT and low affinity for NET (Scheffel *et al.*, 1997).

In PD, striatal DAT density does not seem to correlate with the number of dopaminergic neurons in the SN, and DAT binding may be more a reflector of function rather than neuron count (Saari *et al.*, 2017). In macaques, striatal DAT density correlates with nigrostriatal dopaminergic degeneration until the degeneration reaches 50 % (Karimi *et al.*, 2013) but not in later disease. However, the midbrain DAT density correlates with the level of surviving nigral neurons (Brown *et al.*, 2013), although the DAT levels are substantially lower in the SN than in the striatum (Piccini, 2003). The radiotracer [^{18}F](E)-N-(3-iodoprop-2-enyl)-2β-carbofluoroethoxy-3β-(4'-methyl-phenyl) nortropane ([^{18}F]FE-PE21) has substantial affinity and selectivity for DAT and is therefore able to determine DAT density in the SN, as well as the striatum. According to a study using [^{18}F]FE-PE2I high-resolution PET, degeneration in early PD patients occurs earlier in the striatal axonal terminals rather than in the cell bodies or axons of the SN (Fazio *et al.*, 2018). This finding may be important when new disease modifying treatments for PD are developed.

Striatal DAT binding seems to be lowered in the prodromal phase of PD, as DAT binding correlates with motor symptom severity, hyposmia, rapid eye movement (REM) sleep behaviour disorder (RBD) and PD risk score (PREDICT PD risk estimate that combines several PD risk factors) in non-PD patients (Noyce *et al.*, 2018). When clinical motor symptoms occur in PD, approximately half of the striatal dopamine function has declined (Benamer *et al.*, 2000; Marek *et al.*, 2001). Thus, DAT imaging may be a useful marker of prodromal PD (Barber *et al.*, 2017). PD motor symptom severity negatively correlates with DAT binding with the exception of tremor (Benamer *et al.*, 2000). DAT imaging may be helpful in assessing PD progression as DAT binding decreases in all striatal regions at follow-up (Marek *et al.*, 2001; Simuni *et al.*, 2018b); however, the decline is substantially faster in early PD (Kaasinen & Vahlberg, 2017).

Certain factors may affect DAT SPECT imaging outcome. Imaging outcome may be altered as a consequence of the use of certain medications (Booij & Kemp, 2008). DAT expression is age-dependent, and females seem to have a higher DAT density than males (Varrone *et al.*, 2013; Kaasinen *et al.*, 2015a). However, age and gender are considered in the reference values for striatal specific binding ratios

(SBRs) (Varrone *et al.*, 2013). DAT density may be downregulated in early PD; therefore, the possibility that DAT imaging overestimates dopaminergic degeneration, at least with some DAT ligands, cannot be excluded (Lee *et al.*, 2000).

There are certain limitations in the use of FP-CIT SPECT. There is always a risk for cancer when ionizing radiation is used (de la Fuente-Fernández, 2012). SPECT imaging is also expensive, which limits availability.

2.3 Non-motor symptoms in Parkinson's disease

In addition to motor symptoms, PD is associated with multiple NMSs, and for some patients, these symptoms may dominate the clinical picture (Marras & Chaudhuri, 2016). These NMSs of PD include neuropsychiatric symptoms, sensory deficits, autonomic dysfunction and sleep disturbances (refer to figure 5 for a list of NMSs in PD). NMSs are more prevalent in PD patients than in healthy controls (Bago Rožanković *et al.*, 2017; Marinus *et al.*, 2018), and they have a clear negative influence on health-related quality of life of PD patients (Martinez-Martin *et al.*, 2011).

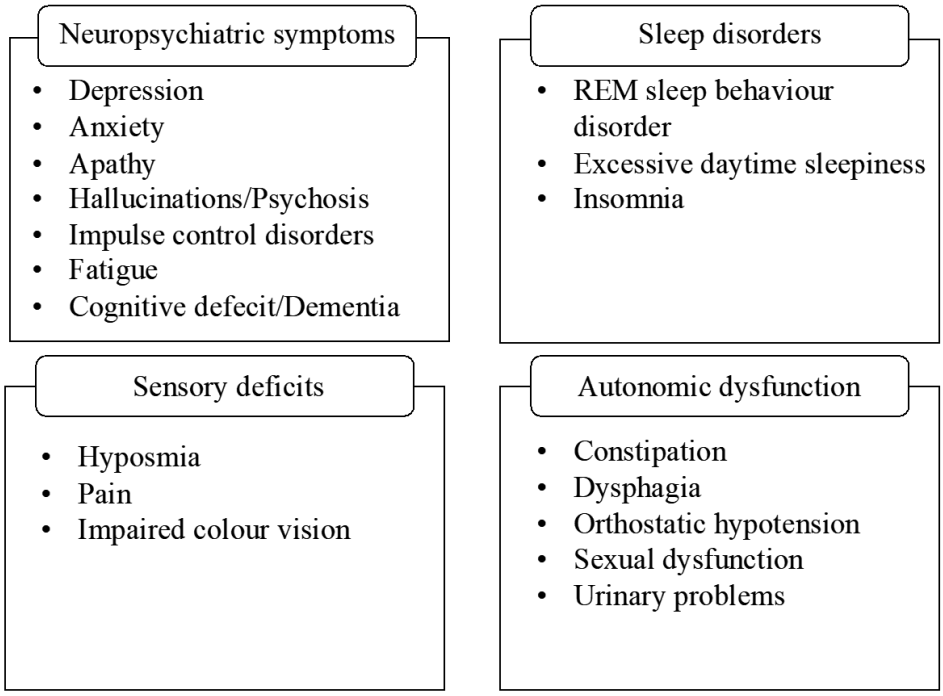

Figure 5. Some non-motor symptoms of Parkinson's disease.

Among PD patients, NMSs are more prevalent in PD patients with the PIGD phenotype than in PD patients with the tremor-dominant motor phenotype (Wu *et al.*, 2016). Several NMSs, such as depression, hyposmia, RBD and constipation, may appear prior to the manifestation of motor symptoms (Reichmann, 2017), whereas other NMSs, such as psychotic symptoms and cognitive deficit, often arise in the later disease stages (Schapira *et al.*, 2017). Since NMSs of PD may be present several years prior to the motor symptoms, diagnostic criteria for prodromal PD have recently been established (Berg *et al.*, 2015) to potentially enable an earlier diagnosis of PD recognition in subjects who have a high risk for developing PD.

The non-motor complications of PD are a heterogeneous group of symptoms, and the underlying pathophysiology is diverse and only partially elucidated (Schapira *et al.*, 2017). NMSs are, at least in part, associated with systemic Lewy pathology in both the central nervous system (CNS) and peripheral nervous systems (PNS). The pathophysiology of the NMSs of PD is, at least in part, dopaminergic (Qamar *et al.*, 2017); however, other neurotransmitters are also involved (Schapira *et al.*, 2017).

Several PD NSMs are discussed in more detail in this chapter, highlighting the symptoms that are investigated in the studies of this thesis.

2.3.1 Neuropsychiatric symptoms

2.3.1.1 Depression

Depression in PD is more common than in healthy controls (Larsen *et al.*, 2017). It has a major negative influence on the quality of life of both patients and caregivers (Schrag, 2006). The prevalence estimates of PD depression vary substantially (from 2.7 to more than 90 %). According to a systematic review, depression affects approximately 35 % of PD patients, with 17 % suffering from major depressive disorder (Reijnders *et al.*, 2008). PD depression often occurs in the premotor phase; however, it is common in all disease stages (Ishihara & Brayne, 2006; Larsen *et al.*, 2017). In a 7-year follow-up study, PD depression improved during the first year after PD diagnosis and subsequently worsened during the next six years (Larsen *et al.*, 2017).

Depression in PD is often underdiagnosed (Timmer *et al.*, 2017). Depressive symptoms may mimic the motor symptoms of PD, thus reducing the recognition of the disorder (Timmer *et al.*, 2017). Moreover, PD depression differs from depression in general elderly individuals; depression in PD includes less sadness and

feelings of guilt and more problems in concentration (Ehrt *et al.*, 2006). PD depression is associated with more severe PD motor symptoms, female gender, pain and dependence on others (Larsen *et al.*, 2017).

Depression is thought to be directly linked to PD neuropathology; however, it may also occur as an independent disorder or related to the psychological burden caused by this chronic disease (Even & Weintraub, 2012). Dopamine plays a key role in the PD depression pathophysiology; mesocortical and mesolimbic dopaminergic pathways are damaged in PD, and this loss of dopaminergic neurotransmission in the limbic and frontal areas is an important factor in the pathophysiology of PD depression (Castrioto *et al.*, 2016). PD depression often responds to dopamine agonist therapy (Barone *et al.*, 2010), and it may be worsened during the off periods (Storch *et al.*, 2013). Moreover, depression is one of the symptoms of dopamine withdrawal syndrome (Yu & Fernandez, 2017).

PD depression has been associated with reduced brain dopamine levels in multiple neuroimaging studies; however, the results are not consistent. A [^{11}C]RTI-32 PET study by Remy and colleagues compared PD patients with and without depression (Remy *et al.*, 2005). They found that PD patients with depression showed significantly lower tracer binding in multiple limbic regions and in the locus coeruleus, which reflects dopaminergic and noradrenergic activity, than PD patients without depression. A mesolimbic dopaminergic deficit has been associated with PD depression severity, as the amount of depressive symptoms has been inversely associated with FP-CIT binding in the left cingulate cortex (Frosini *et al.*, 2015). Hesse *et al* compared PD patients with and without depression and found that the DAT density in the striatum was lower among PD patients with depression than PD patients without depression (Hesse *et al.*, 2009). More severe depressive symptoms in PD have been correlated with lower DAT density in the left caudate (Di Giuda *et al.*, 2012), right caudate (Vriend *et al.*, 2014c), left anterior putamen (Weintraub *et al.*, 2005), left striatum (Rektorova *et al.*, 2008) and bilateral striatum (Wu *et al.*, 2011). In contrast, Ceravolo and colleagues found that more severe depressive symptoms were linked to higher DAT density in the striatum (Ceravolo *et al.*, 2013), and in another study, depressed PD patients exhibited higher striatal DAT density than PD patients with no depression (Felicio *et al.*, 2010). These findings may suggest that dopamine depletion in PD depression could result from the increased DAT levels (leading to greater dopamine clearance from the synaptic cleft). Furthermore, a reduced striatal fluorodopa uptake has been associated with PD depression symptoms (Koerts *et al.*, 2007; Joutsa *et al.*, 2013).

Neurotransmitters other than dopamine are also involved in the pathophysiology of PD depression. For example, noradrenergic deficiency (Remy *et al.*, 2005) and serotonergic dysfunction (Politis *et al.*, 2010; Maillet *et al.*, 2016) are associated

with PD depression. Cholinergic impairment may occur in depressed PD patients with a comorbid cognitive deficit (Thobois *et al.*, 2017).

2.3.1.2 Anxiety

Anxiety disorders, such as panic attacks or generalized anxiety, are frequently occurring neuropsychiatric manifestations of PD, and they are associated with decreased health-related quality of life (D'Iorio *et al.*, 2017). Anxiety may be a premotor symptom in PD; however, it may also be a psychological reaction to PD onset or occur in the later disease stages (Dissanayaka *et al.*, 2014). Anxiety disorders affect approximately 31 % of PD patients on average (Broen *et al.*, 2016; Mele *et al.*, 2018) and, similar to depression, are often underdiagnosed (Dissanayaka *et al.*, 2014). In clinical circumstances, anxiety is often associated with female gender, younger age, history of anxiety, and motor fluctuations and often coexists with depression (Dissanayaka *et al.*, 2014; Schapira *et al.*, 2017).

PD anxiety and the motor symptoms of PD seem to share, at least in part, the same pathophysiology (Péron *et al.*, 2012). In particular, degeneration in the mesocorticolimbic dopaminergic pathways might cause PD anxiety while projecting to the amygdala, which is one of the main structures in the genesis of anxiety in the general population (Craske & Stein, 2016). Furthermore, degeneration and Lewy pathology of the amygdala have been reported in PD (Harding *et al.*, 2002b). Dopaminergic medication diminishes the symptoms of anxiety; however, this effect might result from improvements of the motor symptoms (Chaudhuri & Schapira, 2009). PD anxiety has been associated with a DAT deficit in the right and left caudate (Erro *et al.*, 2012) and right anterior putamen (Weintraub *et al.*, 2005), as well as increased striatal DAT density (Moriyama *et al.*, 2011; Ceravolo *et al.*, 2013), which underlines the involvement of dopamine. In the study of Picillo *et al.,* PD patients with anxiety had a lower DAT density in the caudate than PD patients without anxiety (Picillo *et al.*, 2017), whereas Giuda and colleagues did not identify differences in FP-CIT binding between PD patients with and without anxiety (Di Giuda *et al.*, 2012). Remy *et al* determined that reduced [^{11}C]RTI-32 binding in several limbic regions, the left caudate and the locus coeruleus correlated with more severe anxiety symptoms in PD (Remy *et al.*, 2005), which reflects dopaminergic and noradrenergic dysfunction. According to Braak's staging, Lewy pathology spreads to the noradrenergic locus coeruleus prior to the SN, which may explain the prodromal nature of anxiety in PD (Braak *et al.*, 2004).

2.3.1.3 Psychosis

Illusions, hallucinations and delusions in PD form an entity referred to as PD psychosis (Ffytche *et al.*, 2017). Psychotic symptoms in PD are associated with a greater risk for nursing home placement (Aarsland *et al.*, 2000) and greater mortality (Forsaa *et al.*, 2010). Psychotic symptoms in PD have a severe negative impact on the quality of life of patients and caregivers (McKinlay *et al.*, 2008).

In PD psychosis, minor hallucinations, such as a false sense of presence (feeling that someone is in the room) or passage hallucinations (seeing shadows walking past), often occur first, followed by visual hallucinations and, ultimately, delusions (Ffytche *et al.*, 2017). Hallucinations in PD are predominantly visual hallucinations, which are characteristically complex and well formed, such as animals or people (Fénelon *et al.*, 2000). Delusions and other types of hallucinations, such as auditory hallucinations, are less common than visual hallucinations and often occur in the later disease stages (Ffytche *et al.*, 2017). The insight of the psychotic symptoms in PD mostly remains; however, it may be lost in the later disease stages (Ffytche & Aarsland, 2017).

The prevalence of psychotic symptoms in PD is 26 % according to a study of non-demented PD patients (Mini-Mental State Examination (MMSE) > 23) (Mack *et al.*, 2012); however, the prevalence estimates vary in the literature from 20 to 75 % (Factor *et al.*, 2017). The prevalence of PD hallucinations increases with age (Fénelon *et al.*, 2000). Other risk factors for PD hallucinations include cognitive decline, sleep disturbances, longer disease duration and severe motor symptoms (Fénelon *et al.*, 2000). More severe autonomic dysfunction, excessive daytime sleepiness and RBD predict the development of PD psychosis (Barrett *et al.*, 2018). PD psychosis has been associated with dopaminergic medication, particularly dopamine agonists; however, the results are contradictory (Lenka *et al.*, 2017).

The underlying mechanisms of PD psychosis are only partially elucidated. The dopamine hypothesis of schizophrenia suggests that dopamine D2 receptors are hyperactive in limbic and subcortical areas, which results in the positive symptoms of schizophrenia (Howes & Kapur, 2009). An increased dopamine measure in the mesolimbic dopaminergic pathway (from the VTA to the nucleus accumbens) has an important role in the development of visual and auditory hallucinations in schizophrenia (Rolland *et al.*, 2015). In PD, the mesolimbic and mesocortical dopaminergic pathways are typically better preserved than the nigrostriatal pathway (Kish *et al.*, 1988). Thus, treatment with dopaminergic medication may lead to a relative over-activation of the mesolimbic and mesocortical dopaminergic pathways, thus leading to neuropsychiatric complications associated with increased dopamine neurotransmission, such as hallucinations (dopamine overdose hypothesis)

(Gotham *et al.*, 1988; Vaillancourt *et al.*, 2013). However, there are also unmedicated PD patients with hallucinations, which indicates that PD psychosis is not simply a side effect of dopaminergic medication (Factor *et al.*, 2017).

Serotonin is also involved in the genesis of PD psychosis. Its involvement is supported by the fact that pimavanserin, a 5-hydroxytryptamine (5-HT) 2A receptor inverse agonist, is effective for the treatment of psychotic symptoms in PD (Sarva & Henchcliffe, 2016). The upregulation of 5-HT receptors in cortical areas may lead to PD psychosis (serotonin-dopamine imbalance syndrome) (Stahl, 2016). Furthermore, PD patients with hallucinations show increased serotonin 2A receptor binding in the ventral visual pathways compared to patients with no hallucinations (Ballanger *et al.*, 2010). In brain dopamine imaging studies, the visual hallucinations of PD have been associated with reduced right caudate DAT binding (Kiferle *et al.*, 2014), and a lower striatal DAT density seems to predict the emergence of psychotic symptoms in PD (Ravina *et al.*, 2012).

In addition, Lewy pathology, particularly in cortical areas, is an important factor in the pathophysiology of PD psychosis (Harding *et al.*, 2002a; Papapetropoulos *et al.*, 2006). The pathophysiologies of different psychotic phenomena in PD seem to be distinct. Minor hallucinations that often occur first have been associated with Lewy pathology in the brain stem (Braak stage II), whereas later appearing visual hallucinations have been associated with forebrain Lewy pathology (Braak stage IV) (Ffytche *et al.*, 2017).

2.3.1.4 Impulse control disorders

ICDs in PD include pathological gambling, compulsive shopping, hypersexuality and binge eating disorder. According to the largest study to date, approximately 14 % of PD patients suffer from ICDs (Weintraub *et al.*, 2010); however, the estimates vary depending on the population and methodology (Callesen *et al.*, 2013). In Finnish PD patients, 35 % of PD patients have a positive screen for ICDs (subclinical ICDs included) (Joutsa *et al.*, 2012c). ICDs are characterized by continuing failure to resist an impulsive act that is harmful to the person or other individuals (Ceravolo *et al.*, 2009). Compulsive behaviours, such as punding, hobbyism and dopamine dysregulation syndrome (DDS), are closely related to ICDs. Punding refers to frequent compulsive behaviours with no purpose, such as pointless driving (O'Sullivan *et al.*, 2007). An example of hobbyism is excessive exercise (Weintraub & Claassen, 2017). DDS refers to compulsive antiparkinsonian medication use clearly exceeding the doses required for motor symptom control (Weintraub & Claassen, 2017). ICDs are more common in males than in females, and they are associated with a younger age, younger age at disease onset, not being

married, current smoking and family history of gambling (Weintraub *et al.*, 2010). ICDs have been associated with several NMSs, such as depression and anxiety (Weintraub & Claassen, 2017).

ICDs among unmedicated PD patients are not more common than in the general population (Weintraub *et al.*, 2013), and the development of PD ICDs is often triggered by dopamine replacement therapy, particularly dopamine agonists binding to D2/3 receptors (Weintraub *et al.*, 2010). Although the limbic areas, such as the ventral striatum, are relatively well preserved in PD compared to the dorsal striatum, dopaminergic medication may lead to overactivation of these areas, resulting in the development of ICDs (Joutsa *et al.*, 2015b; Vriend, 2018). Another explanation for the emergence of PD ICDs is that D3 receptors in the ventral striatum are particularly sensitive to dopaminergic medication because of the lack of endogenous dopamine, thus leading to overactivation of these areas (Vriend, 2018).

In brain dopamine imaging studies, PD ICDs have been associated with dopaminergic dysfunction. PD ICDs have been associated with a lower DAT density (Cilia *et al.*, 2010; Lee *et al.*, 2014; Voon *et al.*, 2014) and increased dopamine release in the ventral striatum as a response to stimuli compared to PD patients without ICDs (Steeves *et al.*, 2009; O'Sullivan *et al.*, 2011; Payer *et al.*, 2015; Wu *et al.*, 2015). PD ICDs have also been associated with increased medial orbitofrontal [^{18}F]fluorodopa uptake (Joutsa *et al.*, 2012a). A greater decline in the striatal DAT binding during disease progression predicts the emergence of PD ICDs (Smith *et al.*, 2016). In a longitudinal study by Vriend *et al.,* lowered DAT binding in the right ventral striatum, right anterior dorsal striatum and posterior putamen in *de novo* PD patients predicted the development of ICDs during follow-up, which suggests more severe degeneration or lowered premorbid DAT levels leading to increased dopamine levels (Vriend *et al.*, 2014a). Furthermore, the right ventral and right anterior dorsal striatal DAT density negatively correlated with ICD severity (Vriend *et al.*, 2014a). Thus, dopamine plays a key role in the development of PD ICDs.

2.3.1.5 Other neuropsychiatric symptoms

Apathy and fatigue. Apathy is characterized by a loss of motivation, interest and goal-directed behaviour (Pagonabarraga & Kulisevsky, 2017). Apathy affects 13.9-70 % of PD patients (Santangelo *et al.*, 2013). PD apathy may appear independently or coexist with depression or dementia (Pagonabarraga & Kulisevsky, 2017). Similar to depression, apathy in PD is associated with a mesocorticolimbic hypodopaminergic state (Remy *et al.*, 2005; Santangelo *et al.*, 2013). In an FP-CIT

SPECT study that compared non-demented, non-depressed, drug-naive PD patients with and without apathy, the DAT density was lower in the right caudate nucleus in PD patients with apathy (Santangelo *et al.*, 2015). Furthermore, dopaminergic medication may improve PD apathy symptoms (Thobois *et al.*, 2013). However, the results of dopaminergic involvement in the pathophysiology of PD apathy are inconsistent (Chung *et al.*, 2016a). Furthermore, serotonin plays a key role in the genesis of PD apathy (Maillet *et al.*, 2016), and anticholinesterase treatment may improve PD apathy (Devos *et al.*, 2014). Fatigue affects approximately 50 % of PD patients (Schapira *et al.*, 2017). Fatigue is characterized by exhaustion and shortage of energy. Although fatigue often occurs concurrently with depression or anxiety in PD, it is an independent disorder (Hagell & Brundin, 2009).

Cognitive decline. Cognitive deficits are common in PD. Although PD dementia (PDD) often occurs in advanced disease, mild cognitive impairment (MCI) may be involved in earlier disease stages (Weintraub *et al.*, 2018). PDD is more severe than MCI, disturbing daily life. MCI often leads to the development of PDD (Aarsland *et al.*, 2017). The prevalence of dementia in PD is 24-31 % (Aarsland *et al.*, 2005). The most important pathology underlying PDD seems to be Lewy pathology in cortical and limbic areas (Aarsland *et al.*, 2017). Both dopaminergic deficits, particularly in the mesocorticolimbic dopaminergic pathway, as well as cholinergic deficits occur in PDD (Halliday *et al.*, 2014; Colloby *et al.*, 2016).

2.3.2 Hyposmia, sleep disorders and autonomic dysfunction

2.3.2.1 Hyposmia

An estimated 50-90 % of PD patients suffer from hyposmia (Fullard *et al.*, 2017). Olfaction deficits may be used as a biomarker for PD, for example, when differentiating PD from essential tremor or tauopathies, such as PSP or corticobasal degeneration (CBD) (Fullard *et al.*, 2017). Hyposmia is included as a clinical non-motor marker in the suggested research criteria for prodromal PD (Berg *et al.*, 2015).

Since the Lewy pathology in the olfactory bulb is an early manifestation in PD (Braak *et al.*, 2003; Beach *et al.*, 2009), it probably gives an explanation for the hyposmia, which often precedes the motor symptoms in PD. Other olfaction structures are also affected in PD. The cortical nucleus of the amygdala that participates in olfaction is more severely affected by Lewy pathology than other amygdala areas (Harding *et al.*, 2002b). Moreover, Lewy pathology also spreads to the primary

olfactory cortex (Silveira-Moriyama *et al.*, 2009). Another factor that suggests hyposmia is associated with Lewy pathology is that hyposmia is present in MSA and LBD, whereas olfaction in CBD and PSP is mostly preserved (Müller *et al.*, 2002).

2.3.2.2 Sleep disorders

RBD is a common premotor symptom in alpha-synucleinopathies, including PD (Bassetti & Bargiotas, 2018). RBD is characterized by a lack of normal motor disconnection, which results in disruptive motor behaviours during REM sleep. Probable RBD is associated with many NMSs that are also present in PD, such as hyposmia, which suggests a similar pathological mechanism underlying these diverse symptoms (Mahlknecht *et al.*, 2015). An autopsy study by Postuma *et al* showed that PD patients with RBD had more severe Lewy body deposition widely in both cortical and subcortical regions of the CNS (Postuma *et al.*, 2015a). In DAT imaging studies, PD patients with clinically probable RBD have been shown to have more severe DAT deficits in the putamen (Chung *et al.*, 2017) and the caudate (Arnaldi *et al.*, 2015) than PD patients without RBD, which suggests more severe neurodegeneration in PD patients with RBD. RBD is most accurately diagnosed with polysomnography (Liu *et al.*, 2017b).

In addition to RBD, other sleep disorders, such as excessive daytime sleepiness (EDS), are common in PD (Chahine *et al.*, 2017). PD EDS has been associated with more severe caudate dopaminergic depletion; however, the results require confirmation (Yousaf *et al.*, 2018).

2.3.2.3 Autonomic dysfunction

In PD, Lewy pathology is present in the autonomic nervous system, such as preganglionic sympathetic and parasympathetic neurons, autonomic ganglia and areas that regulate the autonomic nervous system, such as the hypothalamus (Asahina *et al.*, 2013). Autonomic dysfunction of PD includes gastrointestinal (GI) dysfunction, bladder disorders, cardiovascular manifestations, such as orthostatic hypotension, and sexual dysfunction. Autonomic dysfunction is present in all PD stages but worsens when the disease progresses and is associated with a worsened quality of life (Merola *et al.*, 2018). Early autonomic dysfunction in PD has been associated with shorter survival and more rapidly progressing disease (De Pablo-Fernandez *et al.*, 2017). Orthostatic hypotension is an underdiagnosed manifestation of PD and may lead to increased falls (Merola *et al.*, 2018).

The enteric nervous system is affected by Lewy pathology in PD (Beach *et al.*, 2010; Cersosimo & Benarroch, 2012). Constipation is more common in early PD than in age-matched healthy controls (Pagano *et al.*, 2017). Constipation, similar to hyposmia, may be a premotor symptom of PD (Abbott *et al.*, 2007). The underlying mechanisms of PD constipation may be non-dopaminergic, as PD constipation was not associated with DAT deficit in the FP-CIT SPECT study by Pagano and colleagues (Pagano *et al.*, 2017). Additional GI manifestations in PD include dysphagia, decreased or increased saliva secretion and gastric dysfunction (Ali *et al.*, 2016).

3 AIMS OF THE STUDY

The principal aims of the study were to

I Evaluate the relationship between PD ICDs and other psychiatric symptoms.

II Investigate potential factors that predict the outcome in clinical brain DAT imaging.

III Examine whether brain dopamine function, as measured with DAT imaging, predicts which PD patients will develop visual hallucinations.

IV Compare NMSs between PD patients and patients with nondegenerative parkinsonism.

Note: The roman numerals refer to the original publications

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Study I

PD patients from the registry of the Finnish Parkinson Association were asked to participate in the epidemiological study by Joutsa *et al* (n = 575) (Joutsa *et al.*, 2012c). Patients who agreed to be contacted regarding an additional postal survey were invited to participate in study I (n = 376). Two hundred ninety (77 %) patients completed the survey.

4.1.2 Studies II-III

Five hundred fifty-nine patients were scanned with [^{123}I]FP-CIT SPECT in the Department of Nuclear Medicine, Turku University Hospital, during 6 years (2007-2012) (Kaasinen *et al.*, 2014). Of these patients, 545 patients had parkinsonism. The automated image analyses failed in seven cases; thus, the final number of patients in study II was 538.

Patients from the same dataset with PD, as confirmed by a certified neurologist, an abnormal scanning outcome and sufficient description of the clinical details in hospital records, were evaluated at follow-up by the investigators. One hundred sixty-two patients who fulfilled the criteria were identified. The median follow-up was 5.8 years. Patients who developed hallucinations during the follow-up (n = 22) together with matched controls were selected for study III. The control group was matched to the group of patients with hallucinations according to age, gender, follow-up duration, motor symptom duration, Hoehn and Yahr scale at the scan, LEDD at the scan and LEDD at the follow-up. The investigators were blinded to the imaging results when collecting the control group data to avoid bias in subject selection.

The study flowchart and patient selection for studies II and III are represented in figure 6.

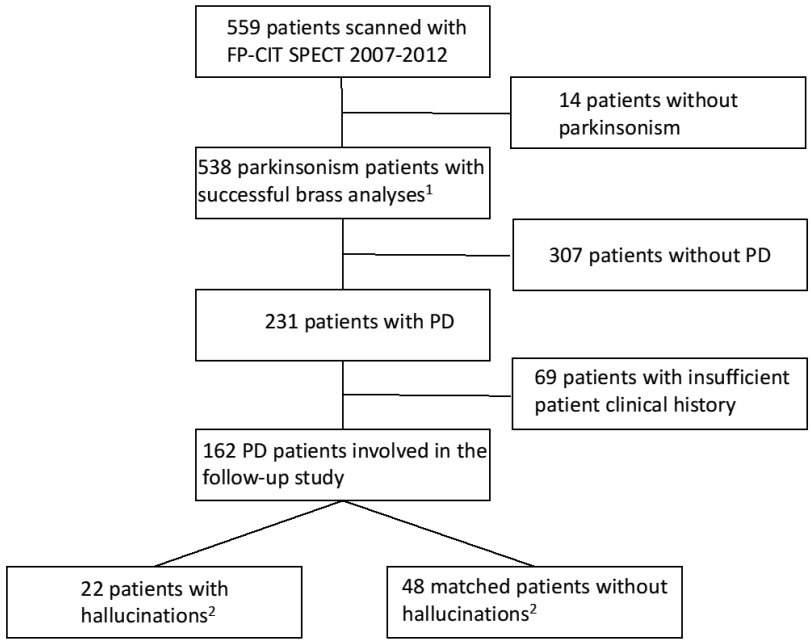

Figure 6. Flowchart and patient selection for studies II and III. [1]Subjects for study II, [2]Subjects for study III. PD = Parkinson's disease.

4.1.3 Study IV

Patients scanned with [^{123}I]FP-CIT SPECT in the department of nuclear medicine, Turku university hospital, or the department of nuclear medicine, Helsinki university hospital, were prospectively recruited for Study IV (NMDAT study; ClinicalTrials.gov Identifier: NCT02650843). Data collection was performed between February 2014 and February 2017, and 221 individuals participated in the study. Clinical investigation of the patients occurred 2-4 hours prior to the scanning. Patients with an MMSE score less than 18 were not included in study IV. Patients who had an abnormal imaging outcome and PD as a final clinical diagnosis were included in study IV (n=84). The control group consisted of patients without PD and a normal imaging outcome (n=109). Thus, the total number of subjects in study IV was 193.

4.2 Methods

4.2.1 Epidemiological survey (study I)

The postal survey for study I included a demographic inquiry, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) (Weintraub *et al.*, 2009), the Symptoms Checklist 90 (SCL-90) (Derogatis *et al.*, 1973) and the Barratt Impulsiveness Scale 11 (BIS-11) (Patton *et al.*, 1995).

Demographic data consisted of age, gender, living environment (rural or urban), smoking, alcohol consumption, predominant motor symptom side, handedness, time when PD was diagnosed and current medication. Levodopa equivalent daily doses (LEDDs) were calculated to estimate the total dopaminergic medication load, as previously described (Tomlinson *et al.*, 2010; Joutsa *et al.*, 2012c).

The QUIP was used to screen ICDs (pathological gambling, hypersexuality, compulsive shopping and binge eating) that were persistent during the previous month. The ICD section of the QUIP consists of five questions that are asked for each ICD (yes / no). Recommended cut-off scores (≥ 2 positive answers for gambling and eating and ≥ 1 positive answer for shopping and sex) were used, as proposed by the original validation of the questionnaire (Weintraub *et al.*, 2009). Other compulsive behaviours included in the QUIP were not assessed in study I because of the lack of validated cut-off scores.

The Finnish version of the SCL-90 was used for screening multiple psychiatric symptoms that occurred during the previous month (Holi *et al.*, 1998). There are 90 questions in the SCL-90. Each question is scored from 0 (no symptom) to 4 (remarkable symptom). The mean score of all 90 questions, referred to as the global severity index (GSI), is used to evaluate the total burden of psychiatric symptoms. The SCL-90 consists of 9 subscores, each of which are calculated as a mean score of the questions included in the dimension. These dimensions include depression (DEP), anxiety (ANX), interpersonal sensitivity (INT), obsessive-compulsive symptoms (O-C), hostility (HOS), phobic anxiety (PHOB), paranoid ideation (PAR), psychoticism (PSY) and somatization (SOM).

Impulsivity was evaluated using the BIS-11, which consists of 30 questions. The BIS-11 total score is the sum of the questions with a range of 30-120. Moreover, there are 3 subscores in the BIS-11, including nonplanning, attentional and motor impulsiveness that reflect failure in planning the future, concentration problems and action without thinking, respectively.

4.2.2 DAT imaging (studies II-IV)

4.2.2.1 Scanning protocol

Patients were scanned with [^{123}I]FP-CIT SPECT in studies II-IV. A GE Infinia II Hawkeye SPECT/CT (GE Medical Systems, Milwaukee, WI, USA) or Picker Irix gamma camera (Picker International, Uniontown, OH, USA) (studies II-III) or GE Infinia II Hawkeye SPECT/CT (GE Healthcare, Tirat Hacarmel, Israel) (Turku), Philips Brightview XCT (Philips Healthcare, Einhoven, the Netherlands) or Siemens Symbia T2 (Siemens Healthineers, Erlangen, Germany) (Helsinki) (study IV) were used for scanning. To prevent thyroid gland uptake, patients received 250 mg 1 % oral potassium perclorate ($KClO_4$) one hour prior to the injection. A 185 MBq intravenous bolus of |^{123}I]FP-CIT was injected 3-4 hours prior to the scanning. A detailed description of the scanning protocol is presented elsewhere (Kaasinen *et al.*, 2014).

4.2.2.2 Image analyses

In the retrospective studies (studies II and III), the scanning outcome was defined as normal or abnormal based on both visual evaluation and semi-quantitative assessment made by a nuclear medicine physician according to previously published guidelines (Darcourt *et al.*, 2010). In the prospective study (study IV), the classifications made by a nuclear medicine physician were reviewed, and the classification was based on the semi-quantitative analyses; the scan was defined as abnormal if the tracer uptake in any of the six regions examined was more than two standard deviations below the reference means (Varrone *et al.*, 2013). Borderline cases were re-evaluated by the investigators and were designated normal or abnormal as previously indicated (Mäkinen *et al.*, 2016).

The reconstruction of the SPECT images was performed using HybridRecon Neurology Software version 1.0.15 (studies II-III) or version 1.3 (study IV) (Hermes Medical Solutions AB, Stockholm, Sweden) with a 3D ordered-subsets expectation maximization (OSEM) algorithm. Image analyses were conducted using BRASS automated semi-quantitative analysis software version 3.6 (studies II-III) or version 2.6H (study IV) (Hermes Medical Solutions, Stockholm, Sweden). All image reconstructions and analyses were performed by the investigators. Scanner specific corrections were applied to the data. Specific binding ratios (SBRs) of striatal DAT binding were calculated for six regions of interest (ROIs): the right and left caudate, anterior putamen and posterior putamen.

As BRASS software does not support other ROIs, the left and right ventral striatum were drawn separately using Carimas software (version 2.9, Turku PET Centre, Turku, Finland), as previously described (Mawlawi *et al.*, 2001). The ROIs for the amygdala and hippocampus were received from the Automated Anatomic Library (AAL). First, Statistical Parametrical Mapping software (SPM, http://www.fil.ion.ucl.ac.uk/spm/software/spm12) running on Matlab (Mathworks Inc., Chicago, IL, USA) was used to spatially normalize the images exported from Hermes into the Montreal Neurological Institute (MNI) space using an in-house template (Kaasinen *et al.*, 2015a). The ROIs were defined in the MNI space and values extracted from the normalized images.

The occipital cortex was used as a reference region (Joutsa *et al.*, 2015a). SBRs were calculated for both the ROI and voxelwise data with the following formula:

$SBR = (ROI_{target} - ROI_{occipital}) / ROI_{occipital}$ (Varrone *et al.*, 2013).

For the voxelwise analyses, the SBR images were smoothed using an 8 mm full width at half maximum (FWHM) Gaussian kernel to improve the signal-to-noise ratio. The statistical analyses were conducted in SPM software as described in the statistics paragraph.

4.2.3 Patient medical history (studies II-IV)

Clinical and demographic data for studies II-III (including the follow-up in study III) were collected from the hospital records. This information included age at scan, gender, duration of motor symptoms prior to the scanning, symmetry, predominant side and type of motor symptoms, Hoehn and Yahr scale, use of antiparkinsonian or antipsychotic medication, self-reported depression, anxiety or impulse-control disorders and scanner type. Detailed indications for scanning were obtained. When there was no specific diagnostic question and the patient suffered from clinically uncertain parkinsonism, clinically uncertain parkinsonian syndrome (CUPS) was set as a scanning indication.

In study IV, all demographical information was obtained during the clinical examination of the patients immediately prior to the scanning with the exception of the final clinical diagnosis, which was obtained from the hospital records at the time of the initiation of the data analyses (February 2017).

4.2.4 NMDAT tasks (study IV)

Study IV included a clinical interview, the MMSE (Folstein *et al.*, 1975), the Non-motor symptoms scale (NMSS) (Chaudhuri *et al.*, 2007), the UPDRS part III (motor part) (Goetz *et al.*, 2008), the Beck Depression Inventory (BDI) (Beck *et al.*, 1961), the Beck Anxiety Inventory (BAI) (Beck *et al.*, 1988) and a single-question screen for RBD (Postuma *et al.*, 2012b).

The MMSE is a screening instrument used to evaluate cognitive function. The MMSE is an interview survey conducted by an investigator. The MMSE consists of 30 questions that are rated as correct (1 point) or incorrect (0 points). Thus, the MMSE is scored from 0 to 30. In study IV, an MMSE score less than 18 was considered a sign of moderate cognitive impairment, and these patients were not included in the study.

The NMSS is a survey that is completed by a health professional based on an interview (Chaudhuri *et al.*, 2007). The NMSS evaluates multiple NMSs in PD. There are 30 questions in the NMSS. The rating for each question (i.e., each symptom) is a product of the symptom severity (from 0 (no symptom) to 3 (severe)) and the symptom frequency (from 0 (never) to 4 (every day)). Every symptom is scored according to the presence of the symptom during the previous month. These 30 scores form 9 domains that include cardiovascular, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, the gastrointestinal tract, the urinary system, sexual function and miscellaneous. Each domain is calculated as a sum of the scores included in the domain. Thus, the total NMSS score varies from 0 to 360.

The MDS-UPDRS is the most widely used tool to assess the clinical state of PD patients. The motor part of the UPDRS, part III, is a clinical evaluation of a patient's motor symptoms. The UPDRS motor part consists of 33 scores, each of which are rated from 0 (normal) to 4 (severe). There are clear instructions for the examiner in each question (Goetz *et al.*, 2008). To ensure consistent ratings, all clinical investigators in study IV passed the MDS-UPDRS Training Program and Exercise (Goetz *et al.*, 2010).

The BDI and BAI are self-reported questionnaires. The BDI is used for screening symptoms of depression, whereas the BAI is used for screening anxiety symptoms. Both questionnaires have been widely used in PD (Schrag *et al.*, 2007; Leentjens *et al.*, 2011). There are 21 questions in both questionnaires. Each question is scored from 0 (no symptom) to 3 (severe symptom), with the total score ranging from 0 to 63.

A single question screen for RBD includes a rapidly performed screening tool for RBD with a very high sensitivity of 93.8 % and specificity of 87.2 % compared to the gold standard, polysomnogram (Postuma *et al.*, 2012b).

4.3 Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics version 21 (study I), version 22 (study II), or version 24 (studies III and IV) (SPSS Inc., Chicago, IL, USA).

Missing variables were handled as previously described (Joutsa *et al.*, 2012c). An ICD assessed with QUIP was considered missing if the missing values prevented a definitive conclusion of the screening outcome (i.e., positive or negative screen). In the SCL-90, BIS-11 (study I), BDI, BAI and NMSS total score (study IV), a patient with more than 20 % of missing values from the total or subscore was removed from the respective analysis of the questionnaire. When there were less than 20 % of missing values, the scores were corrected according to the number of missing values in the SCL-90, BIS-11, BDI, BAI and NMSS total score. The values for the UPDRS part III motor score were corrected as previously indicated if there were missing values (Goetz *et al.*, 2015).

Normality was tested with a combined visual evaluation using histograms and the Shapiro Wilk's test. Group comparisons for studies I (patients with or without ICDs), II (patients with normal or abnormal scanning outcome), III (patients with or without hallucinations) and IV (patients with PD or patients with normal imaging outcome) were performed using independent samples t-tests, Mann-Whitney U-tests or Chi-square tests, as appropriate.

In study I, a Bonferroni correction for 14 comparisons was applied when comparing the SCL-90 and BIS-11 total and subscores to minimize the possibility of false-positive results. For the demographical variables, a Bonferroni correction was not applied to ensure the critical evaluation of group differences. Group comparisons between patients with single and multiple ICDs were performed using Student's t-tests. For the evaluation of possible independent associations between ICDs and psychiatric symptoms or impulsivity, linear regression analyses were performed. For multivariate analyses, only variables with a significant association in the univariate analyses were included.

In study II, a binary logistic regression analysis was performed to assess the factors that were independently associated with the scanning outcome. Only variables that were significantly different between the normal and abnormal scanning outcomes

were selected for the subsequent multivariate analyses. The use of antipsychotic medication was not included in the regression analyses because of collinearity with the scanning indication (patients who are suspected for medication induced parkinsonism use more antipsychotic drugs). Scanning indications with less than 30 patients were not included in the multivariate analyses. Scanning indications of suspected PSP, suspected MSA and suspected parkinsonism plus syndrome were combined as suspected parkinsonism plus syndrome. For scanning indication, CUPS was selected as the reference category.

In study III, logistic regression analyses were performed in the striatal regions where DAT binding was significantly different between patients with and without hallucinations to evaluate the predicting value of a decrease in the in the DAT binding. The group differences in the striatal SBRs were confirmed with voxelwise analysis using SPM software applying a general linear model (GLM). Cluster-level family-wise error (FWE) correction was applied to correct for multiple comparisons across all brain voxels that showed specific binding for ^{123}I-FP-CIT (i.e., SBR≥1.0). The results were confirmed by the addition of age, sex and Hoehn & Yahr as nuisance covariates.

In study IV, Bonferroni corrections for five comparisons were applied for the non-motor total scores (the NMSS, BDI, BAI, MMSE and RBD) and nine comparisons for the NMSS subscores. Analyses were repeated including only patients with no antiparkinsonian medication to exclude the confounding effects of medication. Correlations between the mean putamen or caudate SBRs and other factors and correlations between the motor symptom duration and NMSS total score were calculated using Spearman correlation. The results were confirmed using partial correlation between the mean putamen or caudate SBRs and the NMSS total score, controlling for age, MMSE and UPDRS scores. Variables with skewed distributions were Log transformed. The association between all brain voxels that showed specific binding was investigated using GLM in SPM software. A cluster-level FWE-correction was applied.

In all analyses, *P* values less than 0.05 were considered significant.

4.4 Ethics

Studies I-IV were conducted according to the principles of the Declaration of Helsinki. The local ethical committee approved the study protocols for each study (I-IV). Written informed consent was obtained from all subjects unless the requirement to obtain informed consent was waived by the ethical committee.

5 RESULTS

5.1 Comorbidity of ICDs and other psychiatric symptoms in Parkinson's disease (study I)

In study I, 108 (39 %) PD patients had at least one ICD, and 171 patients did not report ICDs in the QUIP (11 missing values). Of the patients with ICDs, 38 (14 %) patients had multiple ICDs. Compared to the patients with no ICDs, the patients with ICDs were more likely younger men with an early PD onset (table 3). Antiparkinsonian medication among the two groups was similar (table 3).

The differences between the patients with or without ICDs are presented in table 3. The burden of psychiatric symptoms was greater among the patients with ICDs than among the patients without ICDs. The SCL-90 total score (GSI) was greater in the patients with ICDs than in the patients without ICDs (corrected $P = 0.002$). Moreover, the ICD patients scored higher in the O-C (corrected $P < 0.001$), INT (corrected $P = 0.001$), DEP (corrected $P = 0.01$) and PSY (corrected $P < 0.001$) scores of the SCL-90 and in the total (corrected $P < 0.001$), attentional (corrected $P = 0.01$) and nonplanning impulsiveness (corrected $P = 0.03$) according to the BIS-11.

The results of the linear regression analyses are presented in table 4. ICDs were independently associated with GSI ($P < 0.001$), O-C ($P < 0.001$), INT ($P < 0.001$), DEP ($P < 0.001$) and PSY ($P < 0.001$). In addition, ICDs were independently associated with total ($P < 0.001$), nonplanning ($P = 0.002$) and attentional ($P = 0.001$) impulsivity. The PD duration was positively associated with the INT, DEP and PSY scores (table 4). The age at PD onset was negatively associated with the INT score (table 4). Dopamine agonist use was associated with lower O-C, DEP and PSY scores, and alcohol use was associated with lower INT and PSY scores (table 4). When the psychiatric symptoms and impulsivity of the patients with multiple ICDs were compared to those of the patients with a single ICD, the O-C (mean [SD] 1.61 [0.71] vs 1.24 [0.67], respectively, $P = 0.01$) and DEP (mean [SD] 1.28 [0.76] vs 0.99 [0.63], respectively, $P = 0.05$) scores were higher among the patients with multiple ICDs.

Table 3. Patient characteristics, psychiatric symptoms and impulsivity in PD patients with or without ICDs (study I) (modified from tables 1 and 3 of the original publication). Values are means (SD) or n.

	Patients with ICDs (n=108)	***Patients without ICDs (n=171)***	***P value[1]***	***Corrected P value[2]***
Age (years)	63.1 (7.8)	65.8 (7.9)	0.01	
Age of onset (years)	56.5 (8.1)	59.0 (8.8)	0.03	
Gender (m/f)	83/25	92/79	<0.001	
LEDD total[3] (mg)	702.4 (363.4)	649.2 (407.8)	0.28	
Levodopa use	93/15	135/36	0.08	
LEDD levodopa[3] (mg)	577.1 (347.9)	546.6 (353.1)	0.53	
DA use	88/20	127/44	0.11	
LEDD DA[3] (mg)	181.4 (102.1)	188.8 (102.4)	0.61	
SCL-90				
GSI	0.98 (0.54)	0.74 (0.48)	<0.001	0.002
SOM	1.23 (0.68)	1.09 (0.73)	0.11	1
O-C	1.40 (0.72)	1.01 (0.62)	<0.001	<0.001
INT	0.96 (0.68)	0.63 (0.58)	<0.001	0.001
DEP	1.11 (0.69)	0.83 (0.63)	0.001	0.01
ANX	0.90 (0.55)	0.73 (0.57)	0.02	0.21
HOS	0.53 (0.48)	0.40 (0.58)	0.06	0.77
PHOB	0.65 (0.69)	0.47 (0.52)	0.02	0.34
PAR	0.72 (0.61)	0.50 (0.65)	0.007	0.10
PSY	0.72 (0.58)	0.43 (0.46)	<0.001	<0.001
BIS-11				
Total impulsivity	17.47 (5.74)	15.40 (4.46)	0.001	0.01
Attentional	22.11 (3.98)	20.83 (3.79)	0.009	0.13
Motor	26.17 (4.58)	24.44 (4.36)	0.002	0.03
Nonplanning	65.71 (10.09)	60.70 (9.11)	<0.001	<0.001

[1]T-test or Chi-Square test, [2]Bonferroni correction for 14 comparisons, [3]Only patients using the corresponding medication. ANX = anxiety, DA = dopamine agonist, DEP = depression, f = female, GSI = global severity index, HOS = hostility, ICD = impulse control disorders, INT = interpersonal sensitivity, LEDD = levodopa equivalent daily dose, m = male, O-C = obsessive-compulsive symptoms, PAR = paranoid ideation, PHOB = phobic anxiety, PSY = psychoticism, SD = standard deviation, SOM = somatization.

Table 4. Linear logistic regression analyses results (Study I) (modified from table 4 of the original publication).

Dependent variable	*Independent variable*	*Univariate*		*Multivariate*	
		B (95% CI)	***P value***	***B (95% CI)***	***P value***
GSI	ICD	0.24 (0.12-0.37)	<0.001	0.27 (0.15-0.40)	<0.001
	PD duration	0.02 (0.01-0.04)	<0.001	0.02 (0.01-0.04)	<0.001
	DA use	-0.18 (-0.33- -0.04)	0.01	-0.17 (-0.32- -0.03)	0.02
	Alcohol use	-0.22 (-0.37- -0.07)	0.003	-0.17 (-0.31- -0.02)	0.03
O-C	ICD	0.39 (0.22-0.55)	<0.001	0.41 (0.24-0.57)	<0.001
	DA treatment	-0.21 (-0.41- -0.01)	0.04	-0.29 (-0.48- -0.10)	0.003
INT	ICD	0.33 (0.17-0.48)	<0.001	0.32 (0.16-0.48)	<0.001
	Age of onset	-0.01 (-0.02- -0.005)	0.002	-0.01 (-0.02-0)	0.04
	PD duration	0.03 (0.02-0.05)	<0.001	0.03 (0.01-0.05)	0.003
	LEDD total (100mg)	0.02 (0.00-0.04)	0.04	-0.01 (-0.03- -0.01)	0.41
	Alcohol use	-0.29 (0.47- -0.11)	0.002	-0.33 (-0.51- -0.14)	0.001
DEP	ICD	0.28 (0.12-0.44)	0.001	0.34 (0.18-0.50)	<0.001
	PD duration	0.03 (0.01-0.05)	<0.001	0.03 (0.01-0.04)	0.001
	DA use	-0.34 (-0.52- -0.16)	<0.001	-0.32 (-0.51- -0.13)	0.001
	Alcohol use	-0.25 (-0.44- -0.07)	0.008	-0.19 (-0.38-0.003)	0.05
PSY	ICD	0.30 (0.17-0.42)	<0.001	0.32 (0.19-0.44)	<0.001
	PD duration	0.02 (0.01-0.04)	<0.001	0.02 (0.008-0.04)	0.002
	Levodopa use	0.17 (0.008-0.34)	0.04	0.02 (-0.15-0.19)	0.81
	DA use	-0.17 (-0.32- -0.02)	0.03	-0.16 (-0.31- -0.006)	0.04
	Alcohol use	-0.20 (-0.35-0.04)	0.01	-0.16 (-0.31- -0.006)	0.04
Total	ICD	1.73 (0.063-2.84)	0.002		
Nonplanning	ICD	2.07 (0.83-3.31)	0.001		
Attentional	ICD	5.01 (2.66-7.36)	<0.001		

B (95% CI) = regression coefficient (95% confidence interval), Attentional = attentional impulsivity, DA = dopamine agonist, DEP = depression, GSI = global severity index, INT = interpersonal sensitivity, LEDD = levodopa equivalent daily dose, Nonplanning = nonplanning impulsivity, O-C = obsessive-compulsive symptoms, PD = Parkinson's disease, PSY = psychoticism, Total = total impulsivity.

5.2 Factors that predict the outcome of DAT imaging (study II)

Of the 538 patients investigated in study II, the scanning outcome was abnormal in 303 (56 %) cases. Patient characteristics are presented in table 5.

Table 5. Patient characteristics and differences between patients with normal or abnormal DAT imaging outcome (study II) (modified from table 1 of the original publication). Values are mean (SD) on n (%).

	Patients with normal DAT imaging (n=235)	***Patients with abnormal DAT imaging (n=303)***	***P value[1]***
Age at scan (years)	64.3 (12.0)	66.8 (10.7)	0.012
Motor symptom duration (years)	4.4 (7.2)	2.2 (3.0)	<0.001
Gender (m/f)	113/122	178/125	0.014
Asymmetrical/ symmetrical motor symptoms	168/67	243/60	0.024
Tremor/no tremor	153/82	184/119	0.30
Dopaminergic medication	28 (11.9 %)	52 (17.2%)	0.11
Antipsychotic medication	49 (20.9 %)	18 (5.9%)	<0.001

[1]T-test or Chi-square test. DAT = dopamine transporter, f = female, m = male, SD = standard deviation.

In the multivariate binary logistic regression analysis, the patients with an abnormal scanning outcome were older (P = 0.002) and had a shorter symptom duration (P < 0.001) and asymmetrical symptoms (P = 0.005) (table 6). Although males were more likely to have abnormal scans (table 5), this difference did not remain significant in the multivariate analyses (table 6).

Table 6. Independent factors associated with DAT imaging outcome (study II) (modified from table 2 of the original publication). Only variables that showed significant differences between patients with normal and abnormal imaging outcome were included in the multivariate analyses.

Dependent variable	***Independent variable***	***OR (95 % CI)***	***P value***
DAT imaging outcome (normal/abnormal)	Motor symptom duration (years)	0.87 (0.81-0.93)	<0.001
	Age at scan (years)	1.3 (1.1-1.55)	0.002
	Asymmetry of motor symptoms	1.97 (1.23-3.15)	0.005
	Female gender	1.42 (0.97-2.07)	n.s.
	Indication for scanning[1]		0.001
	Re-evaluation of PD diagnosis	3.56 (1.5-8.46)	0.004
	PD or medication related	0.48 (0.24-0.95)	0.036
	Suspected parkinsonism plus[2]	2.34 (0.96-5.7)	n.s.
	PD or essential tremor	0.93 (0.34-2.22)	n.s.
	Suspected PD	1.37 (0.88-2.13)	n.s.

[1]Compared with CUPS, [2]Suspected PSP or suspected MSA. CI = confidence interval, DAT = dopamine transporter, n.s. = not significant, OR = odds ratio.

CUPS (n = 190) and suspected PD (n = 175) were the two most common scanning indications in study II. Other indications for scanning included medication induced parkinsonism (n = 48), re-evaluation of PD diagnosis (n = 39), differentiation between PD and essential tremor (n = 31), suspected LBD (n = 19), suspected PSP (n = 11), suspected MSA (n = 10), suspected parkinsonism plus syndrome (n = 9), suspected vascular parkinsonism (n = 3), akinetic crisis (n = 2) and suspected CBD (n = 2). Indication for scanning was associated with the imaging outcome (table 6, P = 0.001). Re-evaluation of PD diagnosis was independently associated with an abnormal scanning outcome (P = 0.004), whereas suspected drug-induced parkinsonism was independently associated with a normal scanning outcome (P = 0.036) (figure 7).

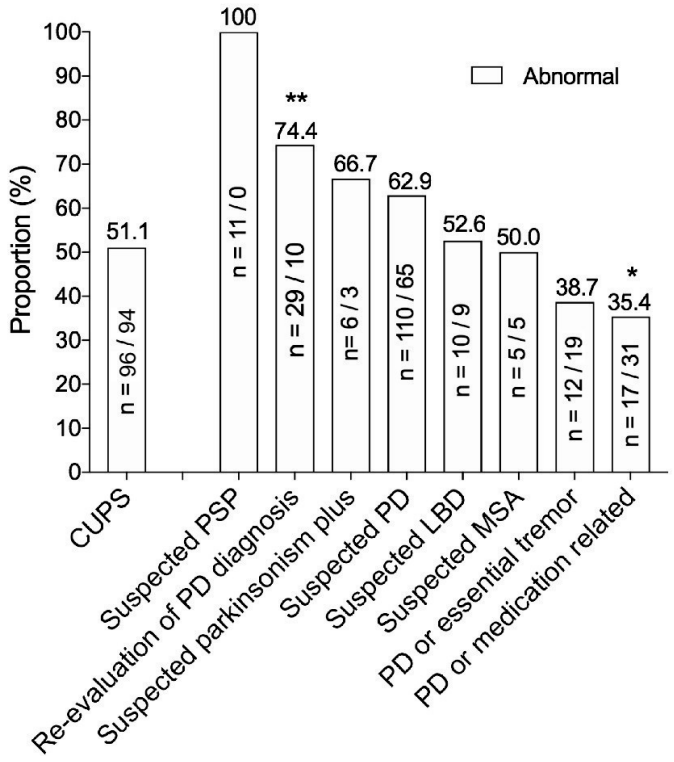

Figure 7. Relative distribution of normal and abnormal imaging outcomes according to the scanning indication (study II) (modified from figure 1 of the original publication). Scanning indication was independently associated with scanning outcome. CUPS was used as a reference category. CUPS = clinically uncertain parkinsonian syndrome, LBD = Lewy body dementia, MSA = multiple system atrophy, PD = Parkinson's disease, PSP = progressive supranuclear palsy. *P < 0.05, **P <0.001.

5.3 Hallucinations and DAT binding in Parkinson's disease (study III)

The patient characteristics for study III and the differences between the patients with or without hallucinations are presented in table 7. The presence of other neuropsychiatric symptoms, which included depression, anxiety or ICDs, did not differ between the two groups at either time point ($P > 0.09$). The patients who subsequently developed hallucinations had a higher Hoehn and Yahr stage at follow-up ($P = 0.03$) but not at baseline ($P = 0.39$) than the patients without hallucinations.

Table 7. Patients characteristics and differences between patients with or without hallucinations (study III) (modified from table 2 of the original publication). Values are mean (SD) or n.

	Patients with hallucinations (n=22)	**Patients without hallucinations (n=48)**	***P* value[1]**
Age (years)	66 (7)	64 (10)	0.49
Gender (m/f)	13/9	27/21	0.82
Duration of follow-up after scan (years)	7.0 (1.7)	6.7 (1.7)	0.39
Symptom duration at scan (years)	1.7 (1)	1.95 (2)	0.52
Predominant side of motor symptoms L/R/S	16/6/0	22/23/3	0.09
H&Y at scan	1.9 (0.8)	1.8 (0.8)	0.39
H&Y at follow-up	3.6 (1.3)	3.0 (1.1)	0.03
LEDD total at scan (mg)	44 (109)	54 (102)	0.73
LEDD DA at scan (mg)	4.3 (27)	6.3 (49)	0.52
LEDD total at follow-up (mg)	664 (235)	683 (300)	0.80
LEDD DA at follow-up (mg)	48 (81)	93 (105)	0.08
Right caudate	1.82 (0.53)	2.02 (0.67)	0.20
Left caudate	1.99 (0.54)	2.12 (0.65)	0.41
Right putamen	1.08 (0.41)	1.33 (0.52)	0.04
Left putamen	1.19 (0.42)	1.34 (0.52)	0.25
Right ventral striatum	1.73 (0.48)	2.12 (0.59)	0.009
Left ventral striatum	1.70 (0.41)	2.04 (0.62)	0.02
Putamen asymmetry index	-0.059 (0.17)	0.0001 (0.19)	0.047

[1]T-test or Chi-Square test for categorical variables. DA = dopamine agonist, f = female, H&Y=Hoehn and Yahr scale, LEDD = levodopa equivalent daily dose, L = left, m = male, R = right, S = symmetrical.

Hallucinations appeared at a median of 4.8 years after the scanning was performed. The type of hallucinations was mainly visual; however, for two patients, the type was not determined. Hallucinations emerged shortly after an increase in the dose or an initiation of dopaminergic medication. The age at the scan, time interval between the scan and the emergence of hallucinations, LEDD at the scan and LEDD at the time when hallucinations occurred are presented in more detail in table 1 of the original publication.

The patients who subsequently developed hallucinations had significantly lower DAT binding in the right putamen (P = 0.04) and the right (P = 0.009) and left ventral striatum (P = 0.02) at the time of scanning than the patients who did not develop hallucinations (table 7, figure 8). Furthermore, the DAT binding in the right amygdala was lower among the patients with hallucinations than among the patients without hallucinations (P = 0.038). There were no differences between the patients with or without hallucinations in DAT binding in the left putamen, right or left caudate, left amygdala or right or left hippocampus. The odds ratio (95 % confidence interval) for a 1.0 decrease in SBR was 3.41 (1.05-11.12) in the right putamen, 4.26 (1.34-13.52) in the right ventral striatum and 3.43 (1.12-10.54) in the left ventral striatum. The patients with hallucinations had a greater putamen asymmetry index than the patients who did not develop hallucinations (P = 0.047). The putamen asymmetry index was calculated as (right – left putamen SBR)/(right + left putamen SBR).

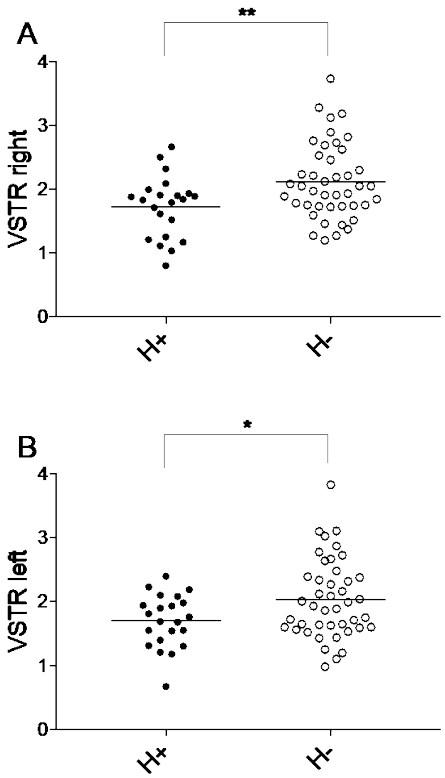

Figure 8. Specific binding ratios of [^{123}I]FP-CIT in the right (A) and left (B) ventral striatum in patients with hallucinations (H+) and patients without hallucinations (H-) (study III) (modified from figure 1 of the original publication). **P < 0.001, *P < 0.05. VSTR = ventral striatum.

In the voxelwise analyses, the patients who developed hallucinations showed lower DAT binding in the ventral and anterior parts of the striatum than the patients without hallucinations (figure 9). The results remained the same after adjusting for covariates (FWE-corrected P = 0.04). There was no correlation between the regional SBRs and the time interval between the scan and the emergence of hallucinations. The difference in the right amygdala DAT binding between the patients with and without hallucinations was not supported by the voxelwise analyses. There were no group differences in the extrastriatal or cortical areas.

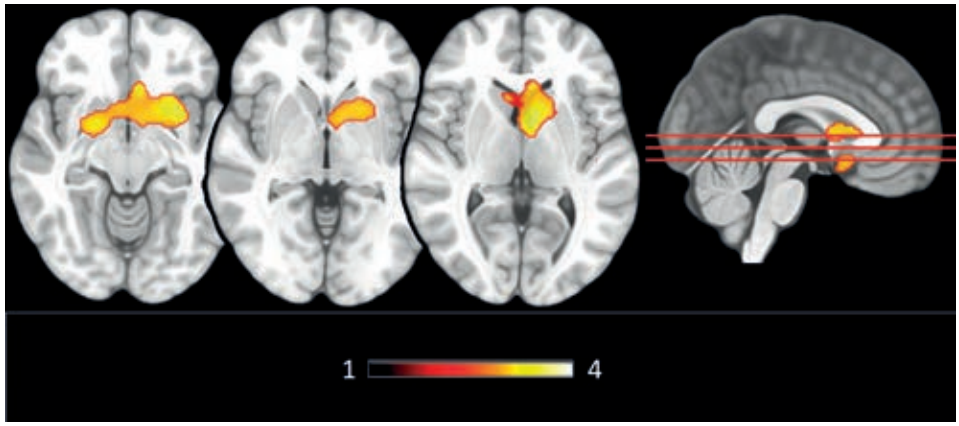

Figure 9. Reduced [^{123}I]FP-CIT binding in patients who developed hallucinations compared to patients who did not develop hallucinations (study III) (modified from figure 2 of the original publication). The cluster with a significant group difference is overlaid on the MNI152 T1 template. The colour bar denotes regional statistical significance. Right side of the image = right side of the brain.

5.4 Comparison of non-motor symptoms between Parkinson's disease and non-degenerative parkinsonism (study IV)

The demographics of the study IV and the differences between the PD patients and the patients with normal DAT binding are presented in table 8. In study IV, there were no significant differences in total NMSS, BDI or BAI scores or the presence of RBD between the PD patients and the patients with nondegenerative parkinsonism (table 8, figure 10). The patients with nondegenerative parkinsonism scored higher in the perception (corrected P = 0.045) and attention/memory (corrected P < 0.001) subscores of the NMSS (table 8). There were no differences in age, gender or motor symptom severity between the two groups (table 8). The non-PD patients

had a longer motor symptom duration than the patients with PD (table 8). However, the NMSS total score and motor symptom duration did not correlate in either group (P > 0.05).

Table 8. Patient characteristics and non-motor symptom scores in PD patients and patients with normal DAT binding (study IV) (modified from table 1 of the original manuscript). Numbers are mean (SD) or n.

	PD (n=84)	**Patients with normal DAT imaging (n=109)**	***P* value[1]**	**Corrected *P* value[2]**
Age (years)	65.3 (9.4)	64.1 (12.1)	0.88	
Gender (male/female)	38/46	57/52	0.33	
Motor symptom duration (months)	30.4 (44.6)	53.0 (68.7)	0.004	
MDS-UPDRS motor score	38.4 (16.1)	35.4 (16.1)	0.21	
H&Y scale	2.0 (0.9)	2.1 (0.8)	0.064	
MMSE score	27.1 (2.4)	26.6 (2.3)	0.052	n.s.
BDI score	8.4 (7.7)	10.1 (9.1)	0.28	n.s.
BAI score	11.1 (6.6)	14.3 (9.3)	0.042	n.s.
RBD (yes/no)	23/57	30/74	0.99	n.s.
NMSS				
Total score	55.5 (46.1)	71.4 (53.4)	0.049	n.s.
Cardiovascular	1.8 (3.3)	3.2 (4.1)	0.013	n.s.
Sleep/fatigue	12.2 (9.9)	12.5 (10.1)	0.86	n.s.
Mood/cognition	11.7 (17.5)	16.9 (21.5)	0.081	n.s.
Perceptional	0.35 (1.6)	0.97 (2.4)	0.005	0.045
Attention/memory	4.4 (6.5)	10.1 (11.0)	<0.001	<0.001
Gastrointestinal	3.5 (4.7)	4.3 (6.7)	0.59	n.s.
Urinary	9.5 (10.3)	8.9 (8.2)	0.70	n.s.
Sexual	3.3 (5.9)	4.8 (6.8)	0.091	n.s.
Miscellaneous	8.3 (7.7)	9.6 (10.3)	0.82	n.s.

[1]T-test or Mann-Whitney U-test as appropriate or Chi-Square test for categorical variables.
[2]Bonferroni-correction for 5 (MMSE, BDI, BAI, RBD, NMSS total score) or 9 (NMSS subscores) comparisons. BAI = Beck anxiety inventory, BDI = Beck depression inventory, DAT=dopamine transporter, H&Y = Hoehn and Yahr scale, MDS-UPDRS=the Movement Disorder Society Unified Parkinson's disease rating scale, MMSE = Mini-mental state examination, NMSS = Non-motor symptoms scale, n.s. = not significant, PD = Parkinson's disease, RBD = REM sleep behaviour disorder.

The NMSS total score in the non-medicated patients did not differ between the PD patients (n=63, NMSS total score mean [SD] = 56.1 [45.7]) and the patients with a normal DAT imaging outcome (n=101, NMSS total score mean [SD] = 72.8 [52.7], corrected P = 0.26) (figure 10). In addition, the PD patients with (n=25, NMSS total score mean [SD] = 54.0 [47.8]) and without antiparkinsonian medication (n=63, NMSS total score mean [SD] = 56.1 [45.7]) had equal NMSS total scores (corrected P = 1.0).

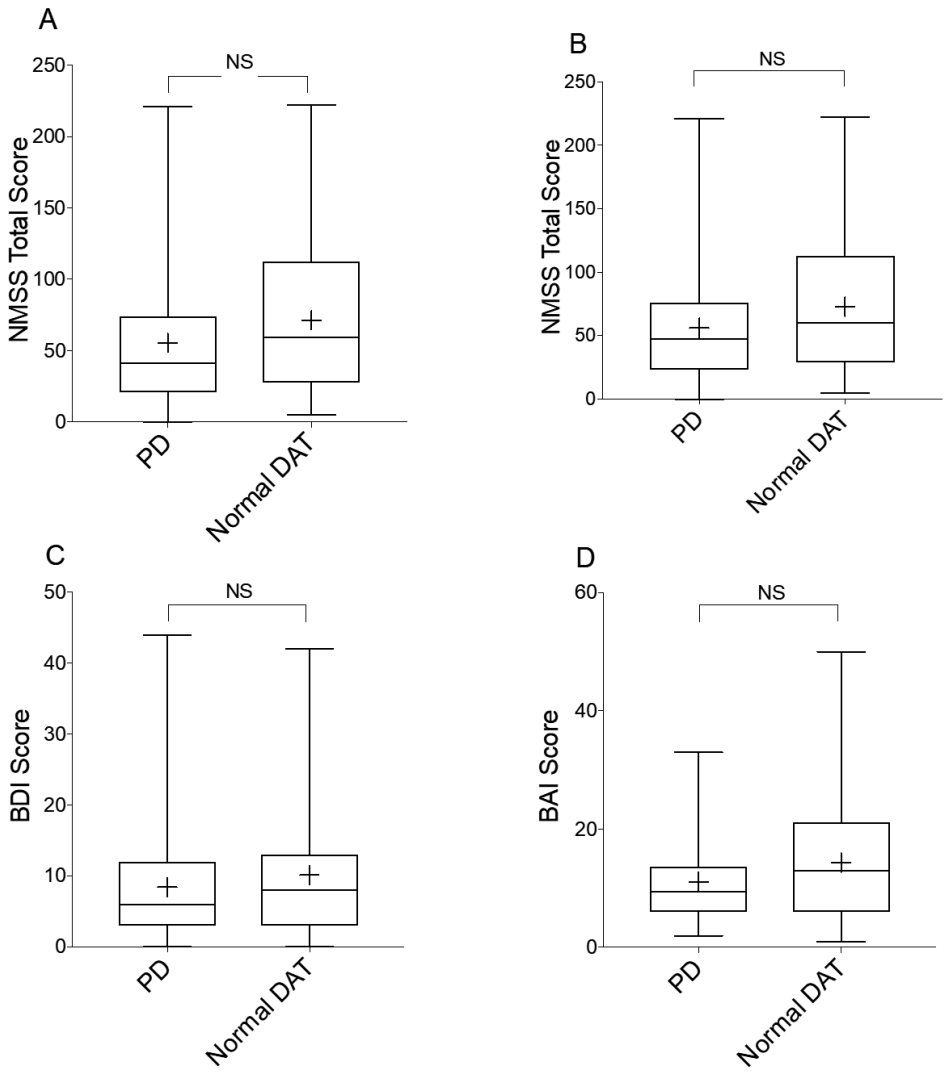

Figure 10. A. NMSS total score in PD patients and patients with normal DAT binding. B. NMSS total score in patients with no dopaminergic medication. C. BDI score and D. BAI score in PD patients and in patients with normal DAT binding (study IV) (modified from figure 1 of the original manuscript). Box plots and whiskers represent the medians, minimums and maximums. ´+' represents the means. BAI = Beck anxiety inventory, BDI = Beck depression inventory, DAT = dopamine transporter, NMSS = Non-motor symptoms scale, NS = not significant, PD = Parkinson's disease.

The striatal SBRs did not correlate with the NMSS total score in the PD patients or in the patients with normal DAT imaging (table 9). The results remained the same after controlling for age, UPDRS motor score and MMSE (table 9). There was a negative correlation between the striatal SBRs and age and a positive correlation between the striatal SBRs and MMSE score in both groups (table 9). The MDS-UPDRS motor score negatively correlated with SBRs in the PD patients (table 9). No associations were identified between SBRs and the NMSS total score in the PD patients in the voxelwise whole-brain analyses.

Table 9. Correlations between mean caudate and putamen DAT binding and age, motor symptom severity, MMSE score and NMSS total score (modified from supplementary table 1 of the original manuscript).

PD patients					
		r^1	P value[1]	r^2	P value[2]
Caudate	Age	-0.65	<0.001	n.a.	n.a.
	Motor MDS-UPDRS	-0.49	<0.001	n.a.	n.a.
	MMSE score	0.28	0.013	n.a.	n.a.
	NMSS total score	-0.14	0.21	0.068	0.57
Putamen	Age	-0.58	<0.001	n.a.	n.a.
	Motor MDS-UPDRS	-0.47	<0.001	n.a.	n.a.
	MMSE score	0.21	0.062	n.a.	n.a.
	NMSS total score	-0.11	0.32	0.085	0.47
Patients with normal DAT binding					
		r^1	P value[1]	r^2	P value[2]
Caudate	Age	-0.39	<0.001	n.a.	n.a.
	Motor MDS-UPDRS	-0.056	0.57	n.a.	n.a.
	MMSE score	0.14	0.14	n.a.	n.a.
	NMSS total score	0.13	0.18	0.037	0.71
Putamen	Age	-0.43	<0.001	n.a.	n.a.
	Motor MDS-UPDRS	-0.12	0.23	n.a.	n.a.
	MMSE score	0.27	0.005	n.a.	n.a.
	NMSS total score	0.11	0.26	0.03	0.77

[1]Spearman correlation, [2]Partial correlation refers to a correlation between DAT binding and NMSS total score while excluding the effects of age, motor symptom severity (motor MDS-UPDRS) and cognitive capacity (MMSE score). DAT = dopamine transporter, MDS-UPDRS=the Movement disorder society Unified Parkinson's disease rating scale, MMSE=Mini-mental state examination, n.a. not applicable, NMSS=Non-motor symptoms scale, PD=Parkinson's disease.

6 DISCUSSION

6.1 Comorbidity of ICDs and other psychiatric disorders in Parkinson's disease

In study I, PD patients with ICDs exhibited higher psychiatric symptom scores, particularly in GSI, depression, psychoticism, obsessive-compulsive symptoms and interpersonal sensitivity, than PD patients without ICDs. Furthermore, impulsiveness among PD patients with ICDs was higher than in PD patients without ICDs. Patients with multiple ICDs had higher scores regarding depression and obsessive-compulsive symptoms than patients with a single ICD.

Only one previous study investigated psychiatric symptoms in PD impulsive-compulsive disorders using the SCL-90. Cabrini *et al* also used the SCL-90 and BIS-11 to compare the psychiatric comorbidity and impulsivity between PD patients with (n=10) and without DDS (n=28) (Cabrini *et al.*, 2009). In line with the study I results, the psychoticism and interpersonal sensitivity scores were higher in PD patients with impulsive-compulsive disorder; however, the researchers did not identify associations between DDS and depression or obsessive-compulsive scores (Cabrini *et al.*, 2009). However, Cabrini *et al* used the DDS-PC inventory for screening DDS in PD, whereas a validated questionnaire, the QUIP, was used in study I. Thus, the definition for ICD-positive patients differed between the two studies. Moreover, in the study by Cabrini *et al*, LEDD was higher in patients with DDS than in those without DDS, whereas in study I, there were no differences in dopaminergic medication between ICD-positive and ICD-negative patients. This difference in medication dose may have an influence on depression symptoms, as dopamine agonists may improve PD depression (Barone *et al.*, 2010). Importantly, the sample size in study I (n=290) was considerably larger than that in the study by Cabrini *et al* (n=38), increasing the power of the study.

6.1.1 ICDs and depression

Consistent with previous studies, PD patients with ICDs showed higher depression scores than patients without ICDs (Isaias *et al.*, 2008; Voon *et al.*, 2011; Joutsa *et al.*, 2012c; Antonini *et al.*, 2017; Hinkle *et al.*, 2018; Terenzi *et al.*, 2018); however, not all studies have confirmed these findings (Vitale *et al.*, 2011). Depression, as well as anxiety, may be more prevalent in PD patients with pathological gambling than PD patients with non-specific ICDs (Pontieri *et al.*, 2015). In the longitudinal study by Joutsa *et al.,* PD patients who developed ICDs during the

follow-up had higher BDI scores at follow-up than the baseline (Joutsa *et al.*, 2012b). These findings suggest that depression in PD ICDs could be a behavioural response to harmful life events rather than a factor that predisposes to the development of ICDs. However, depression may also be a predisposing factor to the development of ICDs (Voon *et al.*, 2011). Although dopamine agonists may trigger ICDs (Weintraub *et al.*, 2010), they may improve PD depression (Barone *et al.*, 2010), which suggests an opposing neural mechanism in terms of dopamine neurotransmission. In our study, dopamine agonist use was associated with lower depression scores but did not differ between patients with and without ICDs.

Limbic basal ganglia-thalamocortical circuits are important in motivation and reward processes. PD depression is presumed to originate, at least in part, from brain dopaminergic hypoactivity (Thobois *et al.*, 2017), which results in relative hyperactivity of the indirect pathway of the limbic circuit, thus leading to increased inhibition that contributes to the symptoms of depression. In PD ICDs, dopamine agonists presumably overstimulate D3 dopamine receptors in the ventral striatum, leading to decreased indirect and increased direct pathway activity in the limbic basal ganglia -thalamocortical circuits, thus causing increased responsivity in the reward system (Vriend *et al.*, 2014b). The pathophysiology of PD depression and the pathophysiology of PD ICDs seem to be somewhat shared but are also in opposition to one another. One explanation is that depression and ICDs occur in a fluctuating manner throughout the day or that other neurotransmitter systems apart from dopamine have a similar role in these two entities (Vriend *et al.*, 2014b). Nevertheless, ICDs and depression often co-occur in PD.

6.1.2 Comorbidity of ICDs with anxiety, obsessive-compulsive symptoms and interpersonal sensitivity

Anxiety has been linked to ICDs in PD (Voon *et al.*, 2011; Hurt *et al.*, 2014; Ricciardi *et al.*, 2018). In study I, ICDs were not associated with symptoms of anxiety. However, obsessive-compulsive symptoms, which have previously been defined as anxiety disorders (Diagnostic and Statistical Manual of Mental Disorders (DSM) IV), were more prevalent in PD patients with ICDs than in patients without ICDs.

Obsessive-compulsive disorder (OCD) is characterized by repetitive actions, such as checking or washing hands, which aim to lessen anxiety. The higher prevalence of obsessive-compulsive symptoms in PD ICD patients identified in study I was also noted in the large multicentre study by Voon *et al* (Voon *et al.*, 2011). However, the results are not directly supported by the study of Isaias *et al* even though they determined that obsessive-compulsive symptoms were more common in PD

patients than in healthy controls (Isaias *et al.*, 2008). ICDs and obsessive-compulsive symptoms share some similar symptomology in that the behaviours are repetitive and cannot be controlled, which may explain the comorbidity of these two phenomena based on self-reported assessment. However, ICDs and obsessive-compulsive behaviours are clearly different in that ICDs are associated with increased reward seeking (Ceravolo *et al.*, 2009), whereas obsessive-compulsive behaviour aims to alleviate anxiety (Hirschtritt *et al.*, 2017). Moreover, obsessive-compulsive symptoms are related to compulsivity more than impulsivity in young adults (Chamberlain *et al.*, 2016). In study I, more severe obsessive-compulsive symptoms were associated with a lower use of dopamine agonists, an opposite finding compared to the association with ICDs, which are often related to greater dopamine agonist use.

Interpersonal sensitivity, which reflects inadequate and inferior feelings compared to other individuals, was more severe in PD patients with ICDs than patients without ICDs in study I. One explanation may be that interpersonal sensitivity is related to the shame related to ICDs. A younger age at PD onset and more advanced disease were also associated with interpersonal sensitivity; thus, interpersonal sensitivity scores may be higher among patients with more disabling disease.

6.1.3 ICDs and psychoticism

PD patients with ICDs showed higher scores on the SCL-90 psychoticism dimension, and ICDs predicted psychoticism even more than PD duration or dopamine agonist medication. Another study reported increased psychotic symptoms in PD patients with non-specific ICDs compared to PD patients with pathological gambling or no ICDs (Pontieri *et al.*, 2015). In a large cross-sectional study by Hinkle *et* al (n=654), PD psychoticism was independently associated with ICDs and DDS (Hinkle *et al.*, 2018). Although an association between ICDs and psychotic symptoms has been shown in several studies (Cabrini *et al.*, 2009; Hinkle *et al.*, 2018), the results are not consistent (Verbaan *et al.*, 2009). In PD, ICDs and psychosis are both often related to dopaminergic treatment, particularly dopamine agonists (Weintraub *et al.*, 2010; Ffytche & Aarsland, 2017), which may be mediated by an overstimulation of dopamine D3 receptors in the limbic areas. This relationship may explain the coexistence of these two phenomena. Furthermore, both ICDs and PD hallucinations have been associated with lowered ventral striatal DAT levels (Vriend *et al.*, 2014a,study III), and more severe autonomic dysfunction predicts the development of both ICDs (Ricciardi *et al.*, 2018) and psychosis in PD (Barrett *et al.*, 2018). Guedes *et al* presented an interesting case report of a PD patient who suffered from both PD psychosis and ICDs. The symptoms were alleviated after

discontinuing dopamine agonist treatment and initiating quetiapine (Guedes *et al.*, 2016). However, in study I, dopamine agonist use was negatively correlated with the SCL-90 psychoticism score. This relationship might be explained with the finding that some patients had discontinued the use of dopamine agonists because of side effects, including psychotic symptoms.

6.1.4 ICDs and impulsivity

Attentional and non-planning impulsivity were more severe in PD patients with ICDs than in non-ICD patients in study I. There were no differences in motor impulsivity, which may be explained by the number of tests used in the study and the conservative statistical approach in which a Bonferroni correction was applied to correct for multiple comparisons. Impulsivity in PD ICD patients seems to be higher than in patients without ICDs (Isaias *et al.*, 2008; Cabrini *et al.*, 2009; Antonini *et al.*, 2011; Voon *et al.*, 2011). Isaias *et al* confirmed these findings in non-PD patients (Isaias *et al.*, 2008), and Antonini *et al* determined that greater attentional impulsivity was also related to PD ICDs in patients with no antiparkinsonian medication use (Antonini *et al.*, 2011). As high premorbid impulsivity may be a risk factor for the development of drug-induced ICDs in PD (Poletti & Bonuccelli, 2012), the initiation of dopamine agonists for patients with high impulsivity scores is not advisable.

6.1.5 Psychiatric comorbidity in single versus multiple ICDs

Study I showed that PD patients with multiple ICDs had higher scores in depression and obsessive-compulsive symptoms than patients with a single ICD. Moreover, Wu *et al* reported that PD patients with multiple ICDs had more depression than PD patients with a single ICD (Wu *et al.*, 2015). However, these results are not in line with the study of Voon *et al*, in which the psychiatric burden was similar regardless of the amount of ICDs (Voon *et al.*, 2011); thus, further studies are required.

6.1.6 Strengths and limitations

The strengths of study I included the large sample size and the use of validated and widely used questionnaires. It should be noted that although ICDs were screened using the QUIP, the QUIP is not a diagnostic instrument and is likely to overestimate the prevalence of ICDs. Furthermore, the SCL-90 is not validated for PD;

however, a number of previous PD studies have used the SCL-90 (Siri *et al.*, 2010; Bugalho *et al.*, 2012; Carrozzino *et al.*, 2018). Although the SCL-90 is a valid tool for screening psychiatric symptoms, it is a self-report questionnaire, and interviews required for formal psychiatric diagnoses were lacking. Furthermore, although the study was based on a postal survey, patients with better motivation and a possibly better physical and/or mental condition might have been more likely to respond. Finally, we were not able to clinically confirm the PD diagnoses, which indicates that there was a possibility that the sample included patients with incorrect clinical diagnoses. However, practically all PD diagnoses are confirmed by board certified neurologists, which is a requirement for medication reimbursement and other benefits. Finally, the study provided no information regarding causality, i.e., whether the psychiatric symptoms are predicting factors in the development of ICDs or *vice versa,* which could only be investigated in a longitudinal study design.

6.2 Factors that predict DAT imaging outcome

In study II, patients with an older age, shorter motor symptom duration and asymmetrical motor symptoms were likely to have an abnormal DAT imaging outcome. Moreover, patients with PD diagnosis confirmation as a scanning indication were more likely to have an abnormal scanning outcome, whereas the suspicion of medication induced parkinsonism was related to normal scans. Although the necessity for scanning should always be considered individually for each patient, these factors should be taken account when making decisions regarding which patients benefit from diagnostic DAT imaging to avoid unnecessary scanning. For example, patients with a relatively short motor symptom duration and typical progressive and asymmetrical symptoms will not likely gain from DAT imaging, as the PD diagnosis is quite clear.

6.2.1 Effects of age and gender in DAT imaging outcome

FP-CIT binding negatively correlates with age in both healthy individuals and patients with PD (Varrone *et al.*, 2013; Kaasinen *et al.*, 2015a). However, age-correction is applied in the reference values of the automated semi-quantitative SBR calculations. Thus, the physiological reduction of the DAT with age does not explain the finding that older patients were more likely to have an abnormal DAT imaging outcome in study II. As age is the most important risk factor for PD (Collier *et al.*, 2011), older patients are expected to be more likely to have a neurodegenerative disease and an abnormal imaging outcome, as observed in the present study II.

Although the DAT density is lower in males than in females (Varrone *et al.*, 2013; Kaasinen *et al.*, 2014), gender did not have an influence on the scanning outcome in study II.

6.2.2 Relationship between motor symptoms and DAT imaging outcome

In addition to older age, a shorter symptom duration predicted an abnormal DAT imaging outcome in study II. Patient selection likely influences these results; patients with a long history of unclear motor symptoms may be scanned to exclude degenerative disease. Furthermore, as PD is a progressive disease, patients with a longer symptom duration rarely require imaging as the diagnosis becomes clear during the follow-up.

Patients with asymmetric motor symptoms more likely exhibited abnormal scans. Early stage PD is typically asymmetric; thus, the results were expected (Djaldetti *et al.*, 2006). Although the atypical parkinsonian syndromes MSA and PSP are more symmetrical (Colosimo *et al.*, 1995; Seppi *et al.*, 2006), PD is substantially more common.

PD patients with tremor appear to show higher DAT levels in the caudate nucleus than PD patients without tremor (Kaasinen *et al.*, 2014); however, the presence of tremor did not influence the scanning outcome in Study II.

6.2.3 Scanning indications predicting the outcome of DAT imaging

Unofficial scanning indications for DAT imaging in clinical practise seem to be substantially broader than the official FDA- and EMA-approved indications (Thiriez *et al.*, 2015). Study II is in line with that while only 9.3 % of patients were scanned for official indications (differentiation between PD and essential tremor or differentiation between Lewy body dementia and Alzheimer's disease). However, as several patients were scanned for clinically uncertain parkinsonian syndrome (CUPS) (n = 190), these patients might have had the official scanning indications, while the indications were obtained from the hospital records and indication was defined as CUPS if the diagnostic question was not clear.

Re-evaluation of PD was associated with an abnormal scanning outcome, and suspected drug-induced parkinsonism was associated with a normal scanning outcome.

Drug-induced parkinsonism results from the blockage of dopamine D2 receptors by antipsychotic drugs (Shin & Chung, 2012), potentially leading to parkinsonism that is mostly symmetrical. The clinical differentiation between PD and medication-induced parkinsonism might be difficult (Brigo *et al.*, 2014). According to study II, patients with suspected drug-induced parkinsonism tend to have a normal scanning outcome, and symmetrical motor symptoms are associated with a normal scanning outcome. As drug-induced parkinsonism should improve in six months after the withdrawal of the predisposing agent (Brigo *et al.*, 2014), the scanning of patients with symmetrical symptoms and suspected drug-induced parkinsonism may be speculated to only need to be performed after withdrawal.

6.2.4 Limitations

Although the results of study II suggest that certain factors could predict the scanning outcome and unnecessary imaging could thus be avoided, the study was unable to evaluate the clinical value of the scans as there were no data concerning the clinicians' evaluation. Furthermore, the retrospective study protocol did not enable clinical examination of the patients.

6.3 Hallucinations and brain DAT imaging in Parkinson's disease

In study III, PD patients who subsequently developed hallucinations showed lower DAT density in the bilateral ventral striatum and right putamen than patients without hallucinations. These findings increased knowledge regarding the neurobiology of PD hallucinations and may aid in the identification of patients who are at risk for developing hallucinations.

6.3.1 Hallucinations and striatal DAT in Parkinson's disease

Schizophrenia, particularly its positive symptoms, has been thought to be a consequence of mesolimbic dopaminergic hyperactivity, which is supported by the results of study III concerning ventral striatal involvement in the genesis of visual hallucinations (Davis *et al.*, 1991; Howes & Murray, 2014). However, in a recent meta-analysis, McCutcheon *et al* determined that patients with schizophrenia have increased presynaptic dopaminergic function in the dorsal (associative and sensorimotor) rather than limbic striatum (McCutcheon *et al.*, 2017). Moreover, studies of PD patients with psychotic symptoms have shown associations between psychotic symptoms and atrophy in limbic brain areas (Ibarretxe-Bilbao *et al.*, 2010;

Gama *et al.*, 2014; Goldman *et al.*, 2014). Ventral striatal DAT deficiency among patients who developed visual hallucinations in study III may have led to the up-regulation of dopaminergic receptors. This theory should be verified using postsynaptic dopamine receptor imaging. Greater D2/3 receptor levels in the ventral striatum have been identified in patients with schizophrenia (Kessler *et al.*, 2009). Furthermore, a lower DAT density, while reflecting more severe degeneration, may be associated with hypersensitivity of postsynaptic dopaminergic receptors.

The right putamen DAT density was lower in PD patients who subsequently developed hallucinations in study III. A right-sided DAT deficit was also identified by Kiferle *et al*, who reported that the right caudate DAT density was lower in PD patients with visual hallucinations than in patients without visual hallucinations (Kiferle *et al.*, 2014). A right caudate DAT deficit was also identified in PD patients with mild cognitive impairment (Ekman *et al.*, 2012). Dementia and psychotic symptoms often coexist in PD in the later disease stages (Schapira *et al.*, 2017) and may thus be localized to the right hemisphere.

In line with the results of study III regarding the right putamen, Ravina *et al* found that PD patients with lower baseline striatal DAT binding had a higher risk for developing psychotic symptoms in a 5-6-year follow-up ([^{123}I]β-CIT SPECT study) (Ravina *et al.*, 2012). This observation may also be an indirect association, as the lowered striatal DAT was associated with several other motor and non-motor symptoms. Furthermore, lowered striatal DAT might also be associated with more severe degeneration in other brain areas. Although psychotic symptoms in PD have been associated with multiple brain region atrophy (Lenka *et al.*, 2015), the pathology of extrastriatal brain areas may explain the genesis of psychosis. Moreover, it should be noted that Ravina *et al* focused on the caudate and putamen and did not investigate the ventral striatal areas.

6.3.2 Hallucinations and extrastriatal DAT in Parkinson's disease

Serotonergic dysfunction has been associated with PD psychosis (Valli *et al.*, 2017). Kiferle *et al* and our group did not identify an association between PD hallucinations and extrastriatal FP-CIT binding (which refers to SERT levels) (Kiferle *et al.*, 2014). These results highlight the role of the striatal dopamine system in the genesis of PD hallucinations. However, it should be noted that the signal-to-noise ratio of [^{123}I]FP-CIT SPECT is not optimal for assessing the extrastriatal areas; thus, the evaluation of serotonergic dysfunction according to these findings is not fully reliable.

6.3.3 Hallucinations and dopaminergic treatment in Parkinson's disease

The hallucinations in study III were mainly associated with dopaminergic medication initiation or a dosage increase. Dopaminergic medication has been postulated to cause hyperstimulation of the mesolimbic dopaminergic pathway (from the VTA to the ventral striatum) and thus induce hallucinations (Wolters, 1999). The control group in study III was matched, and there were no differences in the dopaminergic medication between the two groups at scan or follow-up. Thus, the findings cannot be attributed to higher dopaminergic medication doses. Furthermore, not all PD patients with hallucinations have used dopaminergic medication (Dotchin *et al.*, 2009; Pagonabarraga *et al.*, 2016), and in general, PD psychosis is not associated with the dosage or duration of dopaminergic treatment (Goetz *et al.*, 2011; de la Riva *et al.*, 2014). A subgroup of PD patients is seemingly more vulnerable to the development of medication-induced hallucinations (Ffytche *et al.*, 2017), which may be explained, at least in part, by differences in the underlying brain dopamine function.

6.3.4 Hallucinations and motor symptoms in Parkinson's disease

PD patients with hallucinations had more severe motor symptoms at follow-up but not at baseline than PD patients without hallucinations. This finding is in line with previous studies (Fénelon *et al.*, 2000; de Maindreville *et al.*, 2005), although the predictive value of striatal DAT density in motor symptom progression is not clear (Hubbuch *et al.*, 2011). More severe motor symptom progression in hallucinating PD patients is consistent with the finding that hallucinations are associated with more advanced PD (Ffytche & Aarsland, 2017).

A greater putamen asymmetry index was identified in PD patients with hallucinations in study III. Interestingly, a greater striatal asymmetry index has been associated with a better L-dopa response in PD (DAT SPECT study) (Contrafatto *et al.*, 2011). Thus, patients with a more severe striatal asymmetry may be speculated to be more sensitive to dopaminergic medication and therefore also to medication-induced complications, such as hallucinations.

6.3.5 Limitations

It is important to note that DAT deficiency is also associated with multiple other motor and non-motor manifestations in PD (Benamer *et al.*, 2000; Qamar *et al.*,

2017), and the predictive value of DAT deficiency for the development of hallucinations should be investigated in a separate study. Furthermore, PD patients with hallucinations did not have confirmed diagnoses of PD psychosis; however, the development of hallucinations was based on the information in the hospital records by their treating neurologists. Finally, follow-up scans from the patients would have been valuable to analyse potential changes in DAT binding.

6.4 Total burden of non-motor symptoms in Parkinson's disease and parkinsonism patients with normal brain DAT function

In study IV, the total NMS burden was similar in PD patients and parkinsonism patients with normal brain dopamine function. Although the motor symptom severity assessed with the MDS-UPDRS motor score was associated with striatal DAT binding in PD patients, NMSs did not correlate with striatal SBRs. These results highlight the substantial burden of NMSs in parkinsonism patients with normal brain dopamine function; thus, the total burden of NMSs may not differentiate early PD from nondegenerative parkinsonism.

6.4.1 Non-motor symptom burden in Parkinson's disease versus *patients with nondegenerative parkinsonism*

PD patients have more NMSs than healthy controls (Bago Rožanković *et al.*, 2017; Marinus *et al.*, 2018; Simuni *et al.*, 2018a). When 71 *de novo* PD patients were compared to 60 healthy controls, PD patients had a higher NMSS total score and cardiovascular, sleep/fatigue, mood/cognition, perception, attention/memory and miscellaneous subscores (Bago Rožanković *et al.*, 2017). Simuni and colleagues assessed PD patients and healthy controls from the Parkinson's Progress Initiative Markers (PPMI) cohort at baseline and a two year follow-up (Simuni *et al.*, 2018a). PD patients had a greater increase of NMSs during the follow-up than healthy controls.

When NMSs of PD patients are compared to other parkinsonism patients, the results are not as clear. The control group in study IV reflects real clinical circumstances when patients with unclear parkinsonism/tremor symptoms are scanned, and studies concerning the NMSs of these patients are lacking.

There are patients with suspected PD whose DAT binding is normal. These scans are often referred to as SWEDDs (scans without evidence of dopaminergic deficit) in the literature (Erro *et al.*, 2016), and the patients with SWEDDs likely have a diagnosis other than PD, as the scanning outcome remains normal after follow-up

in most cases (Marek *et al.*, 2014). Thus, the control group in study IV may theoretically be considered SWEDDs, although the patients did not have clinical PD diagnoses, as was the case when SWEDDs were first described.

The results regarding NMSs between PD patients and patients with SWEDDs are controversial. Taylor and colleagues have investigated PD and SWEDD patients from the PPMI cohort and determined that the NMSs between these two groups were similar with the exception of hyposmia. However, Sprenger and colleagues assessed PD patients and patients with SWEDDs from the PPMI cohort and determined that the NMS burden among patients with SWEDDs was higher than in PD, again with the exception of hyposmia (Sprenger *et al.*, 2015). Moreover, patients with essential tremor have less hyposmia than PD patients (Giorelli *et al.*, 2014; Kwon *et al.*, 2016). In study IV, there were no differences in olfaction dysfunction between PD and nondegenerative parkinsonism patients. However, Taylor *et al* and Sprenger *et al* used the UPSIT to measure hyposmia (Sprenger *et al.*, 2015; Taylor *et al.*, 2016), whereas hyposmia was measured with the NMSS olfaction/taste question in study IV, which takes into account taste in addition to olfaction, and the question does not differentiate if the sense is worsened or improved. Studies suggest that PD patients suffer from more NMSs than patients with SWEDDs (Schwingenschuh *et al.*, 2010; Yang *et al.*, 2014). However, these studies had low numbers of PD patients ($n < 30$). Many PD patients in study IV were at an early disease stage, and although the NMS burden in PD increases as PD progresses, the NMSs of SWEDDs tend to remain the same (Taylor *et al.*, 2016; Simuni *et al.*, 2018a). These findings support the unspecificity of NMSs in early parkinsonism patients.

RBD is recognized as a premotor symptom of PD (Liu *et al.*, 2017b). Although the prevalence of RBD in the general population is less than 1 %, RBD may affect 25-50 % of patients with alpha-synucleinopathies, such as PD (Bassetti & Bargiotas, 2018). In study IV, PD patients did not have RBD more than patients with normal DAT binding. Similar results were obtained in the study of Taylor and colleagues that compared PD patients and patients with SWEDDs (Taylor *et al.*, 2016). Although a single question screen for RBD is a sensitive screening instrument, it is not as reliable as a diagnostic polysomnogram (Liu *et al.*, 2017b).

The NMSS perception score was higher in patients with normal DAT binding than in PD patients in study IV. Delusions are often not declared to health professionals in clinical practice (Chaudhuri *et al.*, 2010); thus, the presence of these symptoms may be underestimated using an interview-based questionnaire. Perception symptoms often develop in the later PD stages (Ffytche & Aarsland, 2017), and study IV assessed early PD patients, which may have decreased the amount of perception symptoms.

The attention/memory subscore was also higher in patients with normal DAT binding than the score in PD patients. However, the MMSE score did not differ between the two groups. The result regarding attention/memory should be replicated in future studies.

6.4.2 Striatal DAT binding and non-motor symptoms in Parkinson's disease

In line with previous studies, the UPDRS motor score correlated with striatal SBRs in PD patients, and age correlated with striatal SBRs in both groups in study IV (Varrone *et al.*, 2013; Kaasinen & Vahlberg, 2017). However, the NMSS total score in study IV did not correlate with striatal SBRs in PD patients or patients with normal DAT binding. These results remained the same after controlling for the MDS-UPDRS motor score, age and MMSE score. In accordance with the results of study IV, Simuni and colleagues did not identify an association between DAT binding (FP-CIT SPECT) and NMSs at baseline or NMS progression at the two-year follow-up (Simuni *et al.*, 2018a). Dopamine is currently thought to play at least some role in multiple NMSs (Qamar *et al.*, 2017), but neurotransmitters other than dopamine are also involved in the genesis of NMSs (Schapira *et al.*, 2017). In any case, the total NMS burden in PD seems to be unrelated to the severity of the dopamine deficiency. This finding is supported by the study of Chung and colleagues who compared PD patients with low and high measures of NMSs and determined that the striatal DAT density was not associated with NMS burden (Chung *et al.*, 2016b). Moreover, the NMSS total score is a heterogeneous score, which consists of multiple separate NMSs (frequency x severity) with likely distinct pathophysiologies.

6.4.3 Limitations

There are several limitations in study IV. First, although NMSs were assessed using validated questionnaires, the formal diagnoses were lacking. In particular, the results regarding hyposmia should be considered with caution, as hyposmia was evaluated with NMSS question 28, which is unspecific for hyposmia. Furthermore, an RBD diagnosis would require confirmation with polysomnography. Second, PD patients had a shorter motor symptom duration than patients with normal DAT binding. The same finding was obtained in study II with a different sample of patients (refer to 6.2). Importantly, the motor symptom duration and NMSS total score did not correlate in either group. Third, the PD group in study IV consisted of patients who had clinically uncertain PD prior to the scan that confirmed the diagnosis; thus, this patient group may not represent typical PD. Furthermore, the

control group consisted of a heterogeneous group of patients with parkinsonism and normal brain DAT binding. Nevertheless, this aspect should be considered a strength of the study, as the PD and control groups represent patients in real clinical circumstances.

6.5 SUMMARY

Study I shows that PD patients with ICDs are more impulsive and suffer from multiple psychiatric symptoms, including depression, psychoticism, obsessive-compulsive symptoms and interpersonal sensitivity, compared to other PD patients. Clinicians should take this into account and remember to evaluate the psychiatric comorbidity of PD ICD patients. ICDs and other psychiatric symptoms have a negative influence on the quality of life of a patient (Martinez-Martin *et al.*, 2011; Antonini *et al.*, 2017), thus emphasizing the importance of early recognition and treatment.

In studies II-IV, DAT imaging was used to evaluate the clinical manifestations associated with brain DAT binding. Study II showed that older patients with a shorter motor symptom duration and asymmetrical motor symptoms were more likely to have an abnormal DAT imaging outcome. A longer motor symptom duration among patients with a normal DAT imaging outcome was confirmed in study IV. In study IV, PD patients did not show a difference in the total burden of NMSs compared to non-PD patients with parkinsonism, which suggests that in clinically uncertain parkinsonism, the total NMS burden may not be useful in differentiating PD patients from patients with an intact brain dopamine system.

Patients with decreased striatal DAT binding, particularly in the limbic parts of the striatum, are more vulnerable to developing hallucinations (study III). These findings may help to identify patients who are at a greater risk to develop psychotic symptoms in response to dopamine treatment in the future. However, further validation of the findings and new imaging-based tools may be required before converting these findings into clinical practice.

Dopamine is a key neurotransmitter in PD, and motor symptoms are thought to arise from striatal dopamine depletion (Kalia & Lang, 2015). Dopamine also has a less crucial role in the genesis of PD NMSs (Qamar *et al.*, 2017), but this role has not been fully elucidated. According to the data presented in this thesis, the NMS total burden does not seem to be correlated with striatal DAT in early PD.

To conclude, PD ICDs are associated with increased psychiatric comorbidity. Specific factors, such as age and motor symptom duration, predict DAT imaging outcome. A lower striatal DAT may predispose PD patients to the genesis of hallucinations. A better understanding of the pathophysiology and the dopaminergic basis of PD NMSs is vital, and further studies are required. NMSs in PD should be recognized early and carefully treated to improve the patient care and prevent the worsening of these symptoms.

7 CONCLUSIONS

I PD patients with ICDs suffer from multiple comorbid neuropsychiatric symptoms, including depression, psychoticism, obsessive-compulsive symptoms and interpersonal sensitivity. Acknowledging the high neuropsychiatric comorbidity is important in the clinical care of these patients.

II An older age, shorter motor symptom duration and asymmetry of motor symptoms predict an abnormal DAT imaging outcome. As DAT imaging is expensive and associated with ionizing radiation and its availability is limited, which patients benefit from the imaging must be carefully evaluated. Although clinical decisions should always be made at the individual level, these factors may be helpful in determining the necessity of DAT imaging in clinical practice.

III PD patients who subsequently develop hallucinations show lower DAT binding in the bilateral ventral striatum than PD patients without hallucinations. This finding indicates that some PD patients have a limbic dopaminergic abnormality that predisposes them to the development of psychotic symptoms, particularly in association with dopaminergic medications.

IV Although NMSs are common in PD, parkinsonism patients with normal brain dopamine function seem to also suffer from multiple NMSs. Moreover, in contrast to motor function, the total NMS burden in PD patients is not correlated with striatal DAT density. Thus, PD cannot be differentiated from other causes of parkinsonism purely according to the total NMS burden.

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