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ABSTRACT

Parkinson's disease is a common neurodegenerative movement disorder. The cardinal motor symptoms of Parkinson's disease include bradykinesia, rigidity and rest tremor. The association between rest tremor and nigrostriatal degeneration has remained unclear. Parkinson's disease is also often associated with non-motor symptoms including cognitive and mood problems, with unclear mechanisms despite increased research efforts over the past decades. Dopamine transporter single-photon emission tomography is the most common molecular imaging method used in the diagnostics of Parkinson's disease. The results of this imaging method reflect the monoamine transporter density in brain areas. [^{123}I]FP-CIT, the most commonly used tracer in this context, enables investigating not only dopaminergic but also serotonergic and noradrenergic function.

In this thesis, I explore the association of monoaminergic function with the motor, cognitive and behavioral symptoms of Parkinson's disease as well as the abnormalities in bodily sensations of emotions in the disease. Monoaminergic function and the symptoms of Parkinson's were investigated using the largest available follow-up data of patients with Parkinson's disease, the Parkinson's Progression Markers Initiative. The bodily sensations associated with emotions were studied using a relatively recently developed bodily mapping technique, emBODY.

The results of this thesis show that rest tremor amplitude is associated with increased ipsilateral striatal dopamine transporter availability. In addition, depression seems to be associated with abnormalities in dopamine and serotonin, anxiety with abnormalities in serotonin and noradrenaline, and REM sleep behavior disorder mainly with abnormalities in dopamine function. The emBODY results suggest abnormal bodily sensations of emotions in Parkinson's disease: anger-related sensations on the chest were lesser in Parkinson's disease than among control subjects, and longer disease duration was associated with a shift towards the abdomen. The results provide new insights to the neural mechanisms of both motor and non-motor symptoms in Parkinson's disease, and reveal a new non-motor phenomenon, with each finding having potential future clinical implications.

KEYWORDS: Parkinson's disease, SPECT, rest tremor, depression, anxiety, dopamine transporter, serotonin, noradrenaline, brain network

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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TIIVISTELMÄ

Parkinsonin tauti on yleinen keskushermostorappeumasta aiheutuva liikehäiriösairaus. Taudin motorisia johto-oireita ovat liikkeiden hitaus, jäykkyys, ja lepovapina. Näistä oireista lepovapinan yhteys mustatumake-tyvitumake -järjestelmän rappeutumiseen on kuitenkin jäänyt epäselväksi. Parkinsonin tautiin liittyy usein myös ei-motorisia oireita, kuten kognitio- ja mielialaongelmia, joiden mekanismit ovat edelleen epäselviä viime vuosikymmenten aikana lisääntyneestä tutkimuksesta huolimatta. Dopamiinikuljettajaproteiinien yksifotoniemissio-tietokonetomografia on Parkinsonin taudin diagnostiikassa yleisimmin käytetty isotooppi-kuvantamismenetelmä. Sen tulokset kuvaavat aivoalueiden monoamiinikuljettajaproteiinitiheyttä. [^{123}I]FP-CIT, tässä tavanomaisimmin käytetty merkkiaine, mahdollistaa paitsi aivojen dopamiini-, myös serotoniini- ja noradrenaliinitoiminnan tutkimisen.

Tässä väitöskirjatutkimuksessa tutkittiin Parkinsonin taudin motoristen johto-oireiden ja neuropsykiatristen ei-motoristen oireiden yhteyttä monoamiini-kuljettajaproteiinitoimintaan, sekä Parkinsonin taudissa ilmeneviä muutoksia tunteisiin liittyvissä kehollisissa tuntemuksissa. Monoamiinitoiminnan ja Parkinsonin taudin oireiden välistä yhteyttä tutkittiin suurimmassa, avoimesti saatavilla olevassa seuranta-aineistossa (Parkinson's Progression Markers Initiative). Tunteisiin liittyvien kehollisten tuntemusten poikkeavuuksia tutkittiin käyttäen suhteellisen hiljan kehitettyä emBODY-kehokarttamenetelmää.

Tulokset osoittivat, että lepovapinan laajuus liittyy Parkinsonin tautia sairastavilla samanpuoleisen aivojuovion lisääntyneeseen dopamiinikuljettaja-proteiinin pitoisuuteen. Lisäksi todettiin, että Parkinsonin taudin masennus vaikuttaisi liittyvän dopamiini- ja serotoniinijärjestelmän, ahdistus serotoniini- ja noradrenaliinijärjestelmän, ja REM-unihäiriö ensisijaisesti dopamiinijärjestelmän poikkeavuuksiin. Kehokarttamenetelmän tulokset viittasivat siihen, että Parkinsonin tautia sairastavilla tunteisiin liittyvät keholliset tuntemukset ovat poikkeavat: vihaan liittyvät tuntemukset rintakehän alueella ovat heikompia kuin verrokeilla, ja taudin edetessä vihaan liittyviä tuntemuksia ilmenee yhä enemmän vatsan alueella. Tulokset tarjoavat uusia näkökohtia niin Parkinsonin taudin motorisiin kuin ei-motorisiin oireisiin, ja paljastavat uuden ei-motorisen ilmiön. Kullakin näistä löydöksistä on mahdollisia tulevaisuuden kliinisiä sovellutuksia.

AVAINSANAT: Parkinsonin tauti, SPECT, lepovapina, masennus, ahdistus, dopamiinitransportteri, serotoniini, noradrenaliini, aivoverkosto

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Abbreviations

[^{123}I]FP-CIT	N-(3-Fluoropropyl)-2 β -carbomethoxy-3 β -(4-[^{123}I]iodophenyl)nortropane; [^{123}I]ioflupane
5-HT	5-hydroxytryptamine
α2AR	α2 adrenergic receptor
ACh(E[I])	Acetylcholine (esterase [inhibitor])
AFNI	Analysis of Functional NeuroImages
ANTs	Advanced Normalization Tools
BG	Basal ganglia
BSM	Bodily symptom mapping
CBD	Corticobasal degeneration
CBS	Corticobasal syndrome
CC	Cross correlation
CM	Centromedian (nucleus)
COMT	Catechol O-methyltransferase
D1/2(L)R	Dopamine 1 / 2 (-like) receptor
DAT	Dopamine transporter
DBS	Deep brain stimulation
DDC	Dopadecarboxylase
(d/i)SPN	(Direct/indirect) spiny projection neuron
FDR	False discovery rate
FMRIB	Functional Magnetic Resonance Imaging of the Brain Analysis Group, Oxford, UK
FOG	Freezing of gait
FSL	FMRIB Software Library
FWE	Family-wise error
GABA	ɣ-amino butyric acid
GDS(-15)	Geriatric Depression Scale (15-item)
GPe	Globus pallidus externa
GPi	Globus pallidus interna
HIFU	High intensity focused ultrasound
IC(B/D)	Impulsive-compulsive behavior / disorder
IND	Indeterminate (motor phenotype)
iSPN	Indirect spiny projection neuron
ITK	InSight Toolkit
L-AADC	L-amino-acid decarboxylase

LEDD	Levodopa-equivalent daily dose
LID	Levodopa induced dyskinesia
LRRK2	Leucine-rich repeat kinase 2
MAO-A/-B	Monoamine oxidase A /B
MDS-UPDRS	Movement Disorders Society Unified Parkinson's Disease Rating Scale
MI	Mutual information (alias for Mattes)
MIBG	[^{123}I]metaiodobenzylguanidine
MoCA	Montreal Cognitive Assessment
MRgFUS	Magnetic resonance imaging guided high intensity focused ultrasound
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy
NAT	Noradrenaline transporter; norepinephrine transporter
NIfTI	Neuroimaging Informatics Technology Initiative
NMS	Non-motor symptom
PCA	Principal component analysis
PD	Parkinson's disease
PET	Positron emission tomography
Pf	Parafascicular (nucleus)
PIGD	Postural instability and gait disorder
PPMI	Parkinson's Progression Markers Initiative
PPN	Pedunculopontine nucleus
PSP	Progressive supranuclear palsy
PSP-RS	Progressive supranuclear palsy, Richardson syndrome
PVE	Partial volume error
RBD	Rapid eye movement sleep behavior disorder
RBDSQ	RBD Screening Questionnaire
REM	Rapid eye movement (sleep)
ROI	Region-of-interest
SBR	Specific binding ratio
SERT	Serotonin transporter
SN(c/r)	Substantia nigra (pars compacta/reticulata)
SPECT	Single photon emission computer tomography
SPM	Statistical Parametrical Mapping
SSRI	Selective serotonin reuptake inhibitor
STAI	State-Trait Anxiety Inventory
STN	Subthalamic nucleus
TD	Tremor-dominant (motor phenotype)
VA	Ventral anterior (thalamic nucleus)
VL	Ventrolateral (thalamic nucleus)
VMAT	Vesicular monoamine transporter
VPS35	Vacuolar protein sorting protein 35
VTA	Ventral tegmental area

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Niemi KJ, Sunikka J, Soltanian-Zadeh H, Davoodi-Bojd E, Rahmim A, Kaasinen V, Joutsa J. Rest Tremor in Parkinson's Disease is Associated with Ipsilateral Striatal Dopamine Transporter Binding. *Mov Disord*, 2024; 39(11):2014-2025.

II Niemi KJ, Kaasinen V, Weil R, Joutsa J. Monoaminergic Networks of Anxiety, Depression and REM Sleep Behavior Disorder in Early Parkinson's Disease. *Manuscript*.

III Niemi KJ, Huovinen A, Jaakkola E, Glerean E, Nummenmaa L, Joutsa J. Bodily Maps of Symptoms and Emotions in Parkinson's Disease. *Mov Disord*, 2024; 39(6):1037-1043.

1 Introduction

Parkinson's disease (PD) is a common neurodegenerative movement disorder (Erkkinen et al., 2018). Amongst the growing senior population (Bloom et al., 2015), the prevalence of the disease is approximately 1% (de Lau & Breteler, 2006; Erkkinen et al., 2018). Currently used therapies for PD aim to symptom alleviation, and, at the moment, there are no disease-modifying therapies available despite active research and drug development (Armstrong & Okun, 2020; Vijiaratnam et al., 2021). Thus, better understanding PD and enhanced treatment of the disease could have a marked impact economically and on the quality of life of both patients (Martinez-Martin et al., 2011) and their caregivers (Page et al., 2017).

PD presents with a combination of cardinal motor symptoms, bradykinesia, rigidity and tremor, and at least along the course of the disease, it is accompanied with progressing impairment in gait and balance (Postuma et al., 2015). Despite the diagnostic essence of the motor symptoms, the clinical picture of PD is heavily characterized by non-motor symptoms (NMSs), in many cases affecting quality of life even more than motor symptoms with the current treatments (Martinez-Martin et al., 2011; Prakash et al., 2016). These NMSs include autonomic symptoms, such as abnormal cardiovascular responses and gastrointestinal symptoms, but also a wide variety of neuropsychiatric symptoms (Martinez-Martin et al., 2011).

Molecular imaging techniques, including positron emission tomography (PET) and single photon emission computed tomography (SPECT), provide an opportunity to observe molecular-level phenomena *in vivo* (in living patients) (Theis et al., 2024). Of these imaging techniques, the most commonly used method in the clinical context of PD is N-(3-Fluoropropyl)-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)-nortropane ([^{123}I]FP-CIT) SPECT (Kaasinen & Vahlberg, 2017). Although mainly used to verify diminished striatal presynaptic dopaminergic integrity, [^{123}I]FP-CIT also has affinity for serotonin and noradrenaline transporters (SERT and NET, respectively) (Abi-Dargham et al., 1996; Scheffel et al., 1997). The popularity of the [^{123}I]FP-CIT tracer, with its affinity for multiple molecular-level binding targets, provides a promising platform for exploring multiple different neurotransmitter systems in large cohorts of patients with PD (Arakawa et al., 2008; Qamhawi et al., 2015; Veltman et al., 2010). Bradykinesia and rigidity in PD are known to be associated with contralateral

striatal dopaminergic deficit (H. T. Benamer et al., 2000; Seibyl et al., 1995). However, dopaminergic phenomena underlying rest tremor in PD, suggested by its response to dopaminergic treatment, have remained uncertain. Also, the evidence of monoaminergic abnormalities linked to non-motor phenomena encountered in PD has remained limited (Carey et al., 2021; Laurencin et al., 2023; Maillet et al., 2021; Remy et al., 2005).

Large-scale initiatives facilitate the research of neurodegenerative disorders, eventually offering a better opportunity to understand the different aspects of the disease, and to guide future development towards more effective treatment. Parkinson's Progression Markers Initiative (PPMI) is a large observational study of subjects with PD. It has gathered a large magnitude of longitudinal clinical and imaging data of subjects with early PD and of healthy controls (Marek et al., 2011).

Body sensation mapping (BSM) is a recently developed technique for topographical mapping of subjective sensations (Nummenmaa et al., 2014), and has been used to investigate the bodily sensations associated with emotions in the general population and among individuals with psychiatric and neuropsychiatric conditions (Hietanen et al., 2016; Nummenmaa et al., 2014; Palser et al., 2021; Torregrossa et al., 2019; Volynets et al., 2020). The technique has yielded consistent results across sexes, cultures and developmental stages, indicating that the bodily sensations of emotions are universal across healthy populations (Hietanen et al., 2016; Volynets et al., 2020), and has revealed abnormalities in schizophrenia and autism-spectrum disorders (Palser et al., 2021; Torregrossa et al., 2019). However, it has not been used to study neurological conditions before, although psychiatric features e.g. in PD are common, causing a significant burden for patients (Martinez-Martin et al., 2011; Prakash et al., 2016).

To bridge these gaps in the current knowledge, the aim of this thesis work was to study the monoaminergic abnormalities underlying motor and non-motor symptoms in PD using a new preprocessing algorithm for [^{123}I]FP-CIT SPECT imaging data and to investigate the subjective bodily representations of symptoms and emotions in PD using BSM.

2 Review of the Literature

2.1 Parkinson's Disease

Parkinson's disease (PD) was named after James Parkinson who described it as a syndrome in 1817 in his *Essay on the Shaking Palsy*. In this essay, Parkinson described difficulty and slowness of movement, with tremor of a unique kind, as integral parts of the syndrome. In addition, slow progression, flexed and stooped posture, gait abnormalities, sleeping disorders, constipation, and later cognitive decline were described to belong to this syndrome (Parkinson, 1817). Since this first description, great advances in understanding the role of dopaminergic function in parkinsonism and PD have been achieved, showing the lack of dopamine in the striatum of parkinsonian patients (post-encephalitic parkinsonism and PD), and the efficacy of levodopa in the management of akinesia (slowness or absence of movement) (Birkmayer & Hornykiewicz, 1962; Vilensky, 2011). The cardinal motor symptoms of PD are rigidity, bradykinesia and rest tremor, of which bradykinesia and either rigidity or rest tremor must be present to establish the diagnosis. In addition, a PD diagnosis requires the differential diagnostic possibilities to be excluded to a sufficient degree (Postuma et al., 2015).

PD begins insidiously, and the characteristic motor symptoms necessary for a clinical diagnosis appear only several years after the onset of the underlying pathological process (Berg et al., 2015; Bloem et al., 2021; Hawkes, 2008; Heinzel et al., 2019; Hilker et al., 2005; Mahlknecht et al., 2022; Postuma et al., 2019; Stern et al., 2012). The period during which the underlying pathology is present and progressing but the clinical diagnostic criteria have not been met is the prodromal phase of PD, which can last over a decade (Berg et al., 2015; Bloem et al., 2021; Heinzel et al., 2019; Mahlknecht et al., 2022). Non-motor signs, such as rapid eye movement (REM) sleep behavior disorder (RBD), olfactory deficit, depression, autonomic dysfunction (including gastrointestinal symptoms) and mild cognitive impairment are connected to this phase. Further, subtle extrapyramidal motor signs not yet fulfilling the diagnostic criteria may be present (Berg et al., 2015; Heinzel et al., 2019; Postuma et al., 2019). Striatal dopamine transporter (DAT) density is already declined in the prodromal phase (Cersosimo et al., 2013; Chahine et al., 2021; Iranzo et al., 2011, 2017; Postuma et al., 2019; Ross et al., 2012; Stoessl et al.,

2011). As the understanding of the underlying processes, and the possibilities to identify α-synuclein pathology likely essential in the pathogenesis of at least sporadic PD have improved (Siderowf et al., 2023; Stocchi et al., 2024), novel biological definitions of the disease have been proposed, although, so far, they have not been widely accepted (Höglinger et al., 2024; Simuni et al., 2024).

2.1.1 Epidemiology and Non-Genetic Risk Factors

PD is the second most common neurodegenerative disease, and the most common neurodegenerative disease causing predominantly motor symptoms (de Lau & Breteler, 2006; Erkkinen et al., 2018). In Finland, the epidemiology of PD was elaborately investigated in 1992 in Southwestern Finland (Kuopio et al., 1999). In the study, the age-adjusted prevalence of PD was 139 per 100,000, and the age-adjusted incidence 15.7 per 100,000 per annum. This epidemiological study also showed a possible emerging relative risk ratio in males vs females (risk ratio 1.9 for males) and in rural versus urban populations (risk ratio 1.4 for rural places of living) between 1971 and 1992 (Kuopio et al., 1999). Since then, register-based studies have reported relatively stable age-adjusted prevalence and incidence approximates based on data from 1990s until the late 2010s, and changes in the absolute occurrence of PD appear to follow the changes in the age structure of the Finnish population, with relatively small overall influence from other factors (Dorsey et al., 2018; Sipilä & Kaasinen, 2020). Living in a rural environment has also remained a notable risk factor according to data until the 2010s (Isotalo et al., 2017).

In addition to age, sex and rural place of residence, identified risk factors of PD include the consumption of dairy products, the use of amphetamines or methamphetamines, traumatic brain injury, exposure to pesticides, and many others (Ascherio & Schwarzschild, 2016; Dorsey & Bloem, 2024; Kuopio et al., 1999). There is also evidence supporting postmenopausal estrogen therapy as a risk factor for PD (Ascherio & Schwarzschild, 2016). Schizophrenia spectrum disorders and exposure to antipsychotics appear to be associated with degenerative parkinsonism as well (d'Errico et al., 2022; Kuusimäki et al., 2021).

Although multiple studies have found no association between PD and body mass index, one Finnish study identified a clear positive association between these factors (Ascherio & Schwarzschild, 2016; Hu et al., 2006). Similarly, in most non-Finnish studies, a negative association of blood cholesterol level and the risk of PD has been suggested (Ascherio & Schwarzschild, 2016), in contrast to a Finnish study, which showed that higher blood cholesterol was associated with increased hazard of PD (Hu et al., 2008). It is worth mentioning that these Finnish studies were not controlled for urban or rural living environment (Hu et al., 2006, 2008), while in epidemiological studies in Finland, rural environment has been established as a

relevant factor associated with PD and, in the general population, with obesity and high blood cholesterol (Isotalo et al., 2017; Kuopio et al., 1999; Nuotio et al., 2020). There has been a recent increase in the interest shown towards the importance of gut microbiota properties as a risk factor or even as an etiological factor for PD (Klingelhoefer & Reichmann, 2015; Mertsalmi et al., 2020; Scheperjans et al., 2015). The potential influence of the gut microbiome in the risk of PD has also been implied to possibly explain at least some of the risk associated with living in a rural environment (Vizcarra et al., 2015).

Known factors associated with lower risk of PD include tobacco use (either smoking or using smokeless tobacco), caffeine consumption (R. Liu et al., 2012; Qi & Li, 2014; Ross, 2000), tea consumption (Ascherio et al., 2001; Hu et al., 2007), use of non-steroidal anti-inflammatory drugs and physical activity (Ascherio & Schwarzschild, 2016). Evidence regarding the role of calcium channel blockers has been mixed (Ascherio & Schwarzschild, 2016). Higher serum urate levels have been suggested to be negatively associated with the risk of PD (Chen et al., 2021), although there is no association between gout and PD (Chen et al., 2021; Fazlollahi et al., 2022). There is evidence supporting the possibility that alcohol (especially beer) consumption provides a protecting effect against PD (Ascherio & Schwarzschild, 2016; D. Zhang et al., 2014), although alcohol misuse has been established as a risk factor (Eriksson et al., 2013).

Focusing on tobacco use, a longer history of smoking has been shown to be associated with reduced risk, and a longer time since smoking cessation with increased risk of PD (Thacker et al., 2007). However, stopping smoking seems to be easier and nicotine substitution less common in individuals with PD compared to controls (OR 0.54 for nicotine substitute usage, adjusted for other known protective factors) (Ritz et al., 2014). The latter observations could indicate PD reducing the risk for smoking, rather than tobacco use as a protective factor against PD. However, possible neuroprotective effects of nicotine, especially towards the nigrostriatal system, have also gained some support (Quik et al., 2015).

Coffee consumption and caffeine intake is associated with lower risk of PD (Qi & Li, 2014; Ross, 2000). The consumption of coffee for maximal protective effect has been estimated to be approximately 3 cups per day (Qi & Li, 2014). This connection has been observed in the Finnish population (Hu et al., 2007; Sääksjärvi et al., 2008). The effect has been thought to be related to the adenosine 2A receptor blockade and its subsequent neuroprotection; such properties have also been suggested based on experimental animal models, both with caffeine and selective adenosine 2A receptor antagonists (Ferreira et al., 2015; Kachroo et al., 2010; K. Xu et al., 2010). Caffeine and other, more selective adenosine 2A receptor antagonists might have motor symptom-alleviating properties in patients with PD (Hauser et al., 2014; Postuma et al., 2012), although studies on adenosine 2A receptor antagonists

have shown no considerable beneficial effects in the management of PD (S. H. Fox et al., 2018). Limited PET study series have demonstrated changes of the adenosine 2A receptor binding in patients with PD compared to healthy controls, and a correlation of higher receptor availability with greater motor symptom severity and the presence of levodopa-induced dyskinesias (LIDs) (Ramlackhansingh et al., 2011; Waggan et al., 2023). A recent [^{123}I]FP-CIT SPECT study showed that greater coffee consumption was associated with a lower level and a faster decline in DAT availability, yet with no difference in clinical motor symptom severity (Saarinen et al., 2024).

2.1.2 Heredity and Genetic Risk Factors

Most cases of PD are sporadic, and the impact of genetic factors in the majority of PD is limited (Ben-Shlomo et al., 2024; H. R. Morris et al., 2024). The heritability of PD has been estimated to be 22–40% based on twin studies (Goldman et al., 2019; H. R. Morris et al., 2024), which leaves a considerable role for environmental factors in PD. In total, there are six genes that have been well validated in causing PD (H. R. Morris et al., 2024).

The autosomal dominant genes include *SNCA* encoding α-synuclein, *LRRK2* encoding leucine-rich repeat kinase 2 and *VPS35* encoding retromer protein complex subunit called vacuolar protein sorting protein 35 (Federoff et al., 2015; H. R. Morris et al., 2024; Pihlstrøm et al., 2018; Rahman & Morrison, 2019; Zimprich et al., 2004). The autosomal recessive genes include *PRKN*, an encoding Parkin protein involved in the ubiquitination process essential for some protein degradation processes, including the selective degradation of mitochondria, *PINK1* encoding a kinase activating this kind of ubiquitination process, and *DJ1* (also known as *PARK7*) encoding DJ-1 protein that has a role in oxidative stress sensing (Honbou et al., 2003; Lazarou et al., 2013; Mitsumoto et al., 2001; Mitsumoto & Nakagawa, 2001; H. R. Morris et al., 2024; Seirafi et al., 2015). In addition, mutations in the *GBA1* gene causing Gaucher's disease and encoding a lysosomal protein glucocerebrosidase are associated with PD (Do et al., 2019; Gegg et al., 2022; H. R. Morris et al., 2024). However, most *GBA1* mutation carriers never develop parkinsonism (Do et al., 2019). In summary, all of the most prevalent genetic features predisposing to PD are involved in α-synuclein transcription, autophagy and oxidative stress, leading to the formation of α-synuclein fibrils, oligomers, and eventually Lewy bodies, which are the neuropathological hallmark of PD (H. R. Morris et al., 2024).

The most important autosomal dominant genetic cause of PD is a mutation in the *LRRK2* gene. *LRRK2*-related PD seems to be associated with a slower decline in motor functions and overall, milder cognitive deficits (Saunders-Pullman et al.,

2018; Srivatsal et al., 2015). The mutations in the *SNCA* gene are rarer; they have been suggested to alter the course of PD, making it more severe, although a recent systematic review found convincing evidence only for earlier age of onset (H. R. Morris et al., 2024; Pedersen et al., 2021). Mutations in the *VPS35* gene seem to be associated with late-onset PD (Zimprich et al., 2011).

Of the autosomal recessive genetic causes, the most common cause is homozygous mutation in the *PRKN* gene. Other common recessive genetic causes observed in patients with early-onset PD include mutations in *PINK1* and *DJ1*. In each of these recessive genetic causes, clinical appearance often includes dystonia, relatively good response to levodopa, slow disease progression, and an unconventionally mild tendency to develop cognitive decline. Together, these abnormalities are present in approximately 13% of early-onset PD cases (onset before 40 years of age), and the typical age of onset is 30 years (Kasten et al., 2018; Morales-Briceño et al., 2020).

In Finland, the extent of PD related to the most common single mutations identified worldwide, such as *LRRK2* mutations, seems to be rather limited (Ylönen et al., 2017). However, previous studies on the Finnish population have implied the existence of monogenic forms or genetic susceptibility (Autere, 2000; Ylikotila et al., 2015). Identified genetic variants predisposing to PD in the Finnish populations include *GBA* mutations and *POLG1* CAG repeat length variation (Ylönen et al., 2017). Some case reports on PD and the mutations in *SNCA* and *PARK2* genes have been published during the last decade (Kaasinen et al., 2015; Pasanen et al., 2017). Among the Finnish population, there could also be endemic, pathogenic variants of the genes associated with PD worldwide, but this aspect warrants further studies (Ylönen et al., 2017).

2.1.3 Clinical Motor Features and Assessment

The diagnosis of PD is based on an expert assessment and requires the presence of at least two out of the three cardinal motor symptoms, always including bradykinesia: bradykinesia and rest tremor, or bradykinesia and rigidity. In addition, supportive and exclusion criteria must be taken into account when establishing a diagnosis (Postuma et al., 2015). In clinical assessment, the severity of motor symptoms can be scored using the MDS-UPDRS-III (Movement Disorders Society Unified PD Rating Scale, part III) scale (Goetz et al., 2008).

Bradykinesia is defined as slowness of movement and decrement in amplitude or speed in movement repetition. Rigidity is stiffness of a limb joint in a relaxed position, with velocity-independent “lead-pipe” resistance, not only reflecting failure to relax. Commonly, it may also be accompanied by the “cogwheel phenomenon”. Rest tremor is typically a 4–6 Hz tremor in a fully resting limb, suppressed by the

initiation of movement. Rest tremor might also become present with prolonged posture (re-emergent rest tremor), although the presence in full rest is always required to confirm the presence of rest tremor (Postuma et al., 2015).

Supportive criteria for PD include beneficial response to dopaminergic medications, LIDs, rest tremor during any assessment and either olfactory loss or cardiac sympathetic denervation on [^{123}I]metaiodobenzylguanidine (MIBG) scintigraphy (Postuma et al., 2015). The absolute exclusion criteria include hallmark signs and features of other neurodegenerative disorders or conditions causing parkinsonism (multiple system atrophy [MSA], progressive supranuclear palsy [PSP], fronto-temporal dementia spectrum, drug-induced parkinsonism), a greater probability of any other differential diagnosis, sensory deficits, or functional neuroimaging showing no functional deficit in the presynaptic dopaminergic system (Postuma et al., 2015). Red flags opposing the diagnosis of PD include rapid gait impairment, absence of motor progression, severe autonomic failure, absence of any non-motor features, otherwise unexplained signs of upper motor neuron damage, and bilateral, symmetric parkinsonism (with no anamnestic and no observed side of motor symptom side predominance) (Postuma et al., 2015).

Beginning in the early phases of PD, patients often present with stooped posture, asymmetrical, reduced arm swing while walking, and reduced leg synchrony during gait (Ebersbach et al., 1999; Fearon et al., 2024; X. Huang et al., 2012; Rabin et al., 2016). Sometimes, lower limb dystonia that variably responds to dopaminergic treatment might be present (Jankovic & Tintner, 2001). These appear to be particularly more relevant in patients with young-onset PD (Jankovic & Tintner, 2001; Schrag et al., 1998). Micrographia, small handwriting with a further, progressive reduction in letter size, is also a common fine motor abnormality in PD (Eklund et al., 2022; McLennan et al., 1972; Wu et al., 2016). Of more subtle features, the glabellar tap sign may also be observed in patients with PD (Nuuttila et al., 2021; Sunohara et al., 1985; Vreeling et al., 1993).

In the later course of the disease, freezing of gait (FOG) may become evident (Perez-Lloret et al., 2014). FOG is defined as a sudden, variable and unpredictable stop in walking, and most often presents when initiating gait, walking through doorways or turning (Perez-Lloret et al., 2014). Festination, characterized by footsteps within a long or complex gait trial becoming shorter and shorter, may also be present and is sometimes associated with FOG (M. E. Morris et al., 2008). In advanced PD and on higher concentrations of levodopa used to treat parkinsonian motor symptoms, LIDs may become rather problematic and even disturb balance (Armand et al., 2009; Armstrong & Okun, 2020; Sorbo & Albanese, 2008). In addition to the stooped posture present from early to moderately advanced PD, patients with advanced PD can present with camptocormia, an extremely prominent thoracolumbar flexion of the spine, while sitting or standing; or pleurothotonus (also

known as Pisa syndrome), a syndrome characterized by a marked lateral flexion and axial rotation of the torso and lateral flexion of the head (Rabin et al., 2016). Especially in more advanced PD, difficulty swallowing, dysphagia, and speech problems including dysarthria and oral festination are common (Mekyska et al., 2018; Moreau et al., 2007; J. Müller et al., 2001).

2.1.4 Non-Motor Symptoms

Currently known NMSs of PD include pain, hyposmia, RBD, depression, anxiety, apathy, hallucinations and other psychotic symptoms, cognitive abnormalities, excessive daytime sleepiness, and autonomic symptoms, including cardiovascular, urinary and gastrointestinal systems and sexual function (Armstrong & Okun, 2020; Martinez-Martin et al., 2011; Pfeiffer, 2003; Rabey, 2009; Rodriguez-Blazquez et al., 2021; Seppi et al., 2019; Vriend et al., 2014). Especially in younger patients with PD, using dopamine 2 receptor (D2R) agonist medication, impulsive control disorder (ICD), including a broad spectrum of repetitive behaviors such as gambling, compulsive buying, or abnormal sexual and eating behaviors, might also cause severe problems (Armstrong & Okun, 2020; Garcia-Ruiz et al., 2014; Joutsa et al., 2012; Joutsa et al., 2012; Leroi et al., 2012; Rodriguez-Blazquez et al., 2021; Wirth et al., 2024). Hyposmia, RBD, depression and constipation are among the most typical symptoms to present already in the prodromal phase (Armstrong & Okun, 2020; Roos et al., 2019; Schrag et al., 2015). A summary of the most commonly identified non-motor symptoms associated with PD is presented in **Table 1**.

Table 1. Non-motor symptoms associated with PD.

Category	Symptom
Sensory	Hyposmia
	Pain
Autonomic	Constipation
	Drooling
	Urinary urge and nocturia
	Sexual dysfunction
	Orthostatic hypotension
Neuropsychiatric	Apathy
	Depression
	Anxiety
	Impulsive-compulsive behaviors
	Punding, hobbyism and aimless wandering
	Cognitive impairment and dementia
Sleep and Wakefulness	REM sleep behavior disorder
	Excessive daytime sleepiness

Note that other non-motor symptoms exist, that the presented categorization of the symptoms is crude, and that central mechanisms might also be involved in the autonomic symptoms. REM, rapid eye movement.

Hyposmia is one of the most well-known prodromal NMSs in PD (Armstrong & Okun, 2020; Marrero-González et al., 2020). It appears to occur in at least 55%, perhaps even up to 95%, of all patients with established PD (Haehner et al., 2009; Rodriguez-Blazquez et al., 2021). The interest in hyposmia as a sign of PD has mainly been related to its prodromal character, and its effect on quality of life has been of relatively little interest (Haehner et al., 2009; Marrero-González et al., 2020). RBD is a parasomnia (dream disorder) known to be a prodromal feature associated with PD (Armstrong & Okun, 2020). It is characterized by REM sleep without atonia that leads to the enactment of dreams with motor behaviors or vocalization (Galbiati et al., 2019). Approximately 43% of patients with an established diagnosis of idiopathic RBD (iRBD) will develop PD (Galbiati et al., 2019), and up to 50% of patients with PD are affected by this syndrome (De Almeida et al., 2018; Zimansky et al., 2021). RBD can potentially result in injuries to the patient or their bed partner

(Galbiati et al., 2019), thus affecting the vicinity of the patients in a very concrete way.

Psychiatric symptoms of PD may have an even greater negative effect on quality of life than the well-known motor symptoms (Chaudhuri et al., 2007; Schrag, 2000). Depression and apathy seem to be common and interlinked symptoms in PD, affecting approximately 30–35% and 35–40% of the patients, respectively (Ahmad et al., 2023; Leroi et al., 2012; Weintraub et al., 2022) These symptoms are most common among older patients (Leroi et al., 2012; Rodríguez-Violante et al., 2014). A plausible dopaminergic component in their pathophysiology has been demonstrated by the beneficial effects associated with D2R agonists (Ahmad et al., 2023; Leroi et al., 2012; Ray Chaudhuri et al., 2013; Rodríguez-Violante et al., 2014; Skorvanek et al., 2013). The pathophysiological mechanisms underlying anxiety, affecting 30–35% of patients with PD, are less understood, and the evidence on effective treatments in parkinsonian anxiety have remained limited (Broen et al., 2016; Schneider et al., 2020; Weintraub et al., 2022). Psychotic features in PD tend to be mostly illusions, visual hallucinations and delusions, and manifest well after the motor symptom onset, with a prevalence of 25–50% (Ffytche et al., 2017; Poewe, 2003; Rabey, 2009). They can be provoked by D2R agonists, the use of which may be limited by psychotic symptoms in elderly patients (Biglan et al., 2007; Ffytche et al., 2017; Poewe, 2003; Stowe et al., 2008). At least mild cognitive abnormalities are present in approximately 10% of early PD cases, with a total prevalence of cognitive impairment being 45–60% in cross-sectional studies among patients with PD, including advanced cases (Rodriguez-Blazquez et al., 2021; Weintraub et al., 2015).

The autonomic disturbances associated with PD are broad, and they affect numerous organ systems (R. Liu et al., 2020; Rodriguez-Blazquez et al., 2021). A prevalent cardiovascular presentation in PD is orthostatic hypotension (Bonuccelli et al., 2003; Rodriguez-Blazquez et al., 2021; Senard et al., 1997), which is a dysregulation of blood pressure that manifests depending on posture due to impaired baroreflex-cardiovagal function (Matinolli et al., 2009). Orthostatic hypotension might predispose patients to falling accidents (Martignoni et al., 2006; Matinolli et al., 2009). It is also associated with excessive nocturnal urinary secretion manifested as nocturia, possibly through disturbances in mineralocorticoid receptor activation (Batla et al., 2016; Martinez-Martin et al., 2011). The pathophysiological mechanism of orthostatic hypotension most likely involves the defects in the sympathetic autonomic nervous system (A. H. V. Schapira et al., 2017), best demonstrated in the cardiac sympathetic innervation (Braune et al., 1999; Orimo et al., 2007, 2008).

Gastrointestinal autonomic symptoms may present already in the prodromal phase (R. D. Abbott et al., 2001; Armstrong & Okun, 2020; Berg et al., 2015; Lin et al., 2014; Plouvier et al., 2014; Savica et al., 2009; Schrag et al., 2015). This is one reason why the role of the bowel microbiome, even in the pathogenesis of PD, has

been highlighted in the present literature (Barichella et al., 2019; Bullich et al., 2019; Scheperjans et al., 2015), and there has been hope, but not yet evidence, of modifying disease progression in PD through interventions targeting gut microbiota (Scheperjans et al., 2024). The effects of PD on bowel function are common; constipation, for example, is present in approximately 35–50% (Rodriguez-Blazquez et al., 2021) of patients and, like other NMSs, can have a detrimental effect on the quality of life of patients (Martinez-Martin et al., 2011).

Common urinary symptoms in PD include urge (50–55%) and nocturia (65–70%) (Martinez-Martin et al., 2011) and are associated with abnormal urodynamic findings such as detrusor-external-sphincter dyssynergia (Uchiyama et al., 2011). These symptoms are frequent, but abnormal urodynamic features are even more common in patients with PD (Rodriguez-Blazquez et al., 2021; Uchiyama et al., 2011). Urinary symptoms can cause a variable burden on the quality of life of individuals with PD, although it seems to be less than that of the gastrointestinal symptoms (Araki, 2000; Magerkurth et al., 2005; Rodriguez-Blazquez et al., 2021; Sakakibara et al., 2001; Uchiyama et al., 2011).

ICD includes impulsive-compulsive behaviors (ICBs) such as compulsive gambling, buying, sexual behavior or eating, but also punding, hobbyism and aimless wandering (Armstrong & Okun, 2020; Garcia-Ruiz et al., 2014; Joutsa, Martikainen, Vahlberg, Voon, et al., 2012; J. Kim et al., 2013; Leroi et al., 2012; Rodriguez-Blazquez et al., 2021; Wirth et al., 2024). Punding is different from ICBs and is described as stereotyped, repetitive, non-goal-directed motor behavior (Rajalingam & Fasano, 2023; Spencer et al., 2011). Manifestations of punding seem to be individual (Voon, 2004). ICD is more common in younger males with PD and can be provoked mostly by D2R agonists, although other antiparkinsonian medications may also be associated with these symptoms (Antonini et al., 2017; Garcia-Ruiz et al., 2014; J. Kim et al., 2013; Weintraub, Siderowf, et al., 2006). The impact of ICD on the lives of patients is not limited to daily functionality; it can often have serious economic consequences due to, for example, uncontrollable gambling and shopping (Wirth et al., 2024). ICD is frequently underreported by patients, perhaps due to embarrassment or a lack of insight (J. Kim et al., 2013; Weintraub, Siderowf, et al., 2006).

2.1.5 Differential Diagnostics

Parkinsonism is a symptom entity not unique to PD. As previously mentioned, several differential diagnoses must be considered before establishing a diagnosis of PD. The most typical differential diagnostic options include multiple other primary neurodegenerative diseases. Some of them are predominantly related to pathological tau protein accumulation, such as PSP or corticobasal degeneration (CBD), and some

others involve pathology associated with α-synuclein deposits, such as dementia with Lewy bodies, or MSA. Secondary parkinsonisms, including drug-induced and vascular parkinsonism, and other, clinically mimicking conditions, including essential tremor and normal pressure hydrocephalus, are at least of the same importance (Shin et al., 2022).

2.1.5.1 Synucleinopathies

MSA is a rare, fatal neurodegenerative disorder affecting multiple parts of the brain (Jellinger, 2014; Kwon et al., 2007). The prevalence of MSA has been estimated to be 1.9–4.9 per 100,000, with an incidence of 3 per 100,000 per annum (Jellinger, 2014). Neuropathologically, like PD, this condition belongs to α-synucleinopathies, (Kwon et al., 2007), but instead of Lewy bodies, MSA presents with oligodendroglial cytoplasmic inclusions (also called Papp-Lantos bodies) (Fanciulli & Wenning, 2015; Jellinger, 2014). In addition to parkinsonism, the clinical characteristics of MSA include cerebellar ataxia and more prominent autonomic dysfunction present already in the prodromal phase (Fanciulli & Wenning, 2015; Kwon et al., 2007). Emphasizing its clinical phenomenology, MSA can be further classified into MSA-C (cerebellar) and MSA-P (parkinsonistic) subtypes (Kwon et al., 2007). MSA-P is the most common subtype in Western populations, but MSA-C is more frequent in Japanese population samples (Shin et al., 2022). In clinical evaluation, cerebellar symptoms include gait ataxia, gaze-evoked nystagmus and abnormalities in saccadic eye movements (Fanciulli & Wenning, 2015; Shin et al., 2022). In both MSA subtypes, tremor may be encountered, and positional tremor may also have a myoclonic component that is not present in PD (Shin et al., 2022). Similarly, as in PD, RBD might emerge years before diagnostic manifestations of the disease, as a characteristic of α-synucleinopathies (Shin et al., 2022). A classical structural imaging finding is the “hot-cross bun sign” in the pons, accompanied with pontine and cerebellar atrophy, and hypo- and hyperintense findings in the putaminal regions (Kwon et al., 2007). Response to levodopa may be observed in 30–40% of the cases, but it is usually short-lived (Constantinescu et al., 2007).

Only second to Alzheimer’s disease, dementia with Lewy bodies is one of the most common neurodegenerative disorders predominantly causing dementia, accounting for an estimated 4–30% of all dementia cases (Erkkinen et al., 2018; Vann Jones & O’Brien, 2014; Walker et al., 2000; Zaccai et al., 2005). Dementia with Lewy bodies is characterized by marked cognitive fluctuations, recurrent visual hallucinations and RBD (McKeith et al., 2017). In Alzheimer’s disease, mixed pathological findings with also Lewy bodies have been shown in as much as 15–25% of cases in post-mortem neuropathological autopsies (McKeith et al., 1996). Lewy bodies and their related findings are common hallmark neuropathological

characteristics for both dementia with Lewy bodies and PD (Shin et al., 2022). Previously, it has been conceived that the distribution of α-synuclein pathology in these conditions differ: in clinical dementia with Lewy bodies, the Lewy body pathology is typically more dispersed, accommodating more intensely limbic and neocortical areas while in PD the Lewy body pathology is most pronounced in the midbrain regions and is more associated with ventrolateral substantia nigra (SN) neuromelanin loss (Koga et al., 2021; Matar et al., 2020). Whether PD and dementia with Lewy bodies are one disease entity or two separate diseases continues to be debated (Borghammer et al., 2024; Höglinger et al., 2017; Simuni et al., 2024).

2.1.5.2 Tauopathies

PSP is an uncommon, sporadic, neurodegenerative disorder associated with tau protein accumulation, affecting pons, subthalamic nucleus (STN), globus pallidus (GP) and SN (Shin et al., 2022). The prevalence of PSP has been approximated to be 5.2–9.0 per 100,000 (Swallow et al., 2022). Neuropathologically, PSP belongs to 4 microtubule-binding repeat tauopathies (Höglinger et al., 2017; Respondek et al., 2020; Shin et al., 2022; Williams & Lees, 2009). Although it may clinically mimic PD in the beginning, it has clinical features that develop variably along the disease progression: The hallmark of the classical form, PSP-RS (Richardson syndrome), is characterized by a vertical gaze paresis with slow eye movement saccades (Shin et al., 2022; Williams & Lees, 2009). Also, retrocollis, persistent neck extension posture neither typical of PD, is common in PSP (Shin et al., 2022). As with PD in its later phases, PSP is accompanied with gait and balance abnormalities even early on, eventually resulting in notable tendency to falls. PSP also affects cognitive functions, primarily frontal executive processing speed. Various clinical forms of the disease exist, including ocular-motor predominant, postural instability predominant, parkinsonistic, frontal and speech/language variants, and a variant accompanied by primary lateral sclerosis (Höglinger et al., 2017; Shin et al., 2022; Swallow et al., 2022). Initial levodopa response may be achieved in 30–40% of the cases (Constantinescu et al., 2007), but response of parkinsonistic and postural instability features to levodopa are typically markedly limited and transient (Williams & Lees, 2009). One of the characteristic structural imaging findings is a “hummingbird sign” in the sagittal plane of the midbrain, resulting from dorsal midbrain atrophy (Whitwell et al., 2017).

Corticobasal degeneration (CBD), an even rarer disorder associated with tau protein accumulation, with a prevalence of 1.6–3.0 per 100,000, has numerous clinical reported phenotypes (Doody & Jankovic, 1992; Graff-Radford et al., 2013; Respondek et al., 2020; Shin et al., 2022). Typical clinical characteristics, presently referred to as corticobasal syndrome (CBS), include asymmetric ideomotor or limb

kinetic apraxia, alien limb phenomenon (involuntary motor activity of a limb, in conjunction with the feeling of estrangement from the limb), dystonia, myoclonus, and prominent bradykinesia and rigidity of the most affected upper extremity (Doody & Jankovic, 1992; Graff-Radford et al., 2013; Shin et al., 2022). As clinical features of CBS can be observed in other, neuropathologically different, conditions, the concepts of CBD (neuropathological diagnosis) and CBS (clinical syndrome) have been distinguished in previous literature (Ouchi et al., 2014). Neuropathologically confirmed CBD diagnoses could be accompanied with the clinical features of PSP syndrome, frontal behavioral-spatial syndrome and non-affluent/agrammatic variants of primary progressive aphasia (Armstrong et al., 2013). Structural magnetic resonance imaging in CBD can be characterized by asymmetric cortical atrophy, emphasized on the posterior frontal and parietal cortical structures (Shin et al., 2022). Generally, the motor symptoms in CBS respond poorly to levodopa, but some levodopa response has been reported in approximately 25% of cases in samples of patients with CBS (Constantinescu et al., 2007; Kompoliti et al., 1998).

2.1.5.3 Other Differential Diagnoses

Vascular parkinsonism is a form of parkinsonism associated with cerebrovascular disease, typically ischemic white matter lesions (Korczyn, 2015; Shin et al., 2022). Compared to PD, the emphasis of parkinsonistic features in this condition is more on the lower extremities (Korczyn, 2015; Shin et al., 2022). The gait disorder in vascular parkinsonism typically differs from the one seen in PD, with more prevalent spastic features and an early emergence of freezing and initiation difficulties (Korczyn, 2015; Shin et al., 2022). Akinetic-rigid and postural instability features, symmetric motor symptom onset, early dementia, and the absence of rest tremor are typical in vascular parkinsonism (Glass et al., 2012; Shin et al., 2022). Approximately 25% of patients with vascular parkinsonism seem to variably respond to levodopa (Winikates & Jankovic, 1999).

Normal-pressure hydrocephalus is a disorder classically characterized by a symptom triad consisting of gait disorder, urinary incontinence and cognitive impairment (Shin et al., 2022). Typically, it is idiopathic, as opposed to rarer cases of secondary normal-pressure hydrocephalus resulting after subarachnoid hemorrhage, meningitis or other similar insult (Shiino, 2004; Shin et al., 2022). Bradykinesia, rigidity and postural instability are common, but upper limb motor function is mostly preserved (Shin et al., 2022). Unlike with PD, the gait disorder in NPH is characterized by wide-base, small steps with initiation difficulty, suggesting a frontal lobe disorder (Shin et al., 2022). Structural neuroimaging studies present a large ventricle size compared to the level of cortical atrophy (Shin et al., 2022). Neuropathological findings include subependymal gliosis, fragmented ependymal

lining, white matter rarefaction, and meningeal thickening (Hänninen et al., 2022). The response to the primary treatment, ventricular shunting, may be predicted with lumbar drainage or repetitive lumbar puncture, impaired cerebral blood flow reactivity to acetazolamide established in SPECT imaging, or elevated cerebrospinal fluid flow resistance (Halperin et al., 2015).

Drug-induced parkinsonism has been previously estimated to be the second most common cause of parkinsonism in some population-based studies (Barbosa et al., 2006; Benito-León et al., 2003; Shin & Chung, 2012; Wenning et al., 2005). Most frequently, antipsychotics, but also lithium, typical selective serotonin reuptake inhibitor (SSRI) drugs, gastrointestinal prokinetics (such as D_2 receptor binding metoclopramide), uncommon calcium-channel blockers, some antiarrhythmics (especially amiodarone), and some older anti-epileptic drugs (valproate and phenytoin) have been reported to cause drug-induced parkinsonism (Dotti & Federico, 1995; Klawans Jr. et al., 1973; Lorberboym et al., 2006; Melamed et al., 1991; Werner & Olanow, 1989). Among neuroleptic-treated patients, 10–15% present with clinically notable drug-induced parkinsonism (Dotti & Federico, 1995; Klawans Jr. et al., 1973; Lorberboym et al., 2006; Melamed et al., 1991; Werner & Olanow, 1989). After drug-withdrawal, 60–70% of patients with drug-induced parkinsonism recover in at most 2 months, whereas some experience symptomatic persistence for several years (Dotti & Federico, 1995; Klawans Jr. et al., 1973; Lorberboym et al., 2006; Melamed et al., 1991; Werner & Olanow, 1989). In addition, PD that would otherwise be subclinical but is unmasked by anti-dopaminergic medication exists, with pathological DAT binding being atypical for actual drug-induced parkinsonism (Diaz-Corrales et al., 2010).

Essential tremor is characterized by postural and kinetic tremor (Haubenberger & Hallett, 2018). Although PD is characterized by a wide variety of symptoms other than tremor, in some tremor-dominant cases, essential tremor must be considered in the differential diagnostics (Algarni & Fasano, 2018). While one of the cardinal symptoms of PD is rest tremor, as opposed to the tremor types met in essential tremor, the assessment of tremor may be challenged by rest tremor mimicking postural tremor after prolonged posture (re-emergent tremor) (Algarni & Fasano, 2018). There are also atypical cases of essential tremor, sometimes with additional gait difficulties, cognitive impairment and other mild neurological signs not classically attributed to essential tremor, which may be classified as essential tremor plus, although this kind of classification has received some criticism since its introduction (Bhatia et al., 2018; Louis et al., 2020). These cases might be even more difficult to distinguish from PD. In addition, a higher risk of PD has been proposed for at least some essential tremor subgroups (Tarakad & Jankovic, 2019).

2.1.6 Treatment of Parkinson's Disease

Presently, the treatment of PD focuses on symptom alleviation, and especially strong evidence has been accumulated on therapies for motor symptoms (Armstrong & Okun, 2020). Treatment options for motor symptoms include pharmacological treatments with no invasive interventions, device-aided pharmacological treatments, deep brain stimulation (DBS) and unilateral ultrasound thalamotomy (Armstrong & Okun, 2020).

2.1.6.1 Conventional Pharmacological Treatment

Most of the pharmacological treatments used for motor symptoms are peroral and dopaminergic (levodopa preparations and non-ergot-derivative D2R agonists), or affect the metabolism of administered levodopa and dopamine, promoting and prolonging their dopaminergic effect (dopadecarboxylase [DDC], monoamine oxidase [MAO-B], and catechol O-methyltransferase [COMT] inhibitors) (Armstrong & Okun, 2020; S. H. Fox et al., 2018). Some anticholinergic agents such as biperiden or trihexyphenidyl are used in some cases, but their use has become limited to specific cases (Armstrong & Okun, 2020; S. H. Fox et al., 2018; Rascol et al., 2021). Amantadine, a glutamate-N-methyl-D-aspartate antagonist with several other receptor-level properties, and clozapine, an atypical neuroleptic with serotonergic modulation effects, can be used to treat dyskinesias (S. H. Fox et al., 2018; Newman-Tancredi et al., 1996; Rascol et al., 2021). The effects of common dopaminergic treatments on bradykinesia and rigidity are well established, and it looks like tremulous symptoms generally respond to dopaminergic medications almost as well as akinetic-rigid symptoms (Frequin et al., 2023).

Levodopa was synthesized for the first time in 1911 by Casimir Funk and was purely extracted from *Vicia faba* beans by Marcus Guggenheim in 1913 (A. Abbott, 2010; Hornykiewicz, 2002). It was finally introduced as a medication for parkinsonism in the 1960s (Birkmayer & Hornykiewicz, 1962; Obeso et al., 2000). Levodopa (L-3,4-dihydroxyphenylalanine) is a neutral L-amino acid, and a precursor of dopamine and other catecholamines, noradrenaline and adrenaline (Hornykiewicz, 2002; Mine et al., 2022; Z. D. Zhou et al., 2023). When ingested, its absorption competes with that of other amino acids (LeWitt, 2015). When entered into circulation and tissues, it is converted to dopamine by aromatic L-amino-acid decarboxylase (L-AADC, also termed DDC) (LeWitt, 2015). If administered alone via an enteric route, it is metabolized to dopamine and downstream products systematically, with minimal exposure in the central nervous system (CNS) (LeWitt, 2015). The conversion to dopamine would cause serious dopaminergic side effects, including nausea and blood pressure disturbance (Stocchi, 2003; Van Rumund et al., 2021). When levodopa is used to control the motor symptoms in PD, it is

accompanied by a DDC inhibitor effective in the periphery (LeWitt, 2015). This enables better-targeted dosing of levodopa to the CNS, with less intense systemic side effects (LeWitt, 2015).

Generally, levodopa is the most effective treatment for motor symptoms in PD (S. H. Fox et al., 2018; Stacy et al., 2005; Stowe et al., 2008). Commonly used oral formulations of levodopa are short-acting and are typically administered at least three times per day in equal intervals during the active part of the day (Armstrong & Okun, 2020; S. H. Fox et al., 2018; Hauser et al., 2013). Although previously started at a later course of the disease with serious caution to postpone the appearance of LIDs (Bloem et al., 2021), it is the mainstay treatment for elderly and seriously symptomatic patients for achieving effective symptom control in a more rapid fashion (S. H. Fox et al., 2018; Stowe et al., 2008). The current perception is that LIDs are indeed acutely induced by threshold-exceeding levodopa concentrations, but the concentration threshold needed for the induction of dyskinesias are not relevantly affected by the previous use of levodopa medication, per se (Bloem et al., 2021; Cilia et al., 2014).

The peroral or transdermal, non-ergot-derivative D2R agonists used to treat motor symptoms in PD include pramipexole, ropinirole, and rotigotine (S. H. Fox et al., 2018). Ergot-derivative dopamine agonists, including cabergoline and bromocriptine, can also be used (S. H. Fox et al., 2018), but their use has become rare due to the risk of adverse fibrotic reactions including retroperitoneal and pulmonary fibrosis, and heart valve complications (Antonini & Poewe, 2007; Rasmussen et al., 2011; C.-Q. Zhou et al., 2014). The D2R agonists mimic the effects of dopamine on the D2R receptors, which eventually suppresses the indirect basal ganglia pathway, the relatively increased function of which plays an important role in the symptoms of PD (Albin et al., 1989; DeLong & Wichmann, 2015; McGregor & Nelson, 2019; You et al., 2018). D2R agonists are less effective than levodopa in the treatment of motor symptoms of PD (Armstrong & Okun, 2020). Noteworthy, potential side effects to consider before and during treatment with D2R agonists include ICDs and hallucinations, in addition to nausea, dizziness, somnolence and peripheral swelling (Antonini et al., 2017; Biglan et al., 2007; Ffytche et al., 2017; Garcia-Ruiz et al., 2014; J. Kim et al., 2013; Poewe, 2003; Stowe et al., 2008; Tan & Ondo, 2000; Weintraub, Siderowf, et al., 2006; C.-Q. Zhou et al., 2014).

Apomorphine is a non-selective dopamine receptor agonist, used for sudden motor offs and on-off fluctuations in advanced PD, and is administered subcutaneously as injections or as a continuous infusion, respectively (Armstrong & Okun, 2020; Frankel et al., 1990; Hughes et al., 1993; LeWitt et al., 2019; Stocchi et al., 2008). Apomorphine may also cause severe nausea that in the initiation of apomorphine treatment may be controlled with domperidone, a peripherally acting D2R antagonist (Bacchi et al., 2017; J. A. Barone, 1999; Katzenschlager et al., 2018).

MAO-B inhibitors include the irreversible MAO-B inhibitors selegiline and rasagiline, and also safinamide, a reversible MAO-B inhibitor with sodium and calcium channel blocking effects (Dezsi & Vecsei, 2017; S. H. Fox et al., 2018; Maj et al., 1999; Salvati et al., 1999; Stocchi et al., 2022; Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society, 2022). However, safinamide has been classified as non-efficacious in early PD, and in PD without motor fluctuations according to recent guidelines, although evidence supports benefits in more advanced PD (S. H. Fox et al., 2018; Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society, 2022). On the other hand, zonisamide, an antiepileptic drug with receptor-level properties similar to safinamide, has been classified as useful in PD (Faught et al., 2001; S. H. Fox et al., 2018). MAO-B-inhibitors act by blocking MAO-B, which is responsible for the degradation of dopamine (LeWitt, 2009). This potentiates the effect of both endogenous and levodopa-derived dopamine, and thus also increases the effect of levodopa (Armstrong & Okun, 2020). The irreversible MAO-B inhibitors can be used either as monotherapy or add-on therapy in PD, while the reversible inhibitor zonisamide seems to only be viable as an add-on therapy (S. H. Fox et al., 2018). There is also another elimination pathway for levodopa and its metabolite dopamine: dopamine and other catecholamines are degraded by COMT (Kurth & Adler, 1998). COMT inhibitors, including entacapone, tolcapone and opicapone, block this route of elimination, thus prolonging the effect of levodopa and dopamine (S. H. Fox et al., 2018; Kurth & Adler, 1998; Stocchi, 2003).

Anticholinergic agents used in PD motor symptom control include biperiden and trihexyphenidyl, and mostly act through blocking muscarinic receptors (Armstrong & Okun, 2020; Katzenschlager et al., 2002; Paz & Murer, 2021; Pisani et al., 2007). Although useful, their use should be limited to young and cognitively fit patients, due to potential, mostly cognitive, side effects (Armstrong & Okun, 2020; Katzenschlager et al., 2002; Paz & Murer, 2021; Pisani et al., 2007). Previously, it was believed that anticholinergic agents would offer relatively better control over tremor, but a later interpretation of the available evidence does not support this conclusion (Katzenschlager et al., 2002; Paz & Murer, 2021).

Patients with advanced PD may commonly face disabling motor complications, including wearing off (shortening of the effective time after levodopa administration), delayed onset of dopaminergic medication response and difficult off periods (periods with inadequate response to dopaminergic treatment). On the other hand, motor complications include a lowering threshold of dopaminergic stimulation for LIDs (involuntary, swarming movements in the body, head and neck and limbs) and hallucinations provoked by dopaminergic agents (Armstrong & Okun, 2020; Obeso et al., 2000; Schrag & Quinn, 2000; Stacy et al., 2005; Stocchi, 2003; Stocchi et al., 2008). At the beginning, the loss of response can be handled by increasing the

total amount of dopaminergic medication; although, eventually, the wearing off must be treated by increasing the frequency of levodopa dosing (Armstrong & Okun, 2020; Mouradian et al., 1988; Stocchi, 2003).

However, as the hypodopaminergic complications develop, and LIDs emerge, medical treatment becomes more complicated (Armstrong & Okun, 2020; Stocchi, 2003; Stocchi et al., 2008). To achieve steadier levodopa concentrations, the levodopa dosing interval can be shortened, but this eventually becomes insufficient and may lead to a very unpractical dosing frequency. In this situation, it is possible to either combine a dopamine agonist with the treatment to offer dopaminergic stimulation not solely based on levodopa, or add an MAO-B or COMT inhibitor to prevent dopamine breakdown, thus, prolonging the therapeutic time window after drug administration (Armstrong & Okun, 2020; Parkinson Study Group, 1997; Stocchi, 2003; Stocchi et al., 2008). As the introduction of MAO-B or COMT inhibitor may provoke dyskinesias, especially when dyskinesias were present before the introduction of these inhibitors, compensation of the rise in levodopa and dopamine concentrations by reducing levodopa dosing may be essential (Stocchi et al., 2008). Unfortunately, this might not resolve the dyskinesias in advanced stages (Stocchi et al., 2008). Evidence also supports the use of amantadine up to 300 mg per day to control dyskinesias, thus possibly enabling the use of a sufficient levodopa dose without disrupting dyskinesias (Luginger et al., 2000; Metman et al., 1998; A. Thomas et al., 2004). For difficult or sudden off fluctuations, levodopa inhalations or subcutaneous apomorphine injections may be used (Armstrong & Okun, 2020; Frankel et al., 1990; Hughes et al., 1993; LeWitt et al., 2019; Stocchi et al., 2008).

2.1.6.2 Advanced Therapies

When the motor fluctuations become unmanageable with non-invasive means, device-aided treatments and neuromodulation therapies should be considered (Armstrong & Okun, 2020; S. H. Fox et al., 2018; Stocchi et al., 2008). Device-aided treatments in PD include methods of continuous levodopa or apomorphine regimen delivery (medication pump treatments) and DBS (Armstrong & Okun, 2020; S. H. Fox et al., 2018; Odin et al., 2015). Other treatment options include lesional techniques, such as invasive radiofrequency pallidotomy or thalamotomy, and a relatively recently adopted, less invasive lesional technique using high-intensity focused ultrasound (HIFU), more accurately, magnetic resonance imaging-guided HIFU (MRgFUS) (Armstrong & Okun, 2020; Dobrakowski et al., 2014; Laitinen, 1995; Lozano et al., 1995; Matsumoto et al., 1984).

The pump treatments may be favorable options when the optimal dopaminergic window has become so narrow that a balanced motor symptom control cannot be reasonably achieved with peroral or intermittent subcutaneous medications

(Armstrong & Okun, 2020; Aubignat & Tir, 2024; S. H. Fox et al., 2018). Presently, available pump treatments include enteral delivery of levodopa/carbidopa or levodopa/entacapone/carbidopa gel to the small intestine, through an enteric (jejunal) tube applied through the abdominal wall and ventricle, or subcutaneous delivery of foslevodopa/foscarbidopa or apomorphine regimen (Armstrong & Okun, 2020; Aubignat & Tir, 2024; S. H. Fox et al., 2018; Jost et al., 2023; Katzenschlager et al., 2018; Rosebraugh et al., 2021; Soileau et al., 2022; Viljaharju et al., 2024). For each of these treatment options, the administration program includes the preprogrammed continuous infusion protocol, optionally with patient-controlled on-demand bolus dosing (Armstrong & Okun, 2020; Aubignat & Tir, 2024; Fimea, 2023; S. H. Fox et al., 2018; Jost et al., 2023; Katzenschlager et al., 2018; Rosebraugh et al., 2021; Soileau et al., 2022). The risks in these treatments include primary complications related to the administration route application, administration route malfunction, and possible local reactions (approximately 7.5–25% and 75%, in jejunal levodopa/carbidopa and subcutaneous foslevodopa/foscarbidopa treatment, respectively) and infections (approximately 1–5% and 15–20%, respectively) related to the route of administration (Antonini et al., 2015; Armstrong & Okun, 2020; Katzenschlager et al., 2018; Soileau et al., 2022; Valldeoriola et al., 2016). Levodopa/carbidopa gel treatment also seems to be beneficial in the treatment of NMSs (Kamel & Al-Hashel, 2020).

DBS treatment for PD motor symptoms involves neurostimulation of deep brain structures with electric current, and is used as an additional treatment with the anti-parkinsonian medications (Armstrong & Okun, 2020). Stimulation lead or leads are surgically placed in the deep brain structures involved in the basal ganglia circuits, either uni- or bilaterally (to one or both hemispheres) (Armstrong & Okun, 2020; DeLong & Wichmann, 2015; S. H. Fox et al., 2018; Krauss et al., 2021). A stimulation current generating device (implantable pulse generator) is installed subcutaneously on the upper chest, similar to a pacemaker generator (Armstrong & Okun, 2020; Krauss et al., 2021). Common stimulation targets in PD are globus pallidus interna (GPi) or STN, of which the latter has been more frequently used in Europe (Armstrong & Okun, 2020; Boogers & Fasano, 2024; DeLong & Wichmann, 2015; S. H. Fox et al., 2018). GPi-DBS may be less complicated in terms of lead application, programming, and side effects, but STN-DBS seems to offer better motor symptom control (Boogers & Fasano, 2024). The aim of DBS is to alleviate the motor symptom burden caused by the wearing off phenomenon, thus offering more stable symptom control (Armstrong & Okun, 2020).

Modern DBS systems are bilateral, and include segmented and directional electrodes and advanced, wireless computer programming interfaces allowing fine tuning of direction, amplitude (current), frequency and pulse width of the stimulation (Krauss et al., 2021). The electrodes administer electric pulse modulation on the

stimulation targets (Krauss et al., 2021). The DBS systems also allow multiple patient-switchable programs defined by the physician, and offer patient-controllable current control (Krauss et al., 2021). Some systems may offer remote programming features, or recording of low-field potentials (Krauss et al., 2021). It is even possible to use the low-field potential information, basically beta oscillations, to modulate the stimulation program on demand, to allow a more dynamic stimulation scheme, called adaptive DBS (Arlotti et al., 2018; Habets et al., 2018; Krauss et al., 2021; Little et al., 2013). However, elaborate patient selection is essential for successful DBS treatment: DBS may cause cognitive worsening and increase of falling accidents in patients with pre-existing cognitive decline, and thus, DBS should be targeted to younger and cognitively fit patients (S. H. Fox et al., 2018; Odin et al., 2015). Unsurprisingly, patients non-compliant with non-invasive treatment strategies are also considered to have worse risk-benefit ratios (Odin et al., 2015). Other noteworthy risks associated with DBS treatment include increased hallucinations, pronunciation of apathy and depression after the device application, device-related infections in 5–10% of cases, and possible technical problems that can outweigh the achieved therapeutical benefits (Krauss et al., 2021; Odin et al., 2015).

Lesional techniques can also be used to relieve the symptoms of PD, and more invasive techniques such as invasive radiofrequency pallidotomy or thalamotomy have already been used for decades (Laitinen, 1995; Lozano et al., 1995; Matsumoto et al., 1984). MRgFUS is a lesional technique with no need for craniotomy, and has first been shown effective in essential tremor, but can be used for symptom alleviation, primarily in tremor-dominant PD (Bond et al., 2017; Chang et al., 2015; Elias et al., 2013; Huss et al., 2015; Lipsman et al., 2013). The development of the technique was inspired by previous therapies for tremor with invasive thalamotomy (Elias et al., 2013; Huss et al., 2015; Lipsman et al., 2013; Pahwa et al., 2001; Schuurman et al., 2000). A typical treatment protocol is used for the tremor in PD, and is based on the thermocoagulation of the ventral intermediate nucleus in the thalamus (Armstrong & Okun, 2020; Elias et al., 2013). The procedure needs no open surgery and is conducted with a specialized system with magnetic resonance imaging (MRI) capabilities and a multi-emitter ultrasound system (Armstrong & Okun, 2020; Bond et al., 2017). The basic concept is to produce ultrasound waves at multiple locations and produce an interferential maximum at the lesion target, eventually raising the temperature at the site and creating a permanent lesion there (Elias et al., 2013). The placement of the lesion is determined by anatomical imaging produced during the process, the temperature at the target site is monitored with MRI imaging, and reversible effects are intermittently evaluated when applying increasing sonication energy at the target before the final, permanent lesioning (Elias et al., 2013). The benefits of the technique include the permanent nature of the treatment with a single treatment session, but a similar characteristic might also be

true for the side effects, including long-lasting lower limb weakness and gait and balance problems in 20–35% of cases (Chua et al., 2023). Other side effects include sensory deficits and dysarthria, which, however, tend to recover within a year after the intervention (Chua et al., 2023; Y. Xu et al., 2021). Recurrence of tremor after initial response is possible (Y. Xu et al., 2021). Treating bilateral symptoms with lesions to both ventral intermediate nuclei is not recommended in PD, although this type of stepwise procedure has been approved for essential tremor (Natera-Villalba et al., 2024). Currently, MRgFUS is mostly used for patients with tremor-dominant PD (Natera-Villalba et al., 2024). Unilateral interventions targeting GPi and STN, intended to also relieve other motor symptoms in an asymmetrical manner, have received the approval within the European Union and have been used in asymmetric PD with encouraging results (Armengou-Garcia et al., 2024; Insightec Ltd, 2024; Martínez-Fernández et al., 2018, 2020; Natera-Villalba et al., 2024).

2.1.6.3 Treatment of Non-Motor Symptoms

As the broad spectrum of NMSs may eventually cause an even greater burden on the quality of life than the motor symptoms in patients with PD, placing more emphasis on their management would be essential (Chaudhuri et al., 2007; Schrag, 2000). Unfortunately, the treatments for NMSs are mostly supportive, with much less evidence than for those used to treat the motor symptoms (Armstrong & Okun, 2020). NMSs might also manifest as non-motor fluctuations, in a similar way to motor symptoms (Rodriguez-Blazquez et al., 2021).

Common gastrointestinal symptoms in PD include constipation (in approximately 50–65% of patients) and sphincter relaxation problems (Chaudhuri et al., 2006; Janz et al., 2024; Pedrosa Carrasco et al., 2018). Constipation can be treated with the usual treatments used for constipation, mainly additional diet fiber or laxatives such as macrogol (Pedrosa Carrasco et al., 2018; Seppi et al., 2019). Some studies have suggested potential benefits of 5-HT_4 (5-hydroxytryptamine [serotonin], receptor subtype 4) agonists, but the evidence of their use in parkinsonian constipation is inadequate, and it is likely that their possible serious side effects outweigh the benefits (Pedrosa Carrasco et al., 2018). The use of anorectal botulinum toxin A injections has been studied for defecation difficulties, but the evidence remains inadequate (Pedrosa Carrasco et al., 2018). Other common symptoms involving the gastrointestinal tract are drooling of saliva and nausea (Rodriguez-Blazquez et al., 2021). The current guidelines suggest domperidone as useful for nausea and anorexia, and botulinum toxin A and B injections in salivary glands for drooling (Seppi et al., 2019).

The most common lower urinary tract symptoms are pollakisuria, urinary urge and nocturia (need to urinate during nighttime), present in 40–50% of patients with

PD (Rodriguez-Blazquez et al., 2021). The first-line advocated therapy is bladder training (McDonald et al., 2017). If this does not yield sufficient results, the symptoms can be treated with common antimuscarinic medications used for these symptoms in non-PD populations (McDonald et al., 2017). A newer regimen, a β_3 adrenergic agonist mirabegron, has also been suggested to be beneficial in the treatment of the urinary symptoms in conjunction with non-pharmacological interventions based on a small sample of PD patients (Madan et al., 2022). Sometimes, botulinum toxin A injections in a cystoscopic control might be useful to manage these symptoms in severe cases, if neurogenic detrusor overactivity is present (Badri et al., 2014; Giannantoni et al., 2011).

For orthostatic hypotension, primary treatments include adequate fluid intake, and if pharmacological treatment is warranted, droxidopa may be beneficial (Seppi et al., 2019). Secondarily, midodrine or fludrocortisone may be used (Fanciulli et al., 2020; Seppi et al., 2019). Rescheduling of any possible blood pressure lowering medications may also be helpful (Fanciulli et al., 2020).

RBD is a common symptom in PD, manifesting in up to 50% of patients (De Almeida et al., 2018; Zimansky et al., 2021). The primary medical treatment for insomnia in PD, melatonin, is possibly beneficial in RBD; in some cases, clonazepam may be used (Seppi et al., 2019). It is also important to review the total medication for SSRI, SNRI and tricyclic antidepressant (TCA) medications, as these might cause or worsen RBD symptoms (Seppi et al., 2019). In some cases, RBD might not only lead to sleeping difficulties, but also to physical traumas of the sleeping partner; thus, separating the sleeping sites of the patient and their partner can be helpful (De Almeida et al., 2018; Galbiati et al., 2019).

Common non-psychotic psychiatric problems among people with PD include apathy, depression and anxiety (Ahmad et al., 2023; Broen et al., 2016; Weintraub et al., 2022). D2R agonists are known to be potentially beneficial for parkinsonian apathy and depression, and rivastigmine may also be beneficial for apathy (Ahmad et al., 2023; Seppi et al., 2019; Sethi, 2008). SSRI or SNRI medications, particularly venlafaxine and TCA medications, can be used for both depression and anxiety in PD (Ahmad et al., 2023; Armstrong & Okun, 2020; Schneider et al., 2020; Seppi et al., 2019; Starkstein & Brockman, 2017; Weintraub et al., 2022). As a non-pharmacological intervention, cognitive behavioral therapy might be useful in parkinsonian depression (Seppi et al., 2019). For hallucinations and other psychotic symptoms, quetiapine is used as the mainstay medical treatment, and clozapine has also been found effective (Seppi et al., 2019). Recently, pimavanserin, a 5-HT_{2A} inverse agonist, has been suggested to be efficacious in the management (Seppi et al., 2019). At least mild cognitive decline is common in advanced PD (Rodriguez-Blazquez et al., 2021). Currently, the effective treatments for dementia in PD include

donepezil and rivastigmine, with possible additional beneficial effects of rivastigmine on gait and balance (Henderson et al., 2016; Seppi et al., 2019).

2.1.6.4 Disease-Modifying Treatments

Disease-modifying treatments for PD have been long awaited (Kalia et al., 2015). Until the late 2010s, the trials aiming to prevent or delay the progression of PD had been limited to the common dopaminergic medications used in the treatment of motor symptoms, dietary supplements (including coenzyme Q_{10}, vitamin D, and creatine) and exercise, with no sufficient evidence supporting any of these interventions (S. H. Fox et al., 2018).

Since then, recent promising steps towards disease-modifying treatments have received great interest (Vijiaratnam et al., 2021). However, the trials inspired by the plausible mechanisms related to PD-causing gene mutations, targeting LRRK2 and GBA associated pathways, have mostly been unsuccessful (Vijiaratnam et al., 2021), although previous small, non-randomized and non-controlled study with peroral ambroxol yielded intriguing results (Mullin et al., 2020). Various other treatment targets related to mitochondrial function and calcium-dependent mechanisms have also been investigated (Vijiaratnam et al., 2021).

Previous studies with glucagon-like peptide 1 (GLP-1) regimens include trials with exenatide, with low certainty of therapeutical benefits in motor symptom severity (Mulvaney et al., 2020). A trial with lixisenatide has since shown statistically significant results supporting benefits in motor outcome after one year of GLP-1 treatment in early PD, but the results in general appeared ambiguous (Meissner et al., 2024; Standaert, 2024). Some trials have targeted the centripetal phenomenon of α-synuclein misfolding and aggregation, with either monoclonal antibodies targeting α-synuclein, or small molecular inhibitors of certain α-synuclein misfolding steps (Vijiaratnam et al., 2021). α-synuclein formation could also be modulated with β_2 adrenergic receptor agonists, and some trials have suggested possible symptomatic benefits, albeit with uncertain evidence (Vijiaratnam et al., 2021). One concept is to promote the neuroprotection and regeneration of nigrostriatal axons using the glial cell line-derived neurotrophic factor (Barker et al., 2020; Gash et al., 1998). A previous trial from the early 2000s used intravenous glial cell line-derived neurotrophic factor administration, with no evidence of treatment efficacy (Nutt et al., 2003). Other neurotrophic factors might offer neuroprotective effects. A recent Finnish study with involving intraputaminal administration of recombinant cerebral dopamine neurotrophic factor, suggested to modulate endoplasmic reticulum stress and neuroinflammation, showed possible signs of biological response, and supported the safety and tolerability of the treatment, although few administration-route associated infections occurred (Huttunen et al.,

2023). Further, some studies have investigated the efficacy and safety of fecal transplantation, promoting the safety of the procedure, with potential therapeutic benefits (Bruggeman et al., 2024; Scheperjans et al., 2024).

In summary, the results from the trials aiming to demonstrate disease-modifying treatments for PD have not yet reached their target, but their promising results have strengthened the hope for disease-modifying treatments in the future. Another dilemma with disease-modifying treatments is that, as the current diagnostic criteria of PD are reached in early PD, as much as 35–45% of striatal DAT activity, reflecting the integrity of nigrostriatal pathways, is lost (Heng et al., 2023). Thus, studying the ways to recognize prodromal PD and develop a biological classification of PD, rather than only using the current clinically oriented criteria in clinical trials of disease-modifying treatments, is warranted (Höglinger et al., 2024; Simuni et al., 2024).

2.2 Neurobiology of Parkinson's Disease

2.2.1 Basal Ganglia Anatomy and Connections

Basal ganglia (BG) are a paired subcortical group of structures, consisting of the striatum (nucleus caudatus and putamen), GPi and globus pallidus externa (GPe). Paired SN, including SNr (pars reticulata) and SNc (pars compacta), and STN are essential parts of the BG involving pathways. The (dorsal) striatum is a subsystem of the BG including nucleus caudatus and putamen, and receives neuronal afferents from a wide area of neocortices (glutamatergic), the dopaminergic SNc, and serotonergic dorsal raphe nuclei (Albin et al., 1989; Assous, 2021; Pelloux & Baunez, 2019). The striatum sends afferent connections 1) GPe, connecting further to GPi and SNr. Further, GPe sends projections to STN, with additional efferents projecting to GPi and SNr, 2) directly to GPi and SNr (Albin et al., 1989; Assous, 2021) (**Figure 1**). The striatum is highly interconnected with SNc (Albin et al., 1989; Assous, 2021). Nucleus accumbens, a part of the ventral striatum, has a similar connectivity profile as the dorsal striatum, but receives the main dopaminergic inputs from ventral tegmental area (VTA) (Pelloux & Baunez, 2019).

2.2.1.1 Cell Types

The striatum receives its glutamatergic inputs from the neocortices through intratelencephalic (IT) and pyramidal tract (PT) neurons. The IT neurons appear to have both ipsi- and contralateral striatal projections, while the PT neurons respect the midline with their ipsilateral configurations. These neurons seem to have a mutual hierarchical relationship: the IT neuron axons project to PT neurons, but no reciprocal connections exist (Morgenstern et al., 2022).

The striatum projects to other structures through medium spiny neurons (MSNs; spiny projection neurons [SPNs]) conveying GABA (ɣ-amino butyric acid) neurotransmission, comprising 90–95% of all striatal neurons (Fazl & Fleisher, 2018; Morgenstern et al., 2022). These include direct spiny projection neurons (dSPNs; D1R expressing) and indirect spiny projection neurons (iSPNs; D2R expressing), both of which receive modulatory dopaminergic input from SNc (Fazl & Fleisher, 2018). Some studies have suggested that dSPNs receive a greater proportion of their input from IT neurons than iSPNs, which have a PT-dominant input configuration (D. A. Burke et al., 2017; Martel & Galvan, 2022). The dSPNs and iSPNs also contain opioid peptides, enkephalin and dynorphin (Steiner & Gerfen, 1998). These are believed to participate in the modulation of striatal signaling (Steiner & Gerfen, 1998).

In addition, multiple types of striatal interneurons exist, comprising approximately 10% of all the striatal neurons (Fazl & Fleisher, 2018). The two main groups of striatal neurons are cholinergic interneurons and interneurons conveying GABA neurotransmission (Johansson & Silberberg, 2020). Three main groups of interneurons conveying GABA neurotransmission have been defined: 1) fast-spiking interneurons (parvalbumin expressing), 2) low-threshold spike interneurons (neuropeptide Y and somatostatin expressing) and 3) calretinin-expressing interneurons (Johansson & Silberberg, 2020). The cholinergic interneurons seem to receive solely ipsilateral inputs, mostly from the PT neurons (Johansson & Silberberg, 2020; Martel & Galvan, 2022). The fast-spiking interneurons receive cortical input from cingulate, motor and sensory cortical areas, mostly through IT neurons, and the low-threshold spike interneurons receive input from cingulate and motor cortices (Johansson & Silberberg, 2020). Most of the interneurons receive thalamic inputs with the exception of the striatal calretinin-expressing interneurons, which only receive non-thalamic connections (Martel & Galvan, 2022; Sidibé & Smith, 1999). Some other interneuron groups, such as neurogliaform interneurons and tyrosine hydroxylase-expressing interneurons, have been identified (Martel & Galvan, 2022).

In summary, the main information flow through the corticostriatal connections to MSNs is modulated and converged in complex interactions involving not only the corticostriatal inputs and MSNs, but also nigrostriatal inputs and multiple types of striatal interneurons (Martel & Galvan, 2022).

2.2.1.2 Connectivity Features

In the BG circuitries, the caudate nucleus, putamen and STN are considered to be the input nuclei, GPe and SNc to be the intrinsic nuclei, and GPi and SNr to be the output nuclei (Shipp, 2017). The striatum receives input from the cerebral cortices,

thalamic nuclei, and SNc (Villalba et al., 2021). Through the GPi and SNr, the BG send connections to the thalamus, the most prominent targets being the ventral tier (ventral lateral [VL] and ventral anterior [VA]) and mediodorsal thalamic nuclei (Villalba et al., 2021). Of the thalamic nuclei receiving input from the GPi and SNr, the VL and VA thalamic nuclei have especially robust bidirectional connections with the frontal motor areas (Villalba et al., 2021). These nuclei have efferent glutamatergic thalamocortical projections to the prefrontal cortex (Villalba et al., 2021). Other efferent connections from the GPi and SNr are projected to the midbrain tegmentum, pedunculopontine nucleus (PPN), additional projections from the GPi to the lateral habenula, and from the SNr to the superior colliculus (Albin et al., 1989; DeLong & Wichmann, 2015). In primates, evidence of crossing pallidothalamic and pallidotegmental connections also exists (Hazrati & Parent, 1991; A. Parent & De Bellefeuille, 1982).

Regarding connectivity, the BG can be considered as a set of components contributing to parallel and closed circuits (DeLong & Wichmann, 2015). As may be suggested per the underlying structures, convergence and parallelism are integral features of BG connections (DeLong & Wichmann, 2015; Martel & Galvan, 2022; Shipp, 2017). In addition, BG are known to be functionally segregated, not meaning that such would be any unique feature in the CNS (DeLong & Wichmann, 2015).

Three to four distinguishable striatal main functional circuits covering the majority of the striatum have been described: (sensori)motor, associative and limbic circuits (Basile et al., 2021; Bertino et al., 2020; Obeso et al., 2008) and the oculomotor circuit (DeLong & Wichmann, 2015). Regarding the motor circuit, somatotopical segregation is preserved along all the structures in the BG circuitry, despite convergence (Alexander et al., 1986; DeLong & Wichmann, 2015). Similar persistent segregation has been demonstrated in the circuits originating from frontal cortices (Heilbronner et al., 2018).

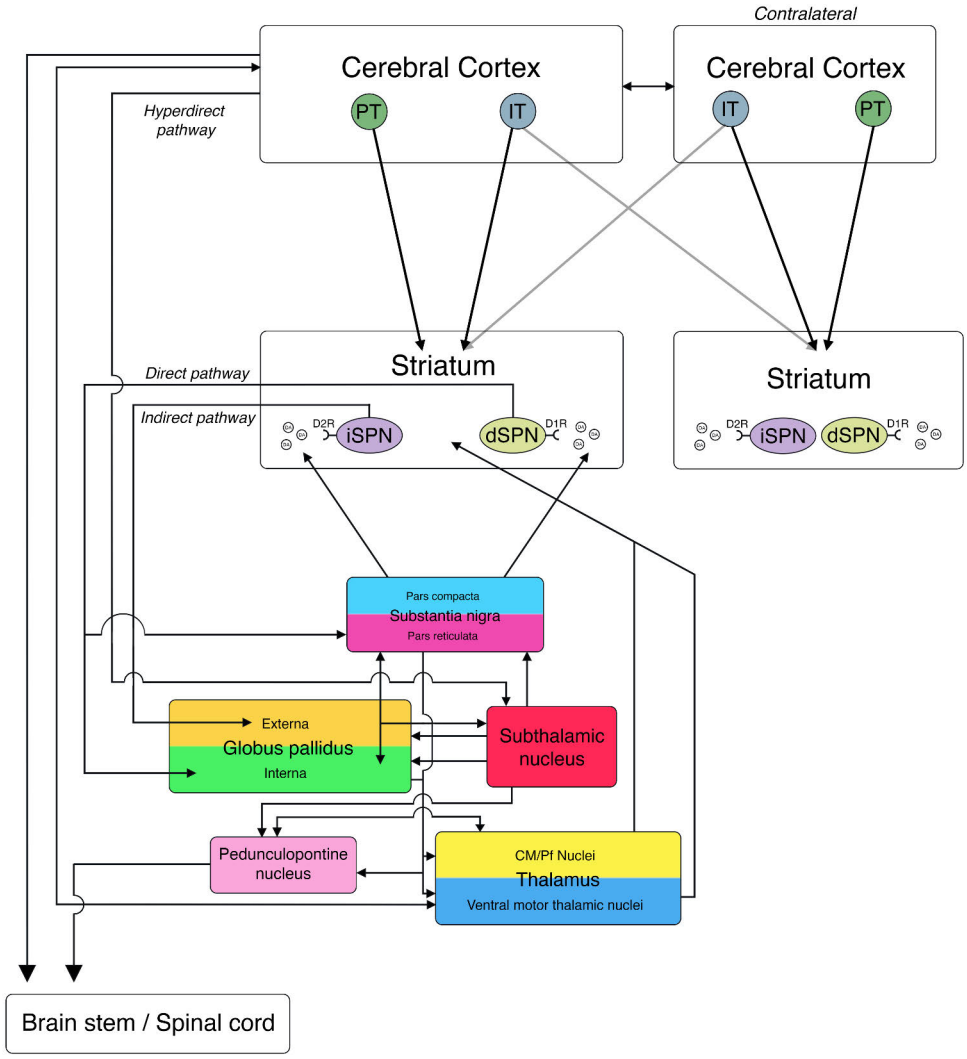

Figure 1. Main connectivity features of the basal ganglia. Cerebral cortex, thalamus, basal ganglia, subthalamic nucleus and pedunculopontine nucleus have vast interconnectivity. The initial routes of direct, indirect and hyperdirect pathways are presented. Note that the connectivity is depicted focusing on one hemisphere. DA, dopamine; iSPN, indirect spiny projection neuron; dSPN, direct spiny projection neuron; CM/Pf, centromedial and parafascicular nuclei; IT, intratelencephalic neurons; PT, pyramidal tract neurons. The figure has been created based on schematics by Delong and Wichmann (2015).

Three main pathways for motor regulation involving the BG system have been identified: direct, indirect and hyperdirect pathways (**Figure 1**) (DeLong & Wichmann, 2015; Neumann et al., 2018). The direct pathway receives input from the cerebral motor cortices to the putamen (DeLong & Wichmann, 2015; Hoover &

Strick, 1993). Subsequent connections, projecting from the MSNs, terminate in the GPi and the SNr. Further, the GPi and the SNr project to the VL thalamic nucleus (DeLong & Wichmann, 2015; Hoover & Strick, 1993). The loop is closed by the thalamocortical connections with frontal cortical motor fields (DeLong & Wichmann, 2015; Hoover & Strick, 1993). These consist of multiple parallel connections following somatotopic organization (DeLong & Wichmann, 2015; Hoover & Strick, 1993). Concerning the direct pathway, the SNc participates in neural modulation of the putamen by dopamine release, with a response in dSPNs through D1Rs (Obeso et al., 2008).

The indirect pathway receives input from the cerebral motor cortices to the putamen, as well (**Figure 1**). With the projections from MSNs, it connects forward to the GPe (DeLong & Wichmann, 2015; Martel & Galvan, 2022). Connections forward from the GPe project 1) directly to the GPi and SNr and 2) indirectly to the GPi and SNr with an additional relay at the STN (DeLong & Wichmann, 2015; Martel & Galvan, 2022). Again, forward connections from the GPi target the VL thalamic nucleus, closing the loop with parallel connections to the different frontal motor cortices (DeLong & Wichmann, 2015; Martel & Galvan, 2022). Concerning the indirect pathway, the SNc exhibits neural modulation in the putamen through dopamine release, with a response in iSPNs (indirect spiny projection neurons) mainly through D2Rs (DeLong & Wichmann, 2015; Martel & Galvan, 2022).

The hyperdirect pathway, differently from the other two, receives input from the cortical areas directly to the STN (**Figure 1**) (DeLong & Wichmann, 2015; Martel & Galvan, 2022). The loop of this pathway is similarly closed with the connections to the GPi and further to the VL thalamic nucleus, which is interconnected to the frontal motor cortices (DeLong & Wichmann, 2015; Martel & Galvan, 2022). As in the other parts of the pathways described, corresponding functional domains have been recognized in the STN (DeLong & Wichmann, 2015; Martel & Galvan, 2022). The connections from the SNr and GPi to the thalamus (nigrofugal and pallidofugal) also send projections to the centromedian (CM; for motor circuits) and parafascicular nuclei (Pf; for associative circuits), these with markedly less connections to cerebral cortices (DeLong & Wichmann, 2015; Smith et al., 2004).

In addition to the corticostriatal inputs, the striatum receives thalamostriatal projections. In primates, the intralaminar nuclei, at least the forementioned CM and Pf nuclei, send projections in a markedly topographical manner to all striatal areas (Smith et al., 2004). The Pf projections mainly innervate the striatofugal (striatum–GP) neurons of the direct pathway, while the CM projections target the dendrites of cholinergic interneurons (Smith et al., 2004). CM stimulation has been shown to reduce the firing rate of tonically active interneurons (electrophysiological term for cholinergic interneurons), resulting in a net effect of decreased acetylcholine (ACh) release (Nanda et al., 2009). Apart from the projections of these intralaminar nuclei,

striatal areas also receive projections from the ventral motor thalamic nuclei (Smith et al., 2004). The principal neurotransmitter of these projections is glutamate (Smith et al., 2004).

The GPi and SNr also send collaterals to the brainstem, mainly to the PPN and superior colliculus (Alam et al., 2011; DeLong & Wichmann, 2015). PPN consists of various types of neurons: at least cholinergic and noncholinergic (glutamatergic and some GABAergic and substance P neurons) (Alam et al., 2011; DeLong & Wichmann, 2015). The cholinergic neurons target the thalamus, cerebellar peduncles and STN (DeLong & Wichmann, 2015; Mena-Segovia et al., 2004). The noncholinergic neurons target SNc, STN, and globus pallidus (DeLong & Wichmann, 2015; Mena-Segovia et al., 2004). In addition, the descending projections of the PPN terminate in the pons, medulla and spinal cord (DeLong & Wichmann, 2015; Mena-Segovia et al., 2004). The variety of functions mediated by PPN, its vast connections, and the thalamostriatal connections it involves, are to some extent unclear. However, PPN is known to be essential for gait and movement in general as well as for rapid cortical rhythms associated with wakefulness and REM sleep (DeLong & Wichmann, 2015; Mena-Segovia et al., 2004). Its thalamostriatal connections seem to have a role in the selection of motor response to sensory stimulus and behavioral flexibility (Kato et al., 2011, 2018).

Dispersed but substantial evidence of crossing collaterals at several sites in the BG pathways have been identified during past decades in non-human primate studies. These include crossing corticostriatal, pallidothalamic and pallidotegmental projections (Fallon & Ziegler, 1979; Hazrati & Parent, 1991; Johansson & Silberberg, 2020; Martel & Galvan, 2022; A. Parent & De Bellefeuille, 1982).

2.2.2 Pathophysiology and Disease Mechanisms

2.2.2.1 Neuropathological Background

Lewy body disorders are characterized by α-synuclein-containing Lewy body inclusions in the brain. Neuropathologically, PD belongs to the spectrum of these Lewy body disorders, dementia with Lewy bodies being the other notable member of the group (Koga et al., 2021). However, it should be noted that Lewy body pathology is not a totally unique feature for these two conditions; it is also seen in POLG-associated neurodegeneration, Niemann-Pick type C1 and Krabbe disease and other rare neurometabolic disorders (Erskine & Attems, 2021).

In autopsies, the first stages of Lewy body disease cannot be macroscopically distinguished from healthy controls when cerebral structures are considered (Koga et al., 2021). Instead, neuromelanin loss in substantia nigra and locus coeruleus (LC)

is usually considered to be a hallmark macroscopic feature, observed even in the clinically early phases (Koga et al., 2021).

The neuropathology of PD is characterized by practically insoluble Lewy neurites (spindle-formed aggregations) in neuronal processes, and Lewy bodies (globular aggregations) in neuronal perikarya (neuronal somas) (Braak et al., 2003). Lewy bodies have a tendency to aggregate to the axonal terminals of nigrostriatal axons, and retrograde (from axon terminal towards perikarya) rather than anterograde spread along the neuron has been proposed based on the data from experimental animal models, including studies in non-human primates (Luk et al., 2012; Recasens et al., 2014; Surmeier et al., 2017). In a non-human primate model, only α-synuclein transferred from a human source to the striatum has been shown to initialize a nigrostriatal degeneration process similar to the process seen in PD (Recasens et al., 2014).

The reason for α-synuclein causing focused damage to the specific sites including SNc dopaminergic neurons, LC, dorsal motor vagal nucleus and PPN is not fully understood (Surmeier et al., 2017). However, the most likely reason behind the destructive effect, which is extremely pronounced in SNc dopaminergic neurons, has been hypothesized to be the oxidative stress related to the dopamine breakdown metabolism, producing oxygen radicals and neurotoxic metabolites, such as with 6-hydroxydopamine used frequently in animal models to cause a PD-mimicking pathological condition (Berman & Hastings, 2001; Bolam & Pissadaki, 2012; A. H. Schapira, 2008; Sulzer, 2007; Sulzer & Zecca, 1999). Additional features that predispose the typical target sites to damage include them having demyelinated, and thus more vulnerable, axons, as well as marked calcium ion flux across the cell membrane with subsequent high and fluctuating intracellular calcium concentrations, in a weakly buffered intracellular environment (Surmeier et al., 2017).

2.2.2.2 Hypotheses on the Disease Progression

The neuropathological hallmark of PD is inarguably its pathology characterized by brain Lewy body deposits (Koga et al., 2021). In 2003, Braak and colleagues proposed a neuropathological staging system for PD based on 110 autopsies (Braak et al., 2003). They defined Stage 1 as when pathological findings are only in the dorsal IX/X nucleus, Stage 2 as when pathology spreads through the pontine tegmentum (including LC and caudal raphe nuclei), Stage 3 as when there is degeneration in the midbrain (especially SNc), Stage 4 as when pathology spreads to the basal prosencephalon and temporal mesocortex, and they considered the eventual more extensive spread to the neocortical areas to happen in Stages 4 and 5 (Braak et al., 2003). Their staging was first widely accepted and applied to theories

of PD pathological mechanisms, but has since received criticism, in part due to the study design and contradictions in findings among other populations (R. E. Burke et al., 2008). On the other hand, prion-like properties of α-synuclein, including cell-to-cell propagation, possibly align with the fundamental concept in Braak's theory are supported by in vitro and animal studies, but at least to date, are not shown in humans (Borghammer, 2018).

Although the hallmark presentation of PD is inevitably due to the pathology in the CNS, Lewy bodies are also found outside the CNS in the cardiac sympathetic nervous structures (Fujishiro et al., 2008; Ghebremedhin et al., 2009; Herzog, 1931; Iwanaga et al., 1999; Orimo et al., 2007, 2008), the enteric nervous system (Klingelhoefer & Reichmann, 2015; Kupsky et al., 1987; Wakabayashi et al., 1990; Wakabayashi & Takahashi, 1997), cutaneous nerves (Ikemura et al., 2008) and salivary glands (Del Tredici et al., 2010). Lewy body-like deposits have also been reported in adrenal glands of patients with PD (den Hartog Jager, 1970). Based on these remarks, a model featuring two alternative starting points of α-synuclein spread and Lewy body pathology has been proposed, most prominently by Borghammer and Van Den Beerge in 2019, in their brain-first and gut-first hypothesis (Borghammer & Van Den Berge, 2019; Clairembault et al., 2015). In Borghammer's refined α-Synuclein Origin site and Connectome model, the hypothesis is that PD pathology either starts outside the brain (body-first PD) in the enteric nervous system, or inside the CNS (brain-first PD), causing two different main classes of PD. According to the hypothesis, in brain-first PD, the pathology starts in the amygdala or its nearby structures such as the olfactory bulb, resulting in a shorter prodromal phase, asymmetric involvement, and a narrower dysfunction of brainstem modulatory neurotransmitter systems. In body-first PD, the pathological processes start in the enteric nervous system, spreading through the vagal nerves quite symmetrically to the dorsal motor nuclei of vagal nerves, with pathology further dispersed to numerous structures in the brain stem, and accompanied with higher initial burden of α-synuclein pathology. This theory, which has received critique, suggests that all this leads to a longer prodromal phase, relatively more symmetrical involvement, more difficult NMSs and accentuated cognitive impairment (Borghammer, 2021; Lövdal et al., 2024).

Similar to the concept of gut-first PD, theories suggesting the initial origin of α-synuclein pathology in the gastrointestinal tract due to microbiome disturbances have been presented (Barichella et al., 2019; Bullich et al., 2019; Scheperjans et al., 2015). The first of these suggestions were based on PD and its postural instability and gait disorder (PIGD) traits being associated with distinct bacterial DNA profiles (Scheperjans et al., 2015). The characteristic feature of peripheral, possibly prodromal, α-synuclein pathology has also led to trials leveraging this to develop methods for diagnosing PD, or its prodromal phase (Gibbons et al., 2024; Orimo et

al., 2008). Such methods include [^{123}I]-meta-iodobenzylguanidine (MIBG) scintigraphy detecting cardiac sympathetic denervation (Orimo et al., 2008) and phosphorylated α-synuclein detection in skin biopsies (Gibbons et al., 2024).

Wherever the α-synuclein and Lewy body pathology initiates, it is associated with nigrostriatal dopaminergic denervation, and other monoaminergic disturbances in PD (P. Barone, 2010; Qamhawi et al., 2015; Seibyl et al., 1995; Shen et al., 2022). These have the potential to lead to other neurotransmitter and electrophysiological disturbances, neuroplastic changes and, eventually, to the broad spectrum of symptoms observed in PD (Albin et al., 1989; P. Barone, 2010; Conti et al., 2018; DeLong & Wichmann, 2015; Kogan et al., 2021; Ma et al., 2007; McCarthy et al., 2011; McGregor & Nelson, 2019; Meles et al., 2020; Qamhawi et al., 2015; Tang et al., 2020; Vo et al., 2017).

2.2.2.3 Pathophysiological Mechanisms

Considering the motor function, the striatum acts as a relay mechanism, in conjunction with the pyramidal system (Shepherd, 2013). Dopamine is an essential neurotransmitter for this function, mediating the control of cortico-striatal connectivity (Honey, 2003). Although dopamine plays a key role in the motor manifestations of PD, and the theories of the pathological mechanisms are related to the dopaminergic deficit, other neurotransmitter systems, particularly noradrenergic, serotonergic and cholinergic systems, appear to be important in the diverse clinical appearance of the disease (P. Barone, 2010).

Of the cardinal motor symptoms, bradykinesia and rigidity have long-lived circuit mechanism theories, explaining the symptoms by the imbalance between direct and indirect striatopallidothalamic circuits associated with dopaminergic deficit (DeLong & Wichmann, 2015). A well-known and generally accepted theory is that nigrostriatal degeneration leads to disproportion of D1R and D2R activation, and consequently to relative overactivity of the D2R-associated indirect basal ganglia circuit (Albin et al., 1989; DeLong & Wichmann, 2015; McGregor & Nelson, 2019). Further, this leads to disinhibition of GABA activity in the SNr, and disinhibition of the motor control circuits (DeLong & Wichmann, 2015). The role of serotonergic variation in PD tremor has also been suggested (Qamhawi et al., 2015).

There is also the electrophysiological point-of-view of parkinsonian motor symptoms: more severe motor symptoms, momentary motor symptom aggravation, and a dopamine-depleted state are associated with pathological beta oscillations (13–30 Hz in the basal ganglia circuits) (Beck et al., 2016; McCarthy et al., 2011), and fewer of these oscillations are associated with symptom alleviation (Morelli & Summers, 2023). This aspect has become more evident as the interest in DBS has

increased, and DBS techniques (low field potential guided programming) have developed towards leveraging this phenomenon (Swinnen et al., 2023).

A parallel theory, supported by motor symptom alleviation with anticholinergic agents, is that dopaminergic depletion not only leads to an imbalance in D1R- and D2R-mediated activity, but also relatively overt cholinergic activity in the striatum (Conti et al., 2018). It has previously been conceived that tremor would better respond to anticholinergic agents than to dopaminergic agents, and thus it has also been thought that tremor would be more mediated through this imbalance between the cholinergic and dopaminergic system (Paz & Murer, 2021). However, the anticholinergic agents seem to relieve both akinetic-rigid and tremulous symptoms, with no emphasis on either (Katzenschlager et al., 2002; Paz & Murer, 2021).

Several studies with animal models, mostly with 6-hydroxydopamine lesioned rodents, have shown that the dopaminergic denervation in the striatum is associated with profound cell-level structural changes, mediated mostly through a loss in D1R-mediated effects in both iSPNs and dSPNs, including dendritic tree atrophy and decreased spine density (Alberquilla et al., 2020; Martel & Galvan, 2022; Suarez et al., 2020; Villalba & Smith, 2018). However, dendritic spine loss seems to be even clearer in dSPNs (Suarez et al., 2020). The effects of a dopaminergic deficit are also reflected in the glutamatergic function, with changes in the glutamatergic synapses targeting SPNs (Ingham et al., 1998; Villalba & Smith, 2018). The hypodopaminergic state also seems to strengthen the glutamatergic synapses targeting iSPNs, and weaken those targeting dSPNs (Shen et al., 2022).

Network mechanisms underlying both the motor and non-motor symptoms in PD have attracted the interest of researchers as well, highlighting brain regions outside the nigrostriatal tract (Joutsa et al., 2018; Kogan et al., 2021; Ma et al., 2007; Meles et al., 2020). Using [^{18}F]fluorodeoxyglucose (FDG) PET and resting-state functional MRI (rs-fMRI), a repeating pattern of metabolic activity related to the motor symptoms of PD, called PD-related pattern, has been identified (Kogan et al., 2021; Ma et al., 2007; Meles et al., 2020; Rommal et al., 2021; Vo et al., 2017). Another pattern, related to the cognitive symptoms of PD, has also been suggested to exist (Tang et al., 2020; Vo et al., 2017). The wide-spread neurotransmitter abnormalities in PD, and their effects through functional networks, have been suggested to underlie these patterns (Gu et al., 2019).

2.3 Molecular Imaging in Parkinson's Disease

In a scientific context, a vast selection of imaging tracers has been utilized in PD research (Beauchamp et al., 2023; Braune et al., 1999; Carey et al., 2021; Hirano et al., 2009; Laurencin et al., 2023; C. S. Lee et al., 2000; Legault-Denis et al., 2021; Liepelt et al., 2009; Maillet et al., 2021; M. L. T. M. Müller et al., 2015; Pappata et

al., 2011; Petrou et al., 2015; Politis et al., 2010; Rektorova et al., 2008; Robert et al., 2012; Shah et al., 2016; Van Der Zee et al., 2021; Yang et al., 2019). However, the purpose of molecular imaging in the clinical context has been rather simple: to enhance the differential diagnostics of PD (H. T. S. Benamer et al., 2000; Catafau & Tolosa, 2004; Lorberboym et al., 2006). Molecular imaging is executed using either single photon emission computed tomography (SPECT) or PET (Rahmim & Zaidi, 2008).

The philosophy underlying both of these imaging techniques, SPECT and PET, is to administer radioactively labelled molecules targeting certain cells, receptors, or other structures or functions in the area of interest (e.g., cells expressing certain receptors, or glucose metabolism), image the local differences in the radioactive radiation or its kinetics based on the distribution phenomena, and eventually obtain an image of certain biological distribution (Beauchamp et al., 2023; H. T. S. Benamer et al., 2000; Hirano et al., 2009; Rahmim & Zaidi, 2008; Robert et al., 2012; Van Der Zee et al., 2021; Wernick & Aarsvold, 2004). While the philosophy of these techniques is very similar, there are a number of critical technical differences between them, which affect their clinical utilization and the information acquired with an individual scan (Rahmim & Zaidi, 2008). In SPECT, a set of projections are acquired with an arch-form detector camera identifying the gamma quants and rotating around the imaging target (**Figure 2A**) (Rahmim & Zaidi, 2008; Wernick & Aarsvold, 2004). Using these projections (**Figure 2B**), a three-dimensional image with tomographic slices is reconstructed using an iterative reconstruction algorithm (**Figure 2C**) (Rahmim & Zaidi, 2008; Wernick & Aarsvold, 2004). Unlike SPECT, PET is based on coincidence detection (Rahmim & Zaidi, 2008). While decaying, the radioisotopes used in PET emit positrons, which annihilate when coming in contact with electrons. Each annihilation results in two 511 kiloelectronvolt (keV) gamma quants directed in completely opposite directions (Levin, 2004). Finally, the emission results in the detection from two detectors on the opposite sides of the place of the annihilation event, at a very specific time determined by the moment of annihilation (Levin, 2004). Thus, in theory, any signal other than that with approximately 511 keV energy and fulfilling the coincidence criteria stay undetected (Levin, 2004; Rahmim & Zaidi, 2008). Based principally on this, PET offers better spatial resolution and an enhanced signal-to-noise ratio (Rahmim & Zaidi, 2008).

PET has an advantage over SPECT in terms of sensitivity and signal-to-noise ratio (Rahmim & Zaidi, 2008). However, the isotopes used in SPECT have a longer half-life than those used in PET, which allows shipping to distant imaging locations and a wider observational time window (Rahmim & Zaidi, 2008). Especially in the clinical context, one of the strengths of SPECT is a better availability of the radionuclides and equipment (Lammertsma, 2001). The longer half-life of SPECT

radionuclides allows their acquisition commercially instead of using an on-site cyclotron (Lammertsma, 2001).

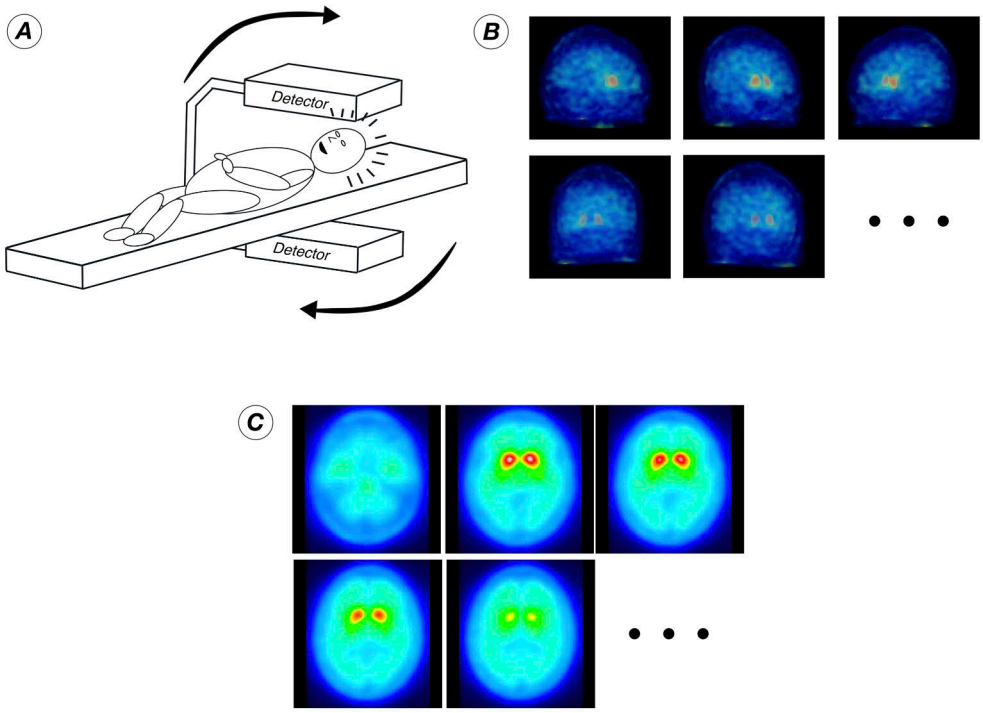

Figure 2. The concept of SPECT image acquisition. (A) An arch-form detector configuration rotates around the subject that has been given a dose of radioactive imaging tracer. **(B)** The detectors collect multiple projections of the target gamma radiation. **(C)** These projections are used to reconstruct tomographic slices and, eventually, a volumetric image using an iterative reconstruction algorithm (Rahmim & Zaidi, 2008; Wernick & Aarsvold, 2004).

Table 2. Most common molecular targets and names of tracers of the dopaminergic system.

Molecular target	IUPAC name	Other names
DAT	2β-carbomethoxy-3β(4-[^{11}C/^{18}F/^{123}I]iodophenyl)tropane	[^{11}C/^{18}F/^{123}I]β-CIT
	N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-[^{11}C/^{18}F/^{123}I]iodophenyl)-nortropane	[^{11}C/^{18}F/^{123}I]FP-CIT, [^{11}C/^{18}F/^{123}I]ioflupane
	N-(3-iodopro-2E-enyl)-2β-carbo[^{11}C/^{18}F/^{123}I]methoxy3β-(4′-methylphenyl)nortropane	[^{11}C/^{18}F/^{123}I]PE2I
	N-(3-iodoprop-2E-enyl)-2β-carbo[^{11}C/^{18}F/^{123}I]fluoroethoxy-3β-(4-methylphenyl)-nortropane	[^{11}C/^{18}F/^{123}I]FE-PE2I
	[2[[2-[[[3-(4-chlorophenyl)-8methyl-8-azabicyclo[3,2,1]-oct-2-yl]-methyl](2mercaptoethyl)amino]ethyl]-amino]ethanethiolato(3-)N2,N2',S2,S2]oxo-[1R-exo-exo)])- [^{99m}Tc]-technetium	[^{99m}Tc]TRODAT-1
L-AADC Activity and DA Storage	[^{18}F]dihydroxyphenylalanine	6-[^{18}F]fluoro-L-dopa, FDOPA
VMAT2	(+)2-hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11bH-bezo[α]-quinolizine	(+)[^{11}C]DTBZ
	(2R,3R,11bR)-9-(3-(18F)fluoranylpropoxy)-10-methoxy-3-(2-methylpropyl)-2,3,4,6,7,11b-hexahydro-1H-benzo[a]quinolizin-2-ol	[^{18}F]AV-133, [^{18}F]FP-DTBZ
D1LR	(5*R*)-8-chloro-3-(1^{11}C)methyl-5-phenyl-1,2,4,5-tetrahydro-3-benzazepin-7-ol	[^{11}C]SCH23390
D2LR	(2S)-3,5-dichloro-N-[(1-ethyl-2-pyrrolidinyl)methyl]-6-hydroxy-2-[^{11}C]methoxybenzamide	[^{11}C]-raclopride, [^{11}C]-RAC
	(S)-N-((1-allyl-2-pyrrolidinyl)methyl)-5-(3-[^{18}F]fluoropropyl)-2-methoxybenzamide	[^{18}F]desmethoxyfallypride, [^{18}F]DMFP
	5-(3-[^{18}F]fluoropropyl)-2,3-dimethoxy-N-[(2S)-1-prop-2-enylpyrrolidin-2-yl]methyl]benzamide	[^{18}F]fallypride
	5-bromo-N-[[(2S)-1-ethylpyrrolidin-2-yl]methyl]-3-methoxy-2-(1-[^{11}C])methoxybenzamide	[^{11}C]FLB 457
	[^{11}C]N-methylspiperone	[^{11}C]NMSP

DA, dopamine; DAT, dopamine transporter; L-AADC, L-amino-acid decarboxylase; VMAT, vesicular monoamine transporter; D1/2LR, D1/2-like receptor; IUPAC, International Union of Pure and Applied Chemistry

2.3.1 PET and SPECT Tracers

A myriad of molecular imaging studies employing various tracers involving the dopamine system in PD have been conducted over the years (Kaasinen & Vahlberg, 2017; Stoessl et al., 2011). Some of the most common tracers targeting the dopamine system are summarized in **Table 2**. The SPECT tracers targeting DAT include the most used 123-iodium (^{123}I) labelled molecules, [^{123}I]FP-CIT and [^{123}I]β-CIT, as well as 99m-tecnetium labelled [^{99m}Tc]TRODAT-1 (Kaasinen & Vahlberg, 2017; Kung et al., 1997). The PET tracers targeting DAT include the ^{11}C- and ^{18}F-labelled derivatives of FP-CIT and β-CIT (Kaasinen & Vahlberg, 2017).

Also, FE-PE2I and PE2I with higher specific binding to DAT, labelled with ^{123}I or ^{125}I for SPECT and with ^{11}C and ^{18}F for PET imaging, have been used in the scientific context (Emond et al., 1997; Guilloteau et al., 1998; Morbelli et al., 2020; Prunier et al., 2003). Based on previous literature, a well-known feature of DAT SPECT in PD is the progressive signal loss associated with longer disease duration, and the negative correlation between rigidity and bradykinesia with contralateral putaminal DAT binding (Kaasinen, 2016; Kaasinen & Vahlberg, 2017; Seibyl et al., 1995).

The imaging of the brain dopamine system is not limited to DAT function. Presynaptically, the conversion and storage function of dopaminergic neurons can be imaged with FDOPA or its ^{11}C-labelled analogue similar to levodopa. L-AADC converts FDOPA to [^{18}F]fluorodopamine (Kaasinen & Vahlberg, 2017; Tong et al., 2011). The produced [^{18}F]fluorodopamine is then transported to intraneuronal storage vesicles by a protein called vesicular monoamine transporter (VMAT); a vesicular protein that is expressed in the synaptic vesicles of monoaminergic presynaptic terminals (Kaasinen & Vahlberg, 2017; Tong et al., 2011). VMAT density can be imaged with molecular imaging methods as well; common PET VMAT tracers include (+)[^{11}C]DTBZ and [^{18}F]AV-133 (Kaasinen & Vahlberg, 2017; Morbelli et al., 2020). In studies of PD, the striatal activity observed utilizing these tracers has been relatively less decreased compared to DAT or VMAT, suggesting that L-AADC is upregulated in these patients (Kaasinen & Vahlberg, 2017).

D1-like (D1LR; including D1 and D5) and D2-like (D2LR; including D2, D3 and D4) dopamine receptors are mostly expressed postsynaptically, and mediate the effects of dopamine in the target cells (C. Liu et al., 2021). Some of these receptors also exist presynaptically, and they function as autoreceptors that, when activated, eventually inhibit the release of dopamine (C. Liu et al., 2021). D1LRs have less specific tracers, but mapping of these receptors in humans has been done with [^{11}C]SCH23390, and other tracers have been under development (Barret et al., 2021; Kaller et al., 2017; National Center for Biotechnology Information, 2024). On the other hand, D2LRs have multiple tracers, and can be mapped using [^{11}C]raclopride

([^{11}C]RAC), [^{18}F]desmethoxyfallypride [^{18}F]DMFP, [^{18}F]fallypride, [^{11}C]FLB 457 or [^{11}C]NMSP (Aalto et al., 2009; Antonini et al., 1994; Hall et al., 1988; Kaasinen et al., 2000, 2004; Mukherjee et al., 1996). Previous studies using the D2LR tracers have demonstrated initial upregulation of striatal D2LR density in early PD with a reversal of density in 3–5 year follow-ups, yet with increased receptor availability after dopaminergic medication withdrawal in advanced PD (Antonini et al., 1997; Ishibashi et al., 2010; Kaasinen et al., 2000, 2021; Rinne et al., 1995; Thobois et al., 2004). Patients treated with LCIG infusions present with increased dopamine availability (reflected as reduced tracer binding) (Politis et al., 2017), and treatment with amantadine has been suggested to upregulate D2 receptor availability in advanced PD (Volonté et al., 2001). Reduction of dopamine receptor density in the hypothalamus has also been demonstrated in patients with advanced PD (Politis et al., 2008).

Apart from the dopaminergic system, other essential molecular systems in the CNS have also been explored in PD populations (Bohnen et al., 2015, 2022; Carey et al., 2021; Joling et al., 2018; K. Kim et al., 2019; Laurencin et al., 2023; Maillet et al., 2021; M. L. T. M. Müller et al., 2015; Remy et al., 2005; Van Der Zee et al., 2021). Some of the most common tracers targeting systems other than the dopaminergic system are summarized in **Table 3**.

In general, serotonin-related molecular imaging tracer targets with specific tracers include serotonin transporter (SERT) and several serotonin receptor subtypes, including 5HT receptor subtypes 1A, 1B, 2A and 4 (Beliveau et al., 2017; Savli et al., 2012). [^{123}I]FP-CIT also binds to SERT (Abi-Dargham et al., 1996; Joling et al., 2018; Maillet et al., 2021; Pasquini et al., 2018, 2020; Qamhawi et al., 2015; Scheffel et al., 1997). The studies in PD patients with SERT binding [^{11}C]DASB or [^{11}C]MADAM, and utilizing the SERT binding capability of [^{123}I]FP-CIT, have suggested not only dopaminergic but also progressing serotonergic lesions along the disease progression, starting from the midbrain structures and proceeding towards cortical regions, as well as associations of serotonergic defects in tremor, apathy, depression and trait-anxiety in PD (Fazio et al., 2020; Joling et al., 2018; Maillet et al., 2021; Pasquini et al., 2018, 2020; Qamhawi et al., 2015). Noradrenalin-related tracer targets in previous human studies include noradrenaline transporter (NAT) and α_2 adrenergic receptors (α_2ARs) (Laurencin et al., 2023; Remy et al., 2005; Severance et al., 2007). [^{123}I]FP-CIT also has affinity for NAT (Abi-Dargham et al., 1996; Scheffel et al., 1997). Previous molecular imaging studies focusing on the noradrenaline system in PD, utilizing NAT binding [^{11}C]RTI-32 and α_2AR binding [^{11}C]yohimbine, have implied noradrenergic deficits along the disease progression, and have suggested an association of noradrenergic deficits with motor symptoms, fatigue, apathy, depression, anxiety and constipation (Ivy Carroll et al., 1995; Laurencin et al., 2023; Remy et al., 2005). Studies focusing on cholinergic changes

in PD, using [^{11}C]PMP targeting ACh esterase (AChE) activity and [^{18}F]FEOBV targeting vesicular ACh transporter, have implied links between cholinergic deficits and cognition and gait (Bohnen et al., 2015, 2022; K. Kim et al., 2019; M. L. T. M. Müller et al., 2015; Van Der Zee et al., 2021). The brain cholinergic system has been suggested to interact with dopaminergic deficits in the cognitive abnormalities of PD (K. Kim et al., 2019).

Table 3. Some of the most common molecular targets and names of SPECT/PET tracers targeting other systems in the CNS.

Molecular target	IUPAC name	Other names
SERT	[^{11}C]-N,N-dimethyl-2-(-2-amino-4-cyanophenylthio)-benzylamine	[^{11}C]DASB
	[^{11}C]-N,N-dimethyl-2-(2-amino-4-methylphenylthio)benzylamine	[^{11}C]MADAM
NAT	3P-(4'-methylphenyl)tropane-2P-carboxylic acid [^{11}C]methyl ester	[^{11}C]RTI-32
α_2AR	[^{11}C]methyl (1*S*,15*R*,18*S*,19*R*,20*S*)-18-hydroxy-1,3,11,12,14,15,16,17,18,19,20,21-dodecahydroyohimban-19-carboxylate	[^{11}C]yohimbine
AChE Activity	[^{11}C]methyl-4-piperidinyl propionate	[^{11}C]PMP
VAchT	[^{18}F]fluoroethoxybenzovesamicol	[^{18}F]FEOBV
μ Opioid Receptor	(1-[^{11}C])methyl 1-(2-phenylethyl)-4-(N-propanoylanilino)piperidine-4-carboxylate	[^{11}C]CAF, [^{11}C]carfentanil
Glucose Metabolism	[^{18}F]fluorodeoxyglucose	[^{18}F]FDG

SERT, serotonin transporter; NAT, noradrenaline transporter; α_2AR, α_2 adrenergic receptor; AChE, acetylcholine esterase; VAChT vesicular acetylcholine transporter

[^{18}F]FDG is used to investigate the glucose uptake and glucose-related metabolic activity. It has numerous clinical applications, for example, in oncology, cardiology and neurology (Wernick & Aarsvold, 2004). The brain metabolic pattern seen in patients with PD, has been replicated in several studies (Kogan et al., 2021; Ma et al., 2007; Meles et al., 2020). Cognitive symptoms in PD have also been suggested to be associated with specific brain metabolic patterns (Tang et al., 2020).

Outside the CNS, one tracer is also viable in the clinical context, in the differential diagnostics of parkinsonian syndromes: [^{123}I]metaiodobenzylguanidine ([^{123}I]MIBG) is used to assess the integrity of cardiac sympathetic nervature, the degeneration of which is a prominent feature in PD. The cardiac sympathetic

denervation is associated with corresponding α-synuclein deposits in PD, and MIBG scintigraphy can be used in the differential diagnostics between Lewy body-related disorders (PD, LBD, iRBD) as well as conditions not associated with Lewy bodies (MSA, PSP, vascular dementia and Alzheimer's disease) (Braune et al., 1999; King et al., 2011; Orimo et al., 2007, 2008). The integrity of the parasympathetic (cholinergic) system in the periphery has also been studied with AChE targeting [^{11}C]donepezil, suggesting that RBD in PD is associated with both earlier sympathetic and parasympathetic deficits peripherally, relative to putaminal dopaminergic deficits (Horsager et al., 2020).

2.3.2 [^{123}I]FP-CIT SPECT Imaging

Until the 1990s, several cocaine analogs targeting monoamine transporters were developed (Abi-Dargham et al., 1996; Kuikka et al., 1995; Neumeyer et al., 1996) After the first imaging studies in human subjects in the mid-1990s (Abi-Dargham et al., 1996; Kuikka et al., 1995), and following evidence of marked benefit in the differential diagnostics between PD and essential tremor, vascular parkinsonism and drug-induced parkinsonism (H. T. S. Benamer et al., 2000; Catafau & Tolosa, 2004; Lorberboym et al., 2006), SPECT with [^{123}I]FP-CIT (commercially known as DATScan™) became the standard DAT imaging protocol used in the clinical context (Kaasinen & Vahlberg, 2017). [^{123}I]FP-CIT preferentially binds to DAT but, as previously mentioned, also has affinity for SERT and NAT; hence, the SERT binding feature has also been previously utilized in PD studies (Abi-Dargham et al., 1996; Joling et al., 2018; Kaasinen & Vahlberg, 2017; Pasquini et al., 2018, 2020; Qamhawi et al., 2015; Scheffel et al., 1997).

The SPECT data itself includes only coarse spatial information, and the signal-to-noise ratio is poorer than in PET imaging. Both of these aspects result in difficulties in image registration with conventional algorithms. This limits the statistical power and compromises the use of voxelwise analyses (statistical analyses over individual image elements).

2.4 Parkinson's Progression Markers Initiative

PPMI (Parkinson's Progression Markers Initiative) is the most comprehensive longitudinal, observational study of subjects with PD (Marek et al., 2011). It has gathered a large magnitude of longitudinal clinical data and, in addition, longitudinal MRI and [^{123}I]FP-CIT SPECT imaging data of both subjects with early PD and healthy controls (Marek et al., 2011, 2018). The target follow-up time of the subjects with PD has been at least 5 years after the recruitment (Marek et al., 2011, 2018). The [^{123}I]FP-CIT SPECT data of PPMI have been analyzed in numerous studies

(Kaasinen, 2016; J.-Y. Lee et al., 2018; R. Liu et al., 2020; Llera et al., 2019; Nicastro et al., 2019; Pasquini et al., 2018, 2020; Picillo et al., 2017; Qamhawi et al., 2015; Rahmim et al., 2016, 2017; Tinaz et al., 2018; Y. C. Zhang & Kagen, 2017). In addition, some studies have explored the associations between [^{123}I]FP-CIT SPECT data and the clinical characteristics of PD (Kaasinen, 2016; J.-Y. Lee et al., 2018; R. Liu et al., 2020; Llera et al., 2019; Marek et al., 2011; Nicastro et al., 2019, 2020; Pasquini et al., 2018, 2020; Picillo et al., 2017; Qamhawi et al., 2015; Rahmim et al., 2016, 2017; Tinaz et al., 2018; Y. C. Zhang & Kagen, 2017), also focusing on SERT deficits utilizing the SERT binding capability of [^{123}I]FP-CIT (Nicastro et al., 2020; Pasquini et al., 2018, 2020; Qamhawi et al., 2015). Most of these studies have utilized region-of-interest (ROI)-based methods, and voxelwise studies have limited their search area to the striatum and nearby structures (Kaasinen, 2016; J.-Y. Lee et al., 2018; R. Liu et al., 2020; Nicastro et al., 2020; Pasquini et al., 2018, 2020; Picillo et al., 2017; Qamhawi et al., 2015; Rahmim et al., 2016, 2017; Tinaz et al., 2018).

3 Aims

This thesis aims to explore both the motor and non-motor manifestations of PD, focusing on the monoaminergic abnormalities underlying the symptoms, and investigating a possible, previously unknown non-motor manifestation in emotion-related bodily sensations. The specific aims of the included studies are:

I To examine associations between striatal DAT binding and the cardinal motor symptoms in early PD

II To examine associations between monoamine transporter binding and depression, anxiety, RBD, and cognition in early PD, and to characterize corresponding monoaminergic brain networks

III To examine the subjective bodily presentations of both sensory and motor symptoms and emotion-related bodily sensations in PD

4 Materials and Methods

4.1 Studies I and II

4.1.1 Study Sample

Data Retrieval

Data for Studies I and II were downloaded from the PPMI database (www.ppmi-info.org/access-data-specimens/download-data, RRID:SCR_006431) on April 12th 2019. The downloaded sample included demographic, clinical and imaging (T1 MRI), original reconstructed [^{123}I]FP-CIT SPECT imaging, and precalculated striatal SPECT ROI data of 215 healthy controls (healthy control group) and 451 patients with PD (PD group) from the PPMI cohort baseline, recruited 2010–2013. In total, 97 patients with PD and 49 controls were excluded due to missing or low-quality anatomical T1 MRI or [^{123}I]FP-CIT SPECT imaging, or failure in the following registration steps, and three patients with PD were excluded due to incomplete or missing MDS-UPDRS-III data. Thus, the final studied sample included 166 healthy controls and 354 patients with PD at baseline (**Figure 3**). In addition, corresponding data from 2-year (n = 275) and 4-year (n =162) follow-up visits were downloaded.

Clinical Data

The clinical data of the PPMI subjects included age, motor symptom duration, and MDS-UPDRS evaluation, including detailed motor symptom severity (measured with MDS-UPDRS-III score); questionnaire data of depression (measured 15-item Geriatric Depression Scale), anxiety, and RBD (measured 15-item Geriatric Depression Scale [GDS-15], State-Trait Anxiety Inventory [STAI], RBD screening questionnaire [RBDSQ], respectively); and cognitive assessments with Montreal Cognitive Assessment [MoCA]) (Knight et al., 1983; Nasreddine et al., 2005; Picillo et al., 2017; Rutten et al., 2017; Spielberger, 2012; Stiasny-Kolster et al., 2007; Wang et al., 2023; Weintraub et al., 2015; Weintraub, Oehlberg, et al., 2006; Yesavage & Sheikh, 1986). The medication data included dopaminergic,

monoaminergically active antidepressant and/or anxiolytic medications and cognition enhancer medications of the subjects at baseline and at 2-year and 4-year follow-ups.

Based on the MDS-UPDRS evaluations, the motor phenotypes (tremor-dominant [TD], indeterminate [IND], and PIGD) were determined as described by Stebbins et al. (Stebbins et al., 2013). In addition, the total MDS-UPDRS-III score and the subscores for rigidity, bradykinesia, and rest tremor amplitude on each side (total and upper limb) as sum scores of items included, and rest tremor severity indices as the product of the side-wise rest tremor amplitude scores and consistency, were calculated. Composite measures of akinetic-rigid symptoms, bradykinesia-rigidity scores, were also calculated as the sum of the corresponding symptom scores.

Monoaminergically active antidepressant and/or anxiolytic medications included SSRI, SNRI, noradrenaline-dopamine reuptake inhibitor (NDRI), noradrenergic and specific serotonergic antidepressant (NASSA), serotonin-modulating, TCA and tetracyclic antidepressant (TeCA) medications. Cognition enhancer medications included AChE inhibitors (AChEIs) and memantine.

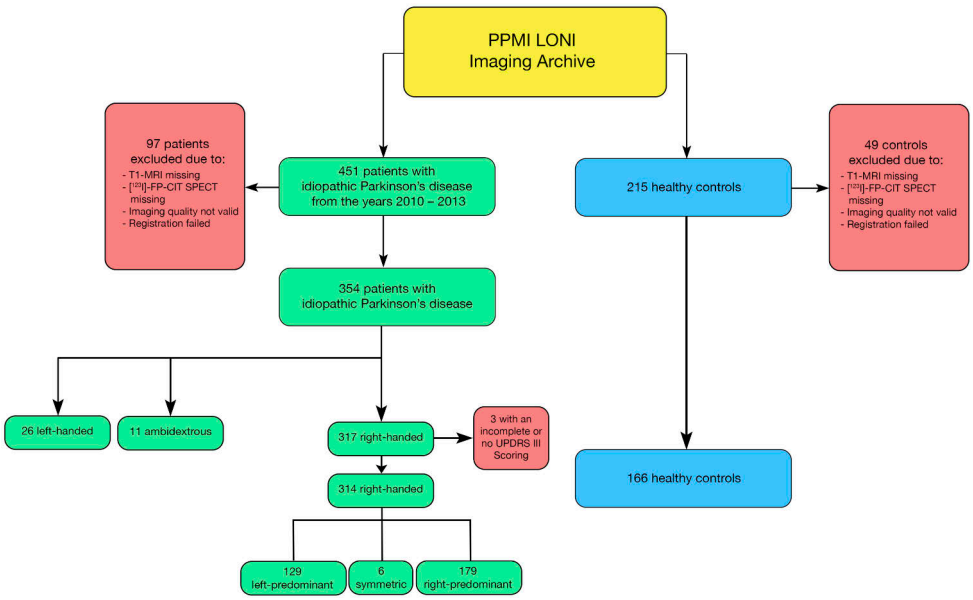

Figure 3. Study I: Sample selection. The group comparisons were run with all patients with PD (n=354) and healthy controls (n=166). Correlations with cardinal motor symptoms were run with right-handed patients only (n=314).

4.1.2 Imaging Data Preprocessing

Image Registration

To register [^{123}I]FP-CIT SPECT in Montreal Neurological Institute (MNI) standard space based on the anatomical data with a resolution of 1x1x1 mm^3, an image preprocessing pipeline was developed. The final SPECT preprocessing pipeline was based on a generic SPECT template, created from 45 pseudorandomly chosen [^{123}I]FP-CIT SPECT images of patients with PD at baseline that had been successfully registered to the MNI standard space according to the workflow principle introduced earlier (Rahmim et al., 2017).

First, to allow nonlinear transformations between each subject's native anatomical and standard space, the T1 MRI imaging of each subject was registered to the MNI standard space with SPM12 (Friston, 2007) software running on MATLAB R2021b (Higham & Higham, 2017) in Ubuntu Linux 20.04 (Zorin OS - branch). This resulted in registered MRI imaging, a nonlinear transformation between these two coordinate spaces, and a tissue segmentation of the MRI image.

The SPECT registration pipeline used the nonlinear transformation information, the generic SPECT template, and a subject's original SPECT imaging data. The programs in the pipeline included SPM12 (Friston, 2007) and Advanced Normalization Tools (ANTs) (Avants et al., 2011), of which the latter was used for all registration steps except nonlinear transformations. The SPECT image registration pipeline **(Appendix 1)** included:

1. linear registration of SPECT imaging (original SPECT) to the generic SPECT template in the subject's T1 native space (1st order registration).
2. nonlinear transformation of the 1st order registration result to the MNI standard space.
3. linear registration of the 1st order registration result in the MNI standard coordinate system to the generic SPECT template in the MNI space (2nd order registration; used as an individual SPECT template for the subject).
4. nonlinear transformation of the 2nd order registration result to the subject's T1 native space.
5. linear registration of the original SPECT imaging to the individual SPECT template instead of the generic template (3rd order registration).
6. nonlinear transformation of the 3rd order registration to the MNI space.

Quality Control

The registration quality was verified for each SPECT scan by visual inspection, focusing on the alignment of striatal and midbrain structures and skull features. The inspection involved the inspection of three image pairs: 1) the nonlinearly registered MRI and the MNI template in the MNI space, 2) the linearly registered [^{123}I]FP-CIT SPECT image and T1-weighted MRI in the native space, and 3) the nonlinearly registered individual [^{123}I]FP-CIT SPECT image and MNI template in the MNI space.

If the registration was not acceptable in the step-by-step inspection, the 1st order SPECT image registration was manually initialized with FSLEyes (Jenkinson et al., 2012), the registration pipeline was rerun, and the quality control was repeated. If the registration failed after two reruns, the image registration was deemed as failed.

Post-Processing

After the image registration, the images underwent partial volume error (PVE) correction, using region-based voxelwise (RBV) and subsequent reblurred van Cittert algorithms (Erlandsson et al., 2012; B. A. Thomas et al., 2016), based on the anatomical segmentation of the T1 MRI image. The PVE correction was conducted in the subject's native space, and the nonlinear transformation was used to transfer the PVE corrected image to the MNI standard space. Finally, the specific binding ratio (SBR) values for each of the [^{123}I]FP-CIT SPECT images were calculated using the bilateral occipital cortex as the reference region:

$$SBR_{i,j,k} = \frac{I_{i,j,k}}{I_{mean,occipital}} - 1 \quad (1).$$

The resulting, post-processed imaging data were used in the consequent voxelwise analyses.

Additional Quality Control

An additional quality measure was conducted for the baseline images that had undergone the image processing pipeline. Voxelwise univariate linear regression was used to determine areas correlated with the precalculated ROI values (left putamen, right putamen, left caudate, right caudate). These analyses demonstrated a strong correlation (voxel-level family-wise error (FWE) corrected P (P_{FWE}) < 10^{-11}) between each ROI and voxels in the corresponding anatomical regions. The relative strength of the association with each of the striatal ROIs was strongest in the corresponding area in these analyses **(Appendix 2)**. Thus, the registered data was anatomically uniform with the traditionally precalculated striatal ROI data.

4.1.3 Voxelwise Statistical Analyses

Study I

In Study I, all voxelwise analyses were performed with SPM12 (Friston, 2007) using the general linear model running on MATLAB R2021b (Higham & Higham, 2017). As a descriptive procedure, the groupwise comparisons between the healthy control and PD groups, between the PD subgroups with right- and left-predominant symptom onset, and association analyses of PD motor symptom severity measured with Hoehn & Yahr staging and MDS-UPDRS-III total score (left, right and total) were conducted, with age and sex as additional covariates. These analyses included the whole brain as the area for voxelwise tests, allowing the identification of the most important SBR abnormalities associated with PD and motor symptom severity.

The main analyses of the association between tracer binding and individual motor symptom properties included the motor symptom severity score, age, and sex as covariates. Several confirmative analyses were repeated by including 1) the Hoehn & Yahr stage, 2) the Hoehn & Yahr stage and MDS-UPDRS-III total score, 3) the Hoehn & Yahr stage and bradykinesia-rigidity total score, 4) the Hoehn & Yahr stage and PD motor phenotype, and 5) the Montreal Cognitive Assessment (MoCA) score as additional covariates. The independence of the motor symptom-associated tracer binding effects was studied in corresponding models, but including two motor features, rest tremor and bradykinesia-rigidity, on the same side as covariates, with age and sex as nuisance covariates. All the analyses included voxels in the search area defined by a 3 mm-dilated striatal mask from Harvard-Oxford Subcortical Atlas. In all the voxelwise analyses, voxel-level P_{FWE} values < 0.05 were considered significant.

Study II: Voxelwise Linear Models

In Study II, all the voxelwise analyses of association between tracer binding and the clinical features were conducted with SPM12 (Friston, 2007) using the general linear model running on MATLAB R2021b (Higham & Higham, 2017). The analysis search area was defined by a mask including the striatum, thalamus, midbrain and brainstem (Harvard-Oxford Subcortical Atlas with 4 mm dilatation).

The cross-sectional analyses of the association of each non-motor symptom separately were conducted for each timepoint (baseline, 2-year follow-up, 4-year follow-up). The analyses at baseline included one of the NMSs, age, sex, and MDS-UPDRS-III scores as covariates; the analyses in the follow-up timepoints included the corresponding variables and medication state (on/off) during clinical examination (medication state x MDS-UPDRS-III total score interaction) as an

additional covariate. Cluster-level $P_{FWE} < 0.05$ at height-threshold of uncorrected $P < 0.001$ were considered significant.

The longitudinal analyses were conducted to study the association between baseline tracer binding and 2- and 4-year follow-up neuropsychiatric symptoms, using the same adjustment covariates (from baseline). Cluster-level $P_{FWE} < 0.05$ at height-threshold of uncorrected $P < 0.01$ were considered significant in these analyses.

Study II: Striatal and Extrastriatal ROIs

To confirm the voxelwise results, equivalent analyses with ROI values were conducted: for these, the mean values from the preprocessed images were extracted for nucleus accumbens and extrastriatal areas (LC, thalamus, and raphe nuclei), according to the Automated Anatomical Labelling Atlas 3 (Rolls et al., 2020).

Study II: Functional Connectivity Analyses

To extend the interpretability of the results from the voxelwise linear models, Study II also included voxelwise network connectivity analyses based on the linear model findings. The identified clusters for each non-motor symptom at the 4-year follow-up cross-sectional analyses were used as seeds for voxelwise whole brain rs-fMRI analyses, using data from 1,000 healthy volunteers (Cohen et al., 2020). As a control measure, a whole brain functional connectivity analysis was conducted with the combined left and right bradykinesia-rigidity clusters from Study I, to identify a network associated with motor symptoms. A detailed description of the rs-fMRI analysis has been reported previously (Joutsa et al., 2022). Briefly, the functional networks of a seed are defined as the temporal correlation of each voxel in the connectome (Joutsa et al., 2022). The resulting Pearson's *r* maps were converted to *z*-maps using Fisher *z*-transformation, and final connectivity maps for each symptom were investigated using one-sample *T*-tests.

As the findings from the deep brain structures had strong mutual connectivity, distinct connectivity profiles for each network were formed. These symptom-specific networks were created by adjusting the raw *z*-connectivity maps for the motor symptom-associated connectivity map in a univariable linear regression model with Wake Forest University Biological Parametric Mapping (Casanova et al., 2007) toolbox running on SPM12 (Friston, 2007). The voxelwise specific connectivity for each neuropsychiatric symptom cluster was defined by subtracting the proportion of its bradykinesia-rigidity network-related connectivity, indicated by a linear regression model. That is:

$$z_{x,y,z,s[Specific]} = z_{x,y,z,s[Non-Specific]} - z_{x,y,z,s[BR]}\beta_{x,y,z[BR]} \quad (2),$$

where for each voxel in the MNI space at coordinates [*x*,*y*,*z*] and normative connectome subject s: $z_{x,y,z,s[Specific]}$ is the specific connectivity, $z_{x,y,z,s[Non\text{-}specific]}$ the (raw) non-specific connectivity, $z_{x,y,z,s[BR]}$ the bradykinesia-rigidity-associated connectivity of a connectome subject, and $\beta_{x,y,z,s}$ is the association (beta coefficient) of the bradykinesia-rigidity cluster connectivity with the original cluster connectivity.

The difference and specificity of the symptom connectivity maps were investigated with pairwise comparisons with linear models, with permutation-based significance approximation (10,000 permutations) implemented in FSL (Jenkinson et al., 2012) Randomise. To assess the relevance of the networks, the connectivity profiles associated with motor parkinsonism and depression were compared to maps derived from brain lesions causing parkinsonism (Joutsa et al., 2018) and depression (Siddiqi et al., 2023). These maps represent the connectivity of lesions causing the corresponding symptoms, in contrast to lesions that do not. The resemblance of these maps with each of the symptom-associated maps from the [^{123}I]FP-CIT analyses was computed as a non-parametric spatial correlation, and the spatial correlation coefficients were compared to a null distribution derived from random permutation of map ROI values 10,000 times, using JuSpace 1.5 (Dukart et al., 2021) with the Neuromorphometrics atlas (*Neuromorphometrics, Inc.*, 2023; Strudwick Caviness et al., 1999), running on MATLAB R2021b (Higham & Higham, 2017).

Study II: Neurotransmitter Receptor Correspondence

The symptom networks were also assessed for spatial correlations with different neurotransmitter receptor distributions. The symptom networks were compared with normative neurotransmitter receptor distribution maps using JuSpace 1.5 (Dukart et al., 2021) (10,000 permutations). These neurotransmitter receptor maps included $5HT_{1A}$ map by Savli and colleagues (Savli et al., 2012), $5HT_{1B}$, $5HT_{2A}$, and $5HT_4$ (serotonin receptor) maps by Beliveau and colleagues (Beliveau et al., 2017), a D_1 map by Kaller and colleagues (Kaller et al., 2017), and a $D_{2/3}$ map by Alakurtti and colleagues (Alakurtti et al., 2015). These tests were corrected for multiple comparisons, for each functional network separately.

4.1.4 Conventional Statistical Analyses

Study I

Statistical analyses of precalculated ROI SBR data other than imaging data were conducted with R 4.1.2 (Bird Hippie) (R Core Team, 2022) running on macOS 10.15. The groupwise comparisons were conducted with a two-sided Mann-Whitney U test or Fisher's exact test, as appropriate. Correlation analyses were conducted using Spearman's rank order correlation coefficient. The striatal binding effects associated with clinical features, and their independence were studied with confirmatory multivariable regression models using the precalculated striatal SBR ROI values. The contributions of each symptom entity to the total model R^2 were estimated using proportional marginal variance decomposition (Grömping, 2007).

The variance inflation factors were inspected to exclude possible multicollinearity issues in the multivariable regression models due to symptom lateralization. Variance inflation factors were ≤ 2.0 for all the covariates in the models. Additional regression analyses included the repetition of these analyses, with non-parametric, empirical significance approximation using 10-fold cross-validation (10,000 repetitions) and bootstrapping (100,000 iterations) methods.

Study II

Statistical analyses of data other than imaging data, as well as analyses of the obtained ROI SBR, were conducted with R 4.1.2 (Bird Hippie) (R Core Team, 2022) running on macOS 10.15. Comparisons between the baseline, 2-year and 4-year follow-up data were conducted using linear mixed models (continuous variables) and partially overlapping sample *Z*-tests (categorical variables). The striatal binding effects associated with clinical features were investigated in multivariable regression models, using the obtained striatal and extrastriatal SBR ROI values according to the Automated Anatomical Labelling 3atlas (Rolls et al., 2020).

4.1.5 Ethics and Approvals

The PPMI study protocol was registered on June 8th 2010 (ClinicalTrials.gov identifier: NCT01141023). The PPMI study protocol was registered on 8 June 2010 (ClinicalTrials.gov identifier: NCT01141023). The study was approved by the institutional review board at each research site. All participants provided written informed consent.

4.2 Study III

4.2.1 Study Sample

Data for Study III included the subject-reported demographic and clinical data, and BSM mapping data of 79 control subjects and 380 subjects with PD. The inclusion criterion for the PD group was a diagnosis of PD established by a neurologist; for the control group the exclusion criterion was evidence of PD or another neurodegenerative parkinsonism syndrome. Data was collected through an online platform that hosted the BSM tool and a questionnaire about demographic and clinical information (Jaakkola et al., 2021). The collected clinical data included age, sex, education, alcohol consumption, and smoking, as well as PD disease duration (from diagnosis), duration of motor symptoms (self-reported), dopaminergic medications, device-aided treatments, and bodily symptom mapping data.

4.2.2 Bodily Symptom Mapping

The BSM data was collected with the emBODY-tool, a relatively novel technique for uniform, quantitative, topographical mapping of bodily sensations (Nummenmaa et al., 2014). The data consisted of maps with a resolution of 171 x 522 pixels (width x height). The participants were instructed to color the bodily locations with currently experienced sensorimotor symptoms (clumsiness, stiffness, tremor, numbness, and pain), and bodily sensations associated with basic emotions (anger, disgust, fear, happiness, sadness, surprise, and neutral) on an outline of the human body. For the sensorimotor symptoms, the patients were instructed to color the experienced symptoms on the ventral (front) side on one map, and on the dorsal (back) side on the other. For the emotions, the patients were instructed to think carefully about the bodily sensations awakened when feeling the emotion in question, and to color the parts with increasing activity on one map and with decreasing activity on the other. The maps were colored by simultaneously pressing a mouse button and dragging the cursor over the area intended to color.

4.2.3 Map Preprocessing

The BSM data were first converted to Neuroimaging Informatics Technology Initiative (NIfTI) format for further processing. To control for the effect caused by minor errors in drawing and clinically insignificant topographical differences in localization, the data were smoothed using a Gaussian smoothing kernel. The smoothing kernel sigma was selected based on a visual inspection of the colored maps to best reflect the primary body part (e.g., lower part of the face or distal lower

limb). Smoothing with $\sigma = 20$ resulted in the most reasonable anatomical resolution and was therefore selected for the statistical analyses. To prevent spillover across distinct anatomical regions (e.g., from hand to hip, which are anatomically distinct but in close proximity in the body outline used in this study), the original maps in anatomical position were nonlinearly warped to a map space with moderately abducted extremities using ANTs (Avants et al., 2011). Finally, the smoothed maps were returned to the original anatomical position and masked with the body outline.

4.2.4 Statistical Analyses of the Bodily Maps

Pixelwise Statistical Analyses

Pixelwise analyses of the BSM data were conducted with SPM12 using generalized linear models (Friston, 2007). First, pixelwise one-sample T-tests were performed to create bodily maps for each sensorimotor symptom and emotion. To facilitate a visual comparison of the PD and control group maps, the obtained T-maps were converted to Cohen's D effect size maps with R 4.3.2 (Eye Holes) (R Core Team, 2022). Second, pixelwise two-sample T-tests between the groups were performed to identify abnormalities associated with PD. Third, the pixelwise association of each map as well as 1) patient-reported motor symptom duration and 2) levodopa-equivalent daily dose (LEDD) were evaluated with univariate linear regression models.

To ensure that the findings were not driven by differences in demographic characteristics between the PD group and the control group, the two-sample *T*-tests and regression analyses of emotions were repeated with sex and education levels as additional covariates. Pixelwise $P_{FWE} < 0.05$ were considered significant. Finally, to account for the imbalance of the group sizes in the comparative analyses, additional analyses were conducted by randomly oversampling the control group. In this approach, the control group data was augmented to the sample size of the PD group by duplicating control subjects with random replaceable sampling. For each comparison analysis, the resampling and pixelwise statistical tests with balanced groups were repeated 10,000 times. From these analyses, the mean together with the 2.5^{th} and 97.5^{th} percentile *T*-maps were extracted. These maps were thresholded to the *T*-value corresponding to $P_{FWE} < 0.05$.

Principal Component Analyses

The covariance patterns from the BSM data were analyzed with principal component analyses (PCA), across both groups and across all pixels, including both symptom and emotion maps, in R 4.3.2 (R Core Team, 2022). The pixelwise values were

centered to the pixelwise mean and scaled to unity. Pixels with all-zero observations were excluded. This PCA analysis resulted in the typical covariance patterns of symptoms and emotion-related sensations for both groups, as indicated by the two first (strongest) principal components, accounting for 13.4% of the total variance across the pixelwise BSM data.

The statistical significance of the principal components were evaluated with permutation tests (1,000 iterations), using the *PCAtest* package (Camargo, 2022). A component value for an individual subject was interpreted as the amount of expression of the corresponding covariance pattern, that is, the pattern expression value. The between-group comparisons of the pattern expression values were conducted using a Mann-Whitney U test and binary logistic regression. *P* values less than 0.05 were considered significant across all analyses. For the covariance pattern expression values, median and 95% bootstrapped confidence interval (CI) of median (10,000 iterations) were chosen as descriptive statistics.

Differences in the pattern expression values between the groups were tested using a Mann-Whitney U test and binary logistic regression with sex or education as covariates. Finally, to provide additional descriptive information, these models , like the linear analyses, were run with data balanced with random oversampling of the control group (10,000 iterations).

Classification with Random Forest Models

To assess the group differences in the BSM patterns between subjects with PD and the controls, random forest models were formed with the *caret* package (Kuhn, 2008) in R 4.3.2 (R Core Team, 2022) for reclassification of the participants to the PD and control groups, with 10 times repeated, 10-fold cross-validation. The main model had the expression values of the two first principal components, age, sex, education level, and smoking status as explanatory variables. The models were trained with 50% of the data and tested on the remaining 50% 1,000 times with group-proportion-saving random data partitioning. Area under the curve, sensitivity, specificity, and kappa values of these runs were calculated to evaluate the performance of the models. For comparison, similar models were run excluding part of the explanatory variables.

4.2.5 Conventional Statistical Analyses

Statistical analyses were performed with R 4.3.2 (Eye Holes) (R Core Team, 2022). Group differences in demographic and clinical data were investigated using a Mann-Whitney U test or Fisher’s exact test, as appropriate.

4.2.6 Ethics and Approvals

The study protocol was approved by Turku University Hospital Clinical Research Services Board. The need for a separate ethics board review was waived. Written informed consent was obtained, and the study was conducted according to the principles of the Declaration of Helsinki.

5 Results

5.1 Study I: DAT Binding and Cardinal Motor Symptoms in PD

Table 4. Study I: Demographic and clinical data at baseline.

Variable	Healthy controls (*n* = 166)	PD (n = 354)	*P* value
Age (years)	61.3 [54.6, 68.4]	62.2 [54.8, 69.0]	0.313
Sex (M/F) [M%]	105 / 61 [63.3%]	227/127 [64.1%]	0.845
Handedness (R/L/A) [R%]	137 / 20 / 9 [82.5%]	317 / 26 / 11 [89.5%]	0.081
Education years	16 [14, 18]	16 [14, 18]	0.087
MoCA total score	28 [27, 29]	28 [26, 29]	<0.0001*
Age at symptom onset	–	60.1 [52.6, 67.3]	–
Disease duration (months)	–	18.5 [11.1, 29.5]	–
With Complete MDS-UPDRS-III Information	*n* = 164	*n* = 349	
Hoehn & Yahr Stage			
0	164	0	
1	0	154	
2	0	193	<0.0001*
3	0	2	
4	0	0	
5	0	0	
MDS-UPDRS-III total score	0.0 [0.0, 1.0]	18.0 [13.0, 24.0]	<0.0001*

The clinical and demographic data for subjects with successfully registered imaging. For continuous variables, median, lower quartile and upper quartile are shown. M, male; F, female; R, right-handed; L left-handed; A, ambidextrous; MoCA, Montreal Cognitive Assessment; MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale, part III. *$P < 0.05$.

The clinical and demographic features of the studied sample at baseline are presented in **Table 4**. There were no significant differences between the healthy control and the PD group in age, gender, handedness, or education. As may be expected, motor symptom severity was greater and cognitive function was slightly more declined in the PD group. The majority of the PD group had the tremor-dominant motor phenotype (62.7%); the next most common motor phenotype was PIGD (21.8%). Of the healthy control and PD groups, 137 (82.5%) and 317 (89.5%) were right-handed, respectively. All the main analyses were conducted with right-handed subjects. Of the right-handed patients with PD, 179 (57.0%) had right-predominant, 129 (41.1%) left-predominant, and 6 (1.9%) symmetrical symptom onset according to the patient.

At baseline, only ten (3.2%) of the right-handed patients included in the main analyses used dopaminergic medications. However, their motor status was assessed without medications. These main analyses were also repeated regardless of dexterity. At the 2-year follow-up, 186 (86.1%) of the patients used dopaminergic medications. For the main analyses at the 2-year follow-up, only patients examined off medications were included. However, all of the main analyses were repeated regardless of the medication state (n = 216, medication state as an additional covariate), and regardless of dexterity (n = 194 with only patients off medication, n = 240 regardless of medication state).

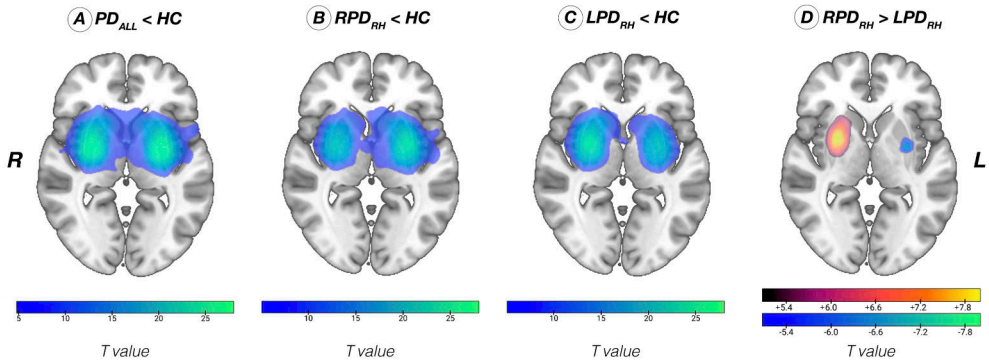

Figure 4. Study I: Group comparisons and correlation with disease severity. Regions showing significant decreased specific binding ratio (SBR) in PD compared to controls or negative correlation (blue–green scale) and higher SBR or positive correlation (red–yellow). MNI space plane coordinates z = 0 for all panels. Only voxels with voxel-level family-wise error (FWE) corrected P < 0.05 are shown. HC, healthy control; L, left; R, right; RPD, PD with right-predominant symptom onset; LPD, PD with right-predominant symptom onset; RH, right-handed.

Expectedly, patients with PD had substantially lower [^{123}I]FP-CIT binding in the striatum compared to the controls (**Figure 4A**), with a more pronounced decline contralaterally to the side of the predominant side of motor symptoms (**Figure 4B–**

D). The measures of overall disease severity were associated with binding deficits in the right striatum, but left and right MDS-UPDRS-III motor scores were negatively associated with contralateral [^{123}I]FP-CIT binding.

Association of the Cardinal Motor Symptoms with [^{123}I]FP-CIT Binding

The association of cardinal motor symptom (rigidity, bradykinesia, and rest tremor) severity was assessed on each side separately. Unsurprisingly, both left and right rigidity and bradykinesia had an association with reduced binding in the contralateral striatum. However, left and right rest tremor amplitude was associated with stronger [^{123}I]FP-CIT binding in the ipsilateral striatum (**Figure 5**). The findings were similar with only upper extremity symptoms, and when controlling for overall disease severity, motor phenotype, or cognitive function. The analyses were also repeated including only patients with any rest tremor, with practically identical results.

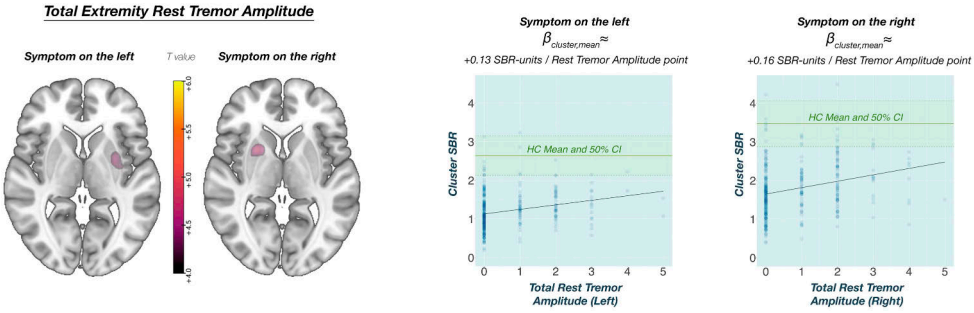

Figure 5. Study I: Association of [^{123}I]FP-CIT binding with rest tremor amplitude. Rest tremor amplitude was associated with higher ipsilateral specific binding ratios (SBRs; volumes of the significant clusters were 1,667 mm^3 [0.70% of the Harvard-Oxford Subcortical Atlas caudate ROI, 8.32% of the putamen] and 1,249 mm^3 [0.70% of the caudate, 6.19% of the putamen] for the total left and right rest tremor, respectively). The analyses were performed in the right-handed PD group, with multivariable linear regression, age, and sex as covariates. On the right side of the figure, the corresponding scatterplots of the association between MDS-UPDRS-III subscores and cluster mean intensity are shown. Note that the scatterplots are only used to illustrate the strength of the association, and *P* values are not calculated because the cluster analyses are circulatory. Only voxels with voxel-level family-wise error (FWE) corrected $P < 0.05$ are shown. L, left; R, right.

The symptoms from each side of the body were also investigated in analyses including akinetic-rigid symptom severity (bradykinesia-rigidity) and rest tremor amplitude in the same model. As bradykinesia and rigidity were strongly intercorrelated (Spearman's $r = 0.70$ and $r = 0.60$ on the left and right side, respectively), the use of the composite was motivated to avoid multicollinearity. The association of rest tremor and increased ipsilateral binding was still evident in these analyses.

The analyses were also repeated with the data from the 2-year follow-up. Both left and right rest tremor were significantly associated with stronger ipsilateral [^{123}I]FP-CIT binding. The inclusion of patients regardless of handedness, or medication state at the 2-year follow-up, did not change the main findings.

Rest tremor severity indices (product of rest tremor amplitude and rest tremor constancy) were associated with stronger ipsilateral tracer binding at baseline and 2-year follow-up, similar to the rest tremor amplitude alone. Rest tremor constancy was not associated with binding.

Motor Symptoms with the Strongest Association with [^{123}I]FP-CIT Binding

The relative association strength of left and right bradykinesia-rigidity and rest tremor amplitude was assessed in the same model, with age and sex as nuisance covariates. In the voxelwise analyses, bradykinesia was the main factor associated with [^{123}I]FP-CIT binding at baseline. At the 2-year follow-up, left rest tremor and left bradykinesia-rigidity were the symptoms most strongly associated with binding (increased ipsilateral and decreased contralateral, respectively). The analysis was replicated with precalculated SBR ROI values, with similar results. With these precalculated values, the contributions of cardinal motor symptoms were also evaluated with linear models equivalent to the voxelwise designs. The proportion of the model R^2 (the amount of variance explained by the model in total) was 21.1% and 9.4% of the anterior striatal (caudate ROI) binding at baseline, and 40.0% and 26.6% at the 2-year follow-up for left and right rest tremor amplitude, respectively (**Figure 6**).

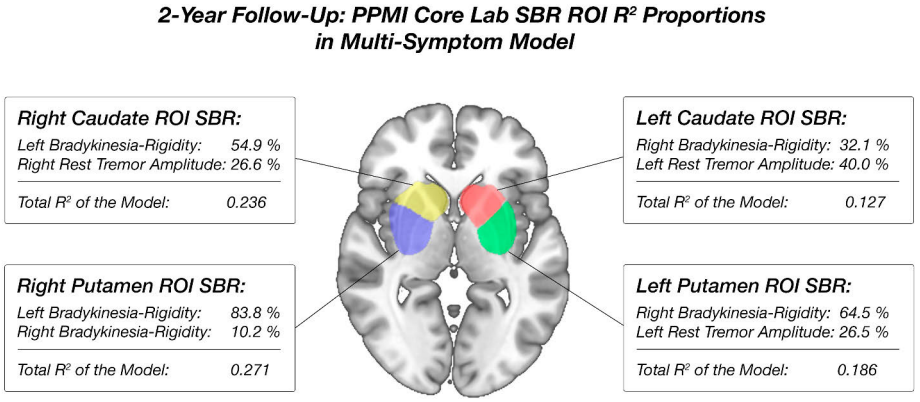

Figure 6. Study II: Cardinal motor symptoms driving [^{123}I]FP-CIT binding at 2-year follow-up. Results of the corresponding multivariate regression model using PPMI Core Lab ROI SBR values. Proportion of the decomposed R^2 values of the total model R^2 are shown. L, left; R, right.

5.2 Study II: Monoaminergic Networks of NMSs in PD

Table 5. Study II: Demographic and clinical data at baseline, 2-year and 4-year follow-up.

Variable	Baseline (*n* = 349)	2-Year Follow-Up (*n* = 268)	4-Year Follow-Up (*n* = 162)
Age (years)	62.1 [54.6, 69.0]	64.3 [56.9, 71.0] *	66.5 [59.1, 72.9] †‡
Sex (M/F) [M%]	224 / 125 [64.2%]	170 / 98 [63.4%]	108 / 54 [66.7%]
Age at Symptom Onset (years)	60.1 [52.6, 67.1]	60.0 [53.0, 67.8]	60.5 [53.4, 67.1]
Time from Symptom Onset to Diagnosis (years)	0.9 [0.5, 1.9]	0.9 [0.5, 1.9]	0.9 [0.4, 1.7]
Disease Duration (years)	1.5 [0.9, 2.6]	3.6 [3.0, 4.5] *	5.6 [5.0, 6.5] †‡
Education Years	16 [14, 18]	16 [14, 18]	16 [14, 18]
MDS-UPDRS-III Total Score	20 [14, 26]	26 [19, 35] *	29 [22, 36] †‡
LEDD	0 [0, 0]	303 [150, 560] *	590 [325, 850] †‡
Hoehn & Yahr Stage			
0	0	1 [0.4%]	0
1	154 [44.1%]	56 [23.2%]	22 [15.6%]
2	193 [55.3%]	171 [71.0%]	109 [77.3%]
3	2 [0.6%]	10 [4.1%]	9 [6.4%]
4	0	3 [1.2%]	1 [0.7%]
5	0	0	0
Not reported	0	27	21

Differences in scalar variables were evaluated with linear mixed models, in categorical variables with partially overlapping samples Z-tests. For numeric variables, the median with the 25th and 75th percentiles [in brackets] are reported. Patients with missing values were excluded from the corresponding analyses. For Hoehn & Yahr stage, no statistical comparison between timepoints was conducted. MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale, part III; LEDD; levodopa-equivalent daily dose. Significant ($P < 0.05$) difference between baseline and 2-year follow-up *, baseline and 4-year follow-up †, 2-year and 4-year follow-up ‡.

The general demographic and clinical characteristics of the studied sample of patients with PD at each timepoint are presented in **Table 5**. The samples from the baseline and the follow-up visits did not differ in terms of sex, delay between symptom onset, or education. Expectedly, age, dopaminergic medication use, disease severity, and disease duration increased during the follow-up period. The

scores of the studied cognitive and behavioral symptoms beyond clinically meaningful cutoffs are presented in **Table 6**. At baseline, 14.9% of patients with PD had a previously established diagnosis of a depressive disorder (median 6.8 years before PD diagnosis), and 10.9% had been diagnosed with an anxiety disorder (median 1.2 years before PD diagnosis). The prevalence of probable depression (14.0–16.5%) and clinically relevant anxiety symptoms (22.0–28.0%) remained stable during the 4-year follow-up time, but probable RBD and at least mild cognitive impairment became more frequent during that period.

Table 6. Study II: Non-motor symptom scores beyond or under significant threshold.

Variable	Baseline (*n* = 349)	2-Year Follow-Up (*n* = 268)	4-Year Follow-Up (*n* = 162)
Number of Subjects beyond Cutoff (number [%])			
Depression: GDS-15 Score ≥ 5	49 [14.0%]	39 [16.3%]	23 [16.4%]
State Anxiety: STAI State Score ≥ 39	97 [28.0%]	54 [23.0%]	30 [21.6%]
Trait Anxiety: STAI Trait Score ≥ 39	76 [22.0%]	61 [26.0%]	35 [25.2%]
RBD Symptoms: RBDSQ Score ≥ 5	89 [26.6%]	76 [31.7%]	44 [31.4%] †
Number of Subjects under Cutoff (number [%])			
Cognition: MoCA Score ≤ 25	71 [20.3%]	76 [31.6%] *	42 [30.0%] †

Differences in scalar variables were evaluated with linear mixed models, in categorical variables with partially overlapping samples Z-tests. For numeric variables, the median with the 25th and 75th percentiles [in brackets] are reported. Patients with missing values were excluded from the corresponding analyses. Significant ($P < 0.05$) difference between baseline and 2-year follow-up *, baseline and 4-year follow-up †, 2-year and 4-year follow-up ‡. GDS-15, 15-item Geriatric Depression Scale; STAI, State-Trait Anxiety Inventory; RBDSQ, RBD Screening Questionnaire; MoCA, Montreal Cognitive Assessment.

Cross-Sectional Association of the Cognitive and Behavioral Symptoms with [^{123}I]FP-CIT Binding

At baseline, none of the symptoms had significant associations with [^{123}I]FP-CIT binding. However, depressive symptoms (GDS-15 score) had a negative association with tracer binding in the right ventral striatum at the 2-year follow-up, and in the left ventral striatum, caudate, and midbrain, including the dorsal raphe nuclei, at the 4-year follow-up (**Figure 7A**). Trait anxiety (STAI-T subinventory score) had a

negative association with tracer binding (including dorsal and median raphe nuclei, and LC) at the 4-year follow-up (**Figure 7B**). However, state anxiety (STAI-S score) was not associated with any of the visits with tracer binding. When patients with antidepressive/anxiolytic monoaminergic medications were excluded, the findings of depressive symptoms and trait anxiety remained similar.

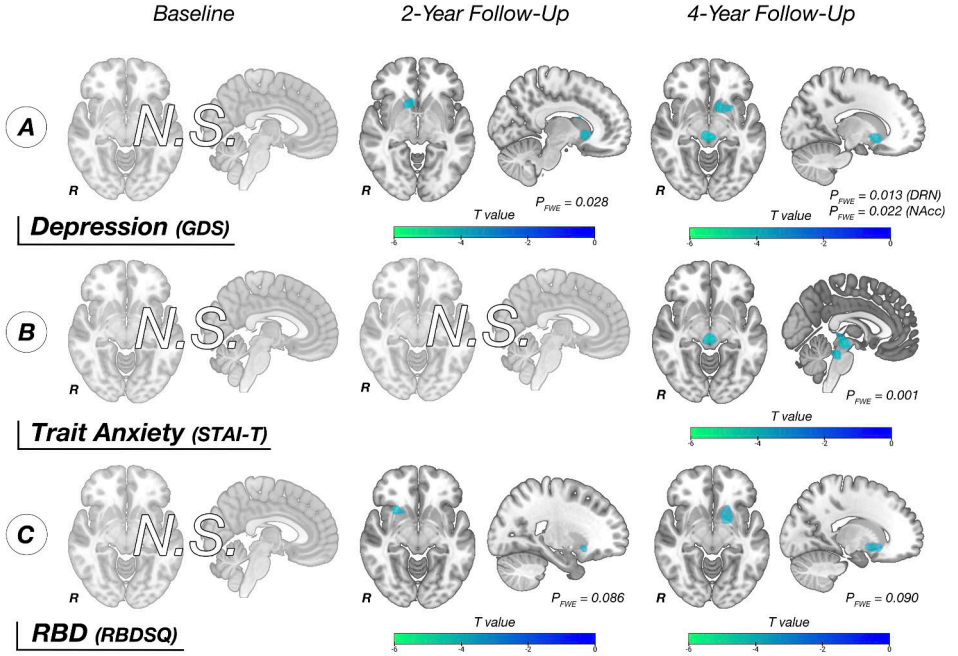

Figure 7. Study II: Association between cognitive and behavioral symptoms and [^{123}I]FP-CIT binding. The association between **(A)** depression, **(B)** trait anxiety, and **(C)** REM sleep behavior disorder symptoms and [^{123}I]FP-CIT binding at baseline, 2-year follow-up and 4-year follow-up. Multivariable linear regression with age, sex, regression, medication state, and MDS-UPDRS-III total score (medication state x MDS-UPDRS-III total score interaction) as covariates. R, right; DRN; dorsal raphe nucleus; NAcc, nucleus accumbens; MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale, part III (motor); P_{FWE}, family-wise error corrected *P* value; N.S., non-significant.

Reported RBD symptoms (RBDSQ score) showed the strongest associations with reduced tracer binding in the right ventral striatum at the 2-year follow-up, and in the left ventral striatum and putamen at the 4-year follow-up but the associations remained statistically unsignificant (**Figure 7C**). Cognition (MoCA score) was not significantly associated with tracer binding during the follow-up period. In the healthy controls, no significant associations with any of the symptoms of interest were present.

The findings in the regression analyses with the anatomical ROI SBR values were similar to those observed in the voxelwise analyses. Depressive symptoms showed strengthening associations with [^{123}I]FP-CIT binding decrement in the ventral striatum, caudates, and raphe nuclei; state anxiety in the raphe nuclei and LC; and reported RBD symptoms in the ventral striatum and putamina. Again, cognition was not consistently associated with binding with any of the anatomical ROI SBR values.

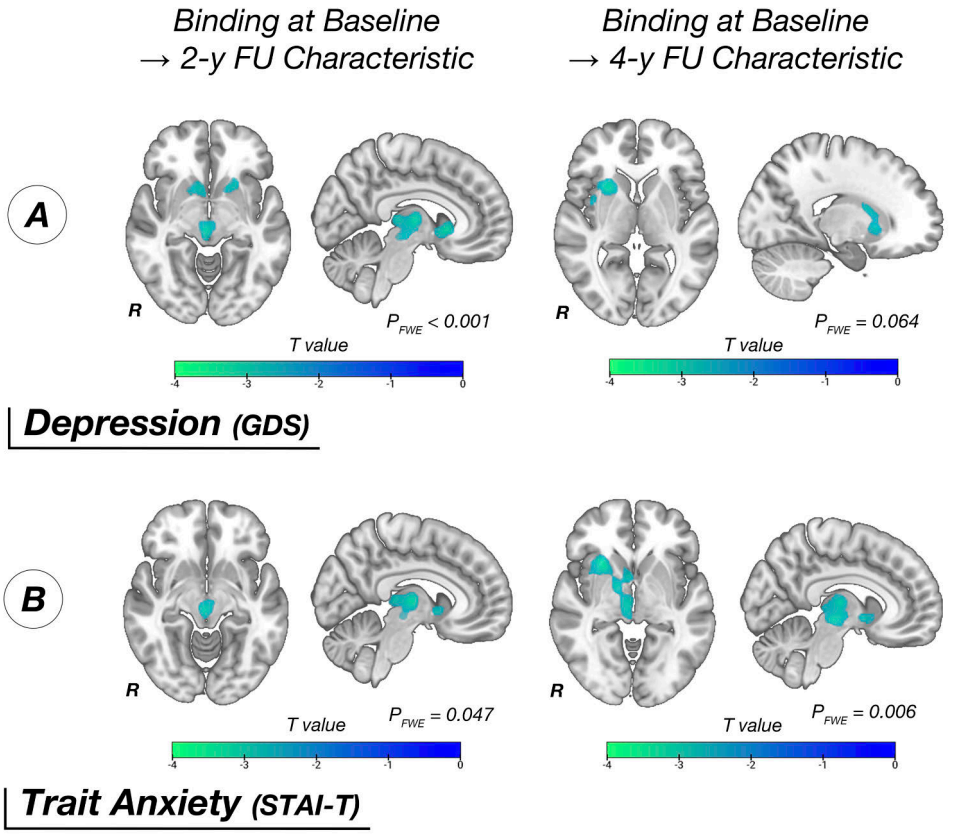

Figure 8. Study II: The association of baseline [^{123}I]FP-CIT binding with depression and trait anxiety at the follow-up visits. (A) Depression was negatively associated with lower dorsal raphe, thalamic (2-year follow-up) and striatal (2- and 4-year follow-up) monoamine transporter binding at baseline. **(B)** Trait anxiety was associated with lower thalamic, dorsal raphe (2- and 4-year follow-up) and striatal (4-year follow-up) binding monoamine transporter binding at baseline. R, right; P_{FWE}, family-wise error corrected *P* value.

Longitudinal Association of the Cognitive and Behavioral Symptoms with [^{123}I]FP-CIT Binding

In the longitudinal analyses, depression at the 2-year follow-up was significantly associated with baseline binding decrement in the ventral striatum, caudate, dorsal raphe nuclei, and thalamus, and depression at the 4-year follow-up showed the strongest negative association with baseline binding in the left caudate and anterior putamen, however, not quite reaching significance (**Figure 8A**). Trait anxiety at the 2-year and 4-year follow-ups was associated with baseline binding decrement in the dorsal raphe nucleus, thalamus, and ventral striatum (**Figure 8B**).

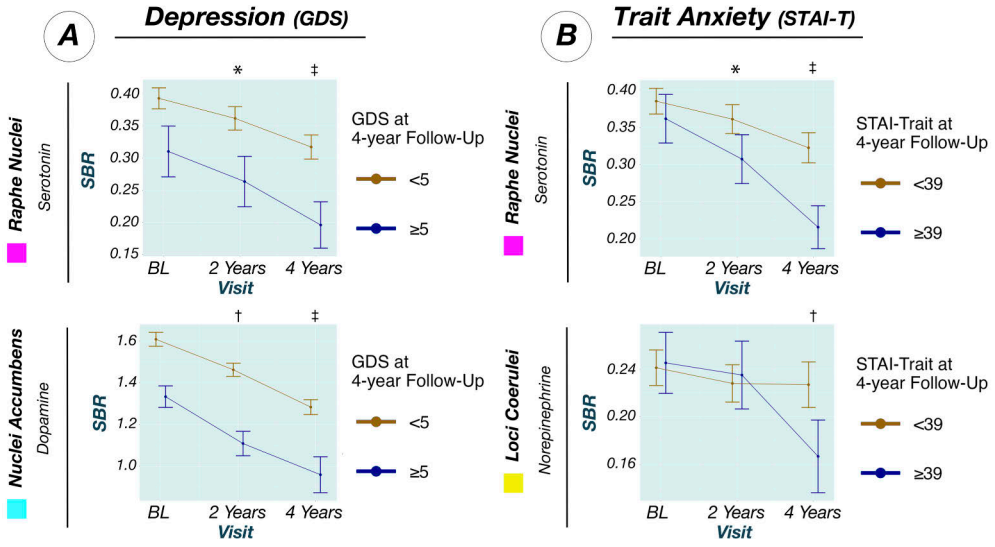

Figure 9. Study II: Progression of monoamine transporter binding deficits in the regions-of-interest. Progression of monoamine transporter binding deficits in the monoaminergic key regions in patients who did and did not develop depression **(A)** and anxiety **(B)** symptoms above the selected cutoffs by the 4-year follow-up. SBR, specific binding ratio; GDS, 15-item Geriatric Depression Scale; STAI-T, State Trait Anxiety Inventory, Trait Anxiety Score; BL, baseline.

Neither the reported RBD symptoms nor cognition at the follow-up visits showed associations with baseline tracer binding. The analyses with anatomical ROI SBR values were confirmative of these findings. Progression of monoamine transporter binding deficits in the identified monoaminergic key areas for patients with probable depression or clinically relevant trait anxiety in the 4-year follow-up are shown in **Figure 9**.

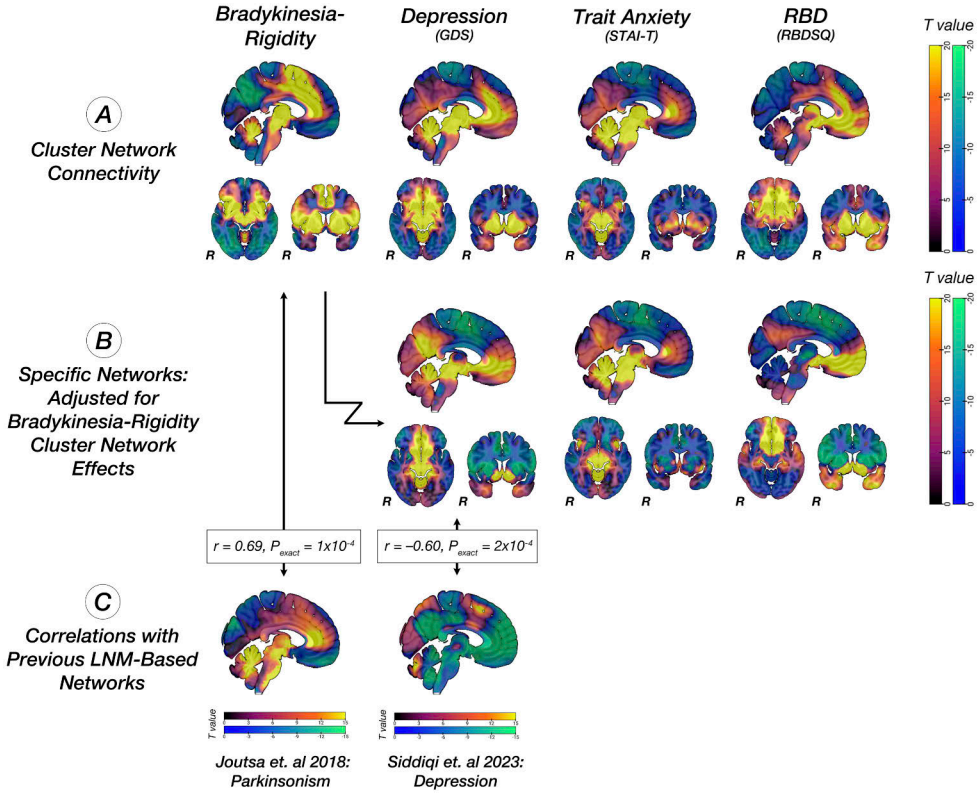

Figure 10. Study II: The whole brain networks corresponding to the monoaminergic deficits associated with the neuropsychiatric symptoms. (A) The networks of the monoaminergic deficits associated with bradykinesia-rigidity, depression, trait anxiety, and REM sleep behavior disorder. **(B)** The specific networks of the monoaminergic deficits associated with depression, trait anxiety, and REM sleep behavior disorder, controlling for bradykinesia-rigidity. **(C)** Spatial correlations between the bradykinesia-rigidity and specific depression network with the corresponding networks identified based on causal lesions (Joutsa et al., 2018; Siddiqi et al., 2021). GDS, 15-item Geriatric Depression Scale; STAI-T, State Trait Anxiety Inventory, Trait Anxiety Score; RBD, REM sleep behavior disorder; RBDSQ, RBD Screening Questionnaire; R, right.

Network Representations of Symptom-Specific Monoaminergic Abnormalities

The monoaminergic networks were constructed for depressive symptoms, trait anxiety and RBD, based on the corresponding, associated monoaminergic clusters in the 4-year follow-up cross-sectional analyses. The motor parkinsonism (akinesia-rigidity) cluster identified in Study I was used as a control cluster, and a similar network was constructed using it as a seed. As expected, the motor parkinsonism cluster presented with most prominent connectivity to motor cortical, striatal, thalamic, midbrain, and cerebellar areas (**Figure 10A**). Depression clusters had the

strongest connectivity with anterior cingulate, dorsomedial frontal, precuneal, and temporal cortices; trait anxiety clusters to the insula, anterior cingulate, and precuneus; and RBD symptom clusters to anterior cingulate, medial frontal, and temporal cortices (**Figure 10A**). The networks of the studied cognitive and behavioral symptoms were also significantly different from the motor network ($P_{FWE} < 0.05$). Adjusting the non-motor symptom network analyses for the motor parkinsonism cluster did not change the observed main patterns (**Figure 10B**).

The topographies of the motor symptom and depression network were similar to the corresponding networks of parkinsonism (Joutsa et al., 2018) and depression (Siddiqi et al., 2023), identified based on causal brain lesions ($r = 0.69$ and -0.60, respectively; $P < 0.001$) (**Figure 10C**). However, the connectivity between the depression maps derived from monoaminergic clusters and lesions were opposite. Spatial correlation analyses were also used to characterize the molecular-level underpinnings of the identified networks. The cluster-derived depression network was characterized by normative maps of $D_{2/3}$ and serotonin $5HT_{1B}$ receptors; anxiety network by that of serotonin $5HT_{1B}$ receptors; and RBD network by those of dopamine D_1, $D_{2/3}$, serotonin $5HT_{1A}$ and $5HT_4$ receptors (**Table 7**).

Table 7. Study II: Spatial correlations of the symptom-specific networks with normative neurotransmitter maps.

Variable	Depression (GDS)	Trait Anxiety (STAI-T)	REM Sleep Behavior Disorder (RBDSQ)
$5HT_{1A}$	0.034	0.057	0.276*
$5HT_{1B}$	-0.237*	-0.330*	-0.138
$5HT_{2A}$	-0.137	-0.308	0.105
$5HT_{4}$	-0.030	-0.189	0.211*
D_{1}	0.126	0.066	0.200*
$D_{2/3}$	-0.322*	-0.077	-0.461*

Spatial correlation analyses based on the Neuromorphometrics atlas, Spearman's r values are reported. *P* values are based on permutation tests (10,000 permutations). *Nested FDR-corrected $P < 0.05$ (across each clinical characteristic separately). FDR, False Discovery Rate; GDS, Geriatric Depression Scale; STAI-T, State-Trait Anxiety Inventory, Trait sub-inventory, RBDSQ, REM Sleep Behavior Disorder Questionnaire; 5HT, 5-hydroxy-tryptamine receptor, subtype subscripted; $D_{1/2/3}$, dopamine receptor 1/2/3.

5.3 Study III: Changes of Emotion-Related Sensations in PD

The clinical characteristics of the studied sample are presented in **Table 8.** The group with PD was more male-predominant than the control group and had relatively lower education levels. The groups did not significantly differ in terms of age, alcohol use, or smoking status.

Sensorimotor Symptoms

The bodily maps of the controls were used as reference for sensorimotor symptoms associated with PD (**Figure 11A**). The group with PD indicated that clumsiness was primarily experienced in distal limbs, stiffness in torso and limbs, and tremor of hands (**Figure 11B**). These topographical findings were expected based on the clinically observed distribution of symptoms in patients with PD. The linear models revealed significant differences in the motor symptoms between the controls and subjects with PD; the group with PD had more motor symptoms (clumsiness, stiffness, tremor), while there was no significant difference in the sensory symptoms (numbness and pain) (**Figure 11C**). The PCA analysis showed PD-related patterns involving all the studied sensorimotor symptoms.

Emotion-Related Sensations

Upon inspection, the maps of the subjects with PD revealed broadly less intensive emotion-related sensations compared to those of the controls (**Figure 12A–B**). In the pixelwise linear models, subjects with PD showed a significant reduction in anger-related parasternal sensations (**Figure 12C**). The findings were similar when sex or education was added as a covariate, or when between-group analysis was balanced with random oversampling (10,000 random oversampling repetitions). Motor symptom duration was significantly associated with anger-related sensation in the abdomen ($P_{FWE} < 0.05$) but not with other emotion-related sensations, with or without the covariates (**Figure 13**). None of the emotion-related sensations were significantly associated with the levodopa-equivalent daily dose (LEDD) of dopaminergic medications.

As with the sensorimotor symptoms, the PCA analyses showed broader PD-related covariance patterns in emotion-related sensations. The finding was clearest for anger that was localized to the abdomen rather than the chest, as implied by the visual analyses. Additionally, the PD-related sensation patterns that were localized to different body regions, whereas the sensations of happiness and sadness were more restricted than in the control-related patterns.

Table 8. Study III: Demographic and clinical characteristics.

Variable	Controls (n = 79)	PD (n = 380)	*P* value
Age (years)	67 [64, 73]	67 [62, 72]	0.522
Sex (M/F) [M%]	31 / 48 [39.2%]	217 / 163 [57.1%]	0.005*
Education			
Primary School Education or Equivalent	1 [1.3%]	36 [9.5%]	
Second Degree Education	37 [46.8%]	184 [48.4%]	0.012*
Higher Education	37 [46.8%]	134 [35.3%]	
Not Reported	4 [5.1%]	26 [6.8%]	
Smoking			
Yes	6 [7.6%]	16 [4.2%]	
Ex-Smoker	6 [7.6%]	50 [13.2%]	0.154
No	65 [82.3%]	269 [70.8%]	
Not Reported	2 [2.5%]	45 [11.8%]	
Alcohol Consumption (doses per week) ($n_{Controls}$ = 71, n_{PD} = 281)	1 [0, 2.5]	1 [0, 4]	0.160
Motor Symptom Duration (years) (*n* = 366)	–	6 [3, 10]	–
Disease Duration (from the diagnosis, years) (*n* = 379)	–	4 [2, 7]	–
Levodopa-Equivalent Daily Dose (LEDD) (*n* = 330)	–	455 [300, 700]	–
Pump Treatment for PD (yes/no [%]) (*n* = 339)	–	5 / 334 [1.4%]	–
DBS Treatment for PD (yes/no [%]) (*n* = 331)	–	16 / 315 [4.8%]	–

The levodopa-equivalent daily dose (LEDD) was calculated as described previously (Tomlinson et al., 2010). For each numeric variable, the median value with 25th and 75th percentiles [in brackets] are reported. DBS, deep brain stimulation.

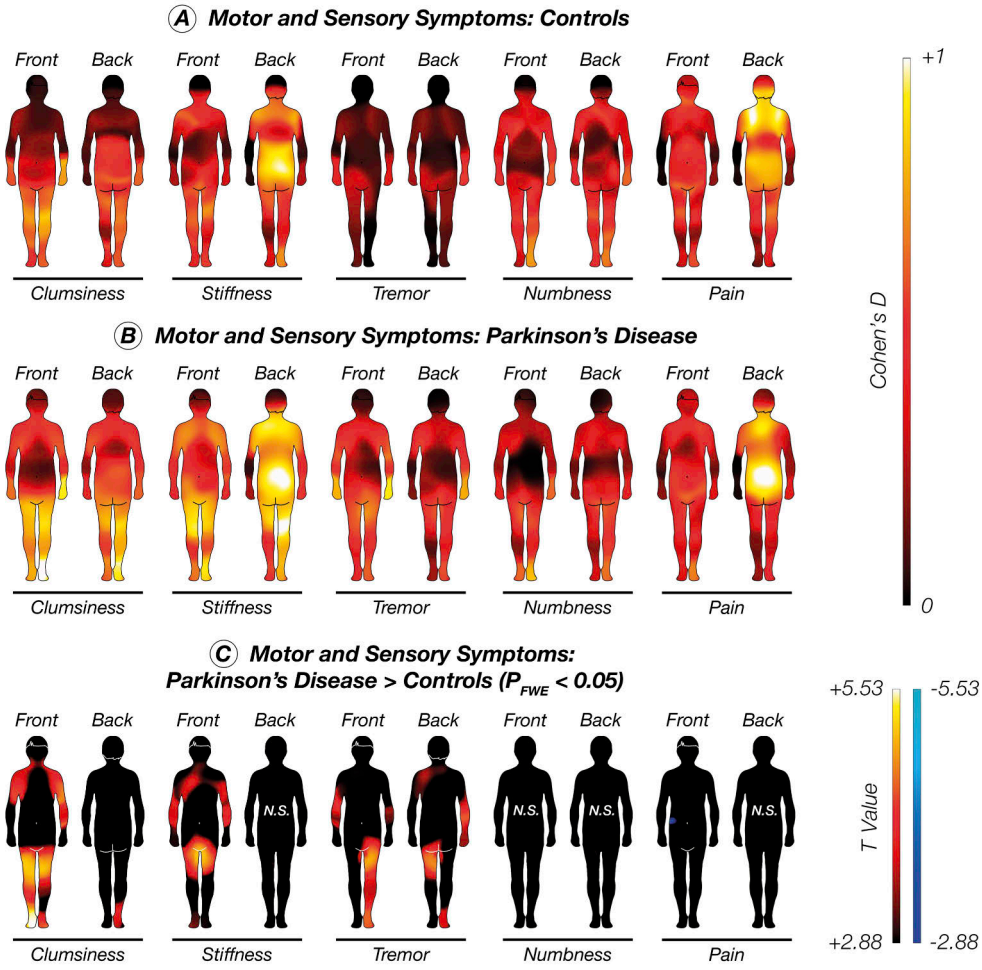

Figure 11. Study III: Symptom-related bodily maps. The pixelwise effect sizes in controls **(A)** and individuals with PD **(B)**, significant differences between groups in the linear model (P_{FWE}<0.05) **(C)**. In PD, clumsiness, stiffness, and tremor map to the body regions commonly affected by bradykinesia, rigidity, and tremor, respectively **(B)**. These motor, but not sensory, symptoms also showed significant regional differences compared to the controls **(C)**. Red–yellow scale indicates positive values, and blue–light blue scale indicates negative values. N.S., non-significant.

Reclassification Task with Random Forest Models

In the main random forest classification model, the subjects were reclassified to control and PD groups using only data of age, sex, education, and the individual expression values of the 1st and 2nd components from the PCA analyses. The main model achieved a median of 100% specificity and 86.3% sensitivity, and the area under the curve of 0.745 in the analyses. Overall, the performance was significantly better compared to the second, otherwise identical, model without the BSM features

(corresponding values 75.0%, 86.7%, and 0.691), characterized by better specificity without a marked loss in sensitivity.

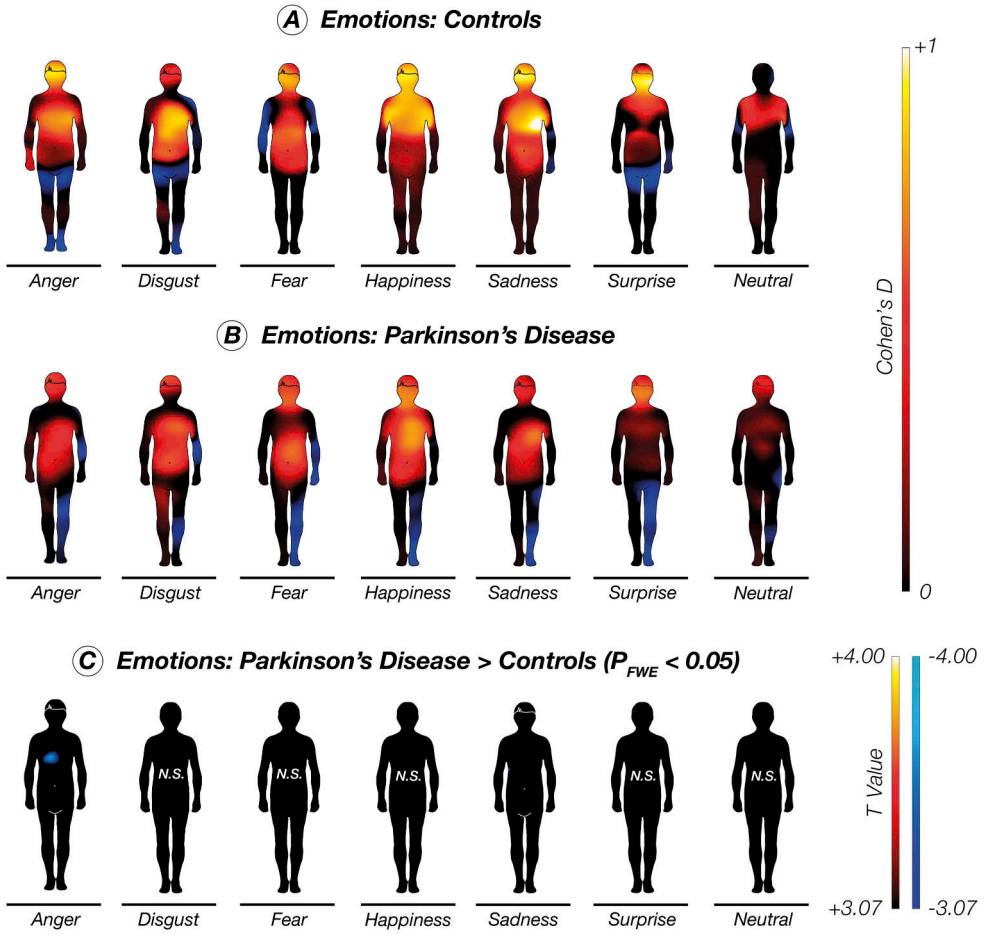

Figure 12. Study III: Emotion-related bodily maps. The pixelwise effect sizes in controls **(A)** and individuals with PD **(B)**, significant differences between groups in the linear model (P_{FWE}<0.05) **(C)**. Visually, the bodily sensations associated with emotions show absent or less intensive expression in PD **(B)** compared to controls **(A)** with a significant difference between the groups in anger-related sensations **(C)**. Red–yellow scale indicates positive values, and blue–light blue scale indicates negative values. N.S., non-significant.

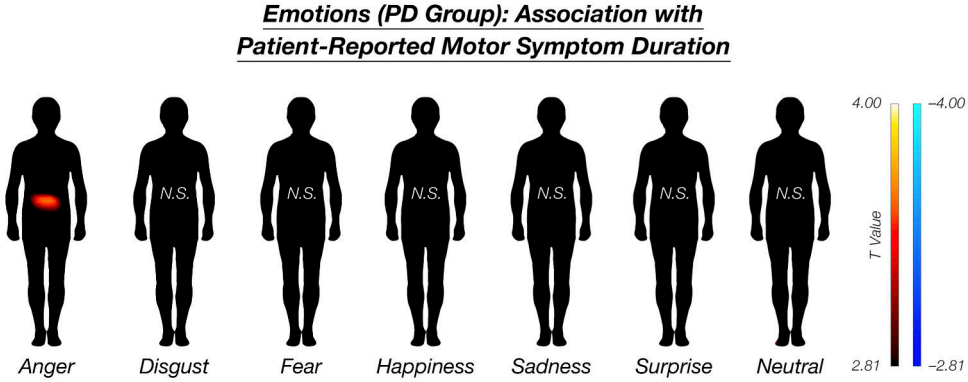

Figure 13. Study III: Motor symptom duration and bodily maps of emotions. Motor symptom duration was significantly associated with more anger-related sensations in the abdomen (P_{FWE} < 0.05). Red–yellow scale indicates positive values, while blue–light blue scale indicates negative values. N.S., non-significant.

6 Discussion

6.1 Study I: DAT Binding and Cardinal Motor Symptoms in PD

Study I showed that in early PD, rest tremor amplitude is associated with stronger ipsilateral striatal DAT binding. This finding was replicated in the 2-year follow-up, in patients examined with or without dopaminergic medications, and regardless of dexterity or other confounding factors. The well-known negative association between akinetic-rigid symptoms and contralateral striatal binding deficit was also replicated.

Patients with tremor-dominant PD are known to have higher DAT binding overall compared to akinetic-rigid patients (A.-Q. Huang et al., 2024; Kaasinen et al., 2014; J.-Y. Lee et al., 2018; Mo et al., 2010; Moccia et al., 2014). However, the association of tracer binding with tremor severity has not been clear, and the interpretations from previous studies have remained inconclusive (H. T. Benamer et al., 2000; Helmich et al., 2011; J.-Y. Lee et al., 2018; Rossi et al., 2010; Seibyl et al., 1995; Spiegel et al., 2007); including the previous work with the PPMI data at baseline, with no observed correlation of tracer binding or rest tremor in the more affected side of the body (J.-Y. Lee et al., 2018). The present study is among the first to observe the positive, lateralized association, with the findings of only one VMAT PET study previously significantly pointing in the same direction (A.-Q. Huang et al., 2024).

There are several possible reasons why the association between rest tremor amplitude and striatal DAT function has not been previously reported. First, most studies investigating [^{123}I]FP-CIT SPECT data and motor symptoms have used composite scores rather than specific measures of tremor characteristics (H. T. Benamer et al., 2000; Helmich et al., 2011; J.-Y. Lee et al., 2018; Rossi et al., 2010; Seibyl et al., 1995; Spiegel et al., 2007). In addition, most of the studies on PD have used ROI-based methods, meaning that the binding values used in these studies have relied on a priori defined anatomical structures (Kaasinen, 2016). This is problematic, as these anatomical regions might not correspond well with the functional anatomy of the striatum, and might lead to neglecting effects localized in more restricted areas or between the areas (McGregor & Nelson, 2019). This study

used a novel registration workflow that, with PVE correction and voxelwise analyses, might offer better sensitivity to detect such effects. Intriguingly, the exact location of the clusters for left and right rest tremor amplitude was different. This may be a result of hemispheric anatomical asymmetry (Güntürkün et al., 2020; Korponay et al., 2022) or differences in functional organization between the hemispheres (Güntürkün et al., 2020; Haaland et al., 2004; Korponay et al., 2022; Simonyan et al., 2013).

The laterality of the rest tremor-associated finding may be counterintuitive, as most motor tracts decussate (cross the midplane), and motor functions of one side of the body are mostly controlled by the contralateral hemisphere (Purves & Williams, 2001). Yet, there are interhemispheric cortical, decussating corticostriatal (M. Parent & Parent, 2006), decussating pallidothalamic and pallidotegmental (Hazrati & Parent, 1991) as well as nigrostriatal (Douglas et al., 1987) connections, and non-decussating dentatorubrothalamic tracts (Meola et al., 2016) also exist and might contribute in the manifestations of the motor symptoms in a pathological state. The relevance of the ipsilateral connections is highlighted by the bilateral beneficial effects of unilateral DBS treatment in PD, although they are more pronounced contralaterally and emphasized in akinetic-rigid symptoms. In addition, the importance of non-decussating dentatorubrothalamic tracts in the MRgFUS treatment of essential tremor has been recently acknowledged in the literature (Feltrin et al., 2022). Rest tremor seems to be controlled both ipsi- and contralaterally, and the relevance of the current findings warrant further research.

Whether the positive association of rest tremor is due to lesser degeneration or functional changes in patients with rest tremor, remains unclear. The matter is underlined by the lack of correlation between [^{123}I]FP-CIT binding and the number of nigral neurons (Saari et al., 2017) or putaminal fibers (Honkanen et al., 2019) in neuropathological studies. Functional or compensatory changes in striatal DAT concentrations have also been identified, at least in association with neurodegenerative conditions (Kaasinen & Vahlberg, 2017) and medications (Chahid et al., 2023). The effects of levodopa on rest tremor (Frequin et al., 2023) would guide towards a concept of DAT upregulation rather than a greater number of dopaminergic neurons.

6.1.1 Limitations

The study includes some limitations that should be acknowledged. First, the cardinal motor symptoms are intercorrelated. This made it difficult to separate the effects of individual cardinal motor symptoms in the analyses, and the use of a composite measure for bradykinesia and rigidity was needed in most of the analyses; thus, it was not completely possible to determine their independent associations with tracer

binding. Second, in the earliest phases of the disease, the main driving factor associated with DAT binding was not ipsilateral rest tremor. Yet, this does not exclude the existence of a link between ipsilateral DAT binding and rest tremor, but rather implies that the effect is weaker than that of bradykinesia-rigidity, especially when the relative effect became stronger during the follow-up. Third, the PPMI study design, with single assessments per follow-up visit instead of separate on and off assessments at each visit, did not allow a study of the differences between tremor responsive and non-responsive to dopaminergic medications (Zach et al., 2020).

6.2 Study II: Monoaminergic Networks of NMSs in PD

Study II demonstrated distinct abnormalities in the monoaminergic function associated with depression, anxiety, and RBD symptoms in PD, also reflecting distinct brain networks. In contrast, tracer binding was not associated with cognitive impairment. Based on the anatomical locations of the findings, the results support the role of serotonin and mesolimbic dopamine function in parkinsonian depression, serotonin and norepinephrine in anxiety, and mesolimbic dopamine in RBD.

The new image registration protocol introduced in Study I enabled the voxelwise analyses across subcortical structures. In these analyses, depression was associated with monoamine transporter deficits in the ventral striatum and raphe nuclei, and by the specific binding properties of these structures. Thus, depression in PD seems to be associated with dopaminergic and serotonergic deficits. In addition, the spatial correlations verified that the connectivity of the clusters was aligned with the distribution of $D_{2/3}$ and serotonin $5HT_{1B}$ receptors. Anxiety was associated with serotonergic and noradrenergic clusters, and its network aligned well with serotonergic $5HT_{1B}$ distribution. The results align well with the clinical observations of beneficial effects with D2R agonists in parkinsonian depression (Ahmad et al., 2023; Saari et al., 2021; Seppi et al., 2019; Sethi, 2008) and are supported by the existing understanding of SSRI and SNRI medication response in parkinsonian depression and anxiety (Ahmad et al., 2023; Schneider et al., 2020; Starkstein & Brockman, 2017; Weintraub et al., 2022).

The implied involvement of monoaminergic deficits in the area of LC, a predominantly noradrenergic structure, in trait anxiety aligns well with previous molecular imaging evidence in PD patients. However, the finding was only apparent after 4 years of follow-up without observable progression in anxiety. This most likely reflects a lack of sensitivity of the present study design to detect changes in LC in an early stage of the disease.

RBD was mostly associated with reduced ventral striatal monoamine transporter binding, and its network primarily with $D_{2/3}$ receptor distribution; yet, the network

correlations also revealed associations with D_1 and two serotonin receptor subtypes ($5HT_{1A}$ and $5HT_4$). Based on the results, it is possible that norepinephrine function in the LC might not be the main factor underlying RBD, although it has been shown to be affected in RBD (García-Lorenzo et al., 2013).

In contrast to other studied non-motor symptoms, no association between cognition and [^{123}I]FP-CIT binding was observed. This supports the previous observations of the marked role of acetylcholine dysfunction in PD cognitive impairment (Bohnen et al., 2015, 2022; K. Kim et al., 2019; M. L. T. M. Müller et al., 2015; Shah et al., 2016; Van Der Zee et al., 2021). However, the PPMI study design, enriched with patients in the early disease stage and with an exceptionally low proportion of patients with dementia, as opposed to most observational cohorts, might have masked our ability to detect associations between monoaminergic dysfunction and cognitive change, as previously it has been expected that the interplay of the dopamine and cholinergic systems is associated with more severe cognitive symptoms in PD (Bohnen et al., 2015, 2022; K. Kim et al., 2019; M. L. T. M. Müller et al., 2015; Van Der Zee et al., 2021).

In the spatial correlation analyses, the networks derived from monoaminergic depression and akinesia-rigidity clusters were similar to the corresponding networks previously identified with causal brain lesions (Joutsa et al., 2018; Siddiqi et al., 2023). This supports the concept of investigating the neurobiological underpinnings of symptoms using network analyses based on molecular imaging clusters.

6.2.1 Limitations

The study also has limitations. First, despite the affinity of [^{123}I]FP-CIT for serotonin and norepinephrine transporters, it has mainly been developed and validated for investigating the striatal dopamine transporters. Thus, none of the findings in any of the studied brain regions can be considered specific for any of the tracer targets, but as a composite of all of them. Second, although the PPMI dataset is the largest available observational molecular imaging dataset in the study of PD, the statistical power to detect weaker associations of the studied non-motor symptoms and tracer binding may have been limited. Despite these limitations, a clear spatial dissociation of the monoaminergic abnormalities was demonstrated. Third, the PPMI cohort included patients with PD in relatively early phases of the disease, and cognitive impairment was rare among the studied sample. This may have limited the power to detect a possible link between cognition and monoaminergic function, possibly important in the later phase of the disease. A similar phenomenon prevented the investigation of hallucinations (prevalence 2.9% at baseline). Fourth, the normative connectome data used for the network analyses consisted of rs-fMRI data of healthy volunteers instead of patients with PD, which would have been optimal. However,

previous work has shown that the effects of the disease on broad patterns of connectivity are minimal, so it is unlikely that this caused any relevant bias in our findings (M. D. Fox et al., 2014). A similar limitation applies to the normative receptor maps (Alakurtti et al., 2015; Beliveau et al., 2017; García-Gómez et al., 2013; Kaller et al., 2017; Savli et al., 2012) used to describe molecular-level underpinnings of the networks, which should be taken into account when interpreting the results.

6.3 Study III: Changes of Emotion-Related Sensations in PD

Study III is the first to study the bodily sensations associated with sensorimotor symptoms and emotions in a neurological disease with BSM. The results show the typical, expected localization of cardinal motor symptoms in PD, and thus demonstrate the feasibility of the BSM method in a neurological disease. Using the methodology, abnormal patterns of emotion-related bodily sensations in PD were also identified. The bodily symptom mapping data also seems to be robust, based on its reasonable performance in the reclassification task between individuals with PD and controls.

The main finding was the decreased parasternal anger-related sensation, with a transition towards the abdomen as the disease progresses. A possible explanation for this may be in cardiac sympathetic denervation, which is very typical of PD (Braune et al., 1999; King et al., 2011; Orimo et al., 2008), likely causing the observable defective cardiovascular responses. It may even be leveraged for the differential diagnostics from other parkinsonian disorders using [^{123}I]MIBG scintigraphy, already in the early phases of the disease (Braune et al., 1999; King et al., 2011; Orimo et al., 2008). The results from previous studies of basic emotions and their autonomic counterparts in non-PD populations have also shown that anger has the strongest association with hemodynamic responses (Siegel et al., 2018), which may also be relevant in cardiovascular health (Alves et al., 2020; Liang et al., 2015; Smyth et al., 2016).

6.3.1 Limitations

This study, too, has some limitations that should be considered when interpreting the results. First, the reported bodily sensations related to emotions are subjective in nature, and little is known how strongly they correlate with the actual physiological responses, or abilities to experience or detect emotions. This matter should be confirmed in an independent study, with objective measures. Second, this was an online study, like previous studies using BSM (Nummenmaa et al., 2014;

Torregrossa et al., 2019; Volynets et al., 2020), and it was not possible to confirm the diagnoses. Third, although all the individuals in the PD group confirmed to have an established diagnosis, the diagnoses of some of them were likely inaccurate, as differential diagnostics of parkinsonism syndromes tend to be difficult even for neurologists (Joutsa et al., 2014). This would have biased the study against the observed findings. Fourth, in terms of the online format, possible selection bias cannot be excluded: probably, patients with more severe cognitive impairment, or those less attached to the patient association that distributed the survey invitations, were less likely to participate in the study. It is also possible that more severe motor symptoms or cognitive impairment, or psychological features associated with the decision to join a patient association or not, may be reflected in the responses. However, as the motor symptom maps aligned well with the known clinical symptom distribution, systematic bias in the observed group differences can be considered unlikely.

7 Summary/Conclusions

This thesis includes three studies, two of which focused on the monoaminergic abnormalities associated with motor and non-motor clinical manifestations of PD. Studies I and II leveraged the largest openly available prospective PD neuroimaging cohort study, PPMI, and a novel image preprocessing protocol developed for [^{123}I]FP-CIT imaging data. The aim was to identify monoaminergic abnormalities underlying motor (Study I), and non-motor (Study II) symptoms in PD, and to characterize monoaminergic networks associated with the studied non-motor symptoms (Study II). Study III utilized a relatively recently introduced bodily symptom mapping tool, and was the first to use this approach in a neurological disease. The aim of this study was to characterize the bodily representations of symptoms and emotions in PD with this subject-driven visual method.

In Study I, the key finding was a significant positive association between rest tremor amplitude and DAT binding in the ipsilateral striatum, with the confirmative findings of a negative association between akinetic-rigid symptoms and contralateral DAT binding. The finding was replicated with the data from the follow-up visits 2 years after the initial assessments, and was independent of age, sex, disease stage, symptom severity, motor phenotype, or cognition. The finding concerning rest tremor provides new insights to the neurobiological mechanisms of rest tremor, possibly also shedding light into the previously observed bilateral effects of unilateral neuromodulatory interventions. In addition, the findings also suggest a possible broader interplay of structures than what has been traditionally thought to underlie rest tremor pathophysiology.

In Study II, depression was associated with monoaminergic deficits in the ventral striatum and raphe nuclei, and trait anxiety with deficits in the raphe nuclei and LC. RBD symptoms were most strongly associated with lesser binding in the ventral striatum. In contrast, cognition showed no association with monoaminergic defects in the data consisting of patients with early PD. Clusters of depression, anxiety, and RBD were associated with distinct brain networks, significantly different from the one of akinetic-rigid symptoms. The networks of these non-motor symptoms also showed distinct receptor-level fingerprints. Thus, the results demonstrate distinct

monoaminergic network abnormalities for different motor and non-motor symptoms of PD.

In Study III, the BSM method demonstrated a typical profile of the cardinal symptoms of PD for sensorimotor symptoms. In terms of the emotion-related sensations, anger-related parasternal sensations were decreased and shifted towards the abdominal area. It is possible that the involvement of the autonomic nervous system underlies these new, previously unreported findings. The sensorimotor and emotion-related sensations also showed a broader covariance pattern associated with PD, significantly different from the pattern more prevalent in controls. These patterns showed a reasonable performance in a reclassification task of the data of controls and subjects with PD. Abnormal emotion-related bodily sensations demonstrated a new, previously unknown non-motor phenomenon in PD. Whether the changes are specific to PD, and whether they are also present in other neurological or non-neurological conditions, needs to be determined in further studies. In addition, the correlation of bodily symptom mapping data with objective measurements, such as motor observations or cardiovascular responses, should be confirmed in dedicated study designs in the future.

To conclude, this thesis demonstrates that both motor and non-motor symptoms in PD are associated with distinct monoaminergic abnormalities, and also identifies a new, previously unrecognized non-motor phenomenon in PD. For possible future clinical applications, the finding of the link between increased ipsilateral DAT binding and rest tremor should be validated in more typical and heterogenic clinical populations, and the underlying network mechanisms behind the finding should be discovered with dedicated designs, to find ways to leverage it towards better differential diagnostics and treatments of PD. The monoaminergic involvement of depression, anxiety, and RBD symptoms, and their spatially dissociated, distinctive monoaminergic networks, could possibly be used to design novel, better-targeted pharmacological and neuromodulation therapies for these debilitating symptoms, with additional cues from confirmative studies using dedicated tracers. Eventually, the recognized non-motor phenomenon of disrupted emotion-related sensations in PD will increase the understanding of the pathophysiological and possibly psychological backgrounds behind the broad clinical manifestation of PD, and may be utilizable in the diagnostics, follow-up and treatment of PD and other neurological diseases, if supported by future studies with more extensive clinical data, and subjects with various neurological conditions.

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List of Figures, Tables, and Appendices

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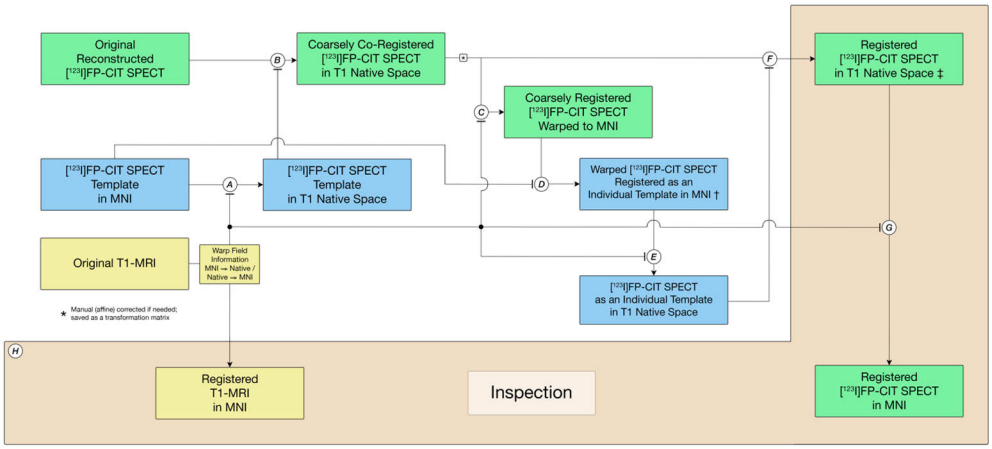
Appendices

Appendix 1. The registration protocol of the [^{123}I]FP-CIT SPECT images.



First, the structural T1-weighted MRI of each subject was processed with SPM12 Segment producing 1) the warp field from the native space to the MNI space, and vice versa, 2) 6 tissue segments of the structural T1-MRI image (used for partial volume error correction) 3) the registered T1-MRI in MNI space.

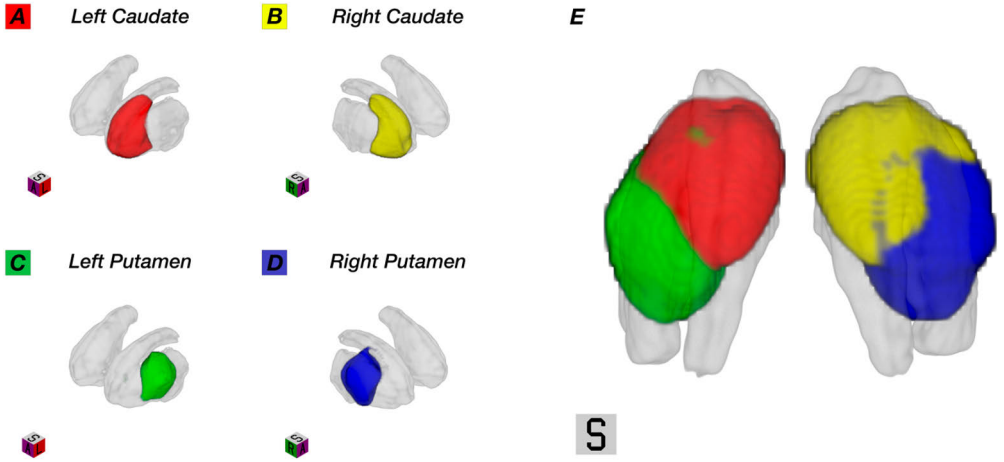
Second, the [^{123}I]FP-CIT-SPECT template was nonlinearly transformed to the individual native T1 space using the obtained inverse warp field from the first step (A). Next, the original reconstructed [^{123}I]FP-CIT-SPECT was coarsely linearly registered with the [^{123}I]FP-CIT-SPECT template in the individual T1 native space (B) and manually corrected if needed (*). The coarsely registered [^{123}I]FP-CIT-SPECT in the T1 native space was then nonlinearly registered to the MNI space (C). The preliminarily registered scan was linearly registered to the initial [^{123}I]FP-CIT-SPECT template in the MNI space, resulting in an individual [^{123}I]FP-CIT-SPECT template (D). This individual template was then nonlinearly transformed back to the individual T1 native space using the inverse warp field obtained in the beginning of the process (E).

Third, the original [^{123}I]FP-CIT-SPECT image was linearly registered to the individual [^{123}I]FP-CIT-SPECT template in the T1 native space, resulting in the original [^{123}I]FP-CIT-SPECT image in the native T1 space with linear transformation only (F). This image was then nonlinearly transformed to the MNI space using the warp field obtained in the first step (G). The preprocessing results were carefully visually inspected, and individuals with suboptimal preprocessing results were excluded from the analyses (H).

The software libraries used: Statistical Parametrical Mapping 126 (for MRI nonlinear registration and warps), Advanced Normalization Tools (Avants et al., 2011) (for mathematical processes [ImageMath] and for the coregistration processes; similarity metrics for the coregistration in the MNI space: Mattes with weight 0.5 + ANTs cross-correlation with weight 0.5; otherwise Mattes similarity metric with weight 1), FSL (Jenkinson et al., 2012) (FSLeyes for inspection and possible correction in step C; fslmaths for mathematical processes), ITK-SNAP (Yushkevich et al., 2006) Convert3D (for transformation matrix format conversions), GNU Parallel (Tange, 2011) (for process parallelization).

† If the registration failed without masking and/or the [^{123}I]FP-CIT-SPECT scan was cropped, both the fixed and moving images were masked with a crop mask. ‡The partial volume error correction for the registered scan was performed in the T1 native space.

Appendix 2. Spatial correspondence with PPMI Core Lab ROI SBR values. The “winner ROIs” of **(A)** left caudate, **(B)** right caudate, **(C)** left putamen, and **(D)** right caudate, with **(E)** a superior presentation of all the “winner ROIs” together on a striatal template defined by the Harvard-Oxford Subcortical Atlas, in the standard MNI space. The “winner ROI” for each voxel within the striatum, defined by the ROI with largest voxel *T* value in the ROI univariate regression models using the PPMI Core Lab SBR regions of interests (ROIs). The results show expected anatomical distribution. S, superior; R, right; L, left.



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