The Role of the Motivational Brain in Parkinson's Disease: A Multimodal Neuroimaging Approach

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Summary

Parkinson's disease (PD) is a progressive multi-system neurodegenerative disease that affects approximately 2% of the population over the age of 80. The accelerated increase in prevalence with age, combined with the rapid aging population in Europe and other Western regions, is leading to a dramatic increase in the (social, economic and personal) burden of PD. Accordingly, there is an urgent need for a better understanding of the disease. So far, almost 200 years of research have yielded significant insights into the pathophysiology of PD. While the precise mechanisms between pathology and clinical presentation are incompletely understood, recent evidence points to a motivational influence on PD motor symptoms. This cumulative thesis aims to investigate the importance of the motivational brain in PD and its associations with PD motor symptoms. To address this aim, this thesis is comprised of three individual research projects, each guided by a different perspective, ultimately addressing the overall research question.

The objective of the first project is to provide an overview of the current literature on neuropathological changes in motivational brain regions and their associated clinical manifestations in PD. The study showed that pathological changes can be observed early on, with some alterations being related to PD motor symptoms. The second project aims to further elucidate the underlying mechanism of motivational contributions to PD motor symptoms. Interestingly, this project showed that the loss of effortful movements may be based on a reduced implicit motivation to move, suggesting that PD motor symptoms may not be a purely motoric issue. Finally, in the third project, it is investigated whether patients can be divided into subtypes based on their observed neurodegeneration in the motivational brain, more specifically the amygdala. However, although the motivational brain seems to play a role in PD motor symptoms, the results of this project suggest that it does not seem to aid classification.

Taken together, the research projects included in this thesis provide an in-depth understanding of the role of motivational brain regions in PD. Collectively, they highlight the far-reaching consequences of neurodegenerative changes that go beyond non-motor symptoms and also contribute to the cardinal motor impairments. In doing so, this work highlights the importance of including motivational brain regions in the scientific discourse and encourages further investigation to promote a better understanding of the disease. Finally, the knowledge gained may contribute to the development of novel therapeutic strategies with the ultimate goal of alleviating the burden of PD.

Zusammenfassung

Die Parkinson-Krankheit (PK) ist eine fortschreitende, neurodegenerative Multisystemerkrankung von der etwa 2% der über 80-Jährigen betroffen sind. Die steigende Prävalenz mit fortschreitendem Alter in Verbindung mit der zunehmend alternden Gesellschaft in Europa und anderen westlichen Regionen führt zu einem drastischen Anstieg der (sozialen, wirtschaftlichen und persönlichen) Belastung durch die PK. Demzufolge besteht ein dringender Bedarf an einem besseren Krankheitsverständnis. Nahezu 200 Jahre an Forschung haben wichtige Erkenntnisse über die Pathophysiologie der PK erbracht. Die genauen Mechanismen, welche die Interaktion zwischen Pathologie und klinischem Erscheinungsbild bedingen, sind jedoch noch nicht gänzlich verstanden und jüngste Erkenntnisse deuten darauf hin, dass es einen Einfluss von motivationalen Prozessen auf die motorischen Symptome der PK geben könnte. Diese kumulative Dissertation untersucht daher die Rolle des motivationalen Gehirns bei der PK und seine Beziehung zu den motorischen Symptomen. Um das Forschungsvorhaben zu adressieren, besteht diese Dissertation aus drei Einzelprojekten, die jeweils aus einem anderen Blickwinkel heraus die Forschungsfrage gemeinsam beantworten.

Ziel des ersten Projekts ist es, einen Überblick über die aktuelle Literatur hinsichtlich neuropathologischer Veränderungen in motivationalen Gehirnregionen und den damit verbundenen klinischen Manifestationen der PK zu geben. Die Studie zeigte, dass pathologische Veränderungen bereits im frühen Stadium zu beobachten sind, wobei einige Veränderungen in Zusammenhang mit den motorischen Symptomen der PK stehen. Das zweite Projekt zielt darauf ab, den zugrundeliegenden Mechanismus zu verstehen, wie Motivationsprozesse zu den motorischen Symptomen der PK beitragen. Interessanterweise zeigte sich in diesem Projekt, dass der Verlust kraftvoller Bewegungen auf eine verminderte implizite Motivation für Bewegungen zurückzuführen sein könnte, was darauf hindeutet, dass die motorischen Symptome der PK möglicherweise nicht ausschließlich ein motorisches Defizit darstellen. Schlussendlich wird im dritten Projekt untersucht, ob sich Patient*innen anhand ihrer Neurodegeneration im motivationalen Gehirn, genauer gesagt in der Amygdala, in Subtypen einteilen lassen. Obwohl das motivationale Gehirn eine Rolle bei den motorischen Symptomen der PK zu spielen scheint, deuten die Ergebnisse dieses Projekts nicht darauf hin, dass es für die Klassifizierung von Bedeutung ist.

Die Forschungsprojekte, welche in der vorliegenden Dissertation zusammengefasst sind, tragen dazu bei, die Rolle der motivationalen Gehirnregionen bei der PK besser zu verstehen. In ihrer Gesamtheit weisen sie auf die weitreichenden Folgen der neurodegenerativen Veränderungen hin, die über die nicht-motorischen Symptome hinausgehen und auch zu den kardinalen motorischen Beeinträchtigungen beitragen. Auf diese Weise zeigt diese Arbeit, wie wichtig es ist, motivationale Gehirnregionen in den wissenschaftlichen Diskurs miteinzubeziehen, und sie regt zukünftige Forschung für ein besseres Krankheitsverständnis an. Letztendlich kann dieses

Wissen dazu beitragen, neue therapeutische Ansätze zu entwickeln, mit dem Ziel die Belastung der PK zu reduzieren.

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1 Introduction

1.1 Parkinson's Disease

The word motivation is derived from the Latin verb "movere" - meaning "to move".

First described in 1817 by James Parkinson in "An Essay on the Shaking Palsy," Parkinson's disease (PD) currently represents one of the leading brain health issues worldwide with enormous global impact. PD is a progressive multi-system neurodegenerative disease, that is associated with the accumulation of α-synuclein and the loss of dopaminergic neurons in the midbrain. Clinically the disease is manifested by the cardinal motor features including rigidity, tremor, and bradykinesia but also by diverse non-motor symptoms, such as depression, cognitive impairment, and disturbed sleep (Bloem et al., 2021). The clinical picture is very heterogeneous, as each patient is affected by a different combination of the diverse symptoms as well as a unique disease progression (Thenganatt & Jankovic, 2014). Even though PD has been known for more than 200 years, the underlying pathological mechanisms are still insufficiently understood and existing treatments focus on relieving symptoms, as to date no cure is available (Oertel & Schulz, 2016).

In recent years, PD has undergone stupendous prevalence growth and current estimates suggest that worldwide 106 per 100,000 (0.01%) adults are affected by PD (Ou et al., 2021). The disease seldom occurs in individuals below 40 years and the prevalence substantially rises above the age of 65, with approximately 2% of individuals over 80 years being affected (Pringsheim et al., 2014), which indicates an accelerated prevalence growth with aging. Due to the rapidly aging population in Europe and other Western regions, it is predicted that the burden of PD (being personal, social, and socio-economical) will continue to grow substantially in future decades, thereby increasing the necessity for a better disease understanding as well as the development of novel therapeutic approaches (Deuschl et al., 2020; Whetten-Goldstein et al., 1997).

For a long time, PD has been seen as a pure motor disorder. However, this classical view might not be entirely correct. PD is not only characterized by alterations in the brain's motor system but also in brain regions associated with emotion, motivation, and reward; also known as the *motivational brain* (Lang & Bradley, 2010; Li et al., 2017). Newer lines of evidence suggest that PD-related alterations in motivational brain regions might also interfere with the brain's motor system and thus, represent a potential modulating factor of the cardinal motor symptoms (Mann et al., 2023). To date, the exact role of the motivational brain in PD pathophysiology, including regional alterations as well as subsequent changes in motor circuits, is incompletely understood. However, neuroimaging methods are a powerful tool to study disease related alterations, as they enable direct in vivo insights into the diseased PD brain (Bidesi et al., 2021). Better knowledge of

the disease mechanisms which orchestrate the interplay between pathology and clinical presentation may provide novel targets for interventions as well as improve diagnosis. For this reason, the overarching objective of this thesis is to elucidate the role of the motivational brain in PD through the use of a multimodal neuroimaging approach.

1.1.1 Pathology

The past years have nourished the development and refinement of many theories on the pathobiology of PD, with the common ground being that it is a complex interplay of multiple factors, which leads to the disease's manifestation and progression (Müller-Nedebock et al., 2023). It has been proposed that factors such as α-synuclein aggregation, mitochondrial dysfunction, synaptic transport issues, oxidative stress, as well as neuroinflammation may be implicated. Collectively these disease mechanisms result in accelerated neuronal death (Bloem et al., 2021). Below, the two most prominent pathological hallmarks of PD will be addressed.

The first key pathological hallmark of PD is the presence of Lewy bodies. Lewy bodies are intraneuronal inclusions, which primarily contain misfolded α-synuclein, a presynaptic neuronal protein (Spillantini et al., 1997). The misfolding and consequent aggregation of α-synuclein is believed to impair mitochondrial, lysosomal, proteasomal, and synaptic functioning, in addition to causing damage to membranes and the cytoskeleton. Ultimately leading to neurodegeneration. Lewy pathology spreads throughout the brain as the disease progresses, whereby the underlying progression mechanism is thought to be based on a cell-to-cell transmission in a prion-like manner (Gómez-Benito et al., 2020; Visanji et al., 2013).

In 2003 Braak et al. (2003) proposed a staging system for PD which classifies the chronological progression of Lewy pathology into six distinct stages (Figure 1). The model posits that the pathological process initiates concurrently in the dorsal motor nucleus of the vagus nerve and the anterior olfactory structures. The disease then progresses rostrally through the rostral brainstem, midbrain, and limbic regions, ultimately reaching the neocortex. As Lewy pathology progresses from the brainstem upwards, the extent of the lesions in the affected brain regions and the clinical manifestations increase substantially. Interestingly, Lewy pathology is not limited to the central nervous system but is also present in the peripheral nervous system, particularly the enteric nervous system (Goedert et al., 2013). Thus, it is unclear whether the brainstem is the actual and sole site of disease origin. Consequently, the first publications of Braak and colleagues were followed up by the more refined *dual-hit hypothesis*, which broadened the view to the peripheral nervous system (Hawkes et al., 2007). According to the hypothesis, an unknown neurotropic pathogen (e.g., a virus or bacterium) enters the body through both a nasal and a gastric pathway. Although the olfactory system is involved early on, the authors do not believe that this is the point from where pathology spreads to the rest of the brain, but rather see the gastric system as the entranceway for pathology to access the brain.

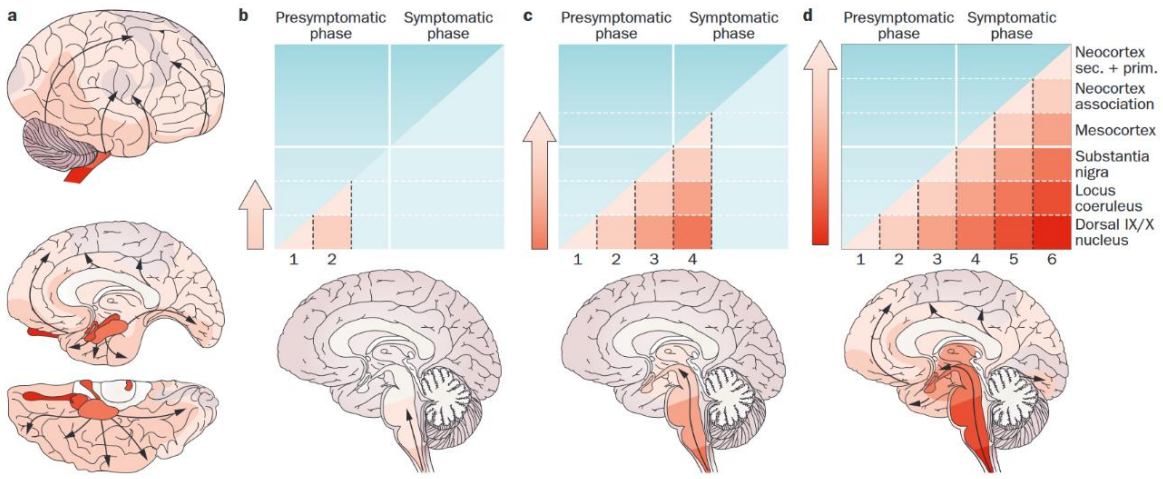

Figure 1: Progression of the Pathological Process in PD. The six stages of PD pathology according to the Braak staging model. The figure was reproduced from 100 years of Lewy pathology (Goedert et al., 2013) with permission from Springer Nature. The figure is licensed by Springer Nature Customer Service Center GmbH, and is NOT part of the overriding OA/Creative Commons license.

The finding of α-synuclein deposits outside the central nervous system, has fostered the development of other models, beside the Braak staging system. Most recently, the *brain-first body-first* idea has gained substantial interest (Borghammer, 2021). This hypothesis was put forward by Borghammer and suggests two PD subtypes with distinct α-synuclein spreading patterns. In the brain-first subtype, α-synuclein aggregates originate unilaterally inside the amygdala from where the pathology disseminates in a more asymmetric fashion downwards to the peripheral autonomic nervous system. On the other hand, in the body-first subtype, α-synuclein aggregates initially arise in the peripheral autonomic nervous system, more precisely in the enteric nervous system. From there the pathology spreads upwards, symmetrically innervating the vagus nerve and finally the brain. It is important to note, that despite various attempts to explain α-synuclein pathology in PD, hitherto a single unifying model is still lacking. Thus, the origin and route of progression including potential subtypes is still a matter of debate and currently under investigation.

The second key pathological hallmark of PD is the loss of dopaminergic neurons, particularly in the substantia nigra pars compacta (Surmeier, 2018). The degeneration of dopamine-containing neurons results in a reduction in dopamine levels within the basal ganglia, particularly within the striatum. This triggers a range of functional alterations in brain circuits in which the basal ganglia control the accurate execution of voluntary movements, and thus it is seen as the biological substrate for the manifestation of PD motor symptoms (Blandini et al., 2000; Graybiel, 2000). Interestingly, neuropathological studies have indicated that up to 50% of dopaminergic neurons may already be lost at the time of motor symptom onset (Heng et al., 2023).

To date, the etiology of PD is incompletely understood and the crucial question of what may be the initial trigger of the disease remains to be answered. However, in the light of today's state of research PD most likely results from the combined effect of environmental (i.e., neurotropic pathogens) and genetic factors (Simon et al., 2020). Most importantly, once the disease manifests, the pathological mechanisms cause a variety of clinically observable symptoms, which are described in the next section.

1.1.2 Clinical Presentation

Some aspects of PD's clinical presentation can be directly linked to neuronal loss, while others seem to be caused by functional and dysfunctional alterations in activity and connectivity of surviving neurons (McGregor & Nelson, 2019). In general, the clinical hallmark of PD is a motor syndrome, however the clinical presentation of PD is multifaceted and can broadly be divided into two categories: motor and non-motor symptoms.

The acronym *TRAP* can be used to describe the defining cardinal motor features of PD: tremor, rigidity, akinesia, and postural instability. Tremor typically presents unilaterally, in the distal part of the extremities and at a frequency between 4 and 6 Hz whereas rigidity refers to the increased resistance of a limb during passive mobilization (Hayes, 2019; Jankovic, 2008). The meaning and use of the term akinesia has varied over the years, and it is sometimes used synonymously with the term bradykinesia, which adds to the confusion regarding the correct definition (Schilder et al., 2017). In order to avoid this ambiguity this thesis uses a more differentiated view, termed the *bradykinesia complex* (Bologna et al., 2023). The bradykinesia complex consists of multiple related symptoms including slowing of movement (bradykinesia), decrease in movement amplitude (hypokinesia), and absence of movement (akinesia). Together they represent the hallmark clinical motor symptom of PD. Finally, postural instability represents the most prevalent underlying cause of falls and injuries, resulting from the loss of postural reflexes (Jankovic, 2008). While motor symptoms have traditionally been the primary focus of PD research, non-motor symptoms have long been underappreciated. However, they constitute a substantial factor in the decline of quality of life. Non-motor features encompass cognitive and affective disorders (such as cognitive decline, apathy, depression, anxiety, and hallucinations), sleep disturbances, autonomic dysfunctions, and sensory symptoms (Sveinbjornsdottir, 2016). The clinical assessment of PD motor and non-motor symptoms is currently based on the MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS; Goetz et al., 2008).

Before the first motor symptoms appear (denoting the onset of clinically manifest PD), individuals may demonstrate a variety of pre-motor symptoms, even as early as 20 years prior. This period is referred to as pre-motor or prodromal phase which is characterized by symptoms such as impaired olfaction, constipation, depression, anxiety, and rapid eye movement sleep behavior disorder. The prodromal phase is of specific relevance to researchers, as it allows investigation of

the pathogenesis as well as the development of disease-modifying interventions, which could potentially delay or even prevent the conversion to clinical PD (Mahlknecht et al., 2015).

In the majority of cases, the disease initially manifests in the form of motor symptoms on one side of the body which extend to the contralateral side with disease progression. While non-motor symptoms are aggravating in the early stages, they are generally mild. The motor dysfunctions cause progressive disability (e.g., freezing, falls, dysarthria, dysphagia) and lead to a growing dependency in daily living. Additionally, the burden of non-motor symptoms increases drastically. Particularly, psychosis and cognitive decline are common in advanced stages. Finally, PD is associated with an increased risk of severe disability and mortality (Poewe & Mahlknecht, 2009; Sveinbjornsdottir, 2016). A representation of the clinical disease course can be found in Figure 2.

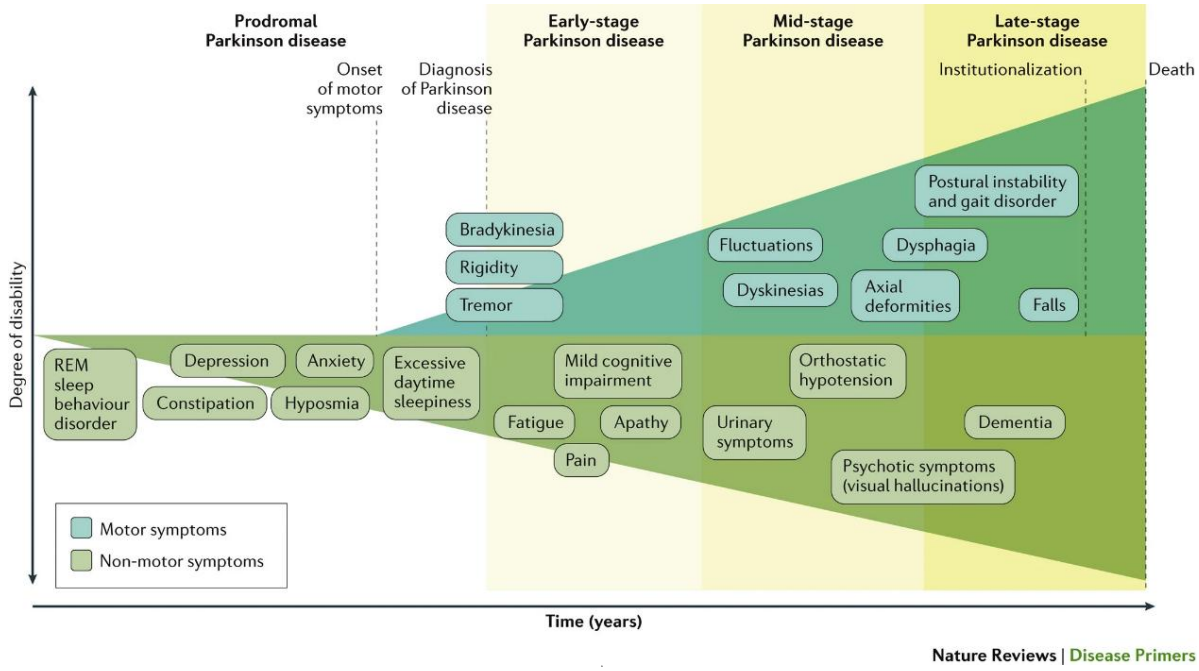

Figure 2: The Clinical Disease Course of PD. The figure was reproduced from *Parkinson disease* (Poewe et al., 2017) with permission from Springer Nature. The figure is licensed by Springer Nature Customer Service Center GmbH, and is NOT part of the overriding OA/Creative Commons license.

1.2 Brain Systems

1.2.1 The Motor System

In order to understand the disease mechanisms that drive PD motor symptoms, one requires knowledge of the underlying systems, their circuits and functions. The ability to generate desired movements (i.e., the decision what to do, how, and when) is essential for our daily living, as we live through interactions with our environment. Based on the respective movement one wants to

perform, the motor system needs to control and coordinate different movement variables, thus execute so-called motor control. The execution of a desired movement requires a representation of the movement goal, its translation into appropriate muscle activations with the correct onset time, speed, force, amplitude, and duration, as well as monitoring of the ongoing movement with instant adjustments if needed (Klaus et al., 2019; Mazzoni et al., 2012).

Research has shown that motor control relies substantially on basal ganglia function. In this regard, dopaminergic neurons project from the substantia nigra to the dorsal striatum (which is composed of the putamen and caudate), constituting one of the brains mayor dopaminergic pathways. This so-called nigrostriatal pathway is known for its involvement in motor control and motor skill learning (Latif et al., 2021). Moreover, the dorsal striatum constitutes the main input gate of the basal ganglia, as it receives excitatory afferents from the frontal, motor, and sensory cortices, and thalamus which supply information about movement goals, internal state, and context. Through integration of this information, basal ganglia outputs are modulated in order to perform the appropriate behavior (Klaus et al., 2019).

Disease models usually represent a considerable oversimplification of the true underlying mechanisms; however, they are an invaluable tool to describe and understand biological processes. As such, the classical circuit model of PD describes two distinct basal ganglia pathways, the direct and indirect pathway, which can be seen as accelerator and decelerator of movements. In PD, nigrostriatal degeneration leads to a disbalance in these basal ganglia pathways which results in diverse motor abnormalities. As such the slowness of voluntary movements and the difficulty to self-initiate movements likely stem from an overactivation of the indirect pathway (Fasano et al., 2022; Graybiel, 2000).

1.2.2 The Motivation System

The motor system does not function independently but is closely intertwined with the motivation system. This becomes especially evident in volitional (i.e., non-automatized) movements, as they rely on the presence of motivation (Fried et al., 2017). Motivation can be defined as “a person’s willingness to exert physical or mental effort in pursuit of a goal or outcome” (https://dictionary.apa.org/motivation). By translating internal states into outcomes, it is a primary source of behavior and adaption. In this sense, motivation determines the energization (i.e., recruitment of needed resources) and direction (i.e., which goals are pursued) of behavior (Brown & Pluck, 2000; Salamone & Correa, 2024). In order to fully grasp the phenomenon of motivation it takes multiple levels of explanation - from the neural level to the psychological and behavioral level.

On the neural level, motivation is driven by a network of striatal and medial frontal regions as well as their associated subcortical-cortical circuits. The underlying dopaminergic pathway is the

mesolimbic pathway, widely known as the reward pathway, which connects the ventral tegmental area in the midbrain to the nucleus accumbens in the ventral striatum (Latif et al., 2021). The release of mesolimbic dopamine has been implicated in the regulation of motivation and desire (also known as *wanting* or *incentive salience*) for rewarding stimuli (Berridge & Robinson, 1998; Salamone & Correa, 2012). Although this pathway is acknowledged for its significant importance, it is but one of numerous components that constitute a more expansive neural network, which regulates motivation. This neural network also encompasses the lateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex which are implicated in the assessment and motivation of behavioral choices. Moreover, limbic regions including the amygdala and hippocampus, are implicated in modulating the network based on internal and external information (Palmisano et al., 2020; Salamone & Correa, 2024). On the subsequent level of explanation, the psychological level, reward is probably one of the most powerful aspects supporting motivational processes. The ability to encode the value of rewarding stimuli and to establish anticipations of when and where rewards will occur are key components, as this information forms the basis of behavioral decisions (O'Doherty, 2004). Finally, motivation can be observed in the form of behavioral choices, effort, duration, and frequency (Kim, 2013).

Research has demonstrated PD-related changes in multiple motivational brain regions which are typically linked to non-motor symptoms (Weintraub et al., 2022; Wen et al., 2016). However, to what extent these changes go beyond the development of non-motor symptoms, potentially contributing to the cardinal motor symptoms remains a matter of investigation.

1.2.3 Movement Motivation – An Intersection

A severely disabled, wheelchair bound patient with PD is suddenly able to move and run to safety out of a burning house. This is probably one of the oldest and most told anecdotes in the field of PD and refers to a phenomenon called *paradoxical kinesia*. Paradoxical kinesia describes the ability of patients with PD to substantially increase movement velocity and reduce bradykinesia under specific conditions, thus suddenly being able to perform tasks which were previously impossible (Glickstein & Stein, 1991; Souques A, 1921). Most of the cited cases have been reported in the context of immediate threat, hence it has been suggested that the critical factor is the presence of salient, external, and preferably visual cues. In an attempt to explain the occurrence of paradoxical kinesia, it was suggested that in these urgent situations basal ganglia reserves are activated. Accordingly, in threatening situations patients are able to release additional dopamine from the dorsal and ventral striatum leading to short-term improved motor abilities (Distler et al., 2016).

Paradoxical kinesia has long been seen as an extreme phenomenon, something that only happens in some patients and under very specific, intense circumstances (Schlesinger et al., 2007). However, more recently this old idea has gained renewed interest in the form of *movement*

motivation. A cardinal feature of PD is the abnormally slow performance of movements (bradykinesia), and it is suggested that it is caused by a shift in the cost-benefit computation of motor behavior (Mazzoni et al., 2007). This idea is grounded in psychological and economic utility theories of motivation, which suggest that movements are the outcome of the brain's economic evaluation (Shadmehr et al., 2019). The core assumptions are as follows: An individual's motivation to perform a specific movement is determined by the expected benefits and costs that are associated with the movement. Benefits entail positive feelings, experiences, and gains which occur either during the performance of the movement or afterwards. On the contrary, cost comprise necessary expenditures such as effort and time but also negative outcomes and missed alternative opportunities. It is assumed that benefits and costs work antagonistically on movement motivation, such that a movement is likely to be performed if the overall benefits outweigh the expected costs but not if the expected benefits are lower than the expected costs (Studer & Knecht, 2016).

The movement motivation idea in PD is supported by several studies. These studies typically use paradigms that utilize varying levels of physical effort and monetary reward and then assess the cost-benefit decisions of patients. For instance, Le Heron et al. (2018) investigated the behavior of patients with PD ON and OFF their dopaminergic medication and found increased physical effort expenditure in the ON state, suggesting an increase of motor vigor by dopamine. Moreover, dopamine also heightened the acceptance for high effort, high reward options. These findings are further corroborated by a study from Le Bouc et al. (2016) which demonstrated lower effort in patients OFF their dopaminergic medication. Finally, Mazzoni et al. (2007) showed that patients with PD were indeed able to produce the required effort but were less likely to do so. Thus, these results suggest that the bradykinesia complex might be due to an increased sensitivity to movement costs or a reduced incentivization by reward, rather than an inability to exert movements.

Taken together these findings indicate that patients with PD might have a shifted cost-benefit computation of movements which results in a reduced implicit motivation. Consequently, this produces abnormally slow movements unless extrinsic stimuli add additional explicit motivation (Herz & Brown, 2023). Embedding these findings into the concept of paradoxical kineasia, it seems that the improvement in motor performance is not the result of recruiting a different neural pathway for motor execution, but a result of external motivators which partly compensate the reduced ability of the basal ganglia to energize movements (Distler et al., 2016).

1.3 Imaging Neurodegeneration

The development and widespread use of neuroimaging techniques has revolutionized our understanding of the brain. Neuroimaging allows non-invasive, in vivo visualization of the brain's

structure, metabolism, and function, thereby aiding our understanding of how different brain regions contribute to different functions such as movement, motivation, and decision-making. In PD, neuroimaging has been used for over 40 years (Politis, 2014), whereby its main purpose lies in the detection of disease related alterations, which may inform diagnosis and monitoring of the disease, but also the development of new therapeutical approaches (Yen et al., 2023).

Multiple neuroimaging biomarkers of PD have been identified, supporting the link between brain pathology and clinical manifestation. It is important to recognize that there is not one perfect biomarker, but specific imaging targets should be utilized for specific aims (Mitchell et al., 2021). Furthermore, the joint use of diverse imaging modalities (i.e., a multimodal neuroimaging approach) can provide a significant advantage (Bidesi et al., 2021). Common neuroimaging techniques of PD research include magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT).

1.3.1 Magnetic Resonance Imaging

MRI is a widely used technique to acquire detailed anatomical images of the human body. In order to acquire an image, a person is placed inside an MRI scanner and the strong magnetic field of the scanner forces the hydrogen nuclei (single protons) of bodily tissues to align with it. Radiofrequency pulses are added, causing the protons to spin out of their alignment. The energy which is released when the protons relax and return to their resting state, thus realigning with the magnetic field, is picked up by sensors on the MRI scanner. Importantly, different bodily tissues relax at different rates, and it is this particular information that is used to generate the MRI images. MRI is a non-invasive imaging method with no known biological hazards, as unlike other imaging modalities, it does not make use of ionizing radiation but instead applies radiation in the radiofrequency range which does not harm bodily tissue (Berger, 2002; Peter, 2009).

For many years, the MRI scans of patients with PD were considered not different from healthy controls. However, technological advances in the last years have enabled the visualization of alterations caused by the neurodegenerative process (Obeso et al., 2017). Whereas in the clinical context MRI aids the differential diagnosis of PD, in research it helps to unravel dysfunctional alterations and mechanisms which underly the disease (Politis, 2014; Theis et al., 2024). Different aspects of brain morphology may be derived from structural MRI scans, with gray matter volume (GMV) being a common proxy for Lewy pathology and neurodegeneration in the broader sense. GMV atrophy in PD is seen as pathological and additive to normal aging and has been associated with α-synuclein presence and inflammation biomarkers (Blair et al., 2019; De Micco et al., 2018; Lin et al., 2021). However, it is important to note that evidence which associates Lewy pathology with GMV loss is not fully straightforward and other aspects such as inflammation and regional vulnerability are likely to be involved as well (Tremblay et al., 2021).

1.3.2 Dopaminergic Imaging

In addition to MRI, dopaminergic imaging provides valuable supplementary information, as it offers the possibility to assess the integrity of the dopaminergic system with high accuracy. A variety of techniques enable the investigation of the dopaminergic system by targeting different sites including the dopamine transporter (DAT), vesicular monoamine transporter 2, dopamine receptors, as well as aromatic-amino-acid decarboxylase (Prange et al., 2022).

Of these techniques in vivo DAT imaging is the most widely employed modality, providing an assessment of the dopamine terminal integrity in the striatum (Ba & Martin, 2015). DAT is a protein which is exclusively located on the presynaptic membrane of dopaminergic nerve terminals. By taking up dopamine from the synaptic cleft into neurons and regulating dopamine storage in synaptic vesicles, it plays a central role in the maintenance of dopamine homeostasis in the central nervous system (Bidesi et al., 2021; Chen & Reith, 2000). DAT imaging uses radiotracers in order to estimate the level of DAT expression in the striatum. There are SPECT and PET radiotracers, both typically consisting of a bioactive molecule which binds to the target as well as a radionuclide which can be picked up by a SPECT or PET camera. PET imaging has some advantages compared to SPECT, such as a higher resolution and sensitivity (Akdemır et al., 2021; Jakobson Mo et al., 2018). However, as DAT SPECT is less costly and more practical in use, it has become the established clinical standard, with [^{123}I]FP-CIT being among the most used radiotracers (Abbasi Gharibkandi & Hosseinimehr, 2019; Theis et al., 2024).

DAT imaging aids the timely and accurate diagnosis of PD in clinical practice and provides important information for researchers seeking to understand the underlying disease mechanisms. In PD, striatal DAT radiotracer uptake is decreased compared to the healthy state, which is seen as an indicator for reduced dopaminergic functioning (Bidesi et al., 2021). Importantly, tracer uptake is already reduced in prodromal individuals, thus representing a powerful indicator of this pre-clinical stage. Reduced tracer uptake appears parallel to the loss of nigrostriatal dopaminergic cells, which is why DAT tracer uptake is utilized as an indirect biomarker of dopaminergic neuron degeneration (Theis et al., 2024).

In PD, the loss of DAT tracer uptake occurs earliest and most prominently in the dorsal putamen. Typically, one brain hemisphere demonstrates a greater decrease, which is located contralaterally to the clinically more affected body side. As the disease progresses the anterior part of the putamen, caudate nucleus, as well as the other hemisphere become affected as well. Finally, in later disease stages this posterior-to-anterior gradient becomes less evident. Importantly, a great body of literature supports the correlation between reduced radiotracer uptake and disease severity (Akdemır et al., 2021). Interestingly, the decrease in DAT tracer uptake is found to be specifically associated with akinesia and rigidity, but to a lesser degree with tremor severity (Brücke & Brücke, 2022). Furthermore, it is of particular significance to note that at the time of initial symptom onset approximately 35–45% of striatal DAT activity is already lost (Cheng et al.,

2010; Heng et al., 2023). This may potentially result in a flooring effect in the DAT measurements at later stages (Kerstens & Varrone, 2020).

1.4 Datasets

1.4.1 Open Access

In recent years, there has been a growing trend towards sharing neuroimaging data. This can be seen in many endeavors, including collective attempts to build up large-scale open access datasets. In the field of PD, the Parkinson's Progression Markers Initiative (PPMI) database, founded by the Michael J. Fox Foundation (https://www.ppmi-info.org), represents such an effort. It is a collection of imaging, genetic, demographic, and clinical data, launched by a group of scientists and industry partners with the goal to identify biomarkers of PD onset and progression. The availability of multimodal neuroimaging data in combination with clinical variables makes it perfectly suited to identify and investigate disease mechanisms underlying the cardinal motor symptoms. Considering the vast amount of resources that are required for the acquisition of neuroimaging data including time, money, as well as access to patients, facilities, and equipment, underscores the immense value of open access datasets. They facilitate the ready availability of high-quality data and thereby accelerate the research progress. This thesis also utilizes the advantages of this open access development and includes data from the PPMI database in addition to data from an in-house study, which is described below.

1.4.2 The DoMoCo Study

The Dopamine and Motoric Control (DoMoCo) study is part of the Deutsche Forschungsgemeinschaft (DFG) - funded Collaborative Research Center 1451 and was launched by our research group, the Multimodal Neuroimaging group, at the University Hospital Cologne, Germany, in 2021. The goal of this study is to investigate the consequences of striatal dopaminergic terminal loss on volitional motor control in the domains of movement vigor, motor planning, and incentive salience of external reward. To this end, we implement a unique combination of behavioral phenotyping and state-of-the-art structural, functional, and molecular neuroimaging methods in prodromal individuals (N=40), early-stage patients with PD (N=40), as well as a sex- and age-matched healthy control group (N=60).

Individuals with prodromal and clinical PD, are recruited at the Department of Nuclear Medicine during their clinical examination, whereas healthy controls are recruited by word of mouth and poster adverts. Each participant is screened for eligibility, which is followed by two study visits. During their study participation, individuals undergo extensive neuropsychological and motor testing as well as various MRI measurements. DAT SPECT images of the prodromal and PD group, which are acquired as part of the clinical examination, are included in the study as well. This

allows the quantification of effects of neuropathology on clinical outcomes. An overview of the study design is depicted in Figure 3.

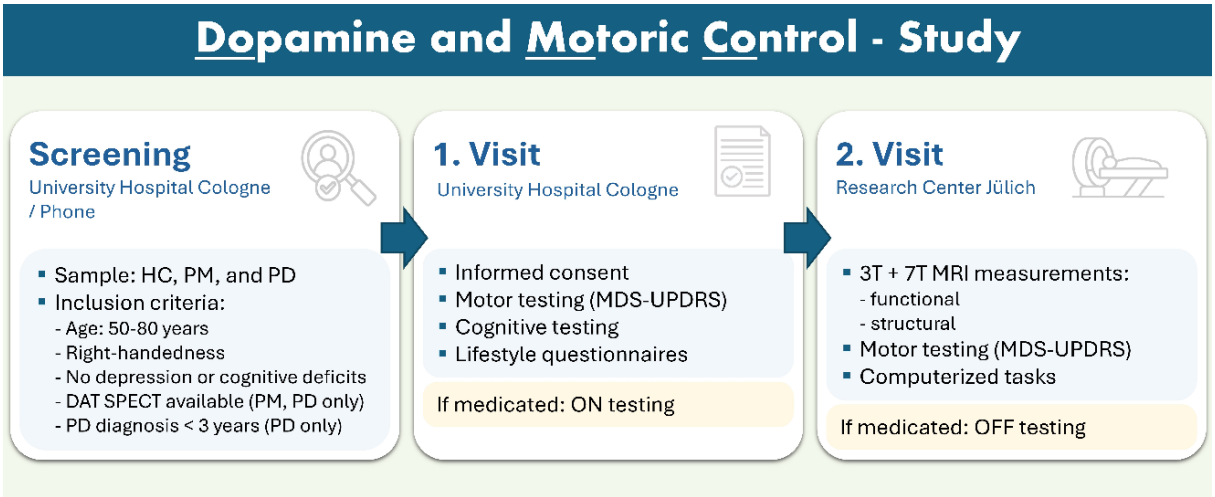

Figure 3: Study Design of the DoMoCo Study. HC = healthy controls, PM = prodromal patients

1.5 Aim and Objectives of this Thesis

For many years the motivational and motor system have been seen as rather separate systems, both being affected by PD, but associated with different symptoms. For instance, loss of dopamine in the mesolimbic system has been associated with deficient reward processing, whereas loss of dopamine in the nigrostriatal system has been directly linked to problems with movement initiation. However, as the abovementioned literature suggests, the motivation and motor system could be more strongly interlinked than previously thought, potentially even providing a novel framework for PD motor symptoms. Currently, the exact mechanisms underlying the interplay between disease pathology and clinical presentation of motor symptoms are not fully understood. Given this lack of knowledge, the aim of this thesis is **to put the spotlight on the motivational brain and investigate its disease related alterations as well as associations with PD motor symptoms**. By using a multimodal neuroimaging approach, the present thesis utilizes powerful tools in order to gain insights into pathological changes of the diseased brain. Importantly, this information may help disentangle why some individuals are differently affected by the disease and provide potential targets for future interventions. The main body of the thesis presents three original contributions (Project 1-3), with the primary objective of each project being described below.

1.5.1 Project 1

In research, PD is frequently considered a pure movement disorder, contradicting the recent framework that PD is actually both a motor and non-motor disease. As a consequence, the majority of research aiming at unravelling the underlying biological cause of PD motor symptoms has strongly focused on the motor system thereby failing to properly capture the motivational system (Chaudhuri et al., 2011). In order to close this gap, Project 1 casts the spotlight on the motivational brain in PD and provides an overview of the latest literature. For this purpose, Project 1 is a systematic review, which specifically addresses PD-related pathological changes in motivational brain regions as well as their associated clinical presentations, whether they are motor or non-motor related. To ensure that the review encompasses a set of clearly defined regions of interest, the limbic system was selected as the conceptual framework due to its pivotal role in motivational and emotional processing (Rolls, 2015). Finally, the new gained insights were then integrated into the current state of knowledge.

Aim of Project 1:

- Provide a systematic review of studies on limbic neuropathological changes and their associated clinical manifestations in PD.

1.5.2 Project 2

The objective of Project 2 is to investigate the movement motivation hypothesis of PD, as proposed by Mazzoni et al. (2007). In particular, the objective of Project 2 is to study the effect of dopamine depletion on the motivation to exert physical effort. As outlined in section 1.2.3, empirical evidence supports the hypothesis that PD may be better characterized as a motivational disorder than a purely motoric one. To date research on the movement motivation hypothesis is limited to investigations ON vs. OFF dopaminergic medication. However, this methodological approach does not come without pitfalls, such as different medication dosages, types, and individual drug efficacy. For this reason, Project 2 implements a more refined approach by using a quantitative measure of striatal dopaminergic degeneration, namely DAT SPECT imaging. In addition to neuroimaging data, this project employes a behavioral incentivized grip-force task to capture movement motivation. The task comprises six distinct monetary rewards, thus encompassing a range of low and high incentives. Thereby this paradigm allows the investigation of the effect of PD-related dopamine loss on the motivation for movement. Data for Project 2 were collected as part of the DoMoCo study and include a group of healthy controls as well as a group of early-stage patients with PD.

Aims of Project 2:

- Investigate the effort patients with PD exert for different incentive levels in an incentivized grip-force task compared to healthy controls.

- Study the effect of striatal dopaminergic degeneration on the effort exertion in the incentivized grip-force task in patients with PD.

1.5.3 Project 3

The longstanding idea that a uniform pattern of α-synuclein progression – namely, from caudal to rostral – can be observed in the majority of patients, has recently been challenged by the brain-first body-first hypothesis (Borghammer, 2021; for details see section 1.1.1). The brain-first subtype is proposed to represent a limbic-dominant subtype, with the amygdala as the initial structure to be affected. This stands in sharp contrast to the traditional view of Braak, which suggest that the amygdala is affected only later on in stage 3 (Braak et al., 1994, 2004; Goedert et al., 2013). In light of the accumulating evidence, indicating the involvement of motivational brain regions in PD motor symptoms, the presence of a limbic-dominant subtype would represent a highly interesting finding. Hence, the main objective of Project 3 is to investigate if support for the brain-first body-first hypothesis can be found. To do so, it was studied if brain-first individuals indeed demonstrate an earlier and more asymmetric involvement of the amygdala as proposed by the hypothesis. For this purpose, MRI data from the PPMI database was downloaded and GMV was utilized as a proxy of neurodegeneration.

Aims of Project 3:

- Investigate if patients with PD demonstrate GMV atrophy, particularly in the amygdala.
- Study if the two proposed PD subtypes demonstrate distinct atrophy patterns. More specifically, if brain-first subjects have a smaller GMV as well as a higher GMV asymmetry in brain regions of Braak stage 3 (including the amygdala) compared to body-first subjects.

2 Publications

2.1 Project 1

Imaging the limbic system in Parkinson's disease – a review of limbic pathology and clinical symptoms

Authors: Banwinkler, M., Theis, H., Prange, S., & van Eimeren, T.

Author contributions: *Banwinkler M.*: Conceptualization; literature search and review; data curation; analysis; preparation of figures; writing of original draft (introduction, discussion, manuscript body); incorporating suggestions of co-authors and external reviewers; steps for submission and publication in journal. *Theis, H.*: Conceptualization; literature search and review; data curation; analysis; writing part of manuscript body. *Prange, S.*: Conceptualization; literature search and review; data curation; analysis; preparation of figures; writing part of manuscript body. *van Eimeren, T.:* Conceptualization; supervision; proofreading of manuscript.

Journal: Brain Sciences

Abstract:

The limbic system describes a complex of brain structures central for memory, learning, as well as goal directed and emotional behavior. In addition to pathological studies, recent findings using in vivo structural and functional imaging of the brain pinpoint the vulnerability of limbic structures to neurodegeneration in Parkinson's disease (PD) throughout the disease course. Accordingly, dysfunction of the limbic system is critically related to the symptom complex which characterizes PD, including neuropsychiatric, vegetative, and motor symptoms, and their heterogeneity in patients with PD. The aim of this systematic review was to put the spotlight on neuroimaging of the limbic system in PD and to give an overview of the most important structures affected by the disease, their function, disease related alterations, and corresponding clinical manifestations. PubMed was searched in order to identify the most recent studies that investigate the limbic system in PD with the help of neuroimaging methods. First, PD related neuropathological changes and corresponding clinical symptoms of each limbic system region are reviewed, and, finally, a network integration of the limbic system within the complex of PD pathology is discussed. In doing so, this review underscores the importance of limbic system alterations in PD symptomatology. In particular, it shows that motor symptoms have been understudied and highlights how motor and non-motor symptoms are deeply intertwined in PD.

brain sciences

MDPI

Systematic Review

Imaging the Limbic System in Parkinson's Disease—A Review of Limbic Pathology and Clinical Symptoms

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Abstract: The limbic system describes a complex of brain structures central for memory, learning, as well as goal directed and emotional behavior. In addition to pathological studies, recent findings using in vivo structural and functional imaging of the brain pinpoint the vulnerability of limbic structures to neurodegeneration in Parkinson's disease (PD) throughout the disease course. Accordingly, dysfunction of the limbic system is critically related to the symptom complex which characterizes PD, including neuropsychiatric, vegetative, and motor symptoms, and their heterogeneity in patients with PD. The aim of this systematic review was to put the spotlight on neuroimaging of the limbic system in PD and to give an overview of the most important structures affected by the disease, their function, disease related alterations, and corresponding clinical manifestations. PubMed was searched in order to identify the most recent studies that investigate the limbic system in PD with the help of neuroimaging methods. First, PD related neuropathological changes and corresponding clinical symptoms of each limbic system region are reviewed, and, finally, a network integration of the limbic system within the complex of PD pathology is discussed.

Keywords: PET; SPECT; MRI; ventral striatum; amygdala; hypothalamus; cingulate; hippocampus; impulse control disorders; depression

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1. Introduction

Parkinson's disease (PD) is a frequent and multisystem neurodegenerative disease, affecting the human central, peripheral, and enteric nervous system. Neuropathology is characterized by intraneuronal inclusions containing misfolded α-synuclein aggregates, called Lewy bodies. The pathophysiology is primarily characterized by a dopamine deficiency due to a progressive loss of dopaminergic neurons innervating the basal ganglia. This pathophysiology is associated with the cardinal motor manifestations and some of the cognitive dysfunctions observed in PD [1–3].

Due to the prominent motor manifestations in PD, for a long time, the main research focus has primarily been set on the pathophysiology of the motor system. Consequently, in the past several decades, there has been remarkable progress in the understanding of the functional organization of the motor system and most notably how pathological changes in the basal ganglia result in motor abnormalities [4]. However, conceptualizing PD as just a disorder of the nigrostriatal dopaminergic system is reductionistic, and it is now well established that the pathophysiology of PD is far more widespread and complex [5]. Histological examination has revealed that damage to the nigrostriatal pathway is accompanied by extensive extranigral pathology. Besides dopaminergic neurons in the motor system, nerve cells of the limbic system have shown to be vulnerable to destruction. In fact, the limbic system and its connections are subject to major pathological changes in the course of the disease [6–8]. For instance, the amygdala, a core limbic structure, harbors dense Lewy

pathology in PD patients, which starts as early as Braak stage 3, i.e., around the same time than the substantia nigra [9,10]. Since the limbic system is integral for emotions, learning, and memory, there has been increasing recognition that changes in this system substantially contribute to the symptom complex which characterizes PD, ranging from neuropsychiatric to vegetative and cardinal motor dysfunction.

1.1. What Is the Limbic System?

The limbic system describes a complex of brain structures central for memory, goal-directed, affective, and emotional behavior. The concept of the limbic system has been highly influential in the field of neuroscience and can look back on a long history. Over time, the entity to what the term "limbic system" refers to underwent substantial changes, but the concept persists to the present day [11]. The term "limbic" stems from the Latin word "limbus" which means "border" and was first used in 1664 by the physician Thomas Willis to denote the curved cortical border around the brainstem [12]. When Broca spoke of the "Great Limbic Lobe", he thought of it as a primarily olfactory structure [13], and it was not until the mid-20th century that Papez and McLean associated the limbic system with emotional functioning in humans [14].

Despite many efforts, to this date, consensus regarding the structures that form the limbic system is still lacking. Most commonly, regions of the limbic system encompass the cingulate gyrus, hippocampus, parahippocampal gyrus, amygdala, mammilary bodies, hypothalamus, as well as the nucleus accumbens [15,16], with dense intrinsic connections [17]. Historically, the ventral striatum was not always seen as an integral part of the limbic system, despite early recognition of the strong reciprocal connections of the ventral striatum and all major limbic structures. However, the ventral striatum, which encompasses the nucleus accumbens, is a central hub for the connection between the motor and limbic system [18]. Therefore, and due to its importance in PD, we decided to include the ventral striatum in the present review and emphasize its role within the limbic system and in neuropsychiatric manifestations related to PD.

Regardless of the absence of a clear definition, the limbic system constitutes a functional concept, and is characterized by dense afferent projections from brainstem and forebrain nuclei, which contributes to behavioral modulation. From this functional standpoint, the limbic system is seen as essential for the regulation of emotional behavior. In fact, the limbic system is a center which links stimuli with social, emotional, or motivational relevance to a set of behavioral outputs; thus, by linking the internal and external world, it controls appropriate behavioral responses [19]. A previous published theory stated that there might not be one limbic system, but rather separate, independent circuits for emotions and memory centered either on the amygdala or the hippocampus [11].

1.2. Imaging Changes

With the progression of PD, limbic structures become increasingly affected by pathology, causing injury to the nerve cells, eventually resulting in cell death [6,20]. Neuroimaging provides insight into these biological changes, which can be due to the underlying neuropathological mechanisms as well as compensatory responses to the disease. To gain a better understanding of the PD related changes of the limbic system, as well as the relationship between changes and clinical presentation, in vivo structural and functional neuroimaging is key, including single photon emission computed tomography (SPECT), positron emission tomography (PET), and novel magnetic resonance imaging (MRI) techniques [21], which, remarkably, were not systematically reviewed to the best of our knowledge.

1.3. Aim of Review

Comprehensive reviews which focus on the pathophysiology of motor impairments in PD exist [4,22], but, to our knowledge, there is currently no review which provides an overview of limbic neuropathological changes and their related clinical manifestations. For this reason, this systematic review puts the spotlight on the limbic system in PD

and gives an overview of the most important structures affected by the disease, their function, disease-related alterations, as well as corresponding clinical symptoms. In this scope, we provide an overview of neuroimaging changes (i.e., MRI, PET and SPECT) and symptoms related to limbic alterations in PD. Furthermore, we develop the network integration of the limbic system within the complex of PD pathology and highlight the role of the ventral striatum. In particular, we seize the suggestion of Rolls [11] concerning two separate limbic systems dedicated to emotion or memory. We transfer these ideas to the cognitive decline in PD, especially PD dementia, and the typical neuropsychiatric symptom complex such as depression, apathy and impulse control disorders (ICD) and how they interact with the motor disturbance in PD.

2. Methods

2.1. Literature Search and Selection Strategy

A systematic literature search was performed in PubMed. Based on the Medical Subject Headings (MeSH) terms provided by the National Library of Medicine and basic literature on the limbic system, we selected the most important regions of the limbic system. These regions included the amygdala, hippocampus, hypothalamus, cingulate gyrus, substantia innominata and septal nuclei, fornix and mammillary bodies, habenula and pineal body, and ventral striatum.

For each limbic region of interest (ROI), we conducted an independent literature search by using the following search query: (Parkinson's disease OR Parkinson) AND (LIMBIC_ROI) AND ((imaging) OR (MRI) OR (PET) OR (SPECT) OR (fMRI) OR (functional MRI)). The searches were limited to human studies only and because we wanted to focus on the most recent literature, studies published between 2018 and 2022 were included. Due to the methodological challenges related to the resolution limits of SPECT, PET and MRI for small, millimetric structures, neuroimaging studies are scarce for the fornix and mammillary bodies as well as the habenula and pineal body [23]. As a consequence, the publication time period was extended, and all available publications were considered for these ROIs. Eligibility for inclusion was determined by predefined criteria.

2.1.1. Inclusion Criteria

A study was included if it met the following criteria:

- English language;
- Parkinson's disease;
- Use of neuroimaging methods (i.e., PET, MRI, SPECT);
- Human study.

2.1.2. Exclusion Criteria

A study was excluded if it met the following criteria:

- The limbic ROI was not explicitly examined in the study;
- Review paper or case report;
- Not accessible and not freely available.

2.2. Limbic Parkinson's Disease Wordcloud

Additionally, we generated a word cloud representing the 200 most discriminant words in the abstracts with 'Parkinson's disease' in the title and containing the word 'limbic'. Specifically, we extracted all nouns and adjectives in 508 abstracts containing 'limbic' and in a random sample of 2500 abstracts (out of 61,565) not containing 'limbic' for articles entitled 'Parkinson's disease' extracted from PubMed between 1977 and March 2022. Stopwords, proper and verbal nouns, and adverbs were filtered out using the Text Mining package and a custom word list following annotation using udpipe in R. This resulted in two corpuses of 4979 and 16,179 words, respectively, with a total of 32,522 and 141,216 occurrences, respectively. Words occurring in at least five abstracts containing

'limbic' were then selected, representing 1052 words with 30,130 and 66,452 occurrences, respectively. We then calculated the Youden's index (also known as bookmaker informedness) for each word, summarizing the performance for a given word to correctly classify an abstract into a given corpus. By analogy, with a diagnostic test, a value of 1 indicates a perfect test, meaning that there are no wrongly classified abstracts using this word, with no false positives or false negatives. Height is proportional to the informedness value.

3. Results

The combined search result of all limbic regions can be seen in Figure 1. Our electronic database search generated a total of 646 studies, of which 224 were identified as relevant and were included in the review. We extracted the following information for each study: key components of general study information (title, author, year, and journal), and study characteristics (main research interest, neuroimaging method, sample size, and outcome). This information is summarized in Supplementary Table S1. In this paper, we first review each limbic region by providing an overview of its anatomy, function, and pathology, and by discussing the most recent evidence for structural and functional imaging and the relationship with PD symptoms. An overview of selected limbic structures and their corresponding PD symptoms can be found in Figure 2. Finally, we conclude and integrate this new information into the limbic system model proposed by Rolls [11].

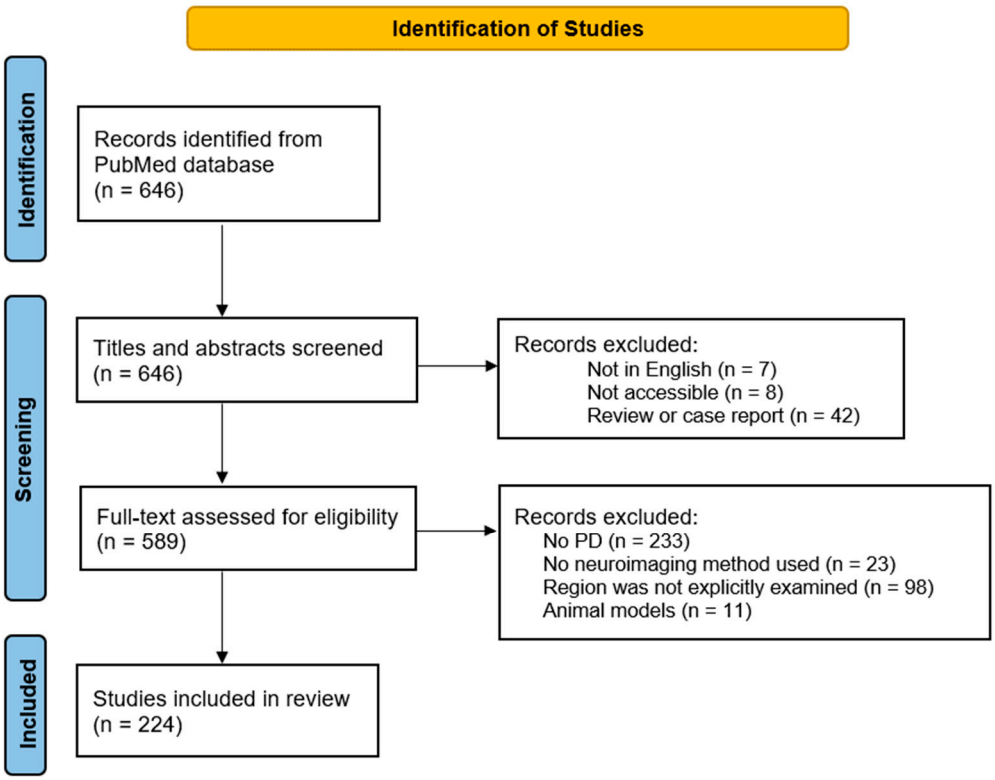

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

In addition, we performed a data-driven, text mining analysis of all abstracts containing the word 'limbic' since 1977 in order to provide an unbiased account of the key components of the limbic system in Parkinson's disease (Figure 3). This illustrates the network organization of the limbic system, involving the frontal and cingular cortico-striatal system and its modulation by brainstem and forebrain small nuclei and their dopaminergic, serotonergic, noradrenergic and cholinergic projections, subjected to multiple pathological processes. Symptoms and disorders involving the limbic system, including memory and dementia, apathy, depression, impulse and reward-related disorders are highlighted.

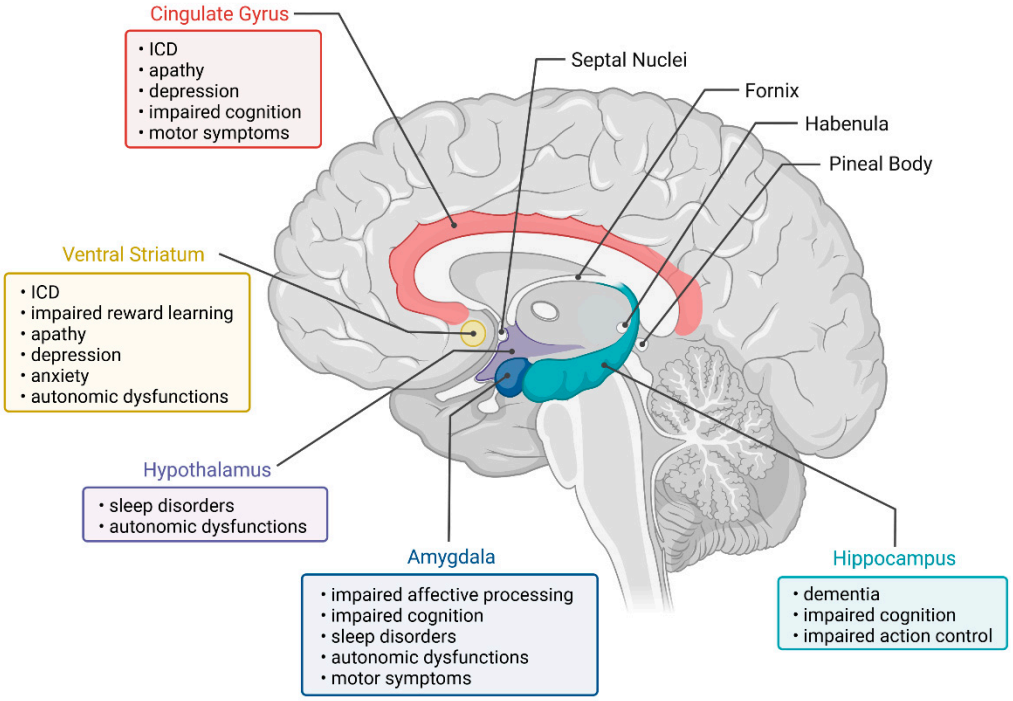

Figure 2. Representation of selected limbic regions affected by PD pathology and their associated clinical symptoms. Created with Biorender.com.

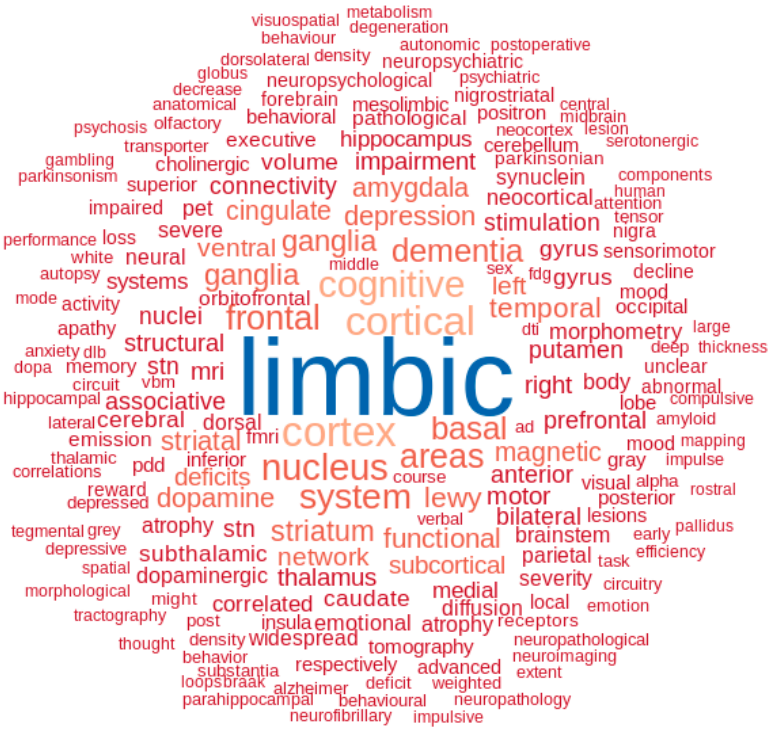

Figure 3. A cloud of the limbic system. The 200 most discriminant words characterizing the abstracts containing the word 'limbic' are depicted in the wordcloud. This illustrates the network organization of the limbic system, involving the frontal and cingular cortico-striatal system, its modulation by dopaminergic, serotonergic, noradrenergic and cholinergic projections from brainstem and forebrain nuclei, and highlights the critical role of the limbic system in dementia, depression, apathy and impulse control disorders.

4. Regions of the Limbic System

4.1. Amygdala

4.1.1. Anatomy and Function

The amygdala is an almond shaped structure nestled deep in the medial temporal lobe. It is a highly differentiated region composed of distinct subareas or nuclei; thus, this is sometimes also referred to as the amygdala complex. One widely acknowledged description divides the amygdala into a phylogenetically primitive group of nuclei, which are associated with the olfactory system (central, medial, cortical, and nucleus of the lateral olfactory tract), and a phylogenetically newer group of nuclei (basal and lateral nucleus) [24].

Information about the external environment is transmitted from the sensory thalamus and sensory cortices to the amygdala. In turn, the amygdala has reciprocal connections with the midline and orbital prefrontal cortex, hippocampus, and sensory areas. Unidirectional outputs encompass the striatum, nucleus accumbens, and the bed nucleus of the stria terminalis, which are involved in translating the input signals into behavioral outputs [25,26]. Most notably implicated in emotion and motivation, the amygdala makes essential contributions to the processing of fearful and rewarding environmental stimuli. It is suggested that the amygdala subserves incentive learning, a process by which stimuli are attributed affective significance, and thereby motivates behavioral responses and actions [27].

4.1.2. Pathology

Severe pathological changes can be observed in the amygdala during the progression of PD. Misfolded proteins are detected early in the amygdala and, according to the Braak PD staging scheme, the amygdala is affected in stage 3 [9,28]. However, the amygdala is not uniformly affected by the pathology. Lewy bodies and Lewy neurites exhibit a specific distribution, with some nuclei undergoing prominent changes and others remaining largely uninvolved. Early and strongly affected nuclei are the central and accessory cortical nucleus [7,10].

4.1.3. Neuroimaging Evidence in PD

Neuropsychiatric Symptoms

Numerous studies have identified reduced gray matter volume in the amygdala [29–32]. While there is inconsistency regarding amygdala atrophy especially in early PD, it becomes more pronounced with increasing disease duration and severity [33–38]. A great body of evidence has revealed a significant relationship between PD-related changes in the amygdala and affective traits. For example, abnormal activation within the amygdala has been observed during affective processing [39], and fMRI studies have found over-activation of the amygdala to be associated with psychotic symptoms and anxiety [40,41]. A study examining early-stage PD patients found no association between the structural covariance of the amygdala and the severity of anxiety symptoms. Thus, it seems that the amygdala-to-whole-brain structural covariance might not be affected early on [42]. However, anxiety levels of PD patients did positively correlate with the functional connectivity between the amygdala and the superior parietal lobule as well as the *weighted degree* (the sum of functional connectivity strengths in a specific brain area with all other brain areas) of the left amygdala [43]. Additionally, anxiety was also associated with a smaller amygdala volume [44] and with a lower dopaminergic binding in females [45]. Furthermore, abnormal connectivity between the amygdala and hippocampus has been related to depression [46].

Molecular imaging studies using [^{11}C]DASB PET report alterations in the serotonergic system in the amygdala starting already in the preclinical stage [47,48] and evidence of [^{18}F]FPEB PET and [^{18}F]FDG PET studies further reveal significantly upregulated glutamate receptors as well as hypometabolism in the amygdala of PD patients [48–51]. In addition, PD patients with ICD had reduced D2/3 receptor binding in the ventral striatum and putamen. In this context, PD patients with ICD exhibited a positive correlation between midbrain and amygdala D2/3 binding [52].

Cognitive Symptoms

Neuroimaging studies have demonstrated a consistent association between hippocampal volume loss and dementia [53]. However, recent evidence also suggests involvement of the amygdala, whereby PD patients with cognitive impairment display even greater amygdala atrophy compared to patients without cognitive impairment [54]. Furthermore, another study reported hypoactivation of the amygdala in PD patients off medication versus healthy controls when generating a successful response in a choice reaction time task [55].

Motor and Other Symptoms

Changes in the amygdala may also contribute to the cardinal motor dysfunction [55]. In this context, a study was able to accurately predict Unified Parkinson's disease rating scale (UPDRS) III scores by using a sparse set of connectivity features, including the putamen and amygdala [56]. Additionally, amygdala mean diffusivity was positively associated with the UPDRS scores for non-motor symptoms as well as activities of daily living impairment, indicating that amygdala changes may affect movement through the regulation of affective states [57]. Dysfunction of the amygdala has further been demonstrated through affected nodal centrality [58,59] and, in line with the diverse functions of the amygdala, studies also report impaired olfaction, sleep disturbances, and autonomic dysfunction in combination with amygdala alterations [60,61].

Regarding connectivity changes, PD patients have demonstrated enhanced coherence of the white matter tract in the amygdala−accumbens−pallidum pathway which can be interpreted as dysfunctional hyperconnectivity [62] and the amygdala to midbrain functional connectivity was found to be modulated by dopamine agonists [63]. Decreased connectivity with the cerebellum has been noted [64], and the white matter structural connectivity showed greater disruption in males compared to females [65]. Increased amygdala connectivity with the putamen and decreased connectivity with the frontoparietal network has been related to freezing of gait, suggesting an increased striato-limbic load in combination with reduced top-down attentional control [66]. Decreased connectivity with the inferior parietal lobule, lingual gyrus, and fusiform gyrus were linked to the severity of hyposmia and cognitive performance [67]. Furthermore, higher D2-like binding in the amygdala was associated with better stopping control [68]. This superior inhibitory control in subjects with higher D2-like binding may indicate limbic regulation of motor control.

Conclusions

In conclusion, PD-related changes in the amygdala are not only linked to alterations in affective processing such as anxiety, but a more extensive symptom complex including cognitive performance, sleep disorders, autonomous symptoms, and cardinal motor dysfunction.

4.2. Hippocampus

4.2.1. Anatomy and Function

The hippocampus is located bilaterally within the medial temporal lobe and its shape grossly resembles a seahorse, which inspired its naming [69]. The hippocampal formation comprises four distinct parts: Cornu ammonis (hippocampus proper), dentate gyrus, entorhinal area, and subiculum. Hippocampus proper and the dentate gyrus form together the C-shaped rings and the hippocampus proper is further subdivided into CA1, CA2, CA3, and CA4 [70]. Decades of research on hippocampal function have established its critical role in learning and memory processes and the link between hippocampal damage and amnesic symptoms [71,72]. In this respect, the hippocampus is critically involved in the formation of new declarative memories [73], as well as spatial navigation involving place and grid cells [74,75]. In addition, the hippocampus also excerpts an influence on the hypothalamic-pituitary-adrenocortical activity and emotional behavior with close reciprocal connections with the amygdala [70].

4.2.2. Pathology

Neuropathological studies have played a critical role in uncovering involvement of the hippocampus in the pathophysiology of PD and indicate increasing α-synuclein deposition that is associated with significant neuronal dysfunction [76,77]. According to Braak staging, the hippocampus harbors significant pathology from stage 4 onwards [9,28]. Accumulating evidence suggests hippocampal involvement not only in dementia but also in motor dysfunctions and other neuropsychiatric aspects of PD [78].

4.2.3. Neuroimaging Evidence in PD

Cognitive Symptoms

Cognitive dysfunction is one of the most prevalent and debilitating non-motor symptoms of PD and 20 years into the disease, and more than 80% of PD patients will develop dementia [79]. In face of this detrimental symptom, extensive research has addressed pathological changes in the hippocampus. Morphological studies have reported reduced hippocampal volume in PD patients, whereby atrophy has inconsistently been reported in early-PD but becomes more pronounced with increasing disease duration and is strongly linked to cognitive decline including memory, spatial working memory, and language impairments [29,31,36,37,54,60,80–97]. The severity of volume loss has also been found to be predictive of conversion to dementia [53,98,99]. Additionally, PD-related alterations in iron content [61,100,101], texture [34], microstructural integrity [102–104], arteriolar-cerebral-blood-volume [105], connectivity [106–108], but not synaptic density [109] have been reported in combination with reduced cognitive performance. Serotonergic binding in the hippocampus of PD patients was not associated with cognitive performance [110]. In addition, serotonin transporter (SERT) loss extended to the hippocampus in PD patients with the A53T mutation in the SNCA gene (associated with autosomal dominant development of PD), but not in premotor carriers [48].

Neuropsychiatric Symptoms

As mentioned earlier, changes in the hippocampus do not only result in cognitive deficits but manifest in other nonmotor symptoms. Hyposmia and sleep disturbance have been associated with hippocampal dysfunction [60,92,111–115] and modulation of the parasympathetic outflow seems to be impaired as well [116]. In addition, decreased left hippocampal volume and altered functional connectivity were reported in depressed individuals [46,117]. Degeneration of the hippocampus was found in combination with psychotic symptoms, which manifest as visual or minor hallucinations, whereby psychosis severity could be predicted from hippocampal volumes [118]. The development of psychotic symptoms was linked to increased signaling in the hippocampus, amygdala, striatum, and the dopaminergic midbrain [41]. Furthermore, the underlying involvement of visual illusions include not only the primary visual cortex and surrounding regions, but also the hippocampus [119]. Finally, dopamine depletion is also linked to attenuated reward signaling in the mesolimbic system, and deficient reward-related processing in the hippocampus has been shown to be partially restorable through the administration of dopaminergic medication [120].

Motor and Other Symptoms

Dysfunction of the hippocampus has recently also been linked to movement dysfunctions [57,121,122]. Patients experiencing freezing of gait, demonstrated reduced activation of the hippocampus and decreased connectivity with the cerebellum relative to controls [123–125]. Higher behavioral impairment scores were related to increased connectivity of the hippocampus with the right caudate head, which may represent a compensatory mechanism [126]. Overall, hippocampal connectivity seems to be more strongly affected in males than in females [65]. Interestingly, a 6-week 'exergaming' intervention (combination of a motivating and visually stimulating computer game with physical exercises) reported a significant volume increase in the left hippocampus, suggesting hippocampal

volume changes in PD patients can be induced by non-pharmacological interventions [127]. Furthermore, the role of the mesocorticolimbic dopaminergic system in action control has been highlighted by [^{18}F]fallypride PET imaging studies, which demonstrated overall reduced binding in PD, but a significant association between faster response inhibition and greater D2-like binding potential in the hippocampus, thereby advocating limbic regulation of the action-control network [52,68].

Reciprocal regulation of dopamine and glutamate has been noted in the nigrostriatal, mesocortical, and mesolimbic system, circuits which are affected by PD pathology. In this context, a study suggests that glutamate is more than 20% upregulated in several mesocortical regions, including the hippocampus, amygdala, and putamen [50]. Furthermore, a specific spatial covariance pattern of the serotonergic system was reported in PD, which comprises decreased binding in the putamen, caudate, and substantia nigra and preserved binding in the hypothalamus and hippocampus. Expression of this pattern was more strongly in PD compared to healthy controls and significantly correlated with disease duration [47,128].

Conclusions

In summary, the hippocampus of PD patients demonstrates substantial volume loss with increasing disease duration, which is strongly linked to cognitive impairment and dementia. However, multiple studies have also highlighted its regulatory role in action control.

4.3. Hypothalamus

4.3.1. Anatomy and Function

Situated at the base of the brain with a size of just 4 cm^3, the hypothalamus constitutes one of the smallest and phylogenetically most conserved parts of the human brain. It is located below the thalamus and above the midbrain. Anteriorly, it is bounded by the optic chiasm, laterally by the optic tracts, and posteriorly by the mammillary bodies. Despite its small size, the anatomy of the hypothalamus is complex, constituting a collection of several distinct nuclei which are commonly organized into the anterior, tuberal and posterior (mammillary) region [129–131].

The functional roles played by the hypothalamus are manifold. It regulates vital functions including thirst, hunger, sleep, temperature, mood, circadian and seasonal rhythms, sex drive as well as the production of some of the body's essential hormones. In the broadest sense, its role is an integrative one. It maintains homeostasis by bringing together sensory and bodily information and accordingly activating endocrine, autonomic, and behavioral responses [130,132].

4.3.2. Pathology

PD related pathological changes in the hypothalamus were noted decades ago by numerous researchers, including Lewy himself [133,134]. These changes include the presence of Lewy bodies, specifically in the tuberomammillary and posterior hypothalamic nuclei, as well as the loss of dopamine. According to the Braak staging scheme, the PD-associated pathology targets hypothalamic nuclei in stage 4, thus in the early symptomatic phase [9,28].

4.3.3. Neuroimaging Evidence in PD

Autonomous Symptoms and Sleep Disturbance

Recent neuroimaging evidence complements early findings. A high-resolution MRI study of >360 participants found no significant difference in the hypothalamus volume of PD and non-PD individuals—thereby implying that the histopathologically detected involvement of the hypothalamus in PD is not observable as global hypothalamic atrophy, and further suggesting that the macrostructure of the hypothalamus remains rather stable throughout the disease course [135]. In line with the regulatory role of the hypothalamus

in the autonomic nervous system, reduced hypothalamic functional connectivity with the thalamus and striatum was observed in PD patients with a higher burden of autonomic symptoms compared to those with a lower burden [136]. Furthermore, excessive daytime sleepiness, a common autonomic symptom in PD, was associated with increased phosphodiesterase 4 (PDE4) expression in brain regions that are involved in sleep regulation, including the hypothalamus. PDE4, an intracellular enzyme expressed in neurons and glial cells, is inter alia implicated in the modulation of dopaminergic activity [113,137]. Loss of SERT was also noted in the hypothalamus in symptomatic and premotor A53T SNCA carriers [48] and a recent [^{11}C]DASB PET study has linked reduced serotonergic function in the hypothalamus to sleep dysfunctions in PD patients [138]. However, lower hypothalamic SERT binding was not observed in early disease stage PD patients [47,128].

Conclusions

To conclude, in accordance with the regulatory role of the hypothalamus, PD-related changes in this region mainly manifest as alterations in autonomic functions.

4.4. Cingulate Gyrus

4.4.1. Anatomy and Function

Anatomically, this brain region spans the corpus callosum and is therefore called "cingulum", which is the Latin word for belt. It was described by Broca in 1877 as a part of the so-called "grand lobe limbique" [139]. The cingulate cortex can be divided into four regions which are again divided into subregions: the anterior cingulate (subgenual and pregenual), the midcingulate (anterior and posterior), the posterior cingulate (dorsal and ventral) and the retrosplenial cortex [140,141]. Among others, the anterior cingulate receives input from the orbitofrontal cortex (OFC), the amygdala, the parahippocampal gyrus, and it projects to other parts of cingulate cortex, the medial prefrontal cortex and to the striatum [142]. The anterior cingulate cortex (ACC) is involved in action-outcome learning, based on the integration of a prediction error signal by taking into account whether an event was expected or not [142,143]. In addition, the subgenual cingulate cortex also integrates the emotional component of reward [144]. The posterior cingulate cortex receives input from the temporal lobe and projects to the hippocampus and has been linked to the spatial component of episodic memory [142]. Furthermore, the posterior cingulate cortex (PCC) is a key structure of the so-called default-mode-network, which is active when an individual is at rest. According to Pearson, this region might be responsible for detecting changes of the environment during rest [145].

4.4.2. Pathology

In PD, the cingulate cortex is affected in the Braak stage 5 [28].

4.4.3. Neuroimaging Evidence in PD

Neuropsychiatric Symptoms

The cingulate cortex has a central role in ICD in PD, mainly involving connectivity changes of the cingulate cortex to other brain regions. Severity of ICD negatively influenced the connectivity between accumbens and ACC [146], whereas another study showed an increase in reward-related connectivity between these two regions, which was independent of dopaminergic medication [63]. A reduced between-network but increased within-network connectivity of the salience network was found in PD with ICD [147]. Apart from connectivity changes, the severity of ICD correlated positively with the volume of the subgenual ACC [146]. Concerning sex differences, greater atrophy in the cingulate was reported for men than women with PD [65]. In addition to the ACC, the PCC is also involved in ICD [146]. In particular, in hypersexual PD patients under dopamine replacement therapy, excessive wanting of reward lead to heightened blood-oxygen-level-dependent (BOLD) activity in the PCC [148].

Similar to the ventral striatum, the ACC is not only involved in ICD and reward processing but also plays an important role in other neuropsychiatric symptoms. Structural imaging revealed a volume reduction of the ACC [149] as well as reduced white matter integrity in PD patients with depression [149–151]. An fMRI study revealed that the anterior cingulate might be a hub region for depression in PD [152]. In this regard, increased connectivity between the ventral tegmental area and the ACC was reported in depressive as compared to non-depressive PD patients [153], in addition to network dysfunction of the PCC in depressive PD patients [154]. Furthermore, apathy was also associated with reduced neuronal activity [155], microstructural alterations [156] and an increase in amyloid depositions in the ACC [157], whereas anxiety was related to thinning of the cingulate cortex [44]. In turn, functional connectivity between the anterior cingulate and the temporo-parietal junction was positively correlated with a higher quality of life in PD [158]. Furthermore, PET studies have reported serotonergic dysfunction in the cingulate of PD patients [159–162]. Notably, increased serotonergic innervation in the ACC and ventral striatum was recently demonstrated in PD patients who were apathetic at diagnosis and reverted apathy under dopamine replacement therapy, suggesting compensatory plasticity in early PD [163]. To conclude, damage of the ACC during the disease course of PD seems to play an important role for the development of behavioral symptoms.

Cognitive Symptoms

Regarding memory and cognition, PD patients with mild cognitive impairment (MCI) had an increased functional connectivity between the posterior cingulate and the thalamus when compared to demented PD patients [164] and fractional anisotropy of PCC bundles correlated positively with cognition [165]. The role of the PCC in cognition and memory was further stressed in functional [108,164,166–168] and structural [169] MRI studies.

In addition, lower structural and functional connectivity between the insula and ACC [170,171] and lower functional connectivity between the caudate and ACC was reported in MCI [126]. Reduced connectivity of the ACC to the dorsolateral prefrontal cortex could be ameliorated by an eight-week cognitive training [172]. However, another study found increased connectivity between the insula and middle cingulate in PD with MCI [173]. Cholinergic innervation of the cingulate cortex was associated with cognitive performance in PD [174]. A multimodal study with dopamine transporter (DAT) SPECT and FDG PET demonstrated that a degeneration of the cognitive striatum, as measured by [^{123}I]FP-CIT binding ratios, is related to a reduced glucose metabolism in the anterior cingulate [175], which emphasizes the link between PD progression and the development of cognitive deficits.

Motor and Other Symptoms

Motor symptoms were linked to imaging changes of the cingulate cortex (e.g., reduced connectivity and metabolism) in particular for hypokinetic symptoms and during motor learning a higher blood flow was reported in the ACC [176]. PD patient with predominant tremor had a higher functional connectivity between the right fronto-insular cortex and the ACC when compared to akinetic-rigid PD [177] and micrographia, a typical early motor symptom, was associated with a reduced glucose metabolism in the middle cingulate gyrus [178]. In PD patients with deep brain stimulation, an impaired drawing ability was related to a reduced perfusion of the cingulate after surgery [179]. Furthermore, a decrease in speech loudness in PD was associated with an increased activation of the anterior cingulate as compared to healthy controls [180].

Regarding sleep disorders, PD patients with rapid eye movement sleep behavior disorder (RBD) had reduced functional connectivity to temporal, frontal, insular and thalamic regions when compared to healthy controls. When compared to PD patients without RBD, PD patients with RBD had a reduced connectivity between posterior cingulate and precuneus [181]. PD patients with pain relieved under deep brain stimulation showed a reduced activity of the anterior cingulate in fMRI as compared to those without relief of

pain [182], with a positive correlation between DAT binding in the posterior cingulate and the pain threshold [183]. Furthermore, a meta-analysis of PET studies, which investigated microglia-mediated neuroinflammation via translocator protein levels, found significantly elevated levels in the ACC as well as PCC of PD patients, thus highlighting the disease related dysfunction of the cingulate [184].

Conclusions

In sum, the cingulate gyrus is critically involved in neuropsychiatric symptoms related to PD, but also influences motor performance. The ACC seems to be rather associated with behavioral symptoms such as ICD, depression and apathy, in connection with the ventral striatum. Furthermore, altered function of the PCC is more related to cognitive decline, with close connection with the temporal lobe and the hippocampus.

4.5. Substantia Innominata and Septal Nuclei

4.5.1. Anatomy and Function

The substantia innominata and septal nuclei (triangular, medial, lateral and dorsal septal nuclei, septofimbrial nucleus, nucleus of diagonal band, nucleus of the anterior commissure) represent telencephalic cortical, predominantly cellular, grey matter regions providing critical cholinergic projections to the amygdala (through the stria terminalis), hippocampus (through the fornix), lateral hypothalamus (through the medial forebrain bundle), habenula (through the stria medullaris thalami) and tegmentum, and receiving major afferents from the amygdala and hippocampus, besides the orbitofrontal, mesiotemporal cortex and insula.

As indicated by its name, anatomical definition of the substantia innominata remains challenging, englobing a collection of cholinergic and non-cholinergic nuclei of the basal forebrain below the anterior commissure within the quadrigone delineated by the anterior perforated substance, and the globus pallidus and ansa lenticularis on each side, in close vicinity to the basal ganglia and amygdaloid complex. Overall, cholinergic neurons are divided into eight groups named Ch1–Ch8, of whom the nucleus basalis of Meynert (nbM, Ch4) gives the chief cholinergic projection to the amygdala and hippocampus, the latter being also innervated by the Ch1 and Ch2 groups. The nbM also project to part of the striatum which receives widespread cholinergic input from the pedunculopontine nucleus (Ch5) and dorsolateral tegmental nuclei (Ch6), also responsible for the cortical cholinergic innervation. As such, the nbM (Ch4), medial septal nucleus (Ch1) and nucleus of the vertical limb of the diagonal band (Ch2) specifically project to the subcortical and cortical limbic system, playing a critical role for attention, memory and arousal.

4.5.2. Pathology

Abundant Lewy bodies are found in the nbM, corresponding to Braak stage 3, with severe accumulation in stage 4 [28], contrasting with often lower density in connected limbic areas [185]. It was postulated that severe extension of Lewy body pathology to the magnocellular nuclei of the basal forebrain (basal nucleus of Meynert, interstitial nucleus of the diagonal band and medial septal nucleus) may represent a prerequisite of neocortical synucleinopathy [28]. Importantly, postmortem studies found consistent cortical cholinergic reduction across PD patients, whereas Ch4 cell loss and hippocampal cholinergic innervation were variable, but strongly depleted in those with PD dementia [76].

4.5.3. Neuroimaging Evidence in PD

Neuropsychiatric and Motor Symptoms

Using in vivo MR imaging, no volumetric difference is found for Ch1-2 and Ch4 between patients with PD and healthy controls in early PD [103,186]. However, lower volume is found in more advanced PD [187,188], correlating with cortical thinning in the bilateral posterior cingulate, parietal, and frontal and left insular regions in patients with PD-MCI [189]. This is in line with decreased metabolism in the parietal and occipital

cortices [190] and decreased functional connectivity between the nbM and the right superior parietal lobe and postcentral gyrus [191]. In addition, patients with lower substantia innominata volume had decreased connectivity between the caudate and frontal, parietal, temporal, precentral and PCC [192]. Furthermore, decreased myelin content is found in its emerging projections [193] together with lower fractional anisotropy within the frontolateral tracts in PIGD-dominant patients [194]. Altered connectivity between the nbM and parietal and occipital cortex may be implicated in visual hallucinations [195] and grey matter density in the Ch4 group and centromedial amygdala was specifically associated with apathy, but not depression, in PD [196]. In addition, recent studies pinpointed the role of cholinergic forebrain nuclei in gait disorders, with lower nbM volume predicting increased gait variability in patients with early PD [197] and in those undergoing STN-DBS.

Cognitive Symptoms

Lower Ch4 density was consistently associated with impaired cognition, including attention and visuospatial dysfunction [198]. Furthermore, free-water using diffusion-weighted imaging is consistently increased in the NbM in those with cognitive impairment at baseline and predicted future cognitive decline together with lower volume [97,199–202]. However, non-corrected DTI metrics were not related to cognitive impairment in the cholinergic forebrain but in the hippocampus [103]. Lower volume of the nbM also predicted cognitive decline in patients undergoing STN-DBS [203]. Notably, single trajectory DBS targeting both the GPi and nbM did not improve cognition in a recent cross-over trial in 6 PD patients [204], consistent with previous trials in PD [205].

Ch1-2 volume might be greater in PD patients without cognitive impairment compared to those with cognitive impairment and to healthy controls [186]. This may indicate greater resilience, although longitudinal atrophy is observed [200]. Notably, the cholinergic projections of the nBM plays a critical role in cortical activation causing desynchronized EEG pattern in the attentional state. Interestingly, volume of the cholinergic basal forebrain correlated positively with alpha reactivity in PD, whereas it was specifically related to EEG changes in pre-alpha power in people with MCI [206]. Importantly, the role of the bidirectional delta/theta band network between the nbM and inferior and mesial temporal lobe structures including the parahippocampal gyrus was recently highlighted in patients with PD dementia [207].

4.6. Fornix and Mammillary Bodies

4.6.1. Anatomy and Function

The fornix represents a small C-shaped projection tract located on each side of the midline, emerging from the flattened fibers of the fimbria, where part of the fibers forms the hippocampal commissure. Thereafter, most of the fibers join, forming a body under the splenium of the corpus callosum, run anteriorly and divide above the interventricular foramen. As such, it connects the hippocampus (subiculum and entorhinal cortex) with the mammillary bodies and anterior thalamic nuclei (postcommissural fibers), and with the septal region (precommissural fibers), through the posterior and anterior columns respectively according to their division around the anterior commissure [208].

In turn, the mammillary bodies send projections in their immediate vicinity to the anterior and dorsal thalamic nuclei (mammillo-thalamic tract, also known as the bundle of Vicq d'Azyr) and to the tegmental nuclei (mammillo-tegmental tract). Importantly, the fornix conveys the cholinergic projections from the septal nuclei to the hippocampus. As such, the fornix and mammillary bodies are part of a hippocampocentric group, critically involved in memory and spatial orientation [208]. Therefore, it is considered as target for DBS in AD. Overall, the fornix is central to the circuit described by Papez and MacLean.

4.6.2. Pathology

Alterations are observed starting in Braak stage 3, although structural alterations of the fornix may be already present in people at risk for PD [209] and be related to peripheral inflammation [210].

4.6.3. Neuroimaging Evidence in PD

Although widespread, white matter alterations were observed in the fornix in patients with MCI [211], advanced stage PD patients with short-term memory impairment [212], and those with excessive daytime sleepiness [213]. Moreover, structural alterations of the fornix using DWI are already found in moderate [214] and early PD [215], as well as in de novo PD patients for whom connectivity of the fornix was associated with hyposmia [216]. In addition, the volume of the fimbria [217] and left hippocampus–amygdala transition area was correlated with visuospatial/executive function in PD patients with MCI [93]. However, decline of the hippocampal formation and fimbria was observed in PD patients progressing to dementia, associated with impairment in the attention and executive domains [99]. This is consistent with altered structural integrity in the fornix and Ch3-Ch4 cholinergic neuronal groups, correlating with impaired Mini-Mental State Examination scores and executive function in early PD. Loss of structural integrity observed in the Ch1-Ch2 groups correlated with the severity of recall memory impairment [104].

In addition, lower fractional anisotropy and higher mean diffusivity were found in the fornix-stria-terminalis in patients with probable RBD [218], possibly restricted to those with concomitant depression [219].

4.7. Habenula and Pineal Body

4.7.1. Anatomy and Function

Together with the pineal body, the habenula and habenular commissure forms the posterior division of the diencephalon, named epithalamus. As such, the habenula can be identified as a small triangular area adjacent to the wall of the 3rd ventricle and to the medial surface of the thalamus, extending into the third ventricle with the habenular commissure. The habenula is further divided into a medial and lateral part, which can be visualized using ultra-high field MRI or susceptibility-weighted imaging at 3T [220].

The lateral habenula receives critical limbic afferent projections through the stria medullaris thalami, from the cortex (ACC, anterior insula, dorsal OFC), but also from the hypothalamus, septal nuclei and brainstem monoaminergic nuclei (ventral tegmental area, median raphe and locus coeruleus), and ventral pallidum for its most lateral part [221]. As such, the lateral habenula is deeply integrated within the emotional limbic system, representing a target for DBS for treatment-resistant depression [222]. In turn, the habenula sends efferent projections to the septal nuclei, ventral tegmental area, dorsal raphe nucleus and locus coeruleus, modulating the mesolimbic dopaminergic, serotonergic and noradrenergic circuits. Hence, the habenula represents a major modulator of the reward circuit, critical for the regulation of impulsive behaviors, next to the amygdala.

4.7.2. Pathology

Even though literature on the neuropathology of the epithalamus is sparse, it is assumed that this brain region starts harboring significant PD pathology in Braak stage 4 [9,28].

4.7.3. Neuroimaging Evidence in PD

Neuropsychiatric Symptoms

Specifically, dysfunction of the habenula was implicated in PD punding, with lower resting-state functional connectivity between the bilateral habenula and left frontal and precentral cortices [223]. In addition, increased connectivity was observed between the habenula and the thalamus bilaterally, and with the striatum and posterior cingulum in the left hemisphere, in comparison to patients without ICDs. Interestingly, increased connectivity between the amygdala and thalamus and striatum was also observed, highlighting the

imbalance of inhibitory control and reward for patients engaging in repetitive behaviors regardless of the lack of reward. Furthermore, patients with punding also had greater severity of apathy and depression relative to healthy controls and patients without ICDs matched for age and disease duration [223]. Interestingly, depressive-like behaviors are observed in Parkinsonian preclinical models related to decreased connectivity between the serotonergic raphe nuclei and the lateral habenula, dentate gyrus of the hippocampus, thalamus and hypothalamus, possibly reversed by dopaminergic treatment [224]. Notably, studies of the habenula remains scarce, which may change with high-resolution imaging using ultra-high field MRI.

The pineal gland is a small neuroendocrine structure derived from the epithalamus and located at the roof of the 3rd ventricle, below the habenular commissure and above the superior colliculus and dorsal to the posterior commissure. Importantly, secretion of small neuropeptides and biogenic amines including melatonin is closely regulated by the anterior hypothalamic nuclei, involving the suprachiasmatic nuclei, considered the central clock within the hypothalamus. Notably, the hypothalamus receives dense projections from the serotonergic midbrain raphe neurons and from the lateral medullary noradrenergic neurons, besides intrinsic dopaminergic neurons. Melatonin is central to the organization of the sleep-wake cycle, and its nychthemeral pattern was found to be dysregulated across neurodegenerative disorders and related to sleep disorders. Specifically, circulating melatonin was found to be reduced in patients with early PD [225], with blunted cycles in those with excessive daytime sleepiness [226]. Furthermore, PD patients exhibited hypothalamic atrophy, likely involving the suprachiasmatic nuclei, and reduced melatonin output over 24 h was correlated to hypothalamic gray matter volume loss [227].

Importantly, [^{18}F]FDOPA PET uptake was reduced in the pineal gland and hypothalamus in patients with advanced PD, possibly related to intrinsic amine synthesis for the pineal gland [228], whereas it was preserved in PD patients with Parkin mutation and in non-symptomatic single parkin mutation carriers [229], who may also have less frequent sleep-related non-motor symptoms [230]. Furthermore, increased [^{18}F]FDOPA uptake was observed in patients with early PD [228,231], possibly indicating early compensatory mechanisms, especially in young-onset PD patients.

4.8. Ventral Striatum

4.8.1. Anatomy and Function

The ventral striatum is phylogenetically older than the neostriatum comprising putamen and caudate. The ventral striatum consists out of the olfactory tubercle and the accumbens. The latter is located in direct continuity with the caudate and the putamen and can be further subdivided into core and shell. The nucleus accumbens is viewed as a signal integration site, based on its diverse afferents, which stem from the hippocampus (contextual information), the amygdala (emotional information), the prefrontal cortex (glutamatergic, executive and cognitive information) and the midbrain (dopaminergic, motivational significance). In turn, its efferents project to the pallidum, hypothalamus, midbrain and cortical areas; brain regions involved in behavior initiation and complex executive functions [232,233]. Due to its connections, Mogenson et al. define the accumbens as a functional interface between the limbic and the motoric system leading from motivation to action [18]. Taking into account its phylogeny, the nucleus accumbens is considered to be important for the biological drives of survival and reproduction [234]. The reinforcing effect of drugs depends principally on dopaminergic signaling in this brain region [235], hence the accumbens can be seen as the key player of the dopaminergic reward system. Nevertheless, labeling the accumbens just as a reward center is reductionist. Floresco concludes that the accumbens is important for action selection facilitating goal-directed behavior. More precisely, the core mediates approaching to relevant motivational stimuli, whereas the shell suppresses irrelevant actions [232].

4.8.2. Pathology

In Braak staging, the accumbens or the ventral striatum are not directly mentioned, but other nuclei of the basal forebrain are severely affected in Braak stage 4 [28]. However, in this context, it is worth mentioning that Lewy Body pathology is not related to dopaminergic cell loss in the striatum, which indicates that Lewy Body pathology in striatal regions might not be an adequate marker for disease progression and symptom severity [236].

4.8.3. Neuroimaging Evidence in PD

Neuropsychiatric Symptoms

Commonly in PD, the accumbens is referred to the pathophysiology of ICD under dopamine replacement therapy. PET imaging of the dopaminergic system revealed that ICDs are associated with a reduction of D2/D3 receptor availability [237,238], dopamine synthesis capacity [146], and DAT density [239] in this region. These "hypodopaminergic" changes of the accumbens are critically involved in ICD and were previously embedded in a vulnerability-stress model for the development of ICD. In this model, a hypodopaminergic state in the accumbens (vulnerability) combined with dopamine replacement therapy (stress) leads to the development of ICD [240]. Task-based fMRI designs shed further light on the involvement of the accumbens in reward learning in ICD: lower BOLD activity was associated with higher subjective value of a delayed reward in hypersexuality [148], and there was a stronger BOLD activity during the initial versus final periods of negative feedback during a gambling task [241]. However, an fMRI paradigm with inhibitory framing and sexual cues could not detect BOLD changes in the accumbens of hypersexual PD patients during a pilot study [242]. Several studies examined connectivity changes of the accumbens in ICD. Whereas larger bet sizes in a virtual casino were associated with a higher structural connectivity to the prefrontal cortex [243,244], ICD severity *per se* was linked to a reduced functional frontostriatal connectivity [146]. Functional connectivity between ventral striatum and subgenual cingulate cortex correlated with reward learning but not with learning from punishment [63]. Therefore, connectivity changes of the accumbens are still ambiguous in ICD.

Concerning reward learning in PD *per se*, abnormal BOLD activity was found in the accumbens during reward anticipation when compared to healthy controls [245] and learning correlated with BOLD activity in this area, which was impaired by dopaminergic treatment [246]. Morphological studies reported on the one hand that implicit risk was associated with higher gray matter volume [247], but on the other hand disinhibition was linked to thinning of the accumbens [248].

An increasing number of studies examined the connection between reward learning and motor activity/skills in order to disentangle the link the between motor symptoms in PD and impaired reward processing. Aerobic motor activity or habitual exercises enhanced reward processing in the accumbens in an fMRI paradigm [249,250]. A raclopride-PET design could show that learning of motor skills in PD leads to a compensatory hyperactivation of the ventral striatum and caudate as compared to healthy controls. However, the controls showed increased dopamine levels in the putamen [251]. Therefore, it seems that motor activity alters reward processing in the accumbens and motor learning itself is processed by the accumbens.

Not only ICDs and learning, but also neuropsychiatric symptoms with reduced impetus such as apathy, depression and anxiety are associated with alterations of the accumbens. There was an inverse correlation between DAT availability and severity of depression [252]. Apathy in PD was associated with reduced amplitude of low-frequency fluctuations as compared to PD controls indicating lower neuronal activity in this brain region [155]. Atrophy of the nucleus accumbens was also reported in patients with apathy [163]. Moreover, apathy was also linked to amyloid deposition in the bilateral accumbens [157].

Cognitive and Other Symptoms

Other non-motor symptoms (e.g., pain, sleep, cognition) also go along with a reduced function of the accumbens: the perception of pain under on and off conditions was referred to functional connectivity changes of the accumbens to the motor and sensory cortex [253]. PD patients with sleep disturbance had a lower availability of SERT in the accumbens when compared to PD patients without sleep disturbance [138], and nocturnal hallucinations were related to a reduced volume of this region [90]. Working memory, frontal executive and visuospatial functions were positively correlated with DAT availability in the accumbens [254]. PD patients with MCI and amyloid depositions showed lower DAT density in this area as compared to PD controls [255]. The severity of autonomic dysfunction correlated negatively with DAT density in this region [256].

Other studies examined general neuroimaging changes of the accumbens in PD during the course of disease such as reduction in VMAT2 density [257], lower gray matter volume [57,258] and a lower orientation dispersion of the amygdala accumbens pathway [62]. In an MRI-study, the volume of the ventral striatum was reduced in later-disease stages of PD as compared to earlier disease-stages. Therefore, the authors conclude that volumetric changes of the ventral striatum might serve as a marker of disease progression [259].

Conclusions

As a conclusion, imaging changes of the accumbens are associated with the typical neuropsychiatric symptoms in PD such as ICD/impaired reward learning, apathy and depression. Despite of the opposing clinical presentation of these symptoms, in the majority, they seem to go along with a vulnerability state of the accumbens.

5. Discussion

The limbic system, a collection of brain structures involved in the processing of emotion and memory, demonstrates marked changes during PD. As outlined above, there is little consensus among researchers on how to precisely define the limbic system, not least on account of its versatile functions. This issue has been a controversial and much disputed subject and has dominated the field for many years, but recent developments offer a new perspective. In this respect, Rolls [11] provides a new framework by postulating not a single but two separate, closely linked limbic systems: the emotion- and memory-centered limbic system.

A useful, operational definition of emotions is that emotions are states associated with stimuli that are either rewarding or punishing and thus emotions are important internal signposts which guide our behavior [260]. The clinical picture of PD is dominated by emotion-related non-motor symptoms such as depression, anxiety, apathy, and ICD. These symptoms place a severe burden on the patient and their caregivers. Therefore, recent neuroimaging evidence has been of critical importance to highlight major contributions of disease-related damage to the amygdala, hippocampus, ventral striatum, and cingulate gyrus to these affective symptoms. According to Rolls, the neural basis of emotions can be divided into three tiers. First, information processing starts at a level at which neurons encode 'what' the input or stimulus represents, independent of its value. This step mainly involves the primary sensory cortices. Second, the value of the stimulus is computed. In this tier, the limbic system comes into play, mainly involving the amygdala. The amygdala as well the OFC (not traditionally seen as part of the limbic system) are implicated in holding representations of stimulus value, learning new reinforcement associations and updating such associations when contingencies change. After the stimulus value has been computed in tier two, brain structures of the final third tier (ACC, medial prefrontal cortex, hypothalamus, basal ganglia) are involved in decision making between stimuli of different value, selecting an appropriate behavior as well as action-outcome learning.

Regarding PD symptomatology, it is important to consider that the connectivity of the emotion system is primarily feedforward—from tier one to three. In this sense, the OFC has projections to the ventral striatum, caudate nucleus, ACC, medial prefrontal

cortex, and hypothalamus. Some of these connections represent pathways particularly important for the production of behavior. A great body of evidence (which has been reviewed in detail above) suggests alterations of these routes in PD. For example, it has been reported that damage in the OFC can cause failure to compute and update the reward value of stimuli and thus might underly emotion impairments, such as lack of affect, irresponsibility, and impulsivity. In PD, ICD (excessive urges and behaviors including pathological gambling, binge eating, hypersexuality, and compulsive buying [261]) is a commonly reported symptom and has been strongly linked to the alterations of processing in hubs as the ventral striatum and cingulate gyrus. In this regard, it has been shown that the connectivity strength of these two regions seems to be negatively correlated with the severity of impulsivity and, furthermore, the severity of impulsivity is also associated with a thicker cingulate cortex [146]. Moreover, ICD is inter alia associated with an altered connectivity between the ventral striatum and prefrontal cortex [243]. Besides the direct disease related alteration of limbic regions, deficient processing on the level of tier two being transmitted to tier three brain regions may also contribute to malfunction and manifestation of PD symptoms such as apathy, depression and anxiety.

In addition, the computation of reward prediction errors (difference between expected and actual reward), which is impaired in PD, is associated with dopaminergic neurons of the midbrain, and computation in the tier two brain regions, whereby tier two output regions represent brain systems concerned with action performance. Now, interestingly, it is hypothesized that PD-motor symptoms may be related to a shift in the cost–benefit computation, downweighting the expected reward [262,263]. In this regard, a study which employed a physical force task found that PD induced dopamine depletion reduced the amount of effort PD patients were willing to produce for a given reward [264]. This further supports the hypothesis of limbic pathology contributing to the cardinal PD motor symptoms, involving the emotion-centered limbic system.

In line with Rolls, it is notable that damage to the emotion-centered limbic system does not severely affect episodic memory or the processing of spatial information, the main functions of the memory-centered limbic system. The amygdala, as part of the emotional limbic system, demonstrates strong connections with the ACC, whereas the hippocampus, the main structure of the memory limbic system, exhibits mayor connections with the PCC, which in turn is connected to areas involved in spatial functioning, including the visual parietal cortex, supporting the existence of two separate limbic systems. However, the systems are not independent of each other, as the hippocampus does receive a signal from reward processing areas such as the OFC and amygdala via the entorhinal and perirhinal cortex.

Dysfunction of the memory-centered limbic system in the form of hippocampal damage, characterized by impaired episodic memory, is observed in many PD patients. In this sense, increased disease duration is strongly linked to cognitive decline, manifesting as dementia in late-stage PD [79]. Neuroimaging evidence suggests that hippocampal volume decreases as the disease advances, whereby the severity of volume loss is a predictor for conversion to dementia [53,98,99]. Additionally, hippocampal cholinergic innervation is also strongly depleted in PD dementia [76]. Now, considering the second major function of the memory-centered limbic system, the processing of spatial information, it has been found that PD related hippocampal alterations are associated with impaired spatial working memory, which can be explained by the essential role of the hippocampus and its connections in object-place memory [95].

Overall, PD pathology is prominent in the limbic system throughout the disease course, responsible for disabling nonmotor, neuropsychiatric, behavioral, and cognitive symptoms. Although the pathophysiology remains complex, neuroimaging helps disentangling specific network injury, supporting the operational dichotomy between memory-centered and emotion-centered limbic systems and related symptoms [11]. Additionally, due to the increasing use of imaging techniques with high spatial resolution such as 7T MRI, more information will also be gained concerning the small limbic structures. Indeed, the two

limbic systems seem to operate in an independent fashion, although neuroimaging in PD patients highlights the network organization and critical role of the ventral striatum and ACC and their modulation by brainstem and forebrain small nuclei.

To conclude, alterations of the limbic system play an important role in PD symptomatology, including affective, but also cognitive and motor symptoms. Particularly, the latter aspect has not yet received adequate attention and highlights how motor and nonmotor symptoms are deeply intertwined in PD.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/brainsci12091248/s1, Supplementary Table S1.

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2.2 Project 2

Putaminal dopamine modulates movement motivation in Parkinson's disease

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Journal: Brain

Abstract:

The relative inability to produce effortful movements is the most specific motor sign of Parkinson's disease, which is primarily characterized by loss of dopaminergic terminals in the putamen. The motor motivation hypothesis suggests that this motor deficit may not reflect a deficiency in motor control per se, but a deficiency in cost-benefit considerations for motor effort. For the first time, we investigated the quantitative effect of dopamine depletion on the motivation of motor effort in Parkinson's disease. A total of 21 early-stage, unmedicated patients with Parkinson's disease and 26 healthy controls were included. An incentivized force task was used to capture the amount of effort participants were willing to invest for different monetary incentive levels and dopamine transporter depletion in the bilateral putamen was assessed. Our results demonstrate that patients with Parkinson's disease applied significantly less grip force than healthy controls, especially for low incentive levels. Congruously, decrease of motor effort with greater loss of putaminal dopaminergic terminals was most pronounced for low incentive levels. This signifies that putaminal dopamine is most critical to motor effort when the trade-off with the benefit is poor. Taken together, we provide direct evidence that the reduction of effortful movements in Parkinson's disease depends on motivation and that this effect is associated with putaminal dopaminergic degeneration.

Putaminal Dopamine Modulates Movement Motivation in Parkinson's Disease

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Running title: Movement motivation and dopamine

Keywords: incentive salience; fatigue; SPECT; imaging; basal ganglia; performance

Abstract

The relative inability to produce effortful movements is the most specific motor sign of Parkinson's disease, which is primarily characterized by loss of dopaminergic terminals in the putamen. The motor motivation hypothesis suggests that this motor deficit may not reflect a deficiency in motor control *per se*, but a deficiency in cost-benefit considerations for motor effort. For the first time, we investigated the quantitative effect of dopamine depletion on the motivation of motor effort in Parkinson's disease.

A total of 21 early-stage, unmedicated patients with Parkinson's disease and 26 healthy controls were included. An incentivized force task was used to capture the amount of effort participants were willing to invest for different monetary incentive levels and dopamine transporter depletion in the bilateral putamen was assessed.

Our results demonstrate that patients with Parkinson's disease applied significantly less grip force than healthy controls, especially for low incentive levels. Congruously, decrease of motor effort with greater loss of putaminal dopaminergic terminals was most pronounced for low incentive levels. This signifies that putaminal dopamine is most critical to motor effort when the trade-off with the benefit is poor.

Taken together, we provide direct evidence that the reduction of effortful movements in Parkinson's disease depends on motivation and that this effect is associated with putaminal dopaminergic degeneration.

Introduction

Dopamine neurons have distinct roles in motivational control, such as investing more physical effort or waiting longer in return for larger rewards.[1–3] Current frameworks suggest that this effect arises from the ability of dopaminergic circuits to promote goal-directed behavior by attributing incentive salience to stimuli and overcoming effort costs.[4,5]

Parkinson's disease (PD) is characterized by a severe depletion of dopaminergic terminals, which occurs earliest and most prominently in the putamen.[6] Notably, evidence demonstrates a close relationship between the loss of putaminal dopamine terminals and the relative inability to produce effortful movements in PD.[7] The recently proposed "*motor motivation hypothesis"* suggests that this distinct motor deficit in PD may not reflect deficient motor control *per se*, but a shift in the cost-benefit consideration for motor effort.[8] In other words, besides the role of dopamine in explicit goal-directed behavior, dopamine may also provide the substrate for *"movement motivation"*.

An increasing body of literature substantiates this motor motivation hypothesis of PD. However, direct evidence of the link between dopaminergic degeneration and movement motivation remains elusive. Studies have demonstrated that the willingness to invest physical effort depends on the medication status of patients with PD, indicating that medicated patients invest more effort than unmedicated patients.[9,10] These results can potentially be explained by low striatal dopamine levels in the unmedicated state, which lead to a shift in the cost-benefit evaluation of effort and, thus, a deficiency in performing effortful movements to obtain a reward.[10–13] Additionally, it has been reported that independent of the medication status, patients with PD invest significantly less effort than healthy controls, especially for low reward options.[14] Previous studies on incentive salience in PD are limited to statistical inference on group (PD vs. HC) and medication (ON vs. OFF dopaminergic medication) effects. Since ON vs. OFF analyses only provide a rough estimate and are swayed by different medication types and dosages, quantitative measures of baseline endogenous dopamine and associated changes in movement are needed.

The objective of our study was to investigate if PD-related motor deficits might relate to the integration of motivation into the motor system. For this purpose, we used dopamine transporter (DaT) SPECT (an established standard for assessing dopaminergic degeneration[15]) as a biological measure of PD severity, i.e., disease severity in the dopaminergic system, and studied the relationship between putaminal dopamine terminal loss and performance in an incentivized grip-force task within a group of unmedicated patients with PD.

We hypothesized that unmedicated patients with PD would invest significantly less effort than healthy controls (HC). Additionally, in the PD group, we anticipated that greater putaminal dopaminergic terminal loss is parametrically associated with lower effort and that this deficit is more evident for low incentives.

Materials and methods

Participants

Twenty-one patients with PD and 26 HC between the age of 49 and 77 years were included in the study. Participants were recruited at the University Hospital Cologne through posters and flyers and from a local register of healthy volunteers. Before inclusion, all participants were screened for eligibility. Exclusion criteria were left-handedness, cognitive deficits (Montreal Cognitive Assessment [MoCA] score of < 24), and depression (Geriatric Depression Scale [GDS] score of > 5), as well as any significant comorbidity. For patients with PD, additional inclusion criteria were early-stage PD (clinical symptoms < 3 years), diagnosis according to the Movement Disorder Society Clinical Diagnostic Criteria for PD,[16] and an available DaT SPECT, acquired shortly before the behavioral assessment at the University Hospital Cologne. For sample characteristics please see Table 1.

Table 1: Characteristics of Study Sample

	HC	**PD**	***p***
N	26	21	
Sex (f/m)	9/17	4/17	.391
Age (years)	63.75 (6.71)	62.4 (8.32)	.548
MoCA	28 (2)	27 (3)	.393
GDS	0 (1)	1 (3)	.078
AES	45 (3)	43.5 (3)	.246
UPDRS-III	0 (0.75)	13 (8)	< .001
Time DaT-SPECT to study visit (weeks)		29.79 (19.2)	
LEDD (mg)		251.36 (153.37)	
Putamen bilateral DaT z-values		-3.72 (0.79)	

Note: MoCA, GDS, AES, and UPDRS-III are provided as median (interquartile range), all others as mean (standard deviation). LEDD = levodopa equivalent daily dose.

Study procedure

The study was approved by the Ethics Committee of the University Hospital Cologne and performed in accordance with the standards of the Declaration of Helsinki. All participants gave written informed consent and received monetary compensation for their participation. The study comprised collecting demographic information, neuropsychological testing (including the Apathy Evaluation Scale [AES]), evaluation of motor symptoms using the Unified Parkinson's Disease Rating Scale (UPDRS-III), and a computerized incentivized force task. DaT SPECTs of patients with PD, which were acquired at the Department of Nuclear Medicine (University Hospital Cologne) as part of the clinical routine to confirm the PD diagnosis, were used for the analysis. Medicated patients (12 out of 21) were asked to pause their medication prior to their study visit; thus, all data

were collected in the medication OFF state. Long-acting dopamine agonists were discontinued for at least 72 and L-DOPA for 12 hours.

Incentivized force task

We used a well-established paradigm, which enables to quantify the effort (i.e. grip force) participants are willing to invest for different monetary incentive levels. More details on the task can be found elsewhere.[9,17,18]

Briefly, a hand dynamometer (Vernier Go Direct, USB connected) was placed in the participant's right hand, and the maximum voluntary grip force was assessed to adapt effort levels in the task to each participant's individual strength. In the task, participants were instructed to maximize their total monetary payoff in two conditions: (A) win and (B) loss avoidance (Fig. 1). Each condition comprised 60 trials. Each trial started with the presentation of a monetary incentive (0.01€, 0.20€, 0.50€, 1.00€, 5.00€, 20.00€; shown in random order for 2-4 seconds), followed by a graduated force scale (4-6 seconds). The force scale ranged from 0 to 100%, with the top representing the maximum grip force of the individual. Visual feedback on the force scale indicated the current (grey bar) and peak in the current trial (red) grip force applied to the dynamometer. Reaching the top of this scale meant reaching one's individual maximum force and thereby (A) winning the full incentive or (B) avoiding any loss. Each increment along the scale corresponded to a fraction of the monetary incentive. Afterwards, the win/loss and the current monetary total was displayed (3.5 seconds).

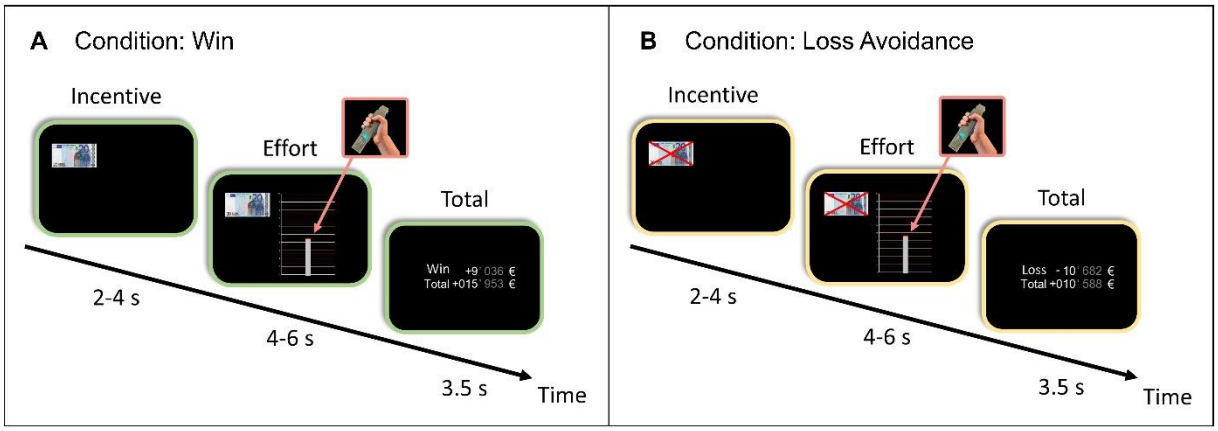

Figure 1: Behavioural Incentivized Force Task. Illustration of one trial of each condition. (**A**) win and (**B**) loss avoidance. The red line moves conjointly with the gray bar upwards the scale when applying grip force to the dynamometer and represents the peak force within each trial.

Data collection and quality checks

Grip force in the incentivized force task was sampled with 100 Hz. The peak force within the effort period (dependent variable) was extracted for each trial. MATLAB R19a was used to implement the task and to extract the dependent variable. Data were plotted and visually inspected for data quality purposes (ensuring that each force profile included the peak force, i.e., making sure that

participants did not start to grip the dynamometer before the effort period, or still grip the dynamometer after the effort period had already ended) using Python 3.10.8.

DaT-SPECT imaging

DaT SPECT images were obtained on a PRISM-3000 three-head SPECT system (Picker) following a standardized clinical procedure (i.e., [123I]Ioflupane injection, reconstruction using Chang's attenuation correction, voxel-values normalized to the occipital cortex). Next, z-transformed deviation maps from age-matched healthy controls were computed, and z-values of the bilateral putamen were extracted using the EARL-BRASS software (Hermes, Sweden).[19,20]

Statistical analyses

Using linear mixed models, we investigated the following effects on peak force: the interaction effect of task condition (win, loss avoidance) and group (HC, PD), the interaction effect of incentive level and group, and the interaction effect of putaminal dopaminergic terminal loss and incentive level in the PD group. Furthermore, to investigate the fatigue effect (decrease in force expenditure over time), we analyzed the interaction effect of trial number and group and the interaction effect of putaminal dopaminergic terminal loss and trial number in the PD group. Incentive level was added to the model as a categorical variable; age, sex, and trial number (except for the fatigue analyses) were added as covariates. Additionally, all analyses were conducted with a second measure of force expenditure, replacing trial number with the cumulative area under the curve of the force-time curves. Participant ID was entered as a random factor to account for repeated measures. Type III Analysis of Variance Tables with Satterthwaite's approximation of the degrees of freedom are reported, and p-values < .05 were considered significant. Outliers were identified using the interquartile range method. All statistical analyses were conducted in R (version 4.1.2)[21], linear mixed models were calculated with the R library lmerTest (version 3.1.3)[22], and plots were created with the R library ggplot2 (version 3.4.0)[23].

Results

The HC and PD group did not significantly differ in age (HC: M = 63.75; PD: M = 62.4; t(38.13) = 0.61, p = .548), sex (χ^2(1) = 0.74, p = .391), MoCA (HC Mdn = 28; PD Mdn = 27; W = 312.5, p = .393), GDS (HC Mdn = 0; PD Mdn = 1; W = 185.5, p = .078), and AES (HC Mdn = 45; PD Mdn = 43.5; W = 243.5, p = .246). By design, patients with PD demonstrated a significantly higher UPDRS-III score (Mdn = 13) relative to HC (Mdn = 0), W = 3.5, p < .001.

843 out of 5640 trials were discarded from the analysis, as force profiles did not pass quality checks. We observed no significant interaction between the two task conditions (win vs. loss avoidance) and group, F(1, 4747.2) = 0.52, p = .469. Thus, the task conditions were jointly analyzed. Analysis of the peak force revealed a significant interaction between group and

incentive level, $F(5, 4739.4) = 3.34$, $p = .005$. Post hoc tests revealed that patients with PD applied significantly less force for the first four incentive levels (0.01€: $p = .044$, Δ = 7.63% of peak force; 0.20€: $p = .006$, Δ = 10.33% of peak force; 0.50€: $p = .027$, Δ = 8.37% of peak force; 1.00€: $p = .019$, Δ = 8.89% of peak force) compared to HC, but not for the highest two levels (5.00€: $p = .06$, Δ = 7.11% of peak force; 20.00€: $p = .139$, Δ = 5.6% of peak force; Fig. 2A). In the PD group, there was a significant interaction between putaminal dopaminergic terminal loss and incentive level, $F(5, 2128.07) = 6.93$, $p < .001$. Lower incentive levels were indeed associated with a steeper reduction of peak force with putaminal dopaminergic terminal loss (Fig. 2B). This this model was also calculated with the UPDRS- III score as an additional covariate, and the result did not significantly change, $F(5, 2128.06) = 6.93$, $p < .001$. The fatigue slopes of two subjects were identified as outliers, and accordingly, these subjects were excluded from the fatigue analyses. A significant interaction was observed between trial number and group, $F(1, 4582) = 7.17$, $p = .007$. Peak force of patients with PD decreased significantly faster across all 120 trials compared to HC (Fig. 2C). In the PD group, there was no significant interaction between trial number and putaminal dopaminergic terminal loss, $F(1, 1970.30) = 0.73$, $p = .392$ (Fig. 2D).

Analyses using the cumulative area under the curve revealed the same results, except for one post hoc test of the significant interaction between group and incentive level. The lowest incentive level only demonstrated trend significance (0.01€: $p = .051$, Δ = 7.49% of peak force).

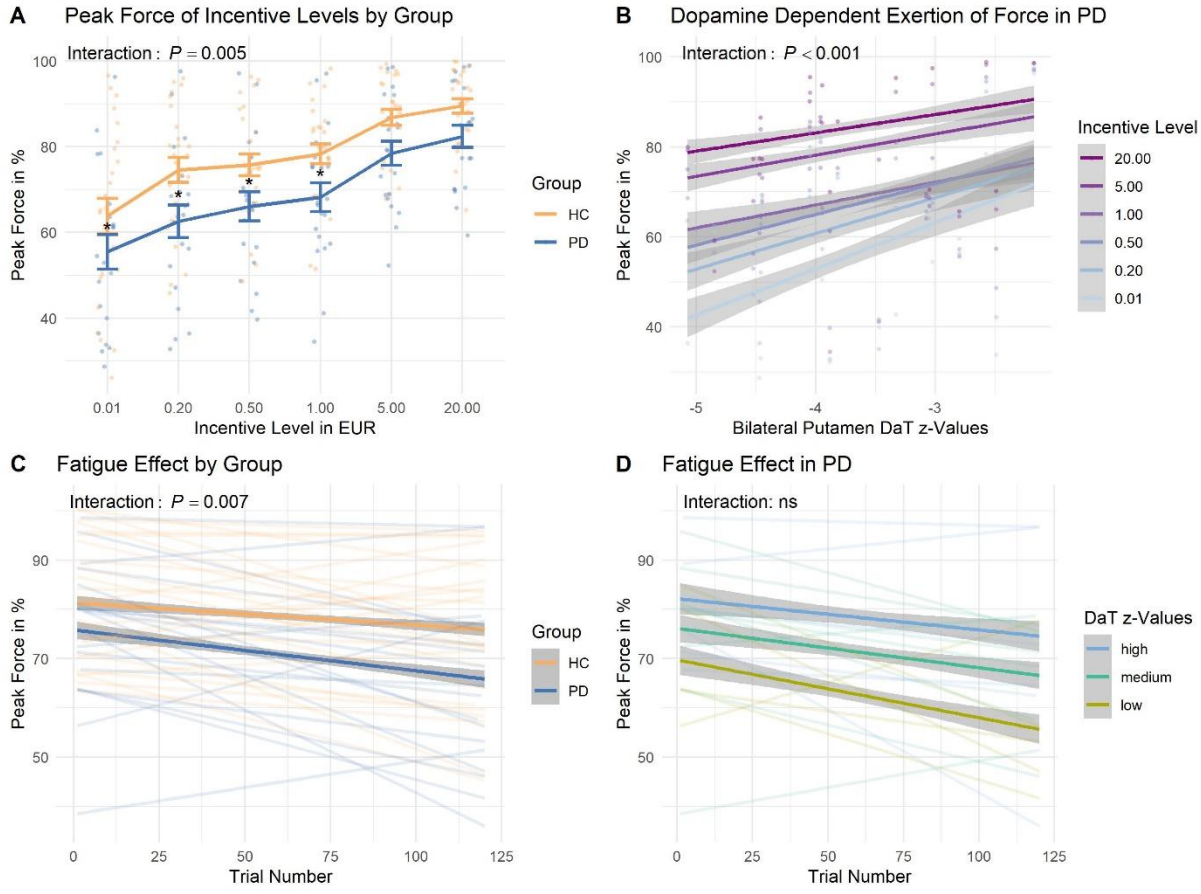

Figure 2: Results of the Incentivized Force Task. (**A**) Peak grip force of patients with PD and HC for each incentive level. Standard error bars are depicted and significant group differences for incentive level 0.01, 0.20, 0.50, and 1.00 EUR are denoted by asterisks. (**B**) Correlation of peak grip force and putamen z-values of dopamine transporter density in the PD group for each incentive level. Lower incentive levels are associated with steeper slopes. (**C**) Peak grip force over all 120 trials of patients with PD and HC. The PD group demonstrates a significantly stronger fatigue effect (decrease in peak force). (**D**) Decrease in peak force over all trials is not associated with putaminal dopaminergic terminal loss in individuals with PD. ns = not significant.

Discussion

Here, we directly investigated if putaminal dopaminergic terminal loss in PD is associated with reduced motor effort in an incentivized force task. Our results demonstrate that patients with PD applied significantly less grip force than HC, especially for low incentive levels. Critically, this deficit was stronger for patients with a greater dopaminergic terminal loss.

In line with previous research, patients with PD could modulate their force expenditure according to the height of the monetary incentive.[24,25] Furthermore, consistent with the motor motivation hypothesis, our findings indicate that patients can attain physical performance levels comparable to healthy controls. However, this performance depended on the presence of high incentives, suggesting that patients normalize motor effort if the motivation is sufficiently high. This finding aligns with previous research, which demonstrated that patients with PD invested less effort than HC, but only for the lowest reward.[14] Moreover, it aligns with the phenomenon known as "paradoxical kinesis", which describes an event where even severely immobilized patients with PD can move when much is at stake (e.g., running out of a burning house).[26,27] Thus, the lack of movement in PD may be overcome through significant extrinsic motivators/incentives.

Importantly, dopamine loss seemed to decrease the motivation to exert physical effort. Previous studies have already indicated this by showing that patients with PD ON dopaminergic medication invest more effort compared to OFF medication.[14,28] Thus, dopamine appears to increase the willingness to work for rewards. In line with previous findings, demonstrating the specificity of dopamine loss to low incentives,[14] in our study the putamen dopamine transporter values were most strongly associated with effort in low incentive levels. Most likely, this means that the willingness to produce high effort is a function of both, incentive level (i.e., incentive-effort conversion rate) and putaminal dopamine level. In the absence of external incentives, the lack of dopamine takes greater effect. Alternatively, the statistical interaction effect could have been produced by a ceiling effect with regard to motor effort. In other words, the cumulative effect of dopamine and external incentives could be "maxed out" at around 90% peak force. An interesting prospect for future studies could be the question whether a greater deficit will also affect high

incentives or leave them intact because they are less dopamine dependent. In this context, we want to emphasize that our patient cohort consisted of individuals with only mild motor symptoms.

We found that patients with PD not only demonstrated grip force which was lower on average, but which also decreased faster over all trials, denoting a greater exhaustion over time, which has also been demonstrated by previous research.[29] Furthermore, based on existing studies and the present findings we expected greater putaminal dopaminergic terminal loss to be linked to a greater fatigue effect. Notably, this was not the case as decreased force expenditure was not associated with the putaminal dopaminergic terminal loss (Fig. 2D). A greater dopaminergic deficit was associated with lower force in general. Still, it did not affect the force expenditure over time. Thus, the effect of dopamine depletion on reducing movement vigor seems stable over physical exertion periods. One potential explanation for the lack of a dopaminergic effect in this regard could be, that fatigue in PD relies more strongly on non-dopaminergic systems, particularly on the serotonergic functioning of the basal ganglia.[30]

A few potential shortcomings need to be considered. First, we only report a correlational link between putaminal dopaminergic terminal loss and incentivized motor effort. As such, the causal relationship between dopamine loss and reduced effort is still uncertain. Second, our analysis was focused on a biological measure of disease severity in the dopaminergic system. It may be of interest in future approaches to focus on the complex interplay of dopaminergic terminal loss, incentivized motor effort and clinical disease severity (e.g. UPDRS). Furthermore, in this regard we focused our analyses on the putamen, whereby we want to stress that our results do not allow a differential consideration of striatal subregions. Third, given that our findings are based on a limited number of subjects, the results should be interpreted with caution and finally, we only had DaT SPECT imaging data of the PD group and thus, some of the analyses were not feasible in HC.

Taken together, our study provides important evidence for a critical role of dopamine in motivating movements. We found that patients with PD demonstrate decreased motivation for effortful behavior if incentives are low. This suggests that dopamine is critical to overcome effort when the trade-off with the benefit is poor. Moreover, for the first time, we can show that this decrease in effort is quantitatively associated with the degree of dopamine depletion in the putamen, as especially manifest in low reward conditions, pointing to a progressive change with dopamine loss severity in the cost-benefit computation of lower yield movements.

Data availability

The data supporting this study's findings are findable in the CRC1451 data registry (https://www.crc1451.uni-koeln.de/), and reasonable requests can be addressed to the corresponding author.

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Competing interests

The authors report no competing interests.

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2.3 Project 3

Gray matter volume loss in proposed brain-first and body-first Parkinson's disease subtypes

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Author contributions: *Banwinkler, M.*: Conceptualization; data retrieval and preparation; data analysis; visualization and interpretation of results; preparation of figures; writing first manuscript draft; incorporating suggestions of co-authors and external reviewers; steps for submission and publication in journal. *Dzialas, V.*: Conceptualization; data retrieval and preparation; proofreading of manuscript. *Hoenig, M. C.*: Conceptualization; data retrieval and preparation; proofreading of manuscript. *van Eimeren, T.*: Conceptualization; supervision; proofreading of manuscript.

Journal: Movement Disorders

Abstract:

α-Synuclein pathology is associated with neuronal degeneration in Parkinson's disease (PD) and considered to sequentially spread across the brain (Braak stages). According to a new hypothesis of distinct α-synuclein spreading directions based on the initial site of pathology, the “brain-first” spreading subtype would be associated with a more asymmetric cerebral and nigrostriatal pathology than the “body-first” subtype. Here, we tested if proposed markers of brain-first PD (ie, higher dopamine transporter [DaT] asymmetry; absence of rapid eye movement sleep behavior disorder [RBD]) are associated with a greater or more asymmetric reduction in gray matter volume (GMV) in comparison to body-first PD. Data of 255 de novo PD patients and 110 healthy controls (HCs) were retrieved from the Parkinson's Progression Markers Initiative. Structural magnetic resonance images were preprocessed, and GMVs and their hemispherical asymmetry were obtained for each of the neuropathologically defined Braak stages. Group and correlation comparisons were performed to assess differences in GMV and GMV asymmetry between PD subtypes. PD patients demonstrated significantly smaller bilateral GMVs compared to HCs, in a pattern denoting stage-dependent disease-related brain atrophy. However, the degree of putaminal DaT asymmetry was not associated with reduced GMV or higher GMV asymmetry. Furthermore, RBD-negative and RBD-positive patients did not demonstrate a significant difference in GMV or GMV asymmetry. Our findings suggest that putative brain-first and body-first patients do not present diverging brain atrophy patterns. Although certainly not disproving the brain-first/body-first spreading hypothesis, this study fails to provide evidence in support of it.

RESEARCH ARTICLE

Gray Matter Volume Loss in Proposed Brain-First and Body-First Parkinson's Disease Subtypes

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ABSTRACT: Background: α-Synuclein pathology is associated with neuronal degeneration in Parkinson's disease (PD) and considered to sequentially spread across the brain (Braak stages). According to a new hypothesis of distinct α-synuclein spreading directions based on the initial site of pathology, the "brain-first" spreading subtype would be associated with a more asymmetric cerebral and nigrostriatal pathology than the "body-first" subtype.

Objective: Here, we tested if proposed markers of brain-first PD (ie, higher dopamine transporter [DaT] asymmetry; absence of rapid eye movement sleep behavior disorder [RBD]) are associated with a greater or more asymmetric reduction in gray matter volume (GMV) in comparison to body-first PD.

Methods: Data of 255 de novo PD patients and 110 healthy controls (HCs) were retrieved from the Parkinson's Progression Markers Initiative. Structural magnetic resonance images were preprocessed, and GMVs and their hemispherical asymmetry were obtained for each of the neuropathologically defined Braak stages. Group and correlation comparisons were performed to assess differences in GMV and GMV asymmetry between PD subtypes.

Results: PD patients demonstrated significantly smaller bilateral GMVs compared to HCs, in a pattern denoting stage-dependent disease-related brain atrophy. However, the degree of putaminal DaT asymmetry was not associated with reduced GMV or higher GMV asymmetry. Furthermore, RBD-negative and RBD-positive patients did not demonstrate a significant difference in GMV or GMV asymmetry.

Conclusions: Our findings suggest that putative brain-first and body-first patients do not present diverging brain atrophy patterns. Although certainly not disproving the brain-first/body-first spreading hypothesis, this study fails to provide evidence in support of it. © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: α-synuclein spread; dopamine transporter; rapid eye movement sleep; rapid eye movement sleep behavior disorder

The key neuropathological feature of Parkinson's disease (PD) is the intracellular protein aggregation of misfolded α-synuclein (α-SN), included in Lewy bodies.[1] It is assumed that progressive intraneuronal accumulation is linked to subsequent neuronal degeneration, whereby strong evidence favors a cell-to-cell propagation

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of misfolded α-SN in a prion-like manner, which is associated with disease progression.[2,3] The spread of α-SN was commonly suggested to occur in a caudal-to-rostral manner, starting in the dorsal motor nucleus spreading upward to the midbrain and limbic structures along six neuropathologically defined Braak stages.[4] Yet recent evidence suggested that this staging scheme may not sufficiently account for the observed interindividual heterogeneity in the pathophysiological progression of PD.[5,6] Interestingly, a recently introduced hypothesis postulates two contrasting subtypes of α-SN spread based on the anatomic location of initial α-SN inclusions (ie, starting point of the propagation), namely the brain-first and the body-first subtype.[7] In body-first PD, α-SN pathology is proposed to first arise in the peripheral autonomic nervous system, from where it enters the brain bilaterally via the vagal nerves and then spreads in a rather symmetric pattern throughout the central nervous system. The body-first subtype of spreading further entails a prolonged phase without PD motor symptoms, including more autonomic symptoms, rapid eye movement (REM) sleep behavior disorder (RBD), and a more bilateral dopaminergic denervation. By contrast, in the brain-first PD subtype, α-SN pathology is suggested to commence unilaterally in the amygdala or a nearby structure of the limbic system. Given the predominantly ipsilateral connectivity of the brain, the pathology is then presumed to spread asymmetrically, resulting in a clinical phenotype with unilateral or largely asymmetric dopaminergic denervation. Around the time of clinically overt motor symptoms of PD, patients with a brain-first spreading history should therefore present with a more asymmetric nigrostriatal dopaminergic degeneration than patients with a body-first spreading history. Conversely, the presence of RBD at that time would indicate a history of body-first spreading.

The aim of the present study was to test specific hypotheses derived from the aforementioned proposition. We examined gray matter volume (GMV) as a marker of neurodegeneration in probable brain-first and body-first subtypes in de novo PD subjects. We reasoned that if pathology in fact starts in the amygdala or nearby structures of one hemisphere in the brain-first subtype, this should result in a more severe atrophy of these regions in the respective hemisphere and, by consequence, in a greater volumetric asymmetry. In contrast, in the body-first subtype, the amygdala and nearby structures should show less and more symmetric atrophy in comparison to the brain-first subtype.

Following the concept described earlier, both higher hemispheric asymmetry of dopaminergic degeneration and absence of RBD would be suitable proxies for the brain-first PD subtype.[7] Nigrostriatal degeneration of dopaminergic neurons in PD is firmly captured by a reduction in dopamine transporter (DaT) binding,[8,9] and therefore, we defined the hemisphere with lower putamen DaT striatal binding ratios (SBRs) as the more affected hemisphere (MAH). We then obtained the GMVs of each Braak stage and hypothesized to find distinct atrophy patterns that are in line with the two subtypes. More specifically, we assumed to find smaller GMV in the MAH and higher GMV asymmetry for brain regions of Braak stage 3 (containing the amygdala) in brain-first compared to body-first subjects.

Therefore, we first explored the association between the asymmetry of dopaminergic degeneration (assessed with putaminal DaT SPECT [single-photon emission computed tomography]) and the GMV of the MAH and less-affected hemisphere (LAH), as well as the GMV asymmetry in each Braak stage. Second, we compared the gray matter measures between a group of RBD-positive and a group of RBD-negative PD patients. Because the amygdala has been proposed to be one of the earliest-affected regions in the brain-first subtype, we repeated our analyses with the amygdala as the region of specific interest.

Patients and Methods

Participants

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/access-data-specimens/download-data). For up-to-date information on the study, visit ppmi-info.org. Data of de novo PD patients as well as healthy controls (HCs) were included in the analysis. The main inclusion criteria were (1) age 50 to 80 years, (2) available magnetic resonance imaging (MRI) scan with <2-mm-slice thickness, and (3) ^{123}I-FP-CIT SPECT information. These criteria resulted in a sample of 259 PD patients and 110 HCs (Table 1). A list of included subject IDs is provided in the Supporting Information (Table S1).

Asymmetry

To assess the asymmetry of dopaminergic degeneration, an asymmetry index (AI) was computed using information of the putaminal DaT SPECT and the formula provided by PPMI. Putamen AI $= |100 \times [(SBR_{left} - SBR_{right})/(\text{mean } (SBR_{left} + SBR_{right}))]|$.

In addition, the degree of motor symptom laterality was calculated using the lateralized items of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III. The items of each side were averaged, and the following formula was applied: $|Items_{Left} - Items_{Right}|$.

RBD Status

To investigate GMVs between patients with and without probable RBD, the 13-item REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) was used to

TABLE 1 *Features of study sample*

	HC	PD	*P*
N	110	259	
Age	64.33 (11.09)	63.18 (11.86)	0.465
Sex	♀37/♂73	♀97/♂162	0.563
Disease duration in months		4.17 (6.83)	
MDS-UPDRS III		20 (11)	
Putamen SBR	2.01 (0.64)	0.78 (0.28)	<0.001

Values are expressed as median (interquartile range).
Abbreviations: HC, healthy control; PD, Parkinson's disease; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; SBR, striatal binding ratios.

define RBD status. Even though polysomnography is considered the gold standard for the diagnosis of RBD,[10] the RBDSQ was used as only very limited polysomnography data were available. The RBDSQ exhibits good diagnostic accuracy, especially for sensitivity in the general population; however, in patient populations inferior performance regarding sensitivity and specificity is observed.[11,12] Therefore, multiple optimal cutoffs have been proposed. To avoid the uncertainty caused by scores close to the originally proposed cutoff of 5 points,[13] subjects with a score of 4 and 5 were removed from the analysis. Therefore, scores ≤3 were classified as having no RBD (RBD–) (n = 120) and scores ≥6 as having RBD (RBD+) (n = 67). The RBD– and RBD+ groups were matched for age, sex, MDS-UPDRS III score, and total intracranial volume (TIV), resulting in 67 subjects per group. To increase comparability with other studies, we also report the results using the original cutoff (see Appendix S1).

Gray Matter Volume

For morphometric analysis of the imaging data, T1 images were processed using the Computational Anatomy Toolbox (CAT12, http://www.neuro.uni-jena.de/cat/) in MATLAB. The default processing pipeline was applied, which includes bias correction of field inhomogeneities, segmentation into gray and white matter and cerebrospinal fluid, and normalization using DARTEL. GMV estimates were extracted from the left and right hemispheres for all 142 regions of interest (ROI) of the Neuromorphometrics atlas. In line with the Braak staging scheme,[14,15] each gray matter ROI (except for cerebellar ROIs) was assigned to the specific Braak stage in which it starts showing significant pathology, resulting in four sets of brain areas (Table 2).

TABLE 2 *Braak stages*

Stage	ROI
1 + 2	Brainstem
3	Amygdala, basal forebrain
4	Hippocampus, entorhinal cortex, parahippocampal gyrus, thalamus, caudate nucleus, globus pallidum, putamen, nucleus accumbens
5 + 6	Remaining cerebral ROIs

ROIs of the neuromorphometrics atlas grouped into Braak stages.
Abbreviation: ROI, region of interest.

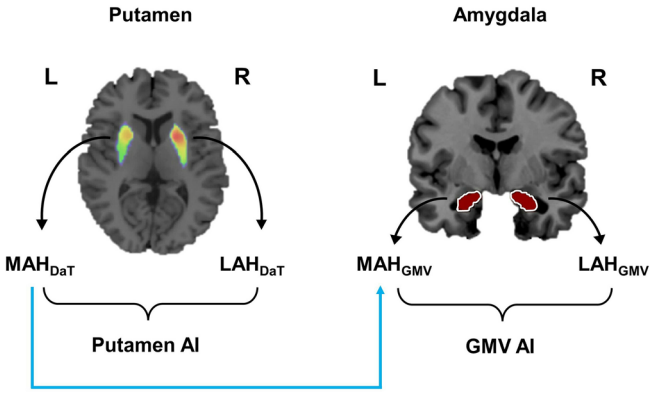

FIG. 1. Representation of important variables. This figure illustrates how the variables of interest were defined. Starting on the left: the hemisphere with the lower putamen DaT SBR (here, the left hemisphere) was defined as the MAH$_{DaT}$. SBRs of both hemispheres were used to calculate the putamen AI. Then, the GMV(z) of the MAH$_{DaT}$ was defined as MAH$_{GMV}$ and used for the analysis. This was also done for the LAH$_{DaT}$. Finally, MAH$_{GMV}$ and LAH$_{GMV}$ were used to calculate the GMV AI. AI, asymmetry index; DaT, dopamine transporter; GMV(z), gray matter volume *z*-value; L, left; LAH, less-affected hemisphere; MAH, more affected hemisphere; R, right; SBR, striatal binding ratios. [Color figure can be viewed at wileyonlinelibrary.com]

The following steps were applied to each of the four sets of brain areas. First, for HCs as well as PD patients, the individual ROI GMVs were averaged to obtain a total GMV score of the respective set of brain areas. This was performed separately for the left and right hemispheres due to inherent hemispheric differences. Second, GMVs of PD patients were *z*-transformed using the volume measures of the HC group as reference, resulting in a GMV$_{(z)}$ score. Third, for PD patients, GMV$_{(z)}$ for the hemisphere ipsilateral to MAH$_{DaT}$ was defined as MAH$_{GMV}$ and the contralateral GMV$_{(z)}$ as LAH$_{GMV}$. Finally, to assess the GMV asymmetry, GMV AI was calculated as follows: |MAH$_{GMV}$ – LAH$_{GMV}$|. For an overview, see Figure 1.

Statistical Analysis

The assumptions for parametric testing were assessed, and nonparametric methods were used when appropriate. The differences between HCs and PD patients were assessed using the Wilcoxon rank-sum tests for continuous variables (age, SBRs, and putamen AI) and Pearson's χ^2 test for the categorical variable sex. To examine the differences in GMV between HCs and PD

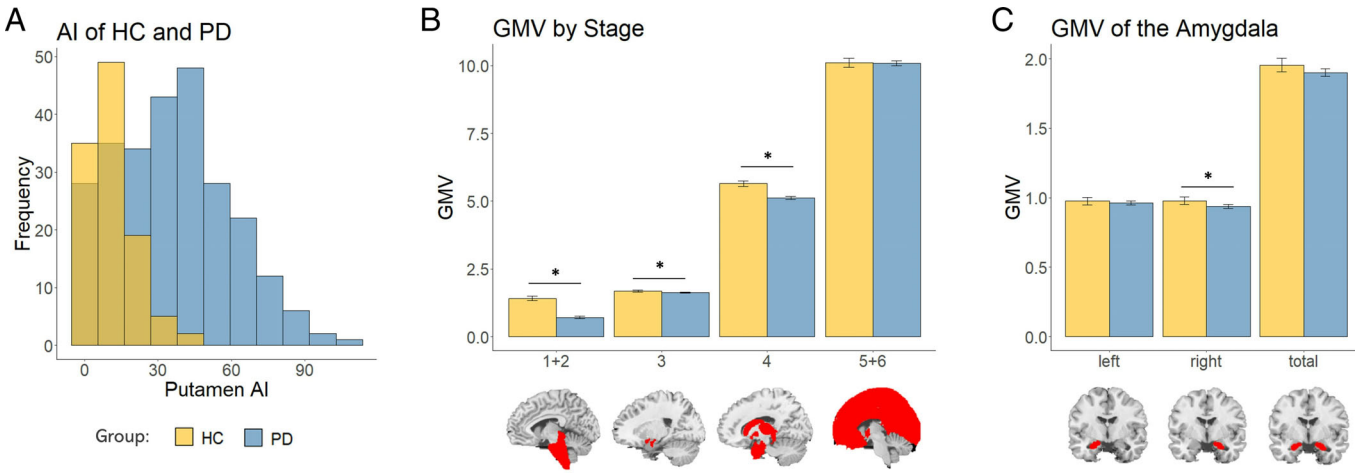

FIG. 2. Results of group comparison of HCs and PD patients. (**A**) Frequency distribution of the putamen AI, depicted as overlay of HC and PD patient data. (**B**) Comparison of the bilateral GMV between HCs and PD patients for Braak stages. Respective ROIs are illustrated. (**C**) Comparison of the amygdala GMV between HCs and PD patients. Amygdala ROIs are depicted. AI, asymmetry index; GMV, gray matter volume; HCs, healthy controls; PD, Parkinson's disease; ROI, region of interest. *$P < 0.05$, corrected. [Color figure can be viewed at wileyonlinelibrary.com]

patients, analysis of covariance (ANCOVA) was used, with age, sex, and TIV as covariates.

In the PD sample, correlations between the putamen AI and the degree of laterality of the MDS-UPDRS III score as well as the total RBDSQ score were examined using Spearman's rank correlations. Putamen SBRs of the left and right hemispheres of 4 PD patients were equal; thus, the MAH_{DaT} of these subjects could not be determined, and they were excluded from all further analyses. Differences between the left and right hemispheres regarding the MAH_{DaT} and LAH_{DaT} were assessed using the Pearson's χ^2 test. Differences between the left and right hemispheres and between the MAH_{GMV} and LAH_{GMV} were tested using a robust analysis of variance (ANOVA) and Wilcoxon rank-sum test. Differences in the GMV AI across stages were tested using the Kruskal–Wallis test.

The following analyses were computed for each Braak stage and for the amygdala: associations between the putamen AI and the MAH_{GMV}, LAH_{GMV}, and GMV AI were computed and adjusted for the covariates age, sex, MDS-UPDRS III score, and TIV using partial Spearman's rank correlations. The differences between the RBD− and RBD+ groups in MAH_{GMV}, LAH_{GMV}, and GMV AI were assessed using the Wilcoxon rank-sum test. The significance level was set to $P < 0.05$, with Bonferroni thresholds for multiple comparison corrections indicated where applicable. All statistical analyses were conducted in R (version 4.0.5).

Results

Group Comparison of HCs and PD Patients

Total putamen SBRs of PD patients ($Mdn = 0.78$) were significantly lower than those of HCs ($Mdn = 2.01$); $W = 28{,}054$; $P < 0.001$. The putamen AI of PD patients ($Mdn = 33.8$) was significantly higher than that of HCs ($Mdn = 8.68$), $W = 4771.5$, $P < 0.001$ (Fig. 2A). Significantly smaller GMV was found in PD patients for brain regions representing stages 1 + 2 ($F(1, 364) = 159.36$, $P < 0.001$); stage 3 ($F(1, 364) = 5.48$, $P = 0.02$); and stage 4 ($F(1, 364) = 54.81$, $P < 0.001$). No significant difference was found for brain regions representing stages 5 + 6, $F(1, 364) = 0.04$, $P = 0.846$ (Fig. 2B). No significant difference was observed in the left amygdala GMV ($F(1, 364) = 0.70$, $P = 0.403$); however, the right amygdala GMV was significantly smaller in PD patients ($F(1, 364) = 5.44$, $P = 0.02$). Bilateral amygdala GMV did not significantly differ between groups ($F(1, 364) = 2.72$, $P = 0.1$; Fig. 2C).

Asymmetry in PD Patients

Putamen AI of PD patients was significantly associated with the degree of laterality of the MDS-UPDRS III score, $r_s = 0.26$, $P < 0.001$, but did not significantly correlate with the total RBDSQ score, $r_s = 0.07$, $P = 0.268$.

There was a significantly smaller $GMV_{(z)}$ in the left hemisphere compared to the right hemisphere in stages 1 + 2 ($F(1, 506) = 29.16$, $P = 0.001$), which was independent of the MAH_{DaT}, $F(1, 506) = 0.07$, $P = 0.797$. There was no significant difference between the hemispheres in stage 3 ($F(1, 506) = 0.74$, $P = 0.39$), stage 4 ($F(1, 506) = 2.24$, $P = 0.136$), or stages 5 + 6 ($F(1, 506) = 0.19$, $P = 0.661$). Neither the left nor right hemisphere was more frequently determined as the MAT_{DaT}, $\chi^2(1) = 2.07$, $P = 0.15$. There was no significant difference between the MAH_{GMV} and LAH_{GMV} in any Braak stage, $F(3, 2032) = 0.58$, $P = 0.9$ (Fig. 3A).

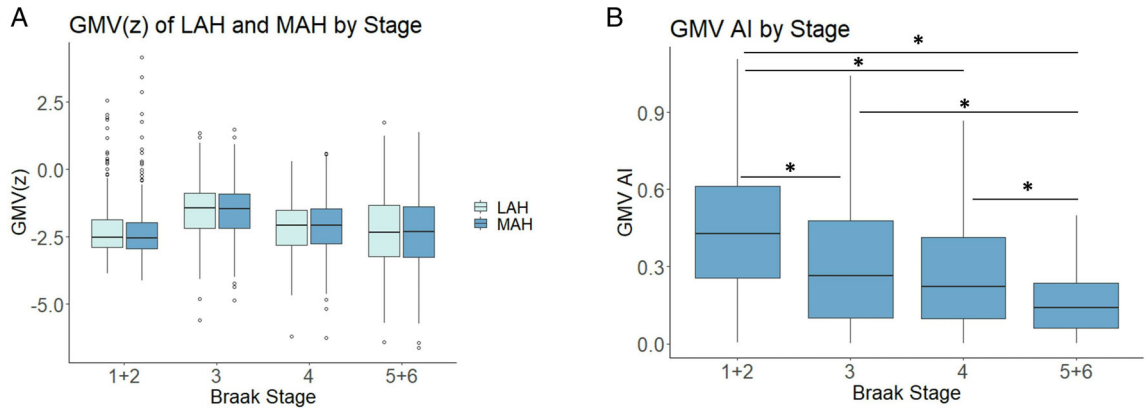

FIG. 3. Asymmetry in PD patients. (**A**) Comparison of MAH_{GMV} and LAH_{GMV} in each Braak stage in the PD sample. (**B**) GMV AI of each Braak stage in the PD sample. AI, asymmetry index; GMV, gray matter volume; HCs, healthy controls; LAH, less-affected hemisphere; MAH, more affected hemisphere; PD, Parkinson's disease. *$P < 0.05$, corrected. [Color figure can be viewed at wileyonlinelibrary.com]

There was also no significant difference between the amygdala MAH_{GMV} ($Mdn = -1.22$) and LAH_{GMV} ($Mdn = -1.21$), $W = 32{,}472$, $P = 0.981$.

GMV AI significantly differed across Braak stages, $H(3) = 158.46$, $P < 0.001$ (Fig. 3B). Comparisons of the mean ranks between stages showed that the GMV AI of stages 1 + 2 significantly differed from that of stage 3 (*difference* = 169.42), stage 4 (*difference* = 194.47), and stages 5 + 6 (*difference* = 326.38). GMV AI of stage 3 did not significantly differ from stage 4 (*difference* = 25.05) but did significantly differ from stages 5 + 6 (*difference* = 156.96). GMV AI of stage 4 significantly differed from stages 5 + 6 (*difference* = 131.91). The critical difference ($\alpha = 0.05$) was 68.83.

GMV of Brain-First and Body-First PD Patients

Increased putamen AI (putative brain-first subtype) was not significantly related to the MAH_{GMV}, LAH_{GMV}, or GMV AI in any Braak stage. Furthermore, after applying the Bonferroni-adjusted threshold of $P < 0.003$, no significant group differences were observed between RBD+ and RBD– in the MAH_{GMV}, LAH_{GMV}, or GMV AI in any Braak stage (detailed statistics are provided in Appendix S1).

Discussion

The aim of this study was to investigate PD-subtype (brain-first, body-first) dependent differences in GMV atrophy. Despite generally finding Braak-stage-dependent brain atrophy in PD, the indicators of the proposed brain-first PD subtype were not associated with more severe or asymmetric atrophy in regions supposedly affected early in this subtype.

Our results demonstrated significantly smaller bilateral GMV volumes in PD patients compared to HCs, denoting disease-related brain atrophy. Despite a plethora of studies, literature on GMV atrophy in early PD is divergent, and MRI studies do not demonstrate a consistent pattern. Discrepancies between studies may be explained, in part, by the great methodological heterogeneity. Studies are quite coherent in report progressive atrophy with increasing disease duration and severity[16,17] but more inconsistent regarding the timepoint when atrophy initially becomes overt. Some studies report no gray matter reduction in de novo PD,[18-20] but more recent studies, which utilized large-scale data sets, strongly imply atrophy in early disease stages.[21-23] In this regard, the brainstem, subcortical structures (especially the putamen) and some cortical regions seem to be the predominant sites of atrophy.[21,23-25] In the present study, we observed reduced GMVs in stages 1 + 2, 3 (including the amygdala), and 4, which is in accordance with not only the literature on PD-related brain atrophy but also the Braak staging scheme. In this staging scheme, the first clinical symptoms emerge in stage 3 and gradually become more pronounced,[15] and our sample included de novo patients who were diagnosed based on the presence of clinical motor symptoms. Therefore, the sparing of atrophy in stages 5 + 6 may reflect the relatively early disease stage of the included subjects.

Our most important finding was that probable brain-first and body-first patients did not present diverging atrophy patterns. The brain-first/body-first spreading hypothesis dichotomizes PD patients into groups of distinct pathology spread. However, regardless of whether a particular brain region was proposed to be affected earlier by the pathology in brain-first or in body-first PD, no difference in GMV was observed. This finding was further substantiated by the same level of GMV asymmetry in both subtypes. In sum, brain-first and body-first PD do not seem to be distinguishable by gray matter atrophy, a result that somewhat challenges fundamental assumptions of the brain-first/body-first

hypothesis. There is accumulating evidence in favor of the brain-first body-first hypothesis in terms of clinical symptoms, with studies reporting higher rates of autonomic dysfunctions (eg, gastrointestinal dysfunction, orthostatic hypotension) and stronger cognitive impairment in PD patients with RBD.[26,27] However, the literature on neuroimaging markers is far more diverse, and the number of studies that used MRI-derived measures is very limited.[28] So far, studies have mainly concentrated on pathological changes of the brainstem,[29-34] and to our knowledge the present study is the first to investigate pathological changes between brain-first and body-first PD across all relevant cerebral regions.

Further challenges of the brain-first/body-first hypothesis come from pathophysiology studies, which suggest α-SN deposition in multiple brain regions of RBD patients[35-37] and a higher α-SN load in the brain of PD patients who were α-SN positive in their stomach or vagus compared to those who were not.[38] Consistent with this, recent neuroimaging studies have linked the presence of RBD in PD patients to decreased volumes in multiple regions, including the striatum and amygdala.[39,40] These neuroimaging results match those observed in our study. Even though our results did not survive the multiple comparison correction, they indicated greater volume reduction in RBD+ patients in stages 3 and 4. In sum, our data and the existing literature suggest that PD patients with preexisting iRBD and early clinical motor symptoms already show significant atrophy of regions belonging to Braak stage 3 or more.

The brain-first/body-first hypothesis is largely based on the assumption that α-SN propagation depends on connection strength. Therefore, brain-first PD would be associated with a predominant ipsilateral spread in the side of pathology onset. Although this concept is very compelling, the spread of pathology may be far more complex. In fact, the exact mechanisms underlying the propagation are only partially understood.[41] For instance, considering the locus coeruleus, we would assume that structures more strongly connected to it demonstrate a higher probability to manifest pathology. However, the cerebellum and the medial reticular formation, some of its most prominent connections, do not demonstrate significant pathology in PD.[41,42] Thus, the spread of pathology does not seem to follow a simple connectivity rule, and other determinants must be considered. Consequently, α-SN spread, which is not solely based on the brain connectome, could be a potential explanation for the absence of greater GMV AI in brain-first PD. However, this would still not explain the general lack of greater atrophy of these regions in the brain-first subtype.

PD is not exclusively determined by α-SN pathology, and other mechanisms such as mitochondrial dysfunction and inflammation are at play.[43] Correspondingly, neurodegeneration may not be due to a single mechanism, but multiple factors contribute to the vulnerability of neurons. As we do not have a direct and exact measure of α-SN in the human brain yet, we have to rely on proxies such as the amount of GMV atrophy, which is not exclusive to α-SN pathology. If the amygdala indeed is the first region to show PD pathology in a proposed brain-first subtype, it would be rather surprising that we did not find more pronounced atrophy. However, the amygdala generally seems to be a highly vulnerable region for pathology in various neurodegenerative diseases,[44,45] and Alzheimer co-pathology seems particularly common in PD patients.[46-48] Therefore, co-pathologies that may also be present could cause neurodegeneration independent of α-SN, which in turn could have interfered with our analysis.

To determine the brain-first and body-first status of PD patients we did not solely rely on one characteristic but instead utilized two separate characteristics. The most straightforward approach to define brain-first and body-first status is to simply dichotomize patients based on their RBD status, and most of the available evidence stems from this approach.[27,30-32] However, this method is highly simplistic, as it does not sufficiently account for the proposed heterogeneity inside the subtypes and the trend of brain-first PD patients to convert to RBD+. Therefore, it has not been spared from criticism.[49] Both our subtype markers, the RBD status and the DaT asymmetry, revealed the same results. Furthermore, we did not find a correlation between these two markers. Because the hypothesis proposes body-first PD to be associated with RBD+ and lower DaT asymmetry, this finding again challenges the hypothesis.

To our surprise, we did not find a correlation between the asymmetry of putaminal DaT and the asymmetry of GMV. PD is considered as a largely asymmetric disorder, with unilateral dominant nigrostriatal dysfunction as one of its typical characteristics.[50] Imaging and neuropathological studies have strongly linked this nigrostriatal asymmetry to the asymmetry of motor symptoms,[51,52] which is further corroborated by our present findings. It is interesting to note that this does not necessarily account for the GMV atrophy as well. Our total PD sample demonstrated smaller GMV in the left hemisphere in stages 1 + 2, which was independent of the MAH_{DaT}. This finding accords with previous studies that found left-hemisphere-dominant atrophy, which was not influenced by the dominant side of motor symptoms.[53,54] It is tempting to speculate that the left hemisphere is particularly susceptible to atrophy, whereby gray matter changes in the left hemisphere may be more pronounced specifically in the early stages of the disease.[54-57] Although there is also contradictory evidence to this account, it seems that this vulnerability of the left hemisphere is also shared by other neurodegenerative disorders.[58,59]

Our research has a number of limitations to be considered. First, we used the RBDSQ score to determine

the RBD status of PD patients and not a proper diagnosis by polysomnography. We did apply more conservative cutoff values, but, nevertheless, we are aware that this approach might still have introduced a degree of uncertainty. If feasible, future studies should aim for polysomnography data to classify subjects into RBD– and RBD+. Importantly, the population investigated in such a study should be in the same stage of disease (in our case "clinical motor onset") for RBD status to be a classifier consistent with the brain-first/body-first hypothesis. Furthermore, we inferred our conclusions from cross-sectional data. Our data represent PD patients specifically in the early disease stage, and because the other stages were not measured, they remain largely speculative. Therefore, it would be of great interest to replicate these analyses with prodromal patients as well as patients in later disease stages. Finally, we note that α-SN pathology cannot be measured directly. Therefore, we used GMV atrophy as a proxy of neurodegeneration. In this regard, it is debatable whether the volumetric approach is the most sensitive method. Certainly, it is highly interesting to further elucidate this research question by utilizing other methods. In this regard methods such as the highly sensitive shape analysis, a functional approach, or diffusion MRI to investigate microstructural differences should be considered.[19,60-62] However, as long as no direct in vivo measure for α-SN is available, studies have to rely on such indirect markers to assess the effects of neuropathology.

Overall, the results of this study dissent the assumptions based on the brain-first/body-first spreading hypothesis. At the least, our findings indicate that the proposed earlier involvement of the central nervous system (in particular the amygdala) in probable brain-first PD is not reflected in a greater volume reduction. However, the hypothesis is very interesting for the investigation of the heterogeneity of PD and should be further investigated. ■

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Data Availability Statement

Any data supporting the findings of this study are available on reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

3 Discussion

3.1 Summary

It was over 200 years ago, that James Parkinson wrote “An Essay on the Shaking Palsy”, the first clear medical document describing PD. Since then, great research efforts have fostered significant advances in deciphering the pathophysiology of PD. However, despite this progress we are currently still lacking a holistic understanding of the disease in its entire complexity. Thus, to date the exact mechanisms of the interplay between disease pathology and clinical presentation of motor symptoms remain inadequately understood. Recently, the field of PD has experienced a change of paradigms: It has been proposed that PD motor symptoms might not be exclusively grounded in the motor system, but in the motivational system as well. At present, it remains uncertain to what extent the motivational brain is involved in the cardinal PD motor symptoms and further research is required. Fortunately, we have powerful technologies at hand that allow the investigation of this matter. As such, neuroimaging constitutes a key methodology to study pathological processes, as it enables direct, in vivo visualizations of the diseased brain. This thesis builds on these qualities and utilizes a multimodal neuroimaging approach in order to investigate the implication of the motivational brain in PD, including the investigation of disease related brain alterations and its associations with motor symptoms. The combined use of neuroimaging and behavioral data in this thesis enabled important insights into the intersection of pathology and symptomatology in PD. Outlined below are the main findings:

1. The systematic literature review revealed that pathological changes in the limbic system are prominent throughout the course of the disease. In this respect, the latest neuroimaging literature highlights the importance of disease-related changes in the limbic system and their contribution to affective, cognitive, as well as motor symptoms. Thus, this review provides support for the idea that limbic pathology may also contribute to motor dysfunctions in PD. Furthermore, the review illustrates that this topic has not been given sufficient attention and requires more in-depth investigations.
2. In light of the movement motivation hypothesis, Project 2 revealed that the reduction of effortful movements in PD could indeed depend on insufficient motivation. Accordingly, the performance in a monetary incentivized effort task indicated that patients with PD applied significantly less grip force than healthy controls, however only for low incentive levels. Furthermore, the association between dopaminergic degeneration and reduced motor effort was most pronounced in low incentive conditions suggesting that dopamine is particularly critical for motor effort, when the trade-off with the benefit is poor.
3. Project 3 does not provide evidence in favor of the brain-first body-first pathology spread hypothesis. The analyses revealed smaller GMV in patients with PD compared to healthy controls. However, despite the proposed earlier affectedness of the brain (particularly the amygdala) the brain-first subtype was not associated with a greater or more asymmetric

volume reduction compared to the body-first subtype. Thus, these results do not support the presence of a limbic-dominant subtype.

The following sections will integrate the results of Projects 1-3 into the current state of knowledge. In this context, it will be discussed if PD should be considered a motivational disorder. Additionally, potential prospects for disease management as well as limitations and future directions will be addressed.

3.2 Parkinson's Disease - A Motivational Disorder?

The question "Is PD actually a motivational disorder?" is not easily answered, as there are many factors which need to be considered. This includes the question whether PD motor symptoms are inherent to the motivational or motor system (section 3.2.1), the circumstance that PD motor symptoms are not only represented in terms of bradykinesia but are manyfold (section 3.2.2) and alternative explanatory models (section 3.2.3). Finally, the circumstance that the dopaminergic system is not the only system that is affected by the disease will be discussed (section 3.2.4).

3.2.1 Motivation System, Motor System, or Both?

Previous research as well as the classic Braak staging model suggest that PD pathology disseminates throughout the brain (Braak et al., 2003). Consistent with this, Project 1 has shown that PD-related pathological changes can be found in multiple limbic/motivational brain regions, even from the early disease stages on. To date, the majority of studies have investigated changes in motivational brain regions in the context of cognitive, affective, or autonomous dysfunctions, whereas studies investigating effects on motor symptoms are rare. However, Project 1 was able to identify studies which demonstrate that disease related changes in regions such as the amygdala, hippocampus, and cingulate cortex are indeed linked to the cardinal motor symptoms.

At present, our understanding of how these alterations in motivational brain regions, particularly those that lie outside of the striatum, are involved in the pathophysiology of PD motor symptoms remains limited. For instance, the amygdala is a structure located bilaterally in the medial temporal lobe with a well-established role in the encoding of affective and reinforcing properties of stimuli (Balleine & Killcross, 2006; Šimić et al., 2021) and shows atrophy in the early stages of PD (Project 1 and 3). Importantly, research findings have revealed an interplay between the amygdala and motor-related areas, and an increasing number of studies provide evidence for limbic regulation of motor output in PD (Grèzes et al., 2014; Mann et al., 2023; Rizzo et al., 2018; Yu et al., 2013). It is assumed that through a limbic-motor loop, temporal structures (including amygdala and hippocampus) are connected to the motor cortex via the ventral striatum, pallidum, and motor thalamus. In this way, limbic regions orchestrate the integration of affective input and

motor output and have thereby an important influence on complex motor behavior (Mann et al., 2023; Sagaspe et al., 2011). Thus, pathological changes outside of primary motor regions might be significantly involved in the cardinal motor symptoms of PD. Nevertheless, it remains to be investigated whether alterations in motivational brain regions are directly related to PD motor symptoms, or whether they result from general progressive degeneration occurring concurrently with other mechanisms that represent the true underlying cause of PD motor symptoms.

On the other hand, alterations of structures located inside the striatum have more frequently been in the focus of research endeavors aiming at understanding the pathophysiology of PD motor symptoms. The striatum is commonly segmented into function-based anatomical divisions: namely the ventral striatum and dorsal striatum. The ventral striatum, which entails the nucleus accumbens and the most ventral part of the caudate and putamen, is usually considered to be a part of the limbic system and is implicated in emotion, reward-processing, and motivation (Fieblinger, 2021; MacDonald & Monchi, 2011). Moreover, it constitutes a limbic-motor interface by transforming limbic input into motor output (Mann et al., 2023). PD-related alterations in the ventral striatum are associated with symptoms such as impulse control disorders and apathy, both representing an imbalance in the motivation domain (Theis et al., 2021). It is of particular importance to note that PD is characterized by a gradient of dopamine depletion, with an earlier and greater deficit occurring in the dorsal compared to the ventral striatum. Consequently, in early to moderate stages of the disease, dopamine depletion is primarily observed in the dorsal striatum (Gepshtein et al., 2014; Morrish et al., 1996). Thus, despite the role of the ventral striatum in the motivational domain, its rather late involvement makes it unlikely to be the sole cause of the motor symptoms, which mark the beginning of clinically manifest PD.

Contrary, the dorsal striatum comprises the bulk of the caudate and putamen and has primarily been associated with sensorimotor functions such as action execution and motor control. It is affected early on, and its degeneration is believed to cause the typical cardinal motor symptoms (Kish et al., 1988; Liu et al., 2020; MacDonald & Monchi, 2011). Traditionally, only the ventral striatum has been linked to motivation, however more recent studies have also demonstrated an important role of the dorsal striatum in motivational processes (Wang et al., 2013). Findings indicate that striatal dopamine is involved in decision-making during goal-directed behavior by modulating the willingness to exert effort in return for rewards. In this context, the dorsal striatum seems to be critical for the encoding of the expected cost-benefit association, which drives the motivation to perform movements, e.g., the response vigor (Balleine et al., 2007; Wang et al., 2013; for details refer to section 1.2.3).

Project 2 provides important evidence in favor of this hypothesis by showing that patients with PD are indeed capable of performing movements comparable to those of healthy controls. However, in order to do so, they need stimuli with a higher incentive salience. This may be explained by the fact that higher rewards have the capacity to outweigh the effort costs in the cost-benefit estimation of movements and thereby elicit the increased performance. In addition, previous

literature suggests that higher dopamine levels are associated with greater movement vigor (Beierholm et al., 2013; Niv et al., 2007). Interestingly, Project 2 also demonstrates this dopamine effect on movement vigor, however it is dependent on the reward level. Strongly dopamine-depleted individuals only exerted high effort for high reward options and appeared to have lost the motivation to exert high effort for low reward options. As the studied patients were in the early stages of the disease, their primary dopaminergic degeneration was located in the dorsal striatum rather than the ventral striatum, pointing towards a motivational computation in the dorsal striatum. In summary, these findings support the idea that motor performance in PD may be significantly influenced by the cost-benefit computation of movements, located in the dorsal part of the striatum.

3.2.2 Motor Symptoms – A Diverse Range

In regard to the pathogenesis of PD motor symptoms, and in particular in the context of motivational approaches, it becomes very evident that there is one significant focus of ongoing debate: the bradykinesia complex. In daily clinical practice, the presentation of "bradykinesia" is highly variable, which is presumably due to the lack of a clear definition. As previously stated in the introduction, the term bradykinesia is currently used interchangeably to describe a number of motor aspects, including reduced movement velocity, reduced amplitude, and even the absence of movement (Schilder et al., 2017). Importantly these bradykinesia aspects represent distinct motor domains with specific underlying biological mechanisms (Bologna et al., 2020). For instance, in healthy controls we can observe an almost linear relationship between movement velocity and amplitude, whereas in PD this close relationship may be lost (Espay et al., 2011; Hallett & Khoshbin, 1980). In line with this rationale, it would be more appropriate to disentangle these motor aspects and interpret them as separate movement parameters. For this reason, Bologna et al. (2023) recently attempted to redefine the term bradykinesia and introduced the term bradykinesia complex, which is also used by this thesis. Accordingly, the bradykinesia complex consists of bradykinesia (reduced velocity), hypokinesia (reduced amplitude), akinesia (inability to perform a movement), sequence effect (progressive reduction in amplitude and/or velocity), hesitations/halts (irregularities in movement timing), and oligokinesia (reduced automatic movements).

In light of these considerations, it is highly important that the specific bradykinesia motor aspect of interest is clearly defined. Furthermore, it is also important to extend the scope of investigation beyond the bradykinesia complex, given that PD is characterized by a range of motor impairments including muscle rigidity, tremor, postural instability, and numerous others (as outlined in section 1.1.2). In this regard, it is widely acknowledged that the different motor symptoms of PD do not necessarily share the same underlying biological substrate and may have distinct pathophysiological mechanisms (Magrinelli et al., 2016). As such, clinical and experimental evidence indicates that PD tremor progresses at its own rate, independently of the bradykinesia

complex and rigidity. Moreover, it cannot be attributed to dopaminergic denervation of the basal ganglia and is likely to depend on other neurotransmitter systems (Dirkx & Bologna, 2022).

Taking this information into account it would be an oversimplification to investigate PD motor symptoms without considering all the individual motor aspects that comprise them. In light of the literature which was discussed above as well as the results of Project 2, it is likely that hypokinesia of the bradykinesia complex can be explained, at least in part, by motivational aspects. However, this finding cannot simply be generalized to other PD-related motor dysfunctions. It becomes apparent that additional research is needed in order to gain a deeper understanding of the diverse pathological mechanisms that underly the distinct motor symptoms, and to investigate whether and how motivational aspects might contribute to them.

3.2.3 Bradykinesia Complex – Explanatory Approaches

Numerous studies have sought to understand and explain the pathogenesis of PD motor symptoms with a particular focus on the bradykinesia complex. While there is accumulating evidence for a motivational component, this represents just one of several explanatory approaches that have been put forward. In order to gain an adequate and comprehensive understanding it is essential to consider other approaches as well, as they may provide further insight. The following section will give a brief overview of these additional explanatory approaches.

Ultimately, all movements can be seen as the result of neural output to muscles, causing them to contract. In PD there are several stages and ways in which bradykinesia symptoms may occur at the level of motor output. Research has shown that both the preparation and execution phases of voluntary movement are affected, suggesting that bradykinesia symptoms may result either from problems in formulating the instructions to move (motor code generation), problems in executing these instructions (motor code execution), or a combination of both (Berardelli et al., 2001).

One explanation which has been put forward is the *speed-accuracy trade-off hypothesis*, which suggests that the bradykinesia complex can be broken down to the level of excessive movement variability. It proposes that patients are unable to program movements correctly, resulting in less accurate movements. Consequently, they have to use corrective mechanisms to compensate for likely errors. This way, patients trade speed for accuracy in a dysfunctional manner, slowing down their movements. Hence, it is suggested that the bradykinesia complex is a consequence of adaptative behavior to the increased movement variability (Fernandez et al., 2018; Sheridan & Flowers, 1990).

Related to this hypothesis is another idea, which proposes that the bradykinesia complex could actually result from proprioceptive deficits combined with poor sensorimotor integration, causing

less accurate movements. According to this hypothesis, it has been shown that patients with PD have reduced sensitivity for detecting changes in limb position and require significantly larger limb displacements in order to detect passive movement. These deficits have been shown to correlate with disease duration and severity, and may occur early in the disease course or even before the onset of motor symptoms. In addition, patients appear to be particularly impaired in motor tasks requiring the integration of proprioceptive and visual information (Fasano et al., 2022; Konczak et al., 2009).

Bradyphrenia, which refers to mental slowness, has also been proposed as a possible explanation for the bradykinesia complex. Bradyphrenia can be seen in many neurodegenerative diseases, including PD, and it is believed that the slowness of thought might interfere with the planning of movements, thereby increasing reaction times (Berardelli et al., 2001; Bologna et al., 2020). Interestingly, an fMRI study has shown that cognitive slowing is indeed associated with dysfunction in basal-ganglia-thalamo-cortical circuits that are implicated in motor processing thereby providing insights into the relationship between cognitive and motor slowing (Hanakawa et al., 2017).

Finally, a rather new concept has recently gained a lot of interest: Research including the study by Le Bouc et al. (2016) demonstrated that patients with PD not only show impairments in active movements but in relaxation as well. Accordingly, they revealed that patients with PD have a slower deceleration of movements as well as relaxation of muscle contractions. These findings imply that motor impairments in PD could actually represent an impairment in switching between movement states. Interestingly, this idea is also based on a cost-benefit calculation, as the transitioning between stable and dynamic motor states may be regarded as an additional effort cost that needs to be taken into account (Herz & Brown, 2023).

Taken together, there are several models that attempt to explain the underlying pathological process of the bradykinesia complex in PD. Currently, considerable research points to an erroneous motor program which may be attributed to an abnormal cost-benefit calculation of movement. Together with other components, such as deficient sensorimotor processing and cognitive slowing, this could give rise to the bradykinesia complex.

3.2.4 Beyond Dopamine

Given that PD is characterized by a pronounced degeneration of the dopaminergic system, research has primarily focused on brain regions situated along the dopaminergic pathways. This approach has led to significant advances in the understanding of pathological mechanisms associated with this particular neurotransmitter system. In addition, the good response of motor and certain non-motor symptoms to dopaminergic medication has reinforced the perspective that PD is primarily driven by dopamine deficiency. However, there is a growing interest in other

neurotransmitter systems and accumulating evidence suggests that PD cannot be considered a pure motor, dopamine depletion driven disease, but a multi-system disease which also involves non-dopaminergic systems (Miguelez et al., 2020; Muñoz et al., 2020).

Project 1 has identified several studies which report non-dopaminergic lesions, highlighting the involvement of different neurotransmitter systems in PD. As such, it has been reported that the cholinergic, serotonergic, glutamatergic, and noradrenergic system show marked changes as well. From a motivational perspective, the profound neuronal loss in the serotonergic and noradrenergic systems is of great interest, as they are involved in the generation of arousal, attention, motivation, and executive function (Dujardin & Sgambato, 2020; Madelung et al., 2022; Paredes-Rodriguez et al., 2020). Most intriguingly, dysfunction in these systems has been linked to the cardinal motor symptoms of PD (Espay et al., 2014; Goyal et al., 2023) and growing experimental evidence suggests that drugs targeting non-dopaminergic receptors have the potential to significantly improve motor complications (Cenci et al., 2022).

In light of the aforementioned evidence, it is important to consider that the brain is a highly integrated network that depends on a well-functioning orchestration of its individual parts. Consequently, while the dopaminergic system exhibits the most pronounced degeneration, other neurotransmitter systems should not be disregarded, as even minor imbalances can result in substantial consequences. It is therefore important to conduct further research to elucidate the role of non-dopaminergic systems and their potential influence on PD motor symptoms.

3.3 Disease Management and Potential Prospects

Currently, PD is still treated exclusively symptomatically and remains an incurable neurological condition, as efforts to modify or halt the progression of the disease have yet to be translated into clinical practice (Wolff et al., 2023). Over the past few decades, a plethora of neuroimaging studies, including those presented in this thesis, have collectively provided invaluable insights into the pathophysiology of PD. Importantly, the identification and characterization of disease-related neurobiological changes can facilitate the detection of new and more precise treatment targets as well as enable more effective monitoring and evaluation of treatment outcomes (Politis, 2014).

As long as no disease modifying therapies are available, a major goal is to increase the quality of life of patients by using symptomatic therapy. Pharmacological approaches have proven very efficacious, especially in the early stages. However, complementary interventions are recommended, as they can significantly improve the overall well-being of patients (Wolff et al., 2023; Zhang et al., 2017). As such, the use of external stimuli might represent a promising strategy. The introduction of additional external cues is employed in *cuing*, a strategy designed to mitigate gait impairment (Rubinstein et al., 2002). The underlying mechanism of cuing is based on the

observation that in contrast to internally generated movements, externally cued movements are less reliant on basal ganglia function. They are primarily attributed to lateral circuits that bypass the dysfunctional basal ganglia and therefore have the capacity to improve motor performance (Fasano et al., 2022; Nonnekes et al., 2019). This concept may also be applied to the bradykinesia complex: The insight that the underscaling of motor effort may stem from an aberrant cost-benefit computation implies that with higher rewards, movement limitations may be compensated to some degree. In this regard, external cues (e.g., in the form of additional reward salience) would likely not circumvent the basal ganglia but may facilitate a shift in the cost-benefit computation of movements towards the desired direction. It may therefore be hypothesized that a motivational signal could assist in the correct execution of motor behavior. Nevertheless, this concept requires further experimental confirmation.

Furthermore, it is important to consider that patients with PD exhibit significant inter-individual variability in both phenotype and progression rates (Wüllner et al., 2023). Consequently, it has been proposed that PD should be conceptualized as multiple sub-disorders, rather than a single unified entity (Farrow et al., 2022; Weiner, 2008). This great disease heterogeneity poses a significant challenge in clinical practice and has prompted various attempts to classify patients into categories. Different approaches have been proposed to stratify patients based on their age of onset (e.g., juvenile parkinsonism, young-onset PD, later-onset PD), predominant motor symptoms (e.g., tremor-dominant, postural instability and gait difficulty, akinetic-rigid), or non-motor symptoms (e.g., individuals with cognitive impairment or rapid eye movement sleep behavior disorder). Despite the efforts, no consensus has been reached regarding this issue (Obeso et al., 2017; Qian & Huang, 2019). In alignment with previous attempts, Project 3 yielded no evidence supporting the existence of discrete PD brain- or body-first subtypes. However, it is important to note that this does not imply that subtyping should be relinquished. In order to provide a more targeted therapeutic approach, it is necessary to break down the complexity of the disease into less heterogeneous subtypes, which then can be specifically targeted. Encouragingly, attempts are being made to use data-driven clustering methods to classify patients. By incorporating a wide range of factors, this appears to be a promising approach. Ultimately, subtyping may help increase treatment success for patients living with PD and thus offers a very encouraging prospect for the future (Qian & Huang, 2019).

3.4 Limitations and Future Directions

Despite the insightful findings of this thesis, some limitations must be considered when interpretating the results. Firstly, this thesis employed state-of-the-art neuroimaging techniques in order to identify disease-related pathological alterations in the brain. However, while MRI and DAT SPECT imaging provide highly valuable information, these methods are merely proxies of the underlying Lewy pathology (Bidesi et al., 2021). Consequently, the possibility that very subtle

brain changes could not be detected with the imaging modalities we currently have at hand needs to be considered. At the moment, there is no validated tracer for α-synuclein in PD available, which would represent a direct measure of PD pathology. The development of a α-synuclein tracer presents particularly challenging, as α-synuclein is deposited intracellularly which limits the accessibility as well as its low abundance relative to other misfolded proteins associated with neurodegeneration. Consequently, a successful α-synuclein tracer needs to express a high affinity and selectivity (Korat et al., 2021). The availability of a α-synuclein tracer in the future would allow a more precise and direct monitoring of the pathological process, as it would enable the direct assessment of the pathology itself, rather than a subsequent pathological process associated with α-synuclein presence. It is also likely that this method would not be subject to the flooring effect (i.e., in stages when all dopamine has been lost), which is observed in DAT SPECT imaging of late-stage patients, and thus allow disease tracking from the pre-clinical to the late disease stage.

In addition, this work examines specific regions of interest and their pathological alterations. However, given the highly integrated nature of the brain, past and present data indicate that PD may be the result of a network dysfunction, rather than the consequence of a deficiency in a single mechanism (Bologna et al., 2020). Although detailed knowledge of individual mechanisms is undoubtedly valuable, a more holistic approach is also warranted. As such, the integration of region-specific and whole-brain data, coupled with behavioral outcome measures, may facilitate a more comprehensive understanding of the pathophysiology of PD.

4 Conclusion

This cumulative thesis investigates the role of motivational brain regions in PD. Contrary to the traditional research focus which is set on the motor system, this body of work puts the spotlight on neurodegenerative processes in the motivation system and assessed the associated clinical presentations. Through three meticulously conducted research projects, it revealed an early involvement of motivational brain regions as well as a direct link between motivational processes and the cardinal PD motor symptoms. In particular, the combination of diverse neuroimaging techniques and behavioral methods contributed to a profound understanding of the motivational aspect underlying the disease.

This thesis highlights the currently underappreciated role of non-motor regions in PD and emphasizes the consideration of motivational brain regions when investigating PD pathophysiology. Thereby it sets an example for more integrated and holistic approaches, which will further enhance the disease understanding and ultimately foster potential for novel therapeutic improvements.

5 References

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6 Appendix

6.1 CV

The CV has been removed due to data protection reasons.

6.2 Eidesstattliche Erklärung

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertationsschrift selbstständig und ohne die Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Stellen - einschließlich Tabellen, Karten und Abbildungen -, die wörtlich oder sinngemäß aus veröffentlichten und nicht veröffentlichten anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, sind in jedem Einzelfall als Entlehnung kenntlich gemacht. Ich versichere an Eides statt, dass diese Dissertationsschrift noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie - abgesehen von unten angegebenen Teilpublikationen - noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss der Promotion nicht ohne Genehmigung der / des Vorsitzenden des IPHS-Promotionsausschusses vornehmen werde. Die Bestimmungen dieser Ordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Prof. Dr. Thilo van Eimeren betreut worden.

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Übersicht der Publikationen:

Banwinkler, M., Theis, H., Prange, S., & Eimeren, T. van. (2022). Imaging the limbic system in Parkinson's disease - a review of limbic pathology and clinical symptoms. *Brain Sciences*, *12*(9), Article 1248. https://doi.org/10.3390/BRAINSCI12091248

Banwinkler, M., Dzialas, V., Rigoux, L., Asendorf, A. L., Theis, H., Giehl, K., Tittgemeyer, M., Hoenig, M. C., & van Eimeren, T. (2024). Putaminal dopamine modulates movement motivation in Parkinson's disease. *Brain*, *147*(10), 3352–3357. https://doi.org/10.1093/BRAIN/AWAE214

Banwinkler, M., Dzialas, V., Hoenig, M. C., & van Eimeren, T. (2022). Gray matter volume loss in proposed brain-first and body-first Parkinson's disease subtypes. *Movement Disorders*, *37*(10), 2066–2074. https://doi.org/10.1002/MDS.29172

Ich versichere, dass ich alle Angaben wahrheitsgemäß nach bestem Wissen und Gewissen gemacht habe und verpflichte mich, jedmögliche, die obigen Angaben betreffenden Veränderungen, dem IPHS-Promotionsausschuss unverzüglich mitzuteilen.

26.05.2025 ..... Magdalena Banwinker .....

Datum Unterschrift