Dopaminergic Degeneration and Resilience: Network-Level Alterations in Early Parkinson's Disease

zur

Erlangung des Doktorgrades
philosophiae doctor (PhD) in Health Sciences
der Medizinischen Fakultät
der Universität zu Köln

vorgelegt von

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Abbreviations

AADC	aromatic L-amino acid decarboxylase
BG	basal ganglia
BOLD	blood-oxygenation-level dependent
DaT	dopamine transpoter
dATN	dorsal attention network
dFC	dynamic functional connectivity
DMN	default mode network
FC	functional connectivity
FPN	frontoparietal network
ICA	independent component analysis
iRBD	idiopathic rapid-eye movement (REM) sleep behavior disorder
LB	Lewy body
LIM	limbic network
MCI	mild cognitive impairment
MDS	Movement Disorder Society
MoCA	Montreal Cognitive Assessment
NAT	network attack tolerance
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PET	positron emission tomography
ROI	region of interest
rsfMRI	resting state functional magnetic resonance imaging
RSN	resting-state network
SMA	supplementary motor area
SMN	somatomotor network
SN /SNc	substantia nigra /substantia nigra pars compacta
SPECT	single photon emission computed tomography
UPDRS	Unified Parkinson's Disease Rating Scale
UPDRS-III	Unified Parkinson's Disease Rating Scale part three
vATN	salience/ventral attention network network
VIS	visual network
VTA	ventral tegmental area

Author's Note: Motivation and Scope

The ability to adapt to change is what makes us humans the currently most successful species on earth (depending of course on how success is defined). From surviving extreme climates to overcoming food scarcity, humans have persistently adjusted to a constantly changing world and inhabit the most diverse places on earth. Crucially this capacity for adaptation is fundamentally rooted within the human body itself and most prominently within the brain.

On an individual scale, the nervous system demonstrates an extraordinary ability to reorganize in response to profound physiological disruption. Recovery after spinal cord injury or the relearning of lost functions following stroke exemplify the brain's immense adaptive potential. In neurodegenerative diseases such as Parkinson's disease (PD), however, this adaptive capacity is challenged continuously. Progressive neurodegeneration constantly reshapes the brains architecture over time, and we suspect that the brains' ability to adapt to these changes plays a decisive role in the clinical expression of the disease. However, a major challenge in PD research is to distinguish brain changes that merely reflect neurodegeneration from beneficial adaptive responses that help maintain function in disregard of the degree of underlying pathology, commonly referred to as resilience. Identifying these resilience-related changes and associating these with individual biological or lifestyle traits could contribute tremendously to our ability to extend pre-clinical phases and identify individuals at elevated risk. Over the past four years, pursuing this distinction has become the guiding mission of my own research.

A critical challenge lies in how such adaptive changes can be assessed. Throughout my academic training, I have explored multiple levels at which neuroscientists investigate brain function: from single-cell recordings using patch clamp techniques, to multi-cellular measurements such as local field potentials, to circuit-level interventions in the context of deep brain stimulation. Each of these perspectives offers valuable insight into neural function at a specific scale. Yet they share a common limitation: none capture the brain as an integrated, global system. This realization ultimately led me to whole-brain resting-state fMRI approaches. Despte their inherent simplifications, they offer a unique perspective on large-scale brain function. In my opinion, regarding a phenomenon as poorly understood as resilience in PD, a perspective that may be highly valuable. Observing large-scale changes associated with PD may thereby represent a first step toward identifying the mechanisms that enable the brain to better cope with progressive neurodegeneration.

Abstract

Although dopamine loss is a central pathological hallmark of Parkinson's disease (PD), the neural mechanisms through which dopaminergic depletion alters large-scale brain function and translates into clinical symptoms remain incompletely understood. Further, individuals with comparable levels of dopamine loss often differ markedly in their clinical presentation. This heterogeneity has given rise to the concept of resilience, which describes mechanisms that mitigate the behavioural impact of neurodegeneration and may explain why some individuals remain relatively asymptomatic despite advanced disease-related changes. Understanding the neural mechanisms underlying resilience represents a key challenge in current PD research.

This dissertation adopts a network-level perspective to investigate how dopaminergic degeneration shapes whole-brain organization and assess how these changes relate to PD symptoms. Specifically, this work aimed to distinguish changes associated with degeneration of the system from changes that may foster resilience against the behavioural consequences of dopamine loss. In this regard, a multimodal imaging approach was chosen, including molecular imaging to quantify individual striatal dopaminergic integrity and advanced resting-state functional MRI to capture global properties of brain function.

Across three projects, this dissertation demonstrated that in early PD, dopaminergic loss and motor symptom severity are closely linked to alterations in connectivity at global and subnetwork levels. Specifically, dopamine depletion and motor symptom severity were associated with decreased network transition flexibility and impaired transitions between highly connected brain states. Disruption of flexible engagement and disengagement of network connections may therefore constitute a mechanism underlying motor impairment in PD. Further, with increasing pathological load the somatomotor network exhibited increased robustness to targeted network disruption, which was associated with better motor performance. Higher levels of lifelong physical activity strengthened the relationship between somatomotor network robustness and preserved motor function, suggesting that behavioural factors may contribute to adaptive resilience mechanisms.

Together, these findings indicate that the consequences of dopamine loss in PD involve complex alterations in the dynamic orchestration and architecture of large-scale functional brain networks that individually shape motor behaviour. By implicating one of these properties as a potential resilience mechanism and demonstrating its association with lifestyle factors, this work asserts a clinical relevance to large-scale network approaches. They thereby pose a valuable intermediate level scope between molecular pathology and clinical manifestation that may yield more specific targets for future therapeutic and lifestyle-based interventions in PD.

Zusammenfassung

Der Verlust dopaminerger Neurone gilt als ein zentrales pathologisches Merkmal der Parkinson-Erkrankung und ist eng mit der Parkinsonsymptomatik verknüpft. Dennoch ist bislang unzureichend geklärt auf welche Weise die dopaminerge Degeneration die globale Organisationsstruktur und Funktion des Gehirns verändert und wie sich diese Veränderungen in der klinischen Symptomatik manifestieren. Auffällig ist vor Allem, dass Patienten mit einem vergleichbaren Dopamindefizit, sich in der klinischen Symptomatik drastisch unterscheiden können. Diese Heterogenität hat zur Entwicklung des Resilienz Konzepts geführt. Resilienz umfasst neuronale Mechanismen, die die funktionellen Folgen neurodegenerativer Prozesse abfedern können und somit erklären können warum manche Individuen trotz fortgeschrittener krankheitsbedingter Veränderungen nur wenig ausgeprägte Symptomatiken aufweisen. Ein besseres Verständnis solcher Mechanismen gilt heute als eine der zentralen Herausforderungen der Parkinson- Forschung.

Vor diesem Hintergrund verfolgt diese Dissertation einen netzwerkbasierten Ansatz, um zu untersuchen, wie das Dopamindefizit bei Parkinson die Organisation und Funktion des gesamten Gehirns beeinflusst und wie diese Veränderungen mit den Symptomen der Erkrankung zusammenhängen. Ziel dieser Arbeit war es insbesondere, zwischen Veränderungen zu unterscheiden, die eine fortschreitende Schädigung des Systems widerspiegeln, und solchen, die potenziell zur Resilienz gegenüber den Folgen des Dopaminverlustes beitragen. Zu diesem Zweck wurde ein multimodaler Bildgebungsansatz gewählt, der molekulare Bildgebung zur Quantifizierung der individuellen striatalen dopaminergen Integrität mit funktioneller MRT Bildgebung zur Erfassung globaler Eigenschaften der Hirnfunktion kombiniert.

Die Ergebnisse aus drei Projekten zeigen, dass in frühen Krankheitsstadien der Parkinsonerkrankung das Dopamindefizit und die motorische Symptomschwere eng mit Veränderungen der funktionellen Konnektivität auf globaler und der netzwerkspezifischer Ebene verbunden sind. Insbesondere ging ein starkes Dopamindefizit und stärkere motorische Einschränkungen mit einer reduzierten Flexibilität zwischen verschiedenen Verknüpfungszuständen von Netzwerken, sowie mit einem verminderten Wechsel in stark vernetze Verknüpfungszustände einher. Eine eingeschränkte Fähigkeit des Gehirns stark vernetze Verknüpfungszustände zu rekrutieren, könnte somit einen zentralen Mechanismus motorischer Beeinträchtigungen bei Parkinsons darstellen. Darüber hinaus zeigte das somatomotorische Netzwerk mit zunehmender pathologischer Belastung eine erhöhte Widerstandsfähigkeit gegenüber gezielter, artifizieller Netzwerkstörungen, die mit einer besseren motorischen Leistungsfähigkeit assoziiert war. Dieser Zusammenhang war besonders ausgeprägt bei Personen mit höherer lebenslanger körperlicher Betätigung. Das weist darauf hin,

dass Verhaltensfaktoren aus unserem früheren Leben die Netzwerkeigenschaften dauerhaft beeinflussen und Resilienz Kapazität positiv unterstützen können.

Insgesamt verdeutlichen die Ergebnisse dieser Arbeit, dass die Folgen des Dopaminverlusts bei Parkinson komplexe Veränderungen in der dynamischen Organisation und Architektur großer funktioneller Hirnnetzwerke umfassen. Diese prägen die motorischen Einschränkungen der Betroffenen individuell und im Rahmen dieser Arbeit wurde eine dieser Veränderungen der Netzwerkeigenschaften (i.e. die gesteigerte Widerstandsfähigkeit gegen Netzwerkstörungen) sogar als potenzieller Resilienz fördernder Mechanismus eingeordnet. Seine zusätzliche Assoziation mit Lebensstilfaktoren unterstreicht die klinische Relevanz solcher Netzwerkanalysen. Sie stellen damit eine wertvolle intermediäre Ebene zwischen molekularer Pathologie und klinischer Manifestation dar, die spezifischere Ansatzpunkte für zukünftige therapeutische und lebensstilbasierte Interventionen bei Parkinson liefern kann.

Introduction

Parkinson's disease (PD) is defined by the progressive degeneration of dopamine producing neurons in the substantia nigra (SN) and the pathological accumulation of α-synuclein, which follows a stereotypical spatiotemporal trajectory throughout the brain. These two processes start unnoticed long before motor dysfunction becomes overt, and clinical PD is diagnosed. The transition to clinical PD is considered a tipping point, reached when compensatory mechanisms in the brain can no longer mitigate ongoing neurodegenerative changes. This tipping point rarely occurs before the age of 50 but shows a sharp increase in prevalence after the age of 60 (de Lau & Breteler, 2006). With more people reaching old age, the number of people living with PD continues to rise. Global prevalence has more than doubled between 1990 and 2016 (Ben-Shlomo et al., 2024; Ray Dorsey et al., 2018), underscoring the growing burden of PD not only for affected individuals but also for families, caregivers, healthcare systems, and society at large. Despite major advances in PD related research, spurred by developments in genotyping (Jia et al., 2022) and fluid/imaging biomarkers (Zarkali et al., 2024), the mechanisms by which neuropathology gives rise to PD symptoms remain incompletely understood. Further, a growing body of evidence suggests that mechanisms compensating pathological processes partially offset the functional consequences of pathology. Individuals with later disease onset often present with more pronounced dopamine loss at diagnosis, while patients with comparable levels of dopaminergic deficit can differ markedly in clinical severity (Bernheimer et al., 1973; Chung et al., 2019; Pagano et al., 2016). These observations indicate the presence of pronounced interindividual differences in the capacity to tolerate or compensate for dopamine loss before and after disease onset, which are summed under the umbrella term of resilience.

Historically, efforts to understand PD pathophysiology have primarily focused on the nigrostriatal dopaminergic system. This focus has yielded the introduction of levodopa therapy and has firmly established dopamine as a key modulator of basal ganglia (BG) circuitry and motor function. However, accumulating evidence indicates that PD pathology extends beyond the nigrostriatal pathway, affecting multiple dopaminergic loops as well as other neurotransmitter systems (Lim et al., 2009). These broader pathological changes highlight the need for models of brain function that move beyond individual regions or isolated dopaminergic loops towards a system level understanding of how the brain copes with rising pathology load. In this context, resting-state functional magnetic resonance imaging (rsfMRI) provides a methodological basis to extend the investigation of PD beyond individual neurotransmitter systems towards large-scale brain organization. While this approach inevitably simplifies biological complexity, it offers a powerful means to capture global alterations in functional brain architecture. How the alterations relate to disease expression and compensatory processes in PD is currently only vaguely understood.

Thereby, this dissertation aimed to characterize dopamine-driven alterations in large-scale brain function and organization and assess how they relate to PD symptoms using a network-based approach. Finally, it was designed to determine whether these alterations reflect global degradation, maladaptive compensatory, or even adaptive resilience-related processes that mitigate the behavioral consequences of dopaminergic pathology.

As a first step toward addressing these questions, the opening chapter of this dissertation provides an overview of the core motor and non-motor symptoms of PD, followed by a summary of current concepts of PD pathology, with a particular focus on dopamine. The second chapter outlines how molecular imaging techniques enable the in vivo assessment of the dopaminergic system and how they contribute to our understanding of PD. Next, the third chapter introduces resting-state fMRI methodology and its contribution to PD research and outlines two advanced rsfMRI approaches applied in this dissertation along with their inherent advantages. Finally, chapter four introduces the concept of resilience and discusses its relevance for understanding individual differences in symptom manifestation in PD.

1.) Hallmarks of Parkinson's Disease and the Associated Heterogeneity of Clinical Symptoms

1.1) The Many Faces of Parkinson's Disease: Clinical Manifestations and Their Variability

The clinical diagnosis of PD is currently based exclusively on the presence of clinical symptoms. According to the Movement Disorder Society (MDS), a diagnosis of PD requires the presence of bradykinesia (slowness of movement), in combination with either rest tremor or muscle rigidity (Postuma et al., 2015). Despite these core features, other motor impairments such as gait disturbances, postural instability, freezing of gait, impaired balance, dystonia, speech or swallowing difficulties, and action tremor can also be present. The fact that the manifestation and severity of each of these motor features vary greatly across individuals, makes the quantitative assessment of overall disease severity in PD inherently difficult. To address this, severity and progression of motor symptoms are most assessed using the Unified Parkinson's Disease Rating Scale part three (UPDRS-III) (Goetz et al., 2008). It includes items assessing speech, facial expression, tremor at rest, action and postural tremor, rigidity, finger taps, hand movements, rapid alternating movements, leg agility, arising from a chair, gait, posture, postural stability, and body bradykinesia on a scale from zero (not present) to four (severely expressed). The total test score is aimed to represent overall severity of motor symptoms and can be categorized into mild (<=32) moderate (33 to 58) and severe (>=59) motor symptoms (Martínez-Martín et al., 2015).

Beyond the motor deficits quantified in UPDRS-III, PD also involves impairments in several non-motor domains, adding to the complexity of the disease phenotype. These non-motor symptoms are captured in UPDRS Parts I and II and include sleep disturbances, chronic pain and autonomic dysfunction (Fanciulli et al., 2025). Notably, although non-motor symptoms may occur at any disease stage, some can precede the clinical manifestation of PD by decades (Chaudhuri et al., 2006). These features thereby act as markers for the early, preclinical (prodromal) stage of PD and their identification enables timely characterization and monitorization of premorbid pathological processes. To guide this effort, the MDS has proposed research criteria for prodromal PD, according to which polysomnography confirmed idiopathic rapid-eye movement sleep behavior disorder (iRBD) represents the strongest predictive value for future development of PD, followed by abnormal dopamine imaging and hyposmia (Heinzel et al., 2019). Among non-motor symptoms, cognitive impairment is one of the most disabling; progressing form subjective cognitive decline to mild cognitive impairment (MCI) and ultimately to PD dementia (PDD) (Aarsland et al., 2021a). In PD, the Montreal Cognitive Assessment (MoCA), the Mattis Dementia Rating Scale-2, and the Parkinson's Disease-Cognitive Rating are considered most suitable for assessing global cognition (Skorvanek et al., 2018). Although cross sectionally roughly 30% of patients have PDD (Svenningsson et al., 2012) and 26% of the non-demented patients meet criteria for MCI (Aarsland et al., 2010), long-term studies estimate that in 70% up to 80% of patients PDD will occur on the long term (Gallagher et al., 2024). Even though the risk of developing PDD increases with age at onset and pathological burden, some individuals progress to dementia early, whereas others remain cognitively stable for decades (Aarsland et al., 2007; Braak et al., 2005). Why some patients appear resistant to cognitive decline, remains poorly understood. While known risk factors include APOE4 carriership, (Tan et al., 2021), iRBD (Gagnon et al., 2009) and hyposmia (Chahine et al., 2016), modifiable risk factors, such as education, smoking, and physical activity, have been linked to dementia risk in the general population (Livingston et al., 2020). Nevertheless, their specific relevance to PD remains to be fully elucidated.

Taken together, the clinical presentation of PD is highly heterogeneous, encompassing a wide range of motor and non-motor symptoms that contribute significantly to patient burden and disease progression. The variability in symptom type, onset, and severity across individuals, substantially add to the complexity of PD symptoms. Importantly, while some patients show a fast decline across motor and non-motor domains after onset of the disease, others appear only mildly affected for a long period (Hähnel et al., 2024). This implies that some individuals express traits that aid in counterbalancing the effects of neurodegenerative progresses. To grasp these traits, understanding how neurodegeneration spreads and how specific neurotransmitter systems contribute to different symptom profiles remains a central goal in PD research. Among these

systems, the dopaminergic system has received the most attention and is currently the best understood.

1.2) Pathophysiology of Parkinson's Disease: From Lewy Bodies to Dopamine

There are two characteristic hallmarks of PD that together serve a definite diagnosis of PD: (1) the presence of Lewy bodies (LBs) in the brain and (2) the degeneration of dopaminergic neurons in the SN pars compacta (SNc). LBs are cytoplasmic aggregations of misfolded, insoluble α-synuclein, a protein believed to play a role in vesicle dynamics, mitochondrial function, and intracellular trafficking (Poewe et al., 2017). This aggregation of α-synuclein is suggested to be induced by the presence of misfolded α-synuclein in adjacent or connected cells: Rodent experiments showed transmission of pathological α-synuclein between cells (Luk et al., 2012; Peelaerts et al., 2015) and postmortem studies found LB pathology in previously healthy neuronal grafts transplanted into patients with PD (Kordower et al., 2008; J. Y. Li et al., 2008). Together these findings suggest that LB pathology originates from a specific "seed" and spreads within the brain, following a pattern dictated by neuronal architecture. Two decades ago, Heiko and Eva Braak proposed a six-stage model describing this spreading pattern of LB pathology, initially emerging in the olfactory bulb and dorsal motor nucleus of the vagus nerve and ultimately progressing through the brainstem and limbic regions to the neocortex (Braak et al., 2002, 2003). In preclinical stages of PD, when LB pathology is mostly restricted to Braak stages one and two (primarily affecting pons and medulla), neurodegeneration is observed in only one specific part of the brain: the SNc (Dijkstra et al., 2014; Milber et al., 2012), which together with the ventral tegmental area (VTA) hosts the majority of dopamine-producing cells in the brain (Dahlström & Fuxe, 1964). Hence, although in later stages of PD LB pathology correlates with neuronal loss, the dopaminergic system seems to be hit most severely and earliest by PD pathology. While the distribution of α-synuclein pathology alone is suggested to insufficiently explain the clinical symptoms of PD (Burke et al., 2008; Jellinger, 2012), the integrity of the dopaminergic system has repeatedly been associated with clinical symptom severity in PD.

Experimental work in the 1980s and early 1990s on basal ganglia (BG) function provided early evidence for a mechanistic link between dopamine signaling and motor function, positing dopamine as a key modulator of BG circuitry and its output (Wichmann et al., 2011). The BG play a central role in facilitating movement by integrating widespread cortical input and relaying filtered feedback via thalamocortical loops (Poewe et al., 2017). The absence of dopaminergic input into the striatum, the input structure of the BG, has been strongly associated with the motor phenotypes of PD (McGregor & Nelson, 2019) and therapeutically, restoring dopamine levels within this circuit through dopamine replacement therapy (e.g., levodopa), or manipulating BG output via surgical interventions like deep brain stimulation, has been remarkably effective in alleviating these phenotypes (Deuschl et al., 2013). Cumulatively, these findings suggest a tight

link between dopamine loss and motor symptoms of PD, with BG circuitry representing the best understood system regarding pathological implications and therapeutical approaches we currently have. However, the broader effects of diminished dopaminergic input onto the BG loops on whole brain function remain poorly understood. Further, in addition to the nigrostriatal pathway interlinking the BG and the SN, dopaminergic neurons in the VTA and medial SN give rise to mesolimbic and mesocortical loops that are suspected to mediate mood, working memory, reward related learning and motivation (Halliday et al., 2014; Speranza et al., 2021). From Braak stage 3 onward LB pathology co-locates with the dopamine populations in medial SN and the VTA (Braak et al., 2003), supposedly similarly affecting mesolimbic and mesocortical loops (Aarsland et al., 2021b; Halliday et al., 2014). Through these pathways, dopamine loss may contribute to several non-motor symptoms of PD. For instance, cognitive functions are suggested to depend on mesocortical input from the VTA and medial SN, striatofrontal loops supporting executive control, and broader dopaminergic networks (Cools, 2006, 2011; Halliday et al., 2014; Owen, 2004). Although the precise mechanisms remain incompletely understood, converging evidence indicates that disturbances across these circuits can contribute to the cognitive impairments observed in PD (Aarsland et al., 2021b). In this regard, in vivo assessment of dopaminergic degeneration is crucial for understanding how dopamine loss across distributed pathways affects behaviour. While circuit models have provided critical theoretical and mechanistic insights, in vivo assessment via molecular imaging have been essential for their validation and extension.

2) Molecular Imaging, Dopamine and Parkinson's Disease

The development of neuroimaging tools in the late 20th century marked a turning point in neurology and neurobiological research. Ever since, molecular neuroimaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT) have substantially added to our understanding of PD and our ability to detect and monitor the disease. Notably, a wide range of imaging modalities are available to assess the dopaminergic system and its degeneration in PD (For recent review see Theis et al., 2024). Still, PET and SPECT represent the two most established methods for assessing dopaminergic dysfunction in PD and offer accurate in vivo evaluation of the presynaptic dopaminergic system (Suwijn et al., 2015). While the clinical diagnosis of PD remains symptom-based (Postuma et al., 2015), PET and particularly SPECT imaging are regularly used in a clinical routine to enhance diagnostic certainty, especially in cases with subtle or atypical presentations (Catafau et al., 2004; Thobois et al., 2019; Tolosa et al., 2007). Both are radiotracer-based methods that detect the radioactive decay of a tracer. While SPECT tracers emit gamma rays directly, PET tracers emit positrons, which subsequently annihilate with electrons, producing detectable gamma photons. These tracers are

part of radiopharmaceuticals that are designed to selectively bind to specific biological targets, thereby enabling the visualization of physiological processes like glucose metabolism, neurotransmitter dynamics, or receptor availability. In PD diagnostics, several tracers are available to assess the integrity of the dopaminergic system. The clinically most widely used SPECT tracer in PD diagnostics is [^{123}I]FP-CIT, which binds to presynaptic dopamine transporters (DaTs) in the striatum and serves as an indirect marker of nigrostriatal terminal integrity. Emerging PET tracers such as [^{18}F]FE-PE2I that also target DaTs offer improved spatial resolution and quantification potential compared to traditional SPECT tracers (Theis et al., 2024). An alternative to targeting DaTs is [^{18}F]DOPA (fluorodopa), a radioactively labeled analogue of levodopa, the precursor of dopamine. Once taken up, fluorodopa is metabolized by aromatic L-amino acid decarboxylase (AADC) in regions with a high density of presynaptic DaTs. The resulting amount of metabolized fluorodopa is used as an indirect measure of AADC activity and dopamine turnover (Sarikaya, 2015). Finally, the availability of vesicular monoamine transporters type two, responsible for packing dopamine (and other monoamines) into vesicles, labeled by [^{11}C]DTBZ can also inform about presynaptic nerve terminal density in the striatum (Stoessl et al., 2014). All imaging techniques described above are summarized in Figure 1, which maps their respective biological targets onto the dopaminergic synapse.

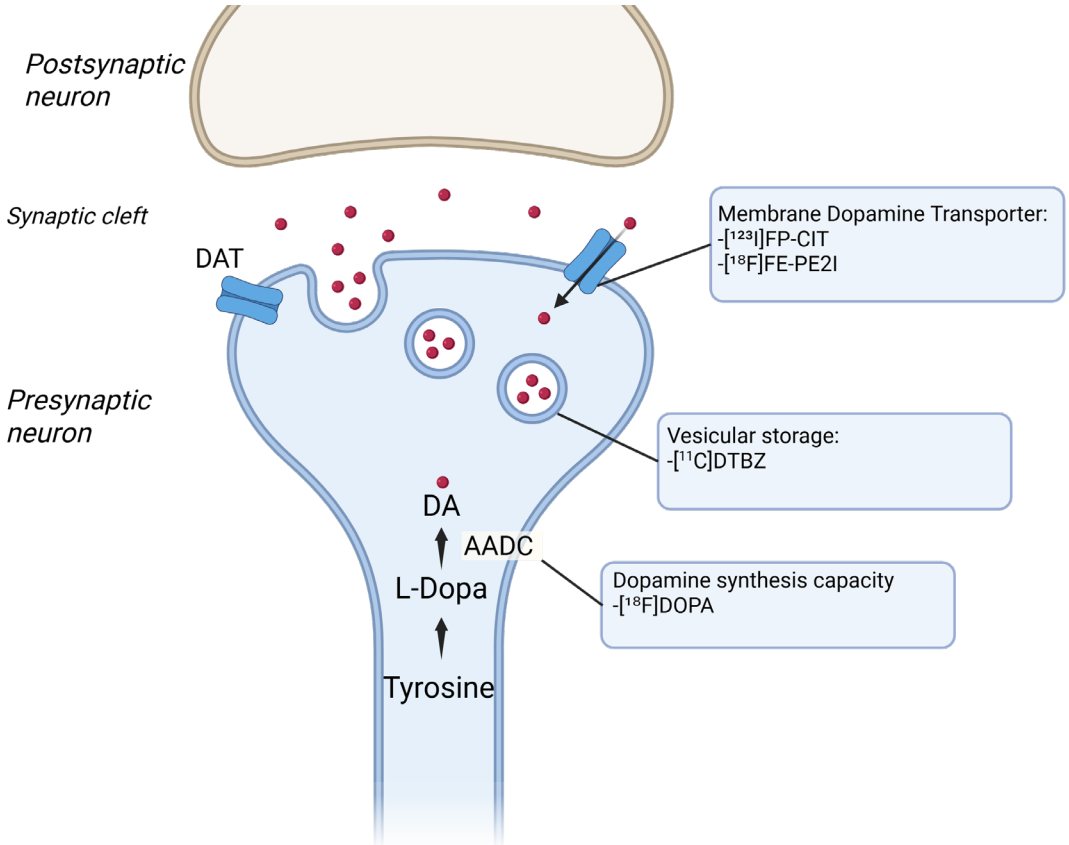

Figure 1: Schematic illustration of presynaptic processes within the dopaminergic synapse and the corresponding PET and SPECT imaging methods that measure them. DA = dopamine, AADC = aromatic L-amino acid decarboxylase, L-Dopa = Levodopa, DAT = dopamine terminal. This illustration was created using Biorender.

Collectively, these tools form the current backbone of dopamine imaging in PD and remain indispensable until novel tracers, such as those targeting alpha-synuclein, have been refined to match to their target and reach broader clinical applicability. Due to the structural complexity, conformational heterogeneity, and overall low abundance of pathological alpha-synuclein in vivo, the development of effective PET imaging agents targeting alpha-synuclein remains one of the key challenges in PD research (Capotosti, 2025; Korat et al., 2021). Very recent first-in-human studies show region-specific uptake of novel alpha-synuclein tracers in patients with multiple system atrophy and PD, that in these very few first patients align with early Braak stages (AD/PD, 2025; Capotosti, 2025). While these findings represent a breakthrough, several technical issues like high off-target binding persist and require further tracer optimization and validation. Therefore, for now, the in vivo assessment of PD pathology, apart from MRI-based evaluation of brain abnormalities and atrophy measures, still primarily relies on imaging of the dopaminergic system.

Beyond their clinical utility, molecular imaging techniques have significantly advanced our understanding of dopamine's involvement in emergence of symptoms in PD. Across PET and SPECT studies, a consistent spatial gradient of dopaminergic loss is observed across the striatum, typically following a posterior-to-anterior gradient: posterior putamen > anterior putamen > caudate nucleus (Kaasinen & Vahlberg, 2017). Early studies demonstrated that reduced striatal DaT binding correlates with motor symptoms such as bradykinesia, rigidity, and axial impairment (Benamer et al., 2000; Pirker, 2003; Seibyl et al., 1995), but not tremor severity, suggesting that tremor may involve non-dopaminergic mechanisms (Benamer et al., 2000; Pirker, 2003). A recent study using advanced statistical approaches even grands repetitive DaT SPECT imaging as valuable biomarker to monitor disease progression in PD (Dzialas et al., 2025). In addition to these findings, depleted dopamine levels were found in iRBD (Arnaldi et al., 2021) and hyposmia (Jennings et al., 2017) patients that have not been diagnosed with PD yet, suggesting DaT as potential preclinical progression marker as well. Notably, DaT reductions have also been linked to several non-motor symptoms. Lower striatal DaT binding has been associated with apathy (Santangelo et al., 2015), increased anxiety (Erro et al., 2012), sleep disturbances (Moccia et al., 2016), hyposmia (Roos et al., 2019; Yoo et al., 2021). Cognitive functions have likewise been linked to dopaminergic signaling. In particular, dopamine loss in the caudate nucleus correlates with executive dysfunction and other cognitive impairments in PD (S. J. G. Lewis et al., 2003; Rinne et al., 2000, Dzialas et al., 2026 under review).

Despite the well-documented association between dopaminergic degeneration and a wide range of PD symptoms, our mechanistic understanding of how these local neurochemical deficits influence global brain function remains incomplete. Importantly, higher order functions, including executive function or motivation, that are impaired in PD, rely on a dynamically coordinated communication across large-scale neural systems. Disruptions of this communication driven by

dopamine deficits are thought to contribute to the emergence of complex motor and non-motor symptoms. Accordingly, understanding how such symptoms arise requires approaches capable of capturing changes in brain-wide communication as pathology accumulates. The concept of functional connectivity (FC) enables a quantification of these system-level interactions. When derived from rsfMRI it is particularly well suited, to assess intrinsic network organization independent of task performance and captures brain-wide architecture as a whole. In this regard combining the quantification of local dopaminergic integrity with assessments of global functional network organization and detailed clinical phenotyping represents a powerful approach to characterize dopaminergic dysfunction and its associated system-level consequences. Such approaches are crucial not only for improving early diagnosis but also for elucidating how dopamine loss underpins both the emergence of, and adaptive compensation against, motor and cognitive deficits in PD.

3) Resting-state fMRI Methods and Their Value to PD Research

Historically, great endeavors in neuroscience have been dedicated to attribute particular neurocognitive functions to discrete regions in the brain. Initiated by lesion-symptom mapping, grounded in observations from Pierre Broca in the late 19th century (Broca, 1861), these endeavors have been accelerated by the advent of functional neuroimaging. Since then, techniques based upon the concept of FC have critically evolved to highly complex and computationally demanding models intended to capture the complexity of brain organization, temporal dynamics, and individual variability. By design, such approaches are well-suited to assess cumulative system-level changes that extend beyond individual neurotransmitter circuits, making them particularly relevant for the study of PD. However, the integration of advanced imaging approaches into PD research is still evolving, and their full potential to characterize disease-related network adaptations remains to be explored. This chapter aims to provide a foundational overview of fMRI concepts, summarize key insights derived from functional neuroimaging, and highlight the potential of advanced functional imaging techniques to further elucidate disease mechanisms in PD.

3.1) Resting-state fMRI – A Tool to Understand PD Mechanisms?

fMRI represents a tool to assess neural activation via the so-called blood-oxygenation-level dependent (BOLD) signal, which shows a rather complex relationship to oxygen metabolism, neurovascular factors and functional brain activity (Gauthier & Fan, 2019). Technically, BOLD signal is based on the different magnetic properties of hemoglobin. While its oxygenated form is diamagnetic, the loss of oxygen causes the deoxygenated form of hemoglobin (deoxyhemoglobin)

to show paramagnetic properties. Hence, the presence of deoxyhemoglobin in venous blood and tissue disturbs the local magnetic field and thereby reduces the T2*-weighted BOLD signal (Ogawa et al., 1990). In presence of a task, brain regions become active, leading to consumption of oxygen and an immediate increase in deoxyhemoglobin levels. Within a few seconds, this is followed by a directed increase in blood flow and blood volume towards the active brain region, that ultimately leads to a local over oxygenation (P. T. Fox & Raichle, 1986; Raichle, 1998). Due to over oxygenation the relative deoxyhemoglobin concentration decreases, causing a local increase in BOLD signal. Hence, BOLD signal does not correspond to increased energetic needs by measuring oxygen consumption, but rather to an overoxidation caused by an increase in cerebral blood flow (Attwell & Iadecola, 2002). It thereby represents an indirect measure of neural activation and opens the door to endless opportunities to assess the brain's function in the presence of a task (i.e. task-based fMRI). For instance, brain activity derived from the occipital cortex entails high spatial specificity enabling receptive field models to identify which specific image from large set of natural images was shown to a participant during scanning (Kay et al., 2008).

While tasks-based fMRI had already been in existence for several years, initial observations by Biswal and colleagues demonstrated that, even in the absence of an explicit task, spontaneous low frequency (<0.1 Hz) fluctuations of the BOLD signal within the motor cortex were temporally correlated with those in other motor-related regions (Biswal et al., 1995). As similar results accumulated across other brain systems, the idea persisted that the brain's activity at rest is not random, but instead reflects a fundamental, and functional organization (Buckner et al., 2013). This gave rise the concept of rsfMRI and FC, which refers to the temporal correlation of low-frequency BOLD signal fluctuations between spatially distinct, but functionally related brain regions. According to the concept, two brain regions are functionally connected (i.e. engaged in the same task) if they show very similar oscillatory patterns of BOLD signal (correlation), or the exact opposite pattern (anticorrelation) (M. D. Fox et al., 2005). Importantly, while FC has been shown to be associated to the brain's anatomical wiring, it is not reducible to it (Buckner et al., 2013), which suggests that FC captures dynamic and flexible aspects of brain communication that transcend static anatomical routes. This concept of FC has given rise to a wide range of analytical methods to assess the brain's functional organization at rest, spanning from simple correlation-based approaches to highly complex, dynamic network models. For clarity, in this work I will differentiate between conventional and advanced analytical approaches. Conventional methods involve seed-based FC analyses or hierarchical clustering, which examine whether one (seed) or several a-priori selected regions of interest (ROIs) are functionally connected with the rest of the brain or with other ROIs. In contrast, advanced network-based techniques, such as independent component analysis, graph theory, or dynamic functional connectivity, aim to capture more complex interactions between brain regions than high and low connectivity values, hence mere

correlation, and are in many cases tightly coupled to a mechanistic paradigm of brain function. Some of these are illustrated in Figure 2 (For overview in PD see: Prodoehl et al., 2014).

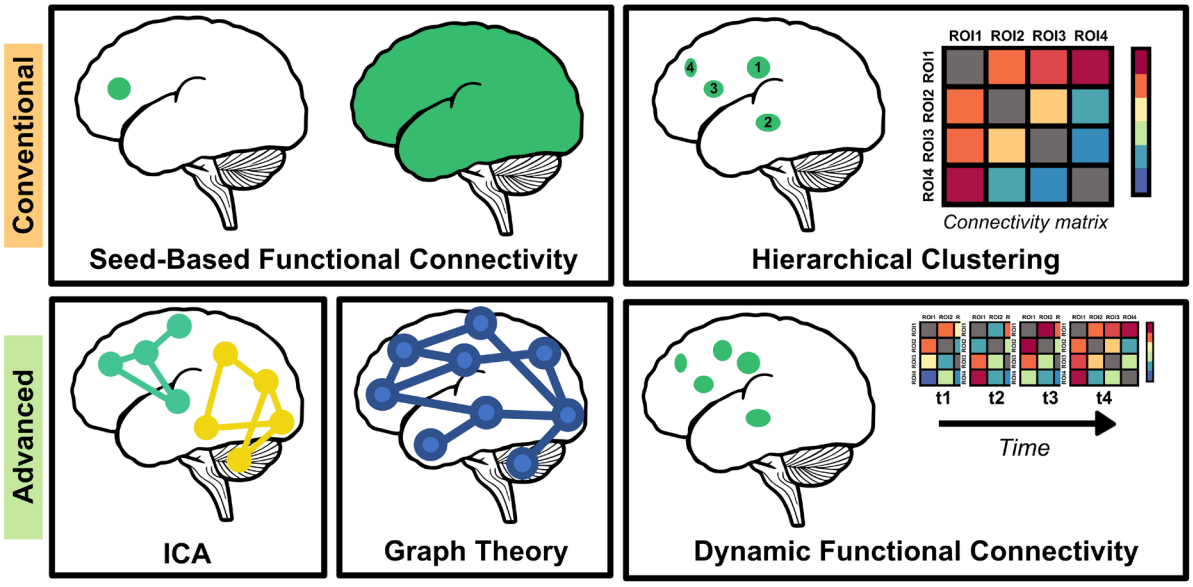

Figure 2: Illustration of conventional and advanced rsfMRI analysis techniques. Top left: Seed-based functional connectivity compares the variation in BOLD signal of a group of voxels or region of interest (ROI) (left) with the rest of the brain (right). Top right: Regional analyses estimate static ROI-to-ROI correlation matrix (connectivity matrix) of clustered ROIs to assess the hierarchical organization of nested modules. Bottom left: Independent Component Analysis (ICA) decomposes the data into spatially independent networks with associated time courses, separating neural signal from noise (data driven network definition). Bottom middle: Graph theory assesses regions as nodes and their temporal covariance in rsfMRI signal as edges to quantify complex network topology (e.g., degree, efficiency, modularity). Bottom right: Dynamic functional connectivity estimates time-varying connectivity (e.g., sliding windows) to identify recurring connectivity states and their transitions over time.

The FC topographies that emerge in the absence of task demands can be summarized into individual functional largescale networks that are termed resting-state networks (RSNs). Each RSN recapitulates an individual system whose particular functional domain (motor, attentional, or default-mode) has largely been derived from task-based fMRI observations (Smith et al., 2009). Over the years, several atlases have been proposed that summarize these RSN into predefined sets of ROIs (Doucet et al., 2019; Schaefer et al., 2018; Seitzman et al., 2020; Shirer et al., 2012; Thomas Yeo et al., 2011). These atlases vary substantially in categorization, spatial distribution and parcellation (Doucet et al., 2019), resulting in distinct methodological advantages and limitations depending on the specific application. Accordingly, driven by methodological considerations, different atlases were employed across the individual projects of this dissertation. For clarity and conceptual consistency, RSNs are introduced here according to the famous atlas by Yeo et al., as all parcellations used throughout this dissertation can be condensed into its major seven-network parcellation consisting of (Yeo et al., 2011): The visual network (VIS) involved in visual processing

(Damoiseaux et al., 2006); the dorsal attention network (dATN), responsible for goal directed attention control (Yeo et al., 2011); the default mode network (DMN), involved in self-reference and spontaneous cognition (Greicius et al., 2003; Raichle, 2015); the salience/ventral attention network network (vATN), associated with consciousness and filtering relevant (salient) from irrelevant information and in initiating appropriate behavioral responses (attention control) (Menon & Uddin, 2010; Sassenberg et al., 2023); the somatomotor network (SMN), involving motor execution and planning and somatosensory integration (Biswal et al., 1995), the frontoparietal network (FPN), responsible for top-down, goal-directed executive and cognitive control (Seitzman et al., 2019), and finally the limbic network (LIM). The spatial topography of these RSNs according to Yeo et al. 2011 can be observed in Figure 3.

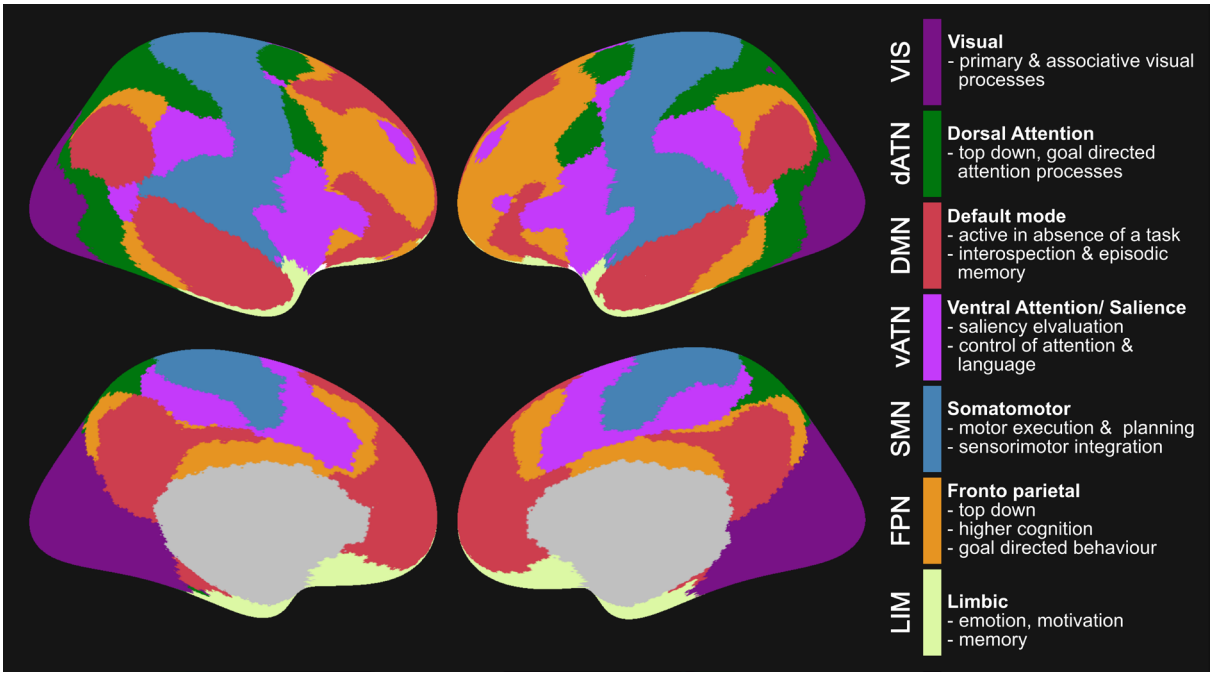

Figure 3: Surface projections of the seven major resting-state networks (RSNs), including the visual network (VIS, purple), the default mode network (DMN, red), the ventral attention network (vATN, pink), the somatomotor network (SMN, blue), the limbic network (LIM, pale lime), the frontoparietal network (FPN, orange) and the dorsal attention network (dATN, green). The surface renderings were projected on an inflated brain (no gyri and sulci) using Freesurfer. Left and right hemispheres are shown on the corresponding sides; upper panel depicts lateral views; lower panel depicts medial views. The ROIs were adopted from Yeo et al. (2011).

As mentioned above many alternative RSN categorizations can be condensed into these core networks. For example, left and right executive control networks show substantial overlap with the FPN, whereas auditory, language, or cingulo-opercular networks largely correspond to salience network/vATN parcellation. Moreover, although not included in the Yeo atlas, the contribution of cerebellar (Buckner et al., 2011) and deep cerebral nuclei, like the striatum (Choi et al., 2012) or the thalamus (Zhang et al., 2008) to RSN architecture, have likewise been characterized. The inclusion and functional assignment of these structures, however, is an aspect

that requires careful consideration depending on the research question. Nevertheless, RSNs have been shown to be highly reproducible across different datasets, participants, scanning protocols, sites, and scanners (Biswal et al., 2010). Therefore, they represent a valuable tool to assess reorganization of the brain's functional architecture in the phase of aging or the presence of neurologic or psychiatric conditions (For recent review see: Snyder, 2022). Each of these networks has been shown to undergo functional reorganization in aging (Du et al., 2023; Jockwitz & Caspers, 2021) or neurodegenerative diseases, including PD, (Baggio et al., 2015; Hohenfeld et al., 2018) highlighting their relevance for understanding both normative and pathological brain function.

In contrast to task-related fMRI, rsfMRI is comparatively independent on task performance and compliance, and thereby more suitable to investigate in clinical populations, such as PD (Tahmasian et al., 2017). Despite the growing application of rsfMRI in disease research, literature concerning PD remains relatively underrepresented compared to that on Alzheimer's disease (Snyder, 2022). So far, in PD seed-based approaches dominate, with the highest number of studies focusing on striatal seed regions (Tahmasian et al., 2015). These studies show that in PD, FC of the striatum with structures, like the cortex, thalamus and midbrain are altered, with findings ranging from increased to decreased connectivity levels (Hacker et al., 2012; Helmich et al., 2010, 2015). Importantly, decreasing connectivity of the striatum and brainstem parallel the deterioration of dopaminergic input onto the striatum (posterior putamen > anterior putamen > caudate) (Hacker et al., 2012). Further, striatal seed connectivity has been associated with motor function (Hacker et al., 2012; Oldehinkel et al., 2022). While a huge body of studies report these alterations to be modulated or even ameliorated by administration of levodopa therapy (Agosta et al., 2014; Gao & Wu, 2016; Kwak et al., 2010; Oldehinkel et al., 2022; Simioni et al., 2017; J. Zhong et al., 2019), studies that associate these changes with a direct assessment of dopamine availability via molecular imaging are comparatively few (Ruppert et al., 2020; Steidel et al., 2022). Nevertheless, together these findings underscore that FC changes are connected to both, the dopaminergic deficit and motor symptom severity, in PD. Similarly, cognitive function in PD patients has been linked to FC changes as well: Compared to cognitively intact PD patients, patients with MCI were shown to exhibit decreased connectivity within the DMN, the FPN and the dATN and decreased coupling between them (Amboni et al., 2015; Baggio et al., 2015). Crucially, FC alterations in the DMN have been suggested to be normalized by dopamine medication in non demented PD patients (J. Zhong et al., 2019), a phenomenon that could similarly affect cognitively impaired patient's FC.

Yet, these findings highlight a fundamental issue in the field: historically, findings have been dominated by seed-based approaches, yielding heterogeneous and region-specific patterns of FC alterations that prevent simple unifying models. Former efforts attempted to synthesize these

patchwork-like observations into single global phenomena (Filippi, Sarasso, et al., 2019; Tahmasian et al., 2017). Filippi et al. proposed that motor symptoms in PD are linked to reduced fronto-striatal-midbrain connectivity, accompanied by increased cerebellar, visual and parietal connectivit while cognitive symptoms are associated with decreased DMN and executive network connectivity (Filippi, Sarasso, et al., 2019). Tahmasian et al emphasized the parietal cortex to play a highly important role in pathophysiology in PD (Tahmasian et al., 2017). Although informative, these models inevitably inherit limitations of seed-based analyses: As these conventional rsfMRI seed-based methods restrict observations to predefined pairings of individually selected pairs of ROIs, predominantly seeded in the striatum (Tahmasian et al., 2015), they underrepresent systems beyond the nigrostriatal circuit. However, and as outlined above, neurodegeneration certainly outgrows the extent of the nigrostriatal system and further affects systems not directly linked to striatal structures. To correct for this historical focus on local striatum-centered FC, we need to shift towards whole-brain, data-driven network-based approaches. Especially the potential of advanced network approaches, that are in many cases coupled to a more mechanistic understanding, has not been investigated to its full capacity.

3.2) Advanced Network-Based Approaches Used in this Dissertation.

In order to further advance more mechanistically rooted methods and to move beyond static, ROI-to-ROI conventional connectivity analyses, this dissertation leveraged two advanced analytic frameworks designed to capture the complexity of brain network dysfunction in PD in a more holistic manner. The first approach applied dynamic functional connectivity (dFC) to characterize the temporal variance of large-scale network connectivity and their relationship to dopaminergic loss. The second approach leveraged graph theoretical models to quantify the resilience of functional networks against progressive degeneration. Both methods addressed different properties entailed in FC metrics that have rarely been assessed in PD. In addition to ROI-to-ROI FC studies, these may offer a system-wide and mechanistically grounded perspective on how PD alters the brain's functional organization. In this chapter, these techniques are conceptually introduced. Full methodological details, critical evaluation, and literature context are presented in the corresponding manuscripts.

3.2.1) Dynamic Functional Connectivity – The Brain is Not Static

As it was shown to be modulated by the presence of a task (Shirer et al., 2012), and recent experience (C. M. Lewis et al., 2009), the functional coupling between networks is constantly changing in the scale of seconds and minutes, irrespective of consciousness or cognitive state (Chang & Glover, 2010; Hutchison et al., 2013). Rather than providing a single time-averaged estimate of inter-network associations, the dFC approach aims to capture and quantify these temporal fluctuations in network interactions. To this end, covariance matrices are estimated that describe how each ROI is functionally connected to all other ROIs. Crucially, these matrices are

computed within short, time windows across the entire acquisition. By repeatedly shifting this window (sliding window) and re-estimating connectivity, a time-resolved series of connectivity matrices is obtained, depicting how functional interactions between ROIs evolved over time for each participant. Clustering algorithms applied to the pooled sets of matrices allow the identification of recurring connectivity patterns across participants and time. Once these patterns are defined, it becomes possible to determine which connectivity states an individual occupied (dwelled in) during the scan, how long each state was maintained, and how frequently transitions between states occurred. dFC can thus be characterized using metrics such as state occurrence, average dwell time, and transition rates, providing a richer description of large-scale network function than static functional connectivity alone (Iraji et al., 2021). An illustrative example comes from a study in chess players. In this study, experts exhibited greater "dynamic fluidity" (for instance higher transition rates) than beginners (Premi et al., 2020), reflecting how complex domains, like skill acquisition are reflected in FC dynamics across time. As mentioned above, dopamine is known to modulate cortico-striatal connections in PD. Yet, whether dopaminergic deficits merely affect average FC strength or also its temporal variability is currently under investigation. In this regard, current endeavors, obtained in small samples, showed contradicting results (Cordes et al., 2018; Díez-Cirarda et al., 2018; Fiorenzato et al., 2019; J. Kim et al., 2017), emphasizing the need for validation across bigger samples. Importantly, direct associations of dFC metrics with the integrity of the dopaminergic system lack completely in the current literature. This thesis aims to clarify how dopaminergic loss relates to FC dynamics, and to assess whether dFC metrics in turn are linked to the severity of cognitive and motor symptoms in PD.

3.2.2) Graph Theory – Assessing the Functional Architecture of the Brain

Advances in neuroimaging techniques such as diffusion MRI, fMRI, and electroencephalography have enabled increasingly detailed mapping of the brain's structural and functional organization (Rubinov & Sporns, 2010). To cope with the increase in size and complexity of these datasets, researchers have turned to the rather old mathematical principles of graph theory that enable the characterization of the brain as a complex network using a huge variety of metrics. Notably, the origins of graph theory trace back to 1736 and Leonhard Euler's solution to the Königsberg bridge problem, which asked whether one could pass all seven bridges of the city and return to the initial starting point without crossing any bridge more than once. By simplifying landmasses as nodes and bridges as edges, Euler demonstrated that the problem at hand was not a geometrical, but a topological problem and that such a route was impossible to take; a verdict now recognized as the first formal analysis of a complex network (Bullmore & Sporns, 2009). When put in graph-theoretical terms, the brain can be similarly modelled as a set of nodes (e.g., brain regions) connected by edges (e.g., structural or functional connections), that define the relation of each node to each other node. Although way more complex than bridge topology in Königsberg, similar

quantitative metrics can be derived from a graph theoretical network based on brain mapping data. These capture key aspects of network topology (Rubinov & Sporns, 2010), such as:

Degree: The number of edges connected to a node, measure of integration

Clustering coefficient: Captures how many of a node's neighboring regions are connected to one another, indicating local segregation

Path length: The shortest number of steps involved to connect any two nodes, reflecting integration

Efficiency: The inverse of the shortest path length, quantifying how many steps need to be taken from any node to any other node in the network, reflecting integration

Modularity: Quantifies the extent to which a network is organized into distinct subnetworks or communities, measure of global segregation.

Using these metrics graph theoretical analyses already revealed fundamental principles of brain organization. They revealed that the brain's network is neither completely regular, where every region is highly locally clustered (segregated), nor entirely random, where connections are spread wide throughout the network. Instead, it follows the principles of *small-world* organization, representing a "sweet spot" between order and randomness that combines high local clustering with short path lengths between regions (Watts & Strogatz, 1998). While partly termed random, this *small world* phenomenon is suggested to be achieved by strategically placed long-range connections that connect regionally tightly interconnected clusters, also known as hub regions, allowing cost-efficient and effective information flow across the whole network (van den Heuvel & Sporns, 2013). Interestingly, specifically these hubs seem to be affected in disorders of the brain (Crossley et al., 2014), making it a suitable surrogate to assess how brain pathology affects the brains architecture. In the context of PD, graph theoretical approaches can elucidate how dopaminergic degeneration reshapes large-scale network organization and how these alterations relate to clinical symptoms. Previous graph theoretical studies suggest that large-scale network topology is altered in PD. Reduced nodal degree in motor-associated regions has been reported and shown to be modulated by levodopa administration (Göttlich et al., 2013; Wu, Wang, et al., 2009). In addition, decreases in clustering coefficient and local efficiency have been associated with motor and cognitive impairments in PD (Luo et al., 2015). Recent advances use graph theory to assess the resilience of network structure against pathology. Importantly, in healthy aging and in PD they show this resilience to be linked with graph theoretical measures (Cascone et al., 2021; Habeck et al., 2024). This resilience can be assessed using the approach of Network Attack Tolerance (NAT), which assesses a network's robustness to simulated node or edge removal. By probing how networks cope with the loss of critical hubs, NAT provides insights into mechanisms that may preserve motor function despite progressive pathology. This thesis leverages graph theory, and NAT in particular, to investigate how dopamine depletion alters brain network architecture and to explore what factors may moderate network resilience in PD.

Importantly, combining advanced rsfMRI-based approaches that characterize distinct properties of functional brain organization and function with molecular imaging measures of dopaminergic integrity provides a powerful framework to assess how the brain responds to changes in dopamine availability. While dFC and NAT alone provide a broader description of PD-related network dysfunction, their integration into a multimodal framework extends their interpretability. Together, these modalities allow a distinction between dopamine-associated network alterations that are linked to deterioration or relative preservation of clinical function. With this distinctive capability, our approach enters the conceptual territory of resilience research. As such the brain-level changes identified might account for variance in clinical outcomes that cannot be explained by dopamine loss alone and might thereby represent a resilience mechanism. To fully introduce the of the concept of resilience in the context of PD, the final chapter of this dissertation is dedicated to address its theoretical origins and the substantial gaps that remain.

4) Beyond Dopamine Loss: Understanding Clinical Heterogeneity Through Resilience

The fact that clinical motor symptoms typically emerge only after approximately 70-80% of striatal DaTs have already been lost (Bernheimer et al., 1973), suggests that until the clinical onset of the disease, mechanisms are at work that sustain the functionality of the motor system, although it constantly degrades. The often more rapid clinical progression observed after symptom onset in these cases supports the notion of a tipping point, at which previously effective mechanisms can no longer counterbalance ongoing degeneration (Chung et al., 2019). Such mechanisms that emerge in response to pathology can be referred to as compensational. However, as compensatory changes may represent universal reactions to pathology that can remain neutral or even become maladaptive over time, the term compensation does not imply that these processes are stable, efficient, or beneficial across individuals or disease stages.

The interindividual variability in disease expression further suggests that compensatory capacity against dopamine loss is not uniform across PD patients. Individuals with later disease onset frequently present with more severe dopaminergic deficits at diagnosis, indicating that only some individuals can prolong the preclinical phase of the disease (Pagano et al., 2016). Moreover, even after disease onset, motor symptom severity varies markedly between individuals with comparable levels of dopaminergic impairment (Bernheimer et al., 1973; Chung et al., 2019). This suggests that only some individuals harbor innate mechanisms that offset motor impairment relative to dopaminergic loss, thereby contributing to heterogeneity in disease trajectories across patients with PD (Kaasinen & van Eimeren, 2025). Such mechanisms are conceptualized as

resilience processes and are thought to reflect traits acquired long before clinical onset, which subsequently buffer the functional impact of neurodegeneration and are able to explain the deviations in symptom expression across PD patients. Hence, compensation and resilience describe related but distinct phenomena. Whereas compensation refers to neural responses that emerge within an individual as a consequence of ongoing pathology, resilience explains why different individuals exhibit divergent clinical outcomes despite comparable levels of neuropathology. In this sense, resilience encompasses mechanisms that mitigate the impact of neurodegeneration in an individualized manner.

While the concept of resilience is well established in Alzheimer's disease, supported by comprehensive theoretical and empirical frameworks (Arenaza-Urquijo & Vemuri, 2018; Hoenig et al., 2017a, 2017b, 2019), it remains less well characterized in PD. Conceptual frameworks developed in Alzheimer's disease distinguish between resistance, that entails processes that prevent neuropathological process to take place (such as tau or amyloid clearing mechanisms in Alzheimer's disease) (Arenaza-Urquijo & Vemuri, 2018), while resilience refers to mechanisms in the brain that mitigate the effect of pathological processes on the brain (Stern et al., 2020). These definitions have recently been adopted in PD: In PD, resilience primarily comprises cognitive reserve and motor reserve, describing active processes that help preserve cognitive and motor function despite neurodegenerative burden (Hoenig, Dzialas, Drzezga, et al., 2023).

Although motor and cognitive reserve share conceptual overlap, the mechanisms through which they manifest at the brain level are suggested to differ and remain insufficiently defined. Within the cognitive reserve framework, three methodological approaches have traditionally been used to identify reserve mechanisms: cross-sectional moderation analyses, longitudinal moderation designs, and residual modelling (Zeller et al., 2024). Among these, particularly residual modelling has been used in the context of motor reserve to isolate resilience effects in PD (Hoenig et al., 2023). In this context, residual modelling quantifies the mismatch between expected symptom severity based on dopaminergic loss and symptoms actually observed, such that positive residuals indicate better-than-expected clinical outcomes and are interpreted as markers of resilience.

Still, despite growing interest, reliable and standardized ways to quantify motor and cognitive reserve in PD remain limited. Many studies interpret altered network properties, such as increased activation, plasticity, or flexibility with increasing dopaminergic deficit or symptom severity, as compensational (Johansson et al., 2024; Passaretti et al., 2024; Shine et al., 2019). However, whether these alterations further reflect resilience mechanisms or instead represent collateral or even maladaptive processes remains unresolved. Residual-based approaches have attempted to address this issue by explicitly modeling symptom severity relative to pathology and have identified structural (Dzialas et al., 2024; Y. J. Kim et al., 2022) and functional (Chung, Kim,

et al., 2020) networks associated with higher motor reserve. Nonetheless, these approaches are constrained by linear modelling assumptions in regard non-linear disease progression (Kaasinen & van Eimeren, 2025), and reliance on UPDRS-III scores, which are subjective and particularly prone to misclassification in patients with mild symptoms (Goetz et al., 2008). Despite these limitations, residual modelling has successfully identified changes to the brain that predicted disease progression in large cohorts, underscoring its high potential in identifying resilience mechanisms in PD (Dzialas et al., 2024).

Data-driven approaches may constitute a promising complementary strategy. The advanced functional connectivity analyses introduced above (i.e. dFC and NAT) have been suggested to conceptually relate to reserve mechanisms and have primarily been explored in the context of cognitive reserve (Cascone et al., 2021; Habeck et al., 2024; Premi et al., 2020). In contrast, comparable data-driven approaches in the motor domain remain underrepresented.

Finally, interindividual differences in resilience capacity are thought to arise from a combination of environmental and genetic factors. Apart from genetic factors, and by definition, resilience reflects traits that are largely acquired prior to disease onset, implying that the ability to actively facilitate resilience mechanisms in PD depends on factors that shape this capacity throughout prior life stages. While the identification of neural network features associated with reserve provides valuable mechanistic insight, a sole focus on brain-level correlates risks narrowing the perspective to descriptive or explanatory accounts. To advance prevention and intervention strategies, it is therefore essential to identify the environmental contributors that give rise to resilience in the first place. In this context, modifiable lifestyle factors, particularly physical activity and educational attainment, have emerged as key candidates and are increasingly investigated in the context of resilience research (Blume et al., 2017; Callow & Smith, 2023; Hoenig, Dzialas, Banwinkler, et al., 2023; Hu et al., 2024; Lin et al., 2018; Olsson et al., 2020; Shih et al., 2019; Sunwoo et al., 2016; Wilson et al., 2019). In cognitive reserve research, such lifestyle and experiential factors have long been employed as proxies to capture interindividual differences in reserve capacity (Buchman et al., 2019; Groot et al., 2018). Within PD, education has consistently been associated with cognitive reserve, with higher educational attainment linked to preserved cognitive functioning and reduced risk of dementia despite ongoing neurodegeneration (Gu & Xu, 2022; Hindle et al., 2014, 2016). In parallel, physical activity has been proposed as a key contributor to motor reserve, supported by evidence from both interventional and observational studies demonstrating that intense exercise programs as well as higher lifetime or habitual physical activity attenuate motor decline and are associated with enhanced dopaminergic function (de Laat et al., 2024; Hu et al., 2024; Sacheli et al., 2018; Schenkman et al., 2018; van der Kolk et al., 2019). Taken together, these findings suggest that education and physical activity may not merely index disease severity or lifestyle differences after diagnosis, but instead reflect long-

standing exposures that shape the brain's capacity to cope with neurodegenerative burden. However, while these factors have been linked to clinical outcomes and dopaminergic markers, it remains unclear whether they contribute to greater resilience at the level of large-scale brain network organization, such as enhanced attack tolerance. Hence, although several approaches are suggested to quantify resilience, their explanatory power still remains limited and lacks a coherent mechanistic framework capable of defining cognitive and motor reserve processes in PD. Thereby key open questions remain, that will be listed in the following Aims and Objectives section.

Aims and Objectives of this Dissertation

Although it is well established that dopamine loss underlies many motor and non-motor symptoms of PD, the precise neural mechanisms through which dopamine depletion alters brain function and gives rise to these symptoms remain poorly understood. Moreover, the specific neural mechanisms that may ameliorate the behavioural impact of dopamine loss remain unknown. In this regard the focus of this work is attributed to unravel mechanistic dopamine-driven changes in network function and determine whether they reflect a global deterioration of the system, or in fact could be attributed to resilience related processes. Identifying these mechanisms and achieving a mechanistic understanding of symptom emergence in PD, is a prerequisite for identifying new targets for disease-modifying interventions. Moreover, clarifying how lifestyle factors interact with and maybe foster these mechanisms could open new avenues for prevention strategies and non-pharmacological interventions.

Previous attempts to address these gaps in PD have largely relied on seed-based FC analyses, that describe increases or decreases in FC between predefined brain regions. As these approaches provide only a fragmented view of brain organization, they cannot be easily translated into mechanistic models of network dysfunction. To overcome these limitations, this dissertation applied two advanced FC metrics - dFC and NAT - that are conceptually designed to characterize how the brain is organized and operates rather than identifying regions that merely coactivate. Using mechanistically meaningful, systems-level network metrics, this dissertation took a network-based perspective to explore how brain organization and function change in the presence of dopaminergic degeneration in PD. The projects were specifically aimed to (1) advance the mechanistic understanding of how dopamine depletion gives rise to PD symptoms, (2) to identify neural and lifestyle-related mechanisms that may foster resilience against the behavioral consequences of dopamine loss and (3) characterize the temporal emergence and modulation of

these mechanisms across preclinical and clinical disease stages. In this regard three interconnected multimodal imaging approaches with distinct purposes were designed:

Project 1: Was designed to identify PD-specific alterations in network flexibility and pattern recurrence associated with both dopaminergic loss and cognitive and motor function to understand how dynamic aspects of brain function may be affected by dopamine loss and how these are implicated in the emergence of PD symptoms.

Project 2: Investigated whether NAT, a graph-theoretical measure of network architecture robustness, reflects interindividual differences in dopaminergic pathology, motor and cognitive performance in PD. Furthermore, this project explored whether lifestyle factors, such as physical activity or education, modulate network robustness and thereby potentially contribute to resilience-related mechanisms.

Project 3: Validated the role of NAT across disease stages, by comparing individuals before and after the onset of overt motor symptoms. This project aimed to determine whether NAT constitutes an inherent property of a healthy, resilient brain, or whether it represents an adaptive mechanism that emerges in response to progressive pathology.

Projects 1 and 2 have been published in peer reviewed journals, whereas Project 3 was accepted for publication in Movement Disorders on 4 August 2026 and is in press at the time of publication of this dissertation. In the following section these projects will be further introduced. The respective publications are appended to this dissertation.

Projects

Project I

P1: Dynamic Properties in Functional Connectivity Changes and Striatal Dopamine Deficiency in Parkinson's disease

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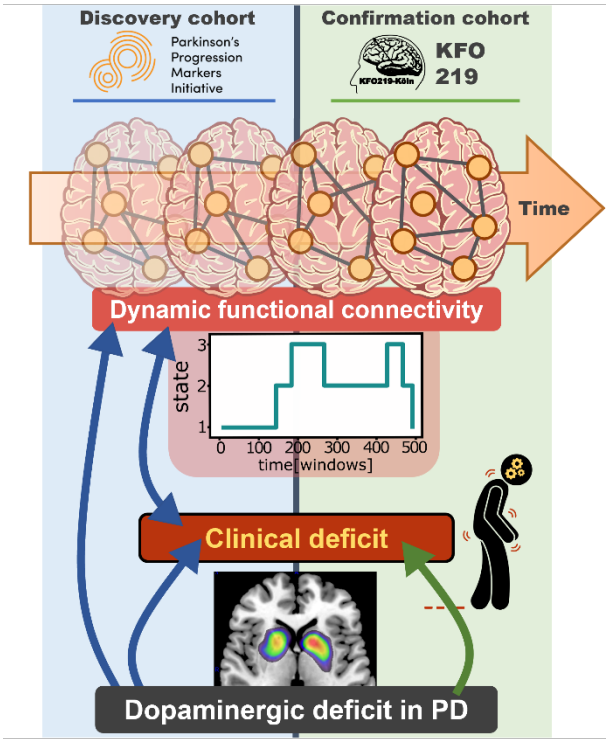

Abstract: Recent studies in Parkinson's disease (PD) patients reported disruptions in dynamic functional connectivity (dFC, i.e., a characterization of spontaneous fluctuations in functional connectivity over time). Here, we assessed whether the integrity of striatal dopamine terminals directly modulates dFC metrics in two separate PD cohorts, indexing dopamine-related changes in large-scale brain network dynamics and its implications in clinical features. We pooled data from two disease-control cohorts reflecting early PD. From the Parkinson's Progression Marker Initiative (PPMI) cohort, resting-state functional magnetic resonance imaging (rsfMRI) and dopamine transporter (DaT) single-photon emission computed tomography (SPECT) were available for 63 PD patients and 16 age- and sex-matched healthy controls. From the clinical

research group 219 (KFO) cohort, rsfMRI imaging was available for 52 PD patients and 17 age- and sex-matched healthy controls. A subset of 41 PD patients and 13 healthy control subjects additionally underwent 18F-DOPA-positron emission tomography (PET) imaging. The striatal synthesis capacity of 18F-DOPA PET and dopamine terminal quantity of DaT SPECT images were extracted for the putamen and the caudate. After rsfMRI pre-processing, an independent component analysis was performed on both cohorts simultaneously. Based on the derived components, an individual sliding window approach (44 s window) and a subsequent k-means clustering were conducted separately for each cohort to derive dFC states (reemerging intra- and interindividual connectivity patterns). From these states, we derived temporal metrics, such as average dwell time per state, state attendance, and number of transitions and compared them between groups and cohorts. Further, we correlated these with the respective measures for local dopaminergic impairment and clinical severity. The cohorts did not differ regarding age and sex. Between cohorts, PD groups differed regarding disease duration, education, cognitive scores and levodopa equivalent daily dose. In both cohorts, the dFC analysis resulted in three distinct states, varying in connectivity patterns and strength. In the PPMI cohort, PD patients showed a lower state attendance for the globally integrated (GI) state and a lower number of transitions than controls. Significantly, worse motor scores (Unified Parkinson's Disease Rating Scale Part III) and dopaminergic impairment in the putamen and the caudate were associated with low average dwell time in the GI state and a low total number of transitions. These results were not observed in the KFO cohort: No group differences in dFC measures or associations between dFC variables and dopamine synthesis capacity were observed. Notably, worse motor performance was associated with a low number of bidirectional transitions between the GI and the lesser connected (LC) state across the PD groups of both cohorts. Hence, in early PD, relative preservation of motor performance may be linked to a more dynamic engagement of an interconnected brain state. Specifically, those large-scale network dynamics seem to relate to striatal dopamine availability. Notably, most of these results were obtained only for one cohort, suggesting that dFC is impacted by certain cohort features like educational level, or disease severity. As we could not pinpoint these features with the data at hand, we suspect that other, in our case untracked, demographical features drive connectivity dynamics in PD.

Contribution to this work:

Adrian Asendorf, Merle Hönig, and Thilo van Eimeren contributed to the development of the research concept, project planning, manuscript preparation, and key decisions throughout the project. Adrian Asendorf conducted all aspects of data inspection, preprocessing, and analysis. He wrote or revised the in-house scripts used in the workflow, performed the statistical analyses, and generated all figures and tables. Adrian Asendorf drafted the first version of the manuscript, which was thoroughly reviewed by the co-authors. The data used in this study were derived from two

cohorts: the completed KFO study and the publicly available PPMI cohort. In both cohorts, data acquisition was carried out by third parties without any involvement of Adrian Asendorf.

Additional information:

This work has been presented as a poster at national and international meetings. In 2022, it was showcased at the MDS Congress in Madrid and at the AD/PD Conference in Barcelona. In the same year it also received best poster awards at the DPG Congress and the SFB 1451 Retreat 2022.

Citation:

Asendorf, A. L., Theis, H., Tittgemeyer, M., Timmermann, L., Fink, G. R., Drzezga, A., Eggers,C., Ruppert-Junck, M. C., Pedrosa, D. J., Hoenig, M. C., & van Eimeren, T. (2024). Dynamic properties in functional connectivity changes and striatal dopamine deficiency in Parkinson's disease. Human Brain Mapping, 45(10), e26776. https://doi.org/10.1002/HBM.26776

Project II

P2: Physical Activity and Network Attack Tolerance Preserve Motor Function in Parkinson's Disease: A Pilot Study in PD

Authors: Adrian L. Asendorf, Elena Guerra, Verena Dzialas, Magdalena Banwinkler, Hendrik Theis, Niklas Hagemann, Kathrin Möllenhoff, Thilo van Eimeren, Merle C. Hoenig

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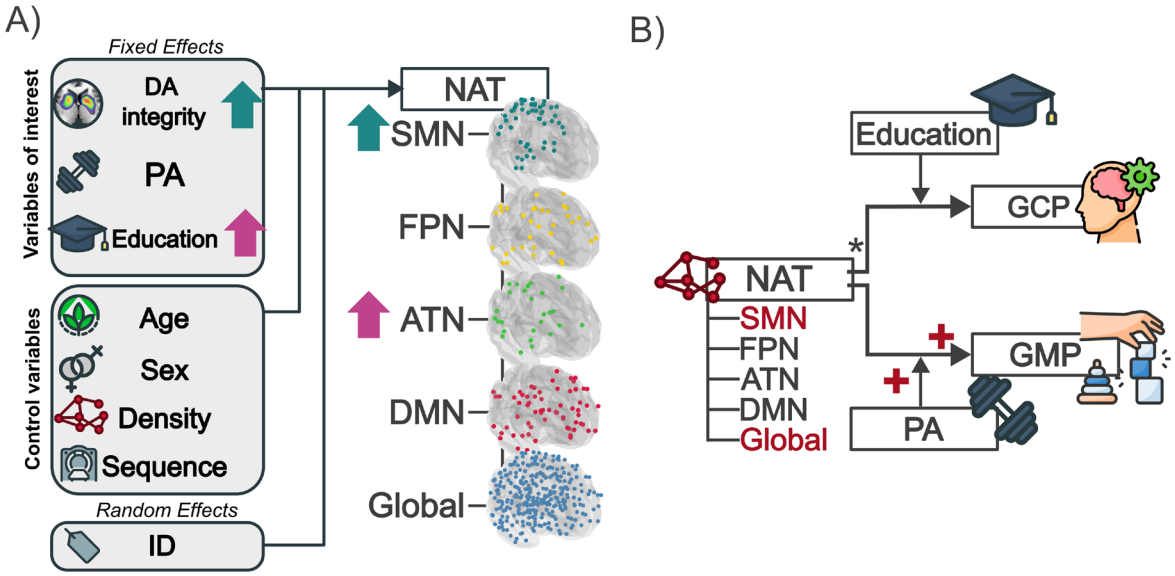

Abstract: We tested whether network resilience, quantified by network attack tolerance (NAT), is associated with dopamine terminal (DaT) integrity, motor function and lifetime factors in Parkinson's disease (PD). Data from 22 individuals with PD and 39 healthy controls included information on lifetime physical activity (PA), cognitive/motor performance, putaminal DaT integrity, and resting-state fMRI. NAT was assessed at global and subnetwork level by calculating global efficiency upon iterative node removal. Generalized linear-mixed-effects models were used to test the effects of PA, education, and dopamine integrity on NAT. Next, the moderating effect of lifetime factors on the association between NAT and motor function were assessed, controlling for DaT integrity. Greater putaminal DaT integrity was linked to higher somatomotor NAT. Higher global and somatomotor NAT supported motor function, especially in patients with moderate lifetime PA. These preliminary results indicate that lifestyle factors serve network-specific attack tolerance, thereby aiding maintenance of motor function in early-stage PD.

Contribution to this work:

Merle Hönig and Adrian Asendorf were involved in outlining the research, planning the project, writing the manuscript, and making key decisions throughout the study. Adrian Asendorf carried out all aspects of the data review, preprocessing and analysis, wrote the inhouse scripts utilized, carried out the statistical analysis, and created all figures and tables included. The data used was taken from the DoMoCo study. Adrian Asendorf, Merle Hönig, Magdalena Banwinkler, Verena Dzialas, Hendrik Theis and Thilo van Eimeren were highly involved in the execution of this study (e.g., data acquisition, patient recruitment, study design, data management). Nils Hagemann and Kathrin Möllenhoff contributed by guiding and overseeing the statistical approach. Elena Guerra established the analytical framework for calculating the lifetime physical activity score. Finally, all authors reviewed the final manuscript.

Additional information:

This work has been presented in several international and national venues. It was showcased as a late-breaking oral presentation at the European Academy of Neurology (EAN) Congress 2024 in Budapest and further selected as the session opener for the Motor Mastery Symposium Cologne in 2024. In addition, the work has been presented as a poster at multiple scientific meetings, most notably at the AD/PD 2025 Conference in Vienna and at the MINC Symposium 2024 in Cologne. It also received a poster award at the SFB 1451 Retreat 2024.

Citation:

Asendorf, A. L., Guerra, E., Dzialas, V., Banwinkler, M., Theis, H., Hagemann, N., Möllenhoff, K., van Eimeren, T., & Hoenig, M. C. (2025). Physical activity and network attack tolerance preserve motor function in Parkinson's disease: A pilot study. Npj Parkinson's Disease 2025 11:1, 11(1), 1–9. https://doi.org/10.1038/s41531-025-01033-9

Project III

P3: Dopamine-Deficiency-Related Reorganization of the Somatomotor Network in Prodromal and Early Parkinson's Disease

Authors: Adrian L. Asendorf, Verena Dzialas, Thilo van Eimeren, Merle C.Hoenig

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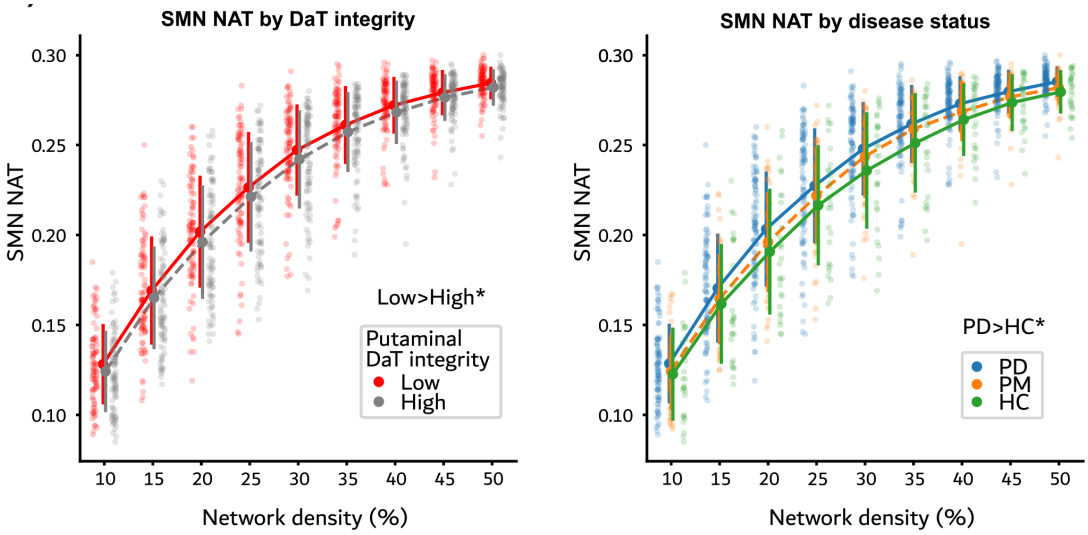

Abstract: Introduction: Network attack tolerance (NAT) measures the brain's ability to sustain information flow despite the loss of critical brain regions. In PD, NAT has been linked to cognitive and motor function. However, it remains unclear how dopaminergic degeneration shapes NAT, and whether it relates to motor symptom progression. Objective: To examine dopamine-deficiency-related changes in NAT across the early PD disease continuum and its association with longitudinal motor outcomes. Methods: We used cross-sectional resting-state functional MRI of 28 healthy controls, 60 prodromal and 94 clinical PD patients to create graph-theoretical networks. NAT was assessed at global and subnetwork level by calculating the global efficiency upon iterative node removal at different network densities. Using linear mixed-effects models, we assessed how putaminal dopamine terminal (DaT) binding, or disease status affected NAT, controlling for network density, age, sex and education. Baseline somatomotor (SMN) NAT was examined as a predictor of motor symptom progression in 145 patients. Results: Lower putaminal DaT signal was associated with higher SMN NAT across groups. PD patients exhibited elevated SMN NAT relative to controls. Neither global nor other subnetworks showed effects. While the effect of baseline SMN NAT on motor progression was not significant, an exploratory analysis

(Johnson-Neyman) suggested that higher SMN NAT may associate with slower motor decline across most of the observed NAT range. Conclusions: Dopaminergic depletion is associated with a targeted SMN reorganization, potentially maintaining network information flow despite progressive hub loss. Whether this reorganization represents compensation or a consequence of progressive pathology requires further longitudinal assessment.

Contribution to this work:

Merle Hönig and Adrian Asendorf were involved in outlining the research, planning the project, writing the manuscript, and making key decisions throughout the study. Adrian Asendorf carried out all aspects of the data review, preprocessing and analysis, wrote the inhouse scripts utilized, carried out the statistical analysis, and created all figures and tables included. Verena Dzialas and Merle Hoenig provided advisory support on the statistical approach. The data used was taken from the publicly available PPMI cohort, where data acquisition was carried out by third parties without any involvement of Adrian Asendorf. Finally, all authors reviewed the final manuscript.

Citation:

Asendorf, A. L., Dzialas, V., van Eimeren, T., & Hoenig, M. C. (2026). Dopamine-Deficiency-Related Reorganization of the Somatomotor Network in Prodromal and Early Parkinson's Disease. *Movement Disorders*, in press. https://doi.org/10.1002/mds.70510

Main Findings of this Dissertation:

In this dissertation, dopamine imaging was combined with advanced resting-state fMRI techniques and detailed behavioural assessments to examine alterations in the brain's functional architecture and dynamic fluctuations in early PD. This multimodal perspective allowed us not only to characterize how complex patterns of FC dynamics and architecture change with loss of striatal dopamine, but also to evaluate how such alterations relate to PD symptoms and whether they are susceptible to modification by lifestyle factors. Using advanced network approaches, including dynamic assessment of resting-state FC (dFC) and graph-theoretical assessment of network resilience (NAT), this work aimed to uncover mechanistic dopamine-driven changes in network function and assess whether they reflect a global deterioration of the system, or could be attributed to resilience related processes. The key findings of this dissertation are threefold, as represented by the three projects arising from this doctoral work:

I. A putaminal dopamine deficit was linked to a change in connectivity dynamics of large-scale neural networks in early PD patients. Specifically, individuals with lower striatal dopamine integrity presented decreased network flexibility and greater network segregation (i.e. the increased presence of lesser connected connectivity configurations). Given that these metrics were likewise associated with an increase in motor symptom severity of PD, they may represent a performance-related consequence of reduced striatal dopaminergic innervation (Asendorf et al., 2024).

II. In the same vein, greater putaminal dopamine deficit across healthy controls, prodromal and clinical PD groups was associated with an increased robustness of the SMN against targeted attacks. Thereby, dopamine loss appeared to result in a targeted reorganization of the SMN architecture towards higher robustness (Asendorf et al., 2026).

III. Interestingly, an increased robustness of the SMN was associated with preserved motor abilities. Importantly, in PD patients with low premorbid physical activity levels this association was weaker than in moderate to highly active patients (Asendorf et al., 2025).

Together, these findings demonstrate that functional connectivity changes are at both the subnetwork and global level (1) closely linked to the integrity of the dopaminergic system and (2) related to motor impairment. Since these metrics are linked to more mechanistically rooted concepts, together, the observations of this dissertation suggest two mechanisms that might add to the complex mosaic of the pathophysiological processes leading to motor impairments in PD.

First, as dopamine is known to modulate the dynamics and stability of neuronal communication, it's striatal absence may accordingly be associated with changes to the time-varying organization of the brain. By assessing constantly fluctuating and recurring global connectivity patterns, it was

found that dopamine loss appears to negatively impact processes that enable a dynamic engagement and disengagement of global integration among large-scale functional networks. This loss of flexibility and the resulting reduced presence of global integration in turn directly related to a deterioration of motor abilities.

Second, FC changes in the brain were assessed using a method that is designed to mimic pathology progression and assesses a networks capacity to cope with this increasing damage. This capacity has not previously been related to dopaminergic loss in PD, and our findings suggest that dopamine depletion may trigger a reorganization of the brain's functional architecture making it more resistant to damage. Across the spectrum from healthy controls to prodromal and early PD, the SMN appears to adopt a more robust architecture that is less vulnerable to the loss of critical hubs and is associated with preserved motor function. Lifestyle factors, particularly lifetime physical activity, may further facilitate this robustness and might thereby enhance the brain's capacity to maintain motor function in the presence of dopaminergic degeneration. Importantly, the directionality of both results points to the possibility that these mechanisms, adaptations of global network dynamics as well as the robustness of the SMN may, to some extent, act as motor reserve mechanisms that help to sustain motor function despite underlying pathology.

In the following, the current results will be discussed. Section 1 will integrate the multimodal findings to delineate how dopaminergic loss shapes large-scale brain networks in early PD. Section 2 will assess how network flexibility and altered dynamic recruitment of large-scale connectivity states are linked to the phenomenon of disconnection in PD. Section 3 will examine whether the observed alterations in network dynamics and architecture reflect passive disease progression or active compensatory adaptation. Finally, Section 4 situates these mechanisms within a broader concept of resilience and will discuss how premorbid lifestyle factors, particularly physical activity and education, may shape the discussed resilience mechanisms in PD.

Discussion

1) A Network perspective on early PD:

Complementary Insights on How Dopamine Loss Shapes Brain Function and Symptoms in Early-Stage PD Patients.

The brain can be conceptualized as a network. Although that frames an approximation that inevitably simplifies the brain's complexity, it provides a powerful framework for understanding how largescale neuronal systems may be organized and how they may adapt in response to neurodegeneration in PD. Dopamine depletion is believed to initiate a cascade of multisystem decline, substantially affecting both the structural and functional architecture of such neuronal systems. Recent efforts to capture these changes at a systems level have resulted in a model describing widespread alterations in structural connectivity (Filippi, Spinelli, et al., 2019). Yet, disentangling which specific alterations are directly associated to dopaminergic loss remains challenging. While, dopamine imaging may provide a critical neurochemical reference point, allowing alterations in structural and functional to be interpreted in the context of striatal dopamine loss, rsfMRI studies that integrate molecular markers, remain scarce.

In this dissertation, all three studies combined molecular and functional imaging and consistently linked connectivity measures across major large-scale networks to dopamine depletion in PD. Despite testing different connectivity measures at global and subnetwork level, the functional network relevant for somatomotor function (i.e. SMN) stood out across analyses. More specifically, the dFC approach of Project 1 yielded that patients with higher dopamine levels spent more time in and transitioned more frequently into a globally integrated state characterized by strong coupling between the DMN, visual network, and the SMN. The NAT analyses of Projects 2 and 3 both revealed dopamine-related alterations within the SMN, but not in any other networks. Hence, across all three projects, the SMN consistently emerged as a core network reflecting altered FC related to dopaminergic loss.

Moreover, our results position the SMN as the network through which dopamine-induced connectivity alterations translate directly into motor symptoms in early PD. Indeed, our first project revealed that the same FC measures that covaried with dopamine loss also covaried with motor performance, as measured by the UPDRS-III. In the Project 2, specifically NAT of the SMN was shown to positively effect motor outcomes derived from a composite of objective motor tests. This is in line with previous observations and highlights the relevance of the SMN in PD. Striatal dopamine depletion was shown to disrupt cortico–striato–thalamo–cortical circuits that project to key SMN regions such as the primary motor and somatosensory cortices and the supplementary motor area (SMA), thereby compromising the integrity of neural systems critical for movement

initiation, execution, and sensorimotor integration (Quarantelli et al., 2022; Ruppert et al., 2020). Our results suggest that in addition to static connectivity changes, lacking reconfiguration of the SMN and reduced flexibility between global large-scale networks and the SMN results in dysfunctional motor control.

Importantly, considering converging evidence highlighting the SMN as a key network in PD, the SMN may thus represent a particularly relevant target for interventional approaches. Several rsfMRI studies demonstrate that dopaminergic loss impacts intrinsic connectivity within the SMN, as well as its coupling with surrounding motor networks and the putamen - effects that are at least partly reversible following dopaminergic supplementation (Esposito et al., 2013; Wu, Long, et al., 2009; Wu, Wang, et al., 2009; Yang et al., 2016). Dopaminergic treatment is thereby suggested to improve motor performance by specifically compensating for the functional impairment in the SMN (Tahmasian et al., 2015). Task-based fMRI studies provide convergent results, showing that levodopa facilitated motor initiation by normalizing activity within the SMA and reducing hyperactivity in lateral premotor and primary motor cortices (Buhmann et al., 2003; Haslinger et al., 2001; Herz et al., 2014). Complementary molecular imaging studies have also demonstrated a similar link: longitudinal Fluorodeoxyglucose PET analyses revealed that the expression of the PD-related spatial covariance pattern, involving a reduction in premotor cortex and SMA connectivity levels, increased as striatal dopamine levels declined and correlated with worsening motor scores (Eckert et al., 2007; Huang et al., 2007). Overall literature thus converges on a common theme: dopaminergic modulation shapes network connectivity of SMN, putamen and cerebellum, and these changes directly influence motor performance and can be modulated by dopaminergic treatment.

Ultimately, determining whether SMN alterations are caused by dopaminergic degeneration in the striatum requires longitudinal designs. To date, only two studies have combined repeated rsfMRI with molecular dopamine imaging (Martín-Bastida & Rodríguez-Oroz, 2025) (Steidelet al., 2022). Steidel et al. (2022) showed that putaminal regions with the strongest [^{18}F]DOPA decline exhibited progressive reductions in coupling with the SMN (Steidel et al., 2022). Li et al. (2020) reported similar DAT-dependent decreases in connectivity between the posterior putamen and thalamic, midbrain, SMA, and sensorimotor regions (W. Li et al., 2020). Both studies indicate that striato-cortical disconnection does not merely co-occur with dopaminergic loss but may be directly shaped by it.

Notably, a few methodological considerations need to be taken into account when considering the results of this dissertation and other studies. Most notably, the varying atlases employed in these studies complicate interpretation and comparability across studies, as structures such as the BG and cerebellum are variably assigned to the SMN, modelled as separate networks, or excluded

altogether. This inconsistency is also present across the projects in this dissertation: while the cerebellum is included in the SMN in all analyses, BG regions were modelled independently of the SMN in the dFC analyses (Project 1) but included within the SMN in the NAT analyses (Projects 2–3). Consequently, the observed association of SMN NAT (Project 2) with dopamine integrity may partly rather reflect striato-cortical disconnection than broader SMN disconnection. Aside from this, also differences in dopaminergic imaging may affect current results. Indeed, while across all three projects, connectivity changes were associated with DAT-SPECT signal, no such associations were observed with [^{18}F]DOPA PET imaging in the KFO cohort (Project 1). Although both DAT-SPECT and [^{18}F]DOPA PET are well-established and sensitive for distinguishing PD from healthy controls (Eshuis et al., 2009), discrepancies have been reported in early or clinically uncertain stages, with DAT-SPECT often indicating larger apparent dopaminergic reductions than [^{18}F]DOPA PET (Kaasinen & Vahlberg, 2017; Wallert et al., 2022). These differences likely reflect their distinct molecular targets. DAT-SPECT indexes presynaptic DaT availability and axonal dysfunction, whereas [^{18}F]DOPA PET measures AADC and thus dopamine synthesis capacity. While [^{18}F]DOPA uptake correlates with post-mortem dopaminergic cell counts (Snow et al., 1993), compensatory upregulation of AADC in surviving terminals increases decarboxylase activity measured by [^{18}F]DOPA, thereby partially preserving tracer uptake and leading to an underestimation of dopaminergic loss in early PD (Kaasinen & Vahlberg, 2017; Stoessl et al., 2014). Consequently, [^{18}F]DOPA PET may have been less sensitive to subtle dopaminergic deficits, potentially explaining the absence of associations with functional connectivity measures in the KFO sample compared to the PPMI sample (DaT-SPECT) of Project 1. Cohort-specific factors, including lifestyle and disease heterogeneity, may have further contributed to this finding.

Conclusively, longitudinal and cross-sectional molecular and MRI-based studies, together with the findings of this dissertation, converge on a coherent global picture of network-level alterations associated with dopaminergic loss in PD. Collectively, this body of work identified a functional disconnection of the SMN - specifically along the BG–SMN axis - as main functional consequence of striatal dopamine loss. As the present approaches identified the SMN within the context of global brain organization, they centre the SMN as a valuable systems-level target for assessing and monitoring the effects of L-Dopa therapy and associated mechanisms of motor symptom alleviation. By combining molecular imaging of dopaminergic integrity with assessments of network dynamics and network robustness to damage, this dissertation leverages one of the first multimodal approaches that link neurochemical pathology and motor symptoms with complex measures of large-scale network organization. The resulting findings provide a strong and literature-compliant foundation for the application of dFC and NAT in future multimodal longitudinal studies. While such designs are methodologically demanding, they constitute a promising next step to further clarify how these network alterations evolve as the disease

progresses, whether they are indeed directly driven by dopaminergic degeneration, and how they contribute to symptom stability in PD. In this context, these approaches may substantially advance our understanding of disease mechanisms, identify targets for therapeutic intervention and support the development of more individualized treatment strategies. What specific mechanistic insights these methods already provided in our cross-sectional approaches, will be discussed in the next sections. In the following this added perspective is explored in the context of network flexibility and its potential role in shaping motor impairment in PD.

2) Is PD a Problem of Flexibility?

PD Might not be a Mere Syndrome of Disconnection.

Regarding this question, the findings from Project 1 suggest two complementary, but not mutually exclusive, interpretations. First, when comparing groups, a smaller proportion of PD patients spent any time at all in the more connected connectivity state (i.e., reduced state prevalence of integrated connectivity state). This absence of integrated states in patients supports the notion that PD is characterized by a system-wide reduction in functional integration and is consistent with the idea of large-scale disconnection as a hallmark of the disease (Göttlich et al., 2013). However, the associations observed with dFC metrics suggest a flip side to this interpretation: Although fewer PD patients entered the integrated state at least once during the approximately eight-minute scanning session (i.e., reduced state prevalence), this measure was not associated with either dopaminergic integrity or motor symptom severity. In contrast, transition-related metrics, such as a lower overall number of transitions and fewer transitions toward the integrated state, were associated with greater dopaminergic deficits and more severe motor symptoms. This pattern suggests that transition metrics may be more sensitive to disease severity than state prevalence per se. Notably, these transition metrics may in part be influenced by the fact that more PD patients did not enter highly integrated states during the scan and therefore could not transition toward them. However, given the limited scan duration of approximately eight minutes, the absence of such states does not necessarily indicate that they are no longer accessible. Thus, while highly integrated states may still be accessible in PD, the likelihood of patients transitioning into these states within the observed time window may be just lower. In this view, the reduced prevalence of integrated states in PD may primarily arise from lower transition rates rather than from a fundamental inability to recruit highly integrated network configurations.

Taken together, while disconnection may represent an apparent endpoint when connectivity is averaged over time, the present data leave room for the possibility that altered network dynamics, rather than structural deterioration per se, are a key driver of these effects. Specifically, in early or potentially prodromal PD, declining dopamine levels may impair the brain's ability to flexibly

transition into highly integrated connectivity states. In this scenario, connections remain largely intact but are underutilized, analogous to a preserved highway that is less frequently travelled on. This would lead to reduced static functional connectivity estimates, even though periods of strong coupling still occur sporadically. As the disease progresses, the ability to disengage from current connectivity states and engage alternate configurations, may become more and more compromised biasing the brain toward more locally organized and less globally integrative regimes (i.e. higher segregation). From this perspective, motor symptoms traditionally attributed to somatomotor network disconnection may instead reflect a loss of functional flexibility, suggesting that dFC could represent a more sensitive marker of early pathology that may precede overt reductions in static connectivity. While a mediative role of static FC on the relationship between dopamine loss and motor symptoms severity has recently been reported (Lorek et al., 2024; Yan et al., 2024), this role remains to tested for FC dynamics. In an independent PD cohort, reduced state transitions and longer dwell times in sparsely connected states were similarly associated with greater motor impairment (Pan et al., 2025), while longitudinal assessments in the same cohort used here (PPMI) showed the prevalence of sparsely connected states to increase with time (Y. Cao et al., 2023). These support the reproducibility of our results and suggest network flexibility to progressively decline alongside motor and dopaminergic deterioration, motivating the assessment of mediation across longitudinal data.

However, considering these findings the precise mechanisms by which dopamine facilitates this network flexibility remain speculative. In this regard, the triple-network model proposed by Vinod Menon (Menon, 2011) might represent a valuable concept to consider. This model focuses on three canonical networks: the central executive network (CEN; corresponding to our FPN), the salience network, and the DMN, and their dynamic interplay. Whereas the central executive network supports externally directed cognition and goal-oriented behavior, the DMN is primarily engaged during interoceptive and self-referential processes. These two networks are thought to operate in an antagonistic manner: when one is active, the other typically is suppressed. The salience network mediates between them, detecting and evaluating relevant internal and external stimuli and orchestrates switching between internally and externally focused states (Menon & Uddin, 2010; Sridharan et al., 2008). According to Menon, disturbances in the engagement and disengagement of these core networks contribute to a wide range of neurological and psychiatric disorders (Menon, 2011). In this light, inappropriate salience attribution and thereby impaired salience network mediated switching could lead to aberrant transitions between internal and external modes of processing. Given that dopamine levels have been shown to affect the salience network in schizophrenia patients (McCutcheon et al., 2019; Rössler et al., 2020), allows for speculation that dopamine loss may disrupt this mediating mechanism of the salience network.

Thus, examining dopaminergic modulation of particularly the salience network and its role facilitating switching flexibility may represent an interesting avenue for future PD research.

Notably, in PD, alterations in dFC have been linked not only to motor but also to cognitive decline. Prior studies showed that the same dFC metrics linked to motor function, such as fewer state transitions and lower engagement of highly integrated states, were likewise associated with emerging cognitive deficits in later PD stages (Díez-Cirarda et al., 2018; Fiorenzato et al., 2019). This suggests that motor and cognitive symptoms could share a common deficit in network flexibility pointing towards shared underlying mechanisms being impaired. Supporting this view, cognitive control is regarded as an integral part of motor function. In PD, freezing of gait and impaired dual-tasking (i.e., performing a cognitive task during movement) represent prime examples of attentional and executive involvement in motor impairment and the required co-recruitment of cognitive and motor networks (Amboni et al., 2008, 2013; Sarasso et al., 2021). Taken together, these observations indicate that alterations in network flexibility may affect mechanisms underlying both cognitive and motor processes, highlighting their close conceptual and functional interdependence. Consequently, reduced flexibility observed in early PD may predominantly manifest as motor impairment, while supporting cognitive function becomes increasingly compromised at later stages (Y. Cao et al., 2023).

Finally, while our multimodal approach moves toward linking dynamics to underlying biology, more focused mechanistic insights are still needed. In Alzheimer's disease research, such approaches have very recently shown promising results: tau pathology, one of the two core pathologies of Alzheimer's disease, has been associated with reduced local dynamics even in healthy individuals (Carrasco-Gómez et al., 2025) and dFC has been shown to mediate the relationship between APOE4 status and trail making test performance (Gong et al., 2025). These findings underscore the value of assessing spatial neuropathological spread with local dynamics changes. Moreover, they reinforce the idea that FC dynamics reflect general (dys-)function rather than a single pathological process. These similar patterns across diseases suggest that the alterations in dFC we observe in PD may amplify both cognitive and motor deficits through widespread disruptions in network coordination.

Together, the findings at hand suggest that what appears as cortico-striatal disconnection in time-averaged connectivity assessments may instead reflect an impaired ability to dynamically recruit highly connected network configurations, rather than an irreversible loss of structural connections. While these observations may be regarded as complementary to the concept of disconnection in later PD stages, the occasional presence of such integrated states in early PD patients suggests that the network architecture required to support these configurations still remains accessible. Importantly, this perspective implies that such alterations may be, at least in

part, modifiable, underscoring their relevance for therapeutic and lifestyle-based interventions. Accordingly, assessing dynamic connectivity changes in preclinical stages of the disease, and particularly their modulation by dopaminergic therapy, may provide valuable insights into the extent to which network dynamics can be altered and their potential utility for early disease detection and monitoring. While global dynamics provide a valuable starting point, future work employing finer-grained spatial and longitudinal approaches will be critical to determine how local dynamic processes and their dopaminergic modulation contribute to symptom progression, and whether preserved network flexibility relates to the concept of compensation and motor reserve. Because rather than merely reflecting progressive deterioration, alterations in FC in PD may also capture the brain's attempt to adapt to an increasing pathological load.

3) Compensation vs. Degeneration in Early PD

Evidence for Active Compensation and Passive Loss of Function

Although converging evidence, including our own findings, consistently implicate dopamine-related changes to be restricted to the SMN, a key challenge is to distinguish changes reflecting passive deterioration from those representing an active compensatory response. Growing evidence suggests that such compensatory mechanisms do emerge in PD and may increase with progressing dopaminergic deficit. At the cellular level, for instance, upregulation of AADC function (Kaasinen & Vahlberg, 2017) and D2 receptor availability (Bezard et al., 2003) have been reported, representing adaptive countermeasures to dopamine loss. Against this backdrop, it remains to be discussed whether the functional alterations observed in this dissertation can be interpreted as active compensation or instead reflect passive decline, and whether such compensation is truly performance preserving or maladaptive. To address this, the following section focuses on dFC and NAT as complementary methodological approaches that may capture distinct, processes related to active compensation in early PD.

Importantly, the SMN consistently emerged as a focus of architectural changes in Projects 2 and 3. Group comparisons indicated that, among major large-scale networks, only the SMN exhibited increased attack tolerance (i.e., NAT) in PD patients. Thereby, compared to healthy controls, the SMN in PD patients showed an increased capacity to preserve its global efficiency despite the progressive artificial removal of crucial network components. Further, it was shown that across the groups of healthy controls, prodromal PD, and clinical PD, NAT of the SMN increased as dopaminergic degeneration progressed, consistent with the notion of a compensatory mechanism that scales with increasing need. However, while NAT increased with dopaminergic impairment, this does not imply that global efficiency of the SMN increases with disease severity. In fact, studies in newly diagnosed and mid-stage PD patients show clear reductions in both global and local

efficiency of the SMN compared to healthy controls (J. Fang et al., 2017; Suo et al., 2017). Thus, although SMN efficiency was not directly quantified in our cohorts, it was likely impaired due to fading striato-cortical input. Consequently, given an already impaired SMN, the ability to preserve the remaining efficiency rises with advancing dopaminergic loss. This implies that in the SMN, NAT is not passively depleted as a mere by-product of degeneration. Rather, the SMN appears to undergo active reorganization to preserve a more resilient network structure.

That said, in our NAT approach, where the most connected nodes were attacked first, participants with more evenly distributed connectivity suffered fewer "casualties" within the first attacks, thereby making them more resilient according to our approach. This raises the possibility that the observed increases in NAT are simply a consequence of reductions in nodal centrality that naturally occur in PD (J. Fang et al., 2017; Suo et al., 2017), rather than constituting an adaptive response to the pathology itself. Yet, evidence from Project 2 strongly argues against a purely artefactual causality: While higher NAT was associated with better motor performance in Project 2, others report a reduction in nodal centrality in the SMN to be associated with worse motor symptoms (Suo et al., 2017). If NAT were merely a by-product of reduced centrality, then both measures should relate to motor impairment in the same direction. Instead, the opposite was observed: whereas a reduction in centrality appeaed to index disease progression, NAT related to preserved function. This dissociation suggests that the degradation of central hubs we observed in PD, and captured with NAT, is not simply a marker of deterioration but may reflect a directed and organized architectural shift. In this interpretation, the brain reduces its reliance on selected highly centralized hubs and redistributes connectivity to maintain global efficiency in response to declining striato-cortical input. This shift would reflect a transition from a more segregated, hub-dominated SMN architecture that strongly depends on striato-cortical projections to a more integrated SMN configuration that may be less sensitive to the loss of striato-cortical input and thereby supports compensation. While these considerations suggest that increased integration may be beneficial, which is consistent with prior work (Mohl et al., 2017; Shine et al., 2019), other studies indicate that decreased integration (i.e. higher segregation) can also support motor execution (Cohen & D'Esposito, 2016; Dzialas et al., 2024). This apparent divergence suggests that the benefits of integration may be context- or task-dependent. However, which specific hubs are degraded to facilitate integration, how this relates to striato-cortical input, and how connectivity is redistributed remain unclear.

With respect to these open questions, visualizations of node centrality distributions across groups in Project 3 may provide initial insights into how the network architecture of the SMN is reorganized in early PD. Although not tested statistically, these visualizations suggest a shift in high node centrality values from predominantly cortical regions in healthy controls to increasingly subcortical and cerebellar regions in prodromal individuals and PD patients.

Although these changes are rather subtle, they suggest that NAT could be closely tied to the ability to recruit additional parts of the SMN that are typically less engaged. This resembles the concept of novel area recruitment, whereby compensation emerges through an expanded spatial extent of cortical engagement (Palmer et al., 2009). Converging task-fMRI evidence supports this view: PD patients show reduced activation in core motor regions during motor tasks alongside increased activation in adjacent areas (Herz et al., 2021), and more recently, hyperactivation in parieto-premotor regions has been linked to better motor and cognitive performance (Johansson et al., 2024). Together, these findings further suggest that NAT may capture a compensatory and targeted redistribution of motor network engagement rather than simple functional decline.

Notably, the two projects revealed associations between NAT and dopaminergic integrity that differed in direction. Specifically, NAT increased with advancing dopamine loss in Project 3, whereas in Project 2 NAT decreased with dopamine loss. These differences likely reflect the distinct study designs: Project 2 was designed to assesses NAT in a single clinical stage with limited interindividual variability while Project 3 was designed to assess NAT across several disease stages. While this design-dependent divergence warrants consideration when interpreting the results, the observations are not necessarily mutually exclusive. Rather, even if NAT decreases with dopamine loss within a given disease stage, the pattern across stages suggest that NAT increases along a more broad disease trajectory.

In summary, this chapter provides converging arguments that increased NAT reflects an adaptive reorganization of the SMN in response to dopamine loss. The findings and considerations at hand not only position NAT as a systems-level marker that may capture compensatory processes, but they also identify specific mechanistic changes to the brain that may be associated with active compensation. While aligning processes like novel area recruitment and increased network integration have been associated with compensation in PD previously, current findings now narrow their implications in motor function to the SMN and wrap them all together in a single framework (i.e. NAT). Although longitudinal studies are required to confirm the temporal trajectory of NAT along the disease course, the present results highlight NAT as a promising target for future work aiming to characterize, monitor, and potentially strengthen compensatory network mechanisms in PD. The current findings illustrate that prodromal participants exhibited intermediate NAT values between healthy controls and PD patients, suggesting that SMN reorganization may even begin before the clinical onset. Thereby, it will be relevant to further assess whether NAT increases within the SMN during premorbid stages and whether such changes may prolong the prodromal phase. In addition to NAT, it will be further important to examine if dynamic changes in FC include compensatory capacity. As the current findings do not suffice for an post hoc assessment, it will be particularly interesting to determine whether preserved network flexibility and the transient engagement of highly integrated states support

motor performance in the face of dopaminergic loss. Future longitudinal studies integrating dFC with measures of motor reserve and salience-network integrity may help clarify whether dynamic network properties reflect true compensatory mechanisms or primarily track global disease progress. Notably, apart from being compensative (a response to dopamine loss), the findings at hand imply that one of the features assessed may be able to explain the heterogeneity in motor symptom severity despite similar dopaminergic integrity and thereby pose a potential mechanism of motor reserve in PD.

4) Lifestyle and Resilience - How are They Linked?

How an Active Lifestyle and Higher Education Might Shape the Brains Resilience to PD.

4.1) Higher NAT as a Resilience Mechanism.

While NAT was initially discussed in the context of compensation, our findings suggest that higher SMN NAT may also reflect an active resilience mechanism supporting motor reserve at the individual level. In Project 2, higher NAT within the SMN was associated with better fine motor performance after accounting for dopaminergic availability, indicating that individuals with comparable levels of dopamine loss differed systematically in motor outcome depending on their network robustness. Importantly, this observation does not rely on residualization or formal mediation frameworks. Rather, the regression models tested whether NAT explained variance in motor performance beyond dopaminergic integrity, thereby capturing inter-individual differences in symptom expression at similar levels of pathology. Accordingly, NAT may account for parts of the discrepancy between dopamine-predicted and observed motor impairment, constituting a potential motor reserve mechanism, and motivating longitudinal studies to establish its role in sustaining motor symptom stability over time.

When assessing motor reserve literature, several residual-based studies have identified greater grey matter integrity or FC of cerebellar regions, alongside other areas, to be predictive of symptom stability (Chung, Kim, et al., 2020; Dzialas et al., 2024; Y. J. Kim et al., 2022). Interestingly, visual assessments of Project 3 suggest that the functional reorganization inside the SMN may also include an increasing recruitment of cerebellar regions along the spectrum from healthy controls to prodromal and early PD. While speculative, these observations suggest that preserving SMN efficiency may depend on the capacity to reroute processing through parallel cerebellar pathways. Mechanistically, the engagement of the cerebello-thalamo-cortical loop, has long been proposed to counterbalance dopamine-related dysfunction in striato-thalamo-cortical circuits (Wu & Hallett, 2013) and has more recently linked to better gait and cognitive performance (Yu et al.,

2025). However, contributions from networks beyond the SMN, such as the DMN, could not be assessed here and should be addressed in future multi-network analyses (J. Fang et al., 2017).

Finally, the fact that another study found higher FPN NAT to be associated with the preservation of cognitive functions despite progressing dopamine loss (Cascone et al., 2021), suggests that cognitive reserve may be linked to similar reorganizational processes that were linked to motor reserve in this dissertation. Although these FPN-related effects were not directly linked to molecular assessments of dopaminergic integrity, the FPN as target of these changes aligns within the known spatial progression of dopaminergic degeneration within the striatum (Kaasinen & Vahlberg, 2017). Along this trajectory, SMN-related circuitry is affected early, whereas frontal networks, including the FPN, become increasingly involved at later stages (Cools, 2011). Hence motor and cognitive reserve might draw on shared resilience mechanisms that are recruited sequentially as pathology spreads, supporting the view that motor and cognitive reserve are intertwined rather than distinct constructs (Zeller et al., 2024). Consistent with this notion, higher motor reserve has been associated not only with motor stability but also with cognitive performance, education, white-matter integrity, and reduced dementia risk in drug-naive PD patients (Chung et al., 2022).

In light of these considerations, if NAT reflects an individual capacity to maintain motor function despite comparable dopaminergic burden, a critical next question concerns the factors that shape this capacity long before clinical onset. While increased exposures to pesticides, solvents, chronic stress, and head injuries have been linked to higher PD risk, coherence to certain lifestyles and behavioural factors, including caffeine consumption, smoking, educational attainment, and physical activity, have been associated with reduced PD prevalence (Blume et al., 2017; Marras et al., 2019; Reichmann et al., 2022). Understanding these opposing influences is essential, as it can directly inform recommendations for modifiable lifestyle strategies, such as adopting healthier diets, increasing physical activity, or minimizing head injury risk, especially for individuals at risk for PD (Marras et al., 2019). In this context, and as a final aim of this dissertation, premorbid engagement in physical activity and educational attainment were examined as potential contributors to the resilience mechanism we identified above (i.e. NAT).

4.2) How Premorbid Physical Activity Levels Might Shape Resilience Mechanisms

Physical activity has long been prime suspect to mitigate motor symptoms in PD. Physiotherapy and ergotherapy are central pillars of current therapeutic strategies (Reichmann et al., 2022) and acute high-intensity exercise interventions have repeatedly been shown to stabilize motor symptoms and enhance striatal dopamine availability in PD (de Laat et al., 2024; Schenkman et al., 2018; van der Kolk et al., 2019). Beyond acute effects habitual and lifetime physical activity have been associated with slower symptom progression and higher dopamine levels (Hu et al.,

2024; Sacheli et al., 2018). Yet, how premorbid physical activity shapes the brain's later capacity to cope with PD-related network dysfunction remains unclear. Therefore, Project 2 tested how midlife (20-50 years) premorbid physical activity exercise affects the ability to cope with dopamine loss. Our findings suggest that particularly the absence of physical activity may have detrimental effects on motor outcomes, as it dampened the positive association between high NAT and motor performance in Project 2. This interpretation aligns with existing epidemiological evidence. A meta-analysis demonstrated that moderate to vigorous physical activity reduced PD risk by 17%, while light PA showed no association at all (X. Fang et al., 2018). Although these studies span heterogeneous age ranges, their focus on mid- to late adulthood points toward a critical window during which no physical activity might limit specific processes that meaningfully reshape the brain.

Supporting this, a recent review reported that even ten months of intensive physical activity during adulthood can lower PD risk (Reichmann et al., 2022), indicating that physical activity associated benefits may not exclusively arise from lifelong continuity, but already from exposure to sufficiently intense episodes. This aligns with our interpretation that the ability to recruit alternative regions within the SMN rather reflects a learned capacity shaped by physical activity experiences, than a mere reflection of general fitness. In theory, repeated engagement in demanding motor situations during midlife may promote the establishment of alternative motor routes, such as cerebello-thalamo-cortical pathways (Wu & Hallett, 2013). While these alternative routes may help maintaining high motor performance in demanding conditions, they might later help to buffer the effect of dopaminergic decline and prolong phases of minimal symptom progression. As such, this theoretical account aligns closely with the definition of resilience outlined above. Consistent with this interpretation, elite athletes show increased efficiency, connectivity, and structural adaptations along global and within motor-related networks (di et al., 2012; Tomita et al., 2021; Wang et al., 2013), suggesting that intense physical activity can induce a reorganization of the motor system, that may, at least in part, endure across the life span.

Complementing these observations, recent accounts suggest that the association between physical activity and brain network organization may further be mediated by physiological fitness. In healthy participants, structural network efficiency and connectivity increased with physical fitness levels, but not with self-reported physical activity (Callow & Smith, 2023; Won et al., 2021). This indicates that beyond experiential exposure, physical fitness may represent a key factor shaping brain network integrity. Supporting this view, mounting biological evidence highlights cardiorespiratory fitness as a central determinant of brain health. In a recent review, Tari et al. showed that cardiorespiratory fitness exerts neuroprotective effects such as improved cerebral blood flow, reduced inflammation, and most importantly increased neuroplasticity (Tari et al., 2025). This rise in neuroplastic potential is thought to be driven by the upregulation of

neurotrophic factors and molecular pathways involved in cell signalling, growth, and structural maintenance (De Sousa Fernandes et al., 2020). Together, this suggests that neuroplasticity may provide the structural conditions required for adaptive network responses. In this context, while physical activity experiences may shape the recruitment and refinement of alternative motor routes, physiological fitness may enable such adaptations by supplying the flexibility necessary for their implementation. As NAT may reflect an active capacity to dynamically redistribute processing load, synaptic plasticity represents a plausible biological substrate enabling NAT by supplying the structural flexibility required for rapid and targeted functional rerouting.

Taking this into account, repeated engagement in physically demanding activities across life may be relevant, when considered from a different perspective. Lifelong participation in exercise may cultivate trained interoceptive awareness (i.e. ability to perceive bodily signals and self-regulate) (Seabury et al., 2023). Individuals experienced in exercise may therefore train more efficiently and with fewer overload related injuries, reducing prolonged interruptions in physical activity across adulthood. Thus, lifelong sport experience may enhance the safety and effectiveness with which individuals maintain physical activity in later life and may thereby positively affect late life physical fitness levels.

Finally, the broader positive effect of physical activity reported on cognitive function, stress and mental health functions (De Sousa Fernandes et al., 2020) might represent another driver of the physical activity motor reserve associations we discussed above. In healthy aging physical activity levels related to measures of cognition in late life (Pucci et al., 2024), and explained changes in networks related to executive function (FPN), attention and learning (dATN,vATN), and memory (DMN) in young adults (Talukdar et al., 2018), while endurance athletes showed increased clustering coefficients interpreted as more efficient executive processing (L. Cao et al., 2023). This raises the possibility that higher physical activity levels support motor function indirectly by strengthening cognitive resources that are required during complex motor actions. A similar notion was reported by Chung et al. (2022), where memory function and fornix integrity explained variance in motor symptom severity in PD (Chung et al., 2022). Altogether, physical activity may strengthen motor reserve by a multitude of potential pathways, which represent promising avenues for future preventative or even therapeutic studies.

4.3) Can Higher Educational Attainment Foster Resilience in PD?

Compared to physical activity, the evidence supporting education as a contributor to resilience in PD is considerably weaker. Initial interest in educational attainment largely originates from cognitive reserve research in healthy aging and Alzheimer's disease, where it has been discussed as a central determinant for decades (Chen et al., 2019; Stern, 2009; Wilson et al., 2019; T. Zhong et al., 2024). Although Stern (2009) proposed education, together with IQ and occupational

demand, as indirect proxy of cognitive reserve in healthy aging and disease early on (Stern, 2009), recent longitudinal studies on aging-associated cognitive decline and cognitive reserve only supply very limited support regarding this assumption: These studies suggest that education is primarily associated with higher baseline cognitive performance, but shows little to no influence on the rate of cognitive decline over time (Sala et al., 2023; Wilson et al., 2019). Still, given its assumed relevance in cognition, education also gained attention as a potential moderator of both cognitive and motor reserve in PD (Blume et al., 2017; Chung, Lee, et al., 2020). Yet the literature remains inconclusive. Only one study demonstrated that individuals with higher educational attainment showed better motor performance despite lower putaminal dopamine availability, suggesting education to be intertwined with a potential resilience mechanism (i.e. motor reserve) in PD (Sunwoo et al., 2016).

Across the projects in this dissertation, the notion that education plays a substantial moderating role in compensating motor or cognitive decline in PD could not be assessed. Educational attainment neither influenced the association between NAT and cognitive outcomes in Project 2, nor was it associated with alterations in connectivity dynamics or dopaminergic integrity in Project 1. Yet, it needs to be considered that many commonly studied lifestyle and sociodemographic factors are known to influence study participation. Individuals who enroll in observational studies tend to be healthier and more socioeconomically advantaged, whereas nonparticipants more frequently exhibit poorer physical and mental health, higher substance use, lower income, and lower educational attainment (Drivsholm et al., 2006; Knudsen et al., 2010; Korkeila et al., 2001). A prominent example is the UK Biobank, where only 5.5% of the approximately nine million individuals contacted ultimately enrolled, resulting in a cohort that differs substantially from the general population with respect to health status and educational attainment (Schoeler et al., 2024; Stamatakis et al., 2021). Accordingly, particularly the lower end of the educational spectrum may have been systematically underrepresented in the early PD cohorts assessed in this dissertation due to volunteer bias. Nonetheless, in Project 2 higher education was associated with increased NAT in the ATN, lending some support to the notion that a greater lifetime cognitive demand may enhance the capacity for information rerouting within higher order association networks. However, in Project 3, ATN NAT did not increase across disease stages. Taken together, these observations imply that at early clinical stages education does not exert substantial influence in early PD resilience processes or may affect only specific network domains that remain relatively spared early stages. These considerations are consistent with findings from a recent complementary study, to which the present author contributed, which examined whether education moderated the association between putaminal dopamine transporter capacity and motor symptom severity in de novo PD patients across three age categories. In that study, a moderating effect of education was observed only in the oldest age

group (70–79 years), suggesting that educational attainment may support resilience mechanisms primarily at advanced age (Hoenig, Dzialas, Banwinkler, et al., 2023). Notably, as all participants were newly diagnosed, this effect may be more closely related to aging-related processes than to disease-specific pathology.

Cumulatively, the findings of this dissertation suggest a shift in how resilience mechanisms in PD may be conceptualized. Rather than representing a fixed trait that is subsequently lost as pathology emerges, the present considerations indicate that some resilience mechanisms may actively fostered once the system is increasingly challenged by disease-related pathology. In this sense, such mechanisms may represent active resilience that is recruited once other forms of compensation or reserve are no longer sufficient. According to our results NAT may provide a quantitative approach to capture these active processes in regard to motor reserve. Importantly, the present results suggest that resilience facilitating adaptations may be established long before clinical onset of the disease. Even limited periods of engagement in physically demanding activities across adulthood showed to contribute to motor reserve in our early PD cohort. From a clinical perspective, these results motivate a move toward earlier and more proactive lifestyle-oriented interventions. Thereby, exercise interventions may not only be therapeutically relevant after diagnosis but may also represent a preventive strategy in at-risk individuals that could facilitate coping with neurodegeneration later on. This perspective aligns with growing efforts to integrate structured exercise programs into standard PD care and extends their relevance to midlife and even presymptomatic stages. Crucially, by establishing NAT as a potential proxy for motor reserve in PD, it may serve as a valuable tool to monitor and predict the impact of individual traits, such as habitual physical activity, on motor reserve capacity in future studies.

5) Current Limitations in rsfMRI Research

While the interpretations discussed above are subject to conceptual limitations, many have been addressed in the respective sections. Further, each analytical approach applied throughout this dissertation entails method-specific constraints that are discussed in detail in the corresponding publications or manuscript. The purpose of the present section is therefore not to reassess these issues, but to acknowledge broader methodological limitations that are inherent to rsfMRI itself and apply equally across all three projects.

Foremost, rsfMRI provides an indirect measure of neural activity based on hemodynamic fluctuations and therefore captures only a proxy of underlying neuronal processes. Consequently, any interpretation of network associations must be considered inferential and some of our interpretations above might necessarily rely on assumptions that extend beyond what rsfMRI can directly measure. Beyond this conceptual limitation, rsfMRI is affected by several methodological constraints that impair comparability and reproducibility across studies. First, the technique is highly sensitive to non-neural sources of variance, including head motion, physiological noise, and fluctuations in vigilance, that are particularly pronounced in PD populations (Tahmasian et al., 2015). Continuous monitoring of attentional state or physiology represents a minimal standard to address these confounds. However, such measures were not available in the cohorts analysed here, limiting our ability to correct for these. Second, comparability is affected by the lack of consensus regarding standardized preprocessing pipelines for rsfMRI. Across the literature, substantial variability exists in motion correction, denoising strategies, nuisance regression, temporal filtering, and spatial normalization. Even when identical analytical frameworks are applied, differences in preprocessing alone can yield markedly divergent results (Ciric et al., 2017; Luppi et al., 2024). Thereby, comparability of the results at hand to other studies adopting identical paradigms may still remain limited. Although all datasets in this dissertation were processed using unified pipelines to ensure internal consistency, methodological considerations required different parcellation schemes. In this dissertation, dynamic FC analyses relied on data-driven ROIs labelled using the Shirer atlas (Shirer et al., 2012), whereas NAT analyses were based on predefined spherical ROIs from the Seitzman atlas (Seitzman et al., 2020).

Taken together, these limitations underscore that, while powerful, rsfMRI is a fragile tool. The high interpretative flexibility inherent to the advanced network analyses at hand must therefore be balanced against the indirect nature of the signal and susceptibility to confounds. Future progress in the field will critically depend on harmonized preprocessing frameworks, standardized network definitions, improved physiological monitoring, and larger longitudinal datasets. Only under such conditions can rsfMRI findings be more confidently linked to disease mechanisms and individual differences in resilience.

Resume

In current PD research, two fundamental questions remain particularly important yet incompletely understood: (1) How does dopaminergic degeneration translate into clinical symptoms? And (2) Why do patients with a comparable biological burden experience different clinical outcomes? This dissertation addressed these questions from a large-scale network perspective, proposing that the organisation and communication of brain networks critically determine how strongly PD pathology manifests clinically.

Across three multimodal projects, the findings of this work converge on the notion that complex network metrics are closely linked to both striatal dopamine loss and motor impairment in early PD. In this sense, the results provide preliminary mechanistic insight into how dopaminergic degeneration may translate into motor symptoms: not solely through local neurotransmitter depletion and an associated disconnection of the striatum, but by altering the brain's ability to flexibly engage and disengage large-scale network configurations. At the same time, the adaptive reorganization of the somatomotor network observed in early PD may offer a partial answer to the second question: by adaptively increasing its robustness, the somatomotor network may better compensate for pathological load, thereby preserving motor function. Thus, individual differences in network robustness may partly explain clinical heterogeneity.

While these findings highlight the potential of advanced rsfMRI network analyses to refine our understanding disease mechanisms in PD, their true strength originates from multimodal assessments. The integration of DaT-SPECT, resting-state fMRI, detailed motor phenotyping, and lifestyle assessment in deeply characterized cohorts such as DoMoCo enabled insights that would not have been accessible from any single modality alone. In particular, the observation that premorbid physical activity strengthened the buffering effect of network robustness on motor symptom decline provides a proof of concept that network-level properties may be shaped by lifelong behavioural exposures. This link illustrates how multimodal, phenotypically rich approaches can begin to explain clinically relevant symptom variability and inform about possible intervention mechanisms.

Taken together, this dissertation demonstrates that advanced network-based approaches can move the field beyond descriptive disconnection models toward a mechanistic understanding of how dopaminergic degeneration reshapes large-scale brain organization. More broadly, it emphasizes that future progress in PD research will depend on integrative study designs, large well-characterized cohorts, and the combination of molecular, functional, and behavioural data. Developing such approaches to better understand the concept of resilience and disease progression in neurodegenerative diseases represents the direction I aim to pursue.

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Appendix

Publications Included in This Dissertation:

Publication Project 1:

Dynamic properties in functional connectivity changes and striatal dopamine deficiency in Parkinson's disease

In the following the accepted manuscript version of the article published in Human Brain Mapping is displayed. The final published version of record is available at:

Asendorf, A. L., Theis, H., Tittgemeyer, M., Timmermann, L., Fink, G. R., Drzezga, A., Eggers,C., Ruppert-Junck, M. C., Pedrosa, D. J., Hoenig, M. C., & van Eimeren, T. (2024). Dynamic properties in functional connectivity changes and striatal dopamine deficiency in Parkinson's disease. *Human Brain Mapping*, 45(10), e26776. https://doi.org/10.1002/HBM.26776

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Running title: dFC and Dopamine in PD

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Abstract

Introduction: Recent studies in Parkinson's disease (PD) patients reported disruptions in dynamic functional connectivity (dFC, i.e., a characterization of spontaneous fluctuations in functional connectivity over time). Here, we assessed whether the integrity of striatal dopamine terminals directly modulates dFC metrics in two separate PD cohorts, indexing dopamine-related changes in large-scale brain network dynamics and its implications in clinical features.

Methods: We pooled data from two disease-control cohorts reflecting early PD. From the Parkinson's Progression Marker Initiative (PPMI) cohort, resting-state functional magnetic resonance imaging (rsfMRI) and dopamine transporter (DaT) SPECT were available for 63 PD patients and 16 age- and sex-matched healthy controls. From the clinical research group 219 (KFO) cohort, rsfMRI imaging was available for 52 PD patients and 17 age- and sex-matched healthy controls. A subset of 41 PD patients and 13 healthy control subjects additionally underwent ^{18}F-DOPA-PET imaging. The striatal synthesis capacity of ^{18}F-DOPA PET and dopamine terminal quantity of DaT SPECT images were extracted for the putamen and the caudate. After rsfMRI pre-processing, an independent component analysis was performed on both cohorts simultaneously. Based on the derived components, an individual sliding window approach (44s window) and a subsequent k-means clustering were conducted separately for each cohort to derive dFC states (reemerging intra- and interindividual connectivity patterns). From these states we derived temporal metrics, such as average dwell time per state, state attendance, and number of transitions and compared them between groups and cohorts. Further, we correlated these with the respective measures for local dopaminergic impairment and clinical severity.

Results: The cohorts did not differ regarding age and sex. Between cohorts, PD groups differed regarding disease duration, education, cognitive scores and L-dopa equivalent daily dose. In both cohorts the dFC analysis resulted in three distinct states, varying in connectivity patterns and strength. In the PPMI cohort, PD patients showed a lower state attendance for the globally integrated (GI) state and a lower number of transitions than controls. Significantly, worse motor scores (UPDRS-III) and dopaminergic impairment in the putamen and the caudate were associated with low average dwell time in the GI state and a low total number of transitions. These results were not observed in the KFO cohort: No group differences in dFC measures or associations between dFC variables and dopamine synthesis capacity were observed. Notably, worse motor performance was associated with a low number of bi-directional transitions between the GI and the lesser connected (LC) state across the PD groups of both cohorts.

Conclusion: In early PD, relative preservation of motor performance may be linked to a more dynamic engagement of an interconnected brain state. Specifically, those large-scale network dynamics seem to relate to striatal dopamine availability. Notably, most of these results were obtained only for one cohort, suggesting that dFC is impacted by certain cohort features like educational level, or disease severity. As we could not pinpoint these features with the data at hand, we suspect that other, in our case untracked, demographical features drive connectivity dynamics in PD.

Key points:

- Exploring dopamine's role in brain network dynamics in two Parkinson's disease (PD) cohorts, we unravelled PD-specific changes in dynamic functional connectivity (dFC).
- Results in the PPMI and the KFO cohort suggest motor performance may be linked to a more dynamic engagement and disengagement of an interconnected brain state.
- Results only in the PPMI cohort suggest striatal dopamine availability influences large-scale network dynamics that are relevant in motor control

Key words:
Dynamic functional connectivity, resting state fMRI, imaging, network, F-Dopa PET, DAT SPECT,

Introduction:

Parkinson's disease (PD) is characterized by a degeneration of the nigrostriatal dopaminergic neurons, causing a wide range of motor and non-motor symptoms. Region-specific associations have revealed a strong relationship between striatal dopamine availability, motor symptom severity (Asenbaum et al., 1997; Benamer et al., 2001; Pirker, 2003)), and higher-order cognitive tasks (Cools, 2011; Costa et al., 2014). From a network-based perspective, this suggests dopamine is a crucial player in effectively recruiting large-scale networks associated with these cognitive and motor domains. Using resting-state functional MRI (rsfMRI) to investigate connectivity across different networks has repeatedly shown that the putamen, which is known to express the most prominent striatal dopamine reduction in clinical PD, loses connectivity strength with frontal brain structures (Rolinski et al., 2016). Further, in recent multimodal approaches incorporating dopamine positron emission tomography (PET) or dopamine transporter (DaT) single-photon emission computed tomography (SPECT), it has been illustrated that the degeneration of nigrostriatal connectivity functionally impairs distinct striatocortical (Ruppert et al., 2020) and putamen-midbrain (Rieckmann et al., 2015) projections.

Additionally, an increase in dopaminergic deficit was associated with decreased putaminal interconnectivity over time (Li et al., 2020). These studies suggest that dopamine is fundamental for the efficient interplay between motor processing areas and parts of the basal ganglia. Interestingly, PD-specific changes in large-scale network organization normalize after taking dopaminergic medication (P. T. Bell et al., 2015; Cole et al., 2013; Wu et al., 2009). Thus, network consequences of dopamine loss may not be limited to brain regions directly connected to the basal ganglia. However, how striatal dopamine deficiency specifically perturbs the interplay of large-scale brain networks remains unresolved.

Notably, most of these studies assessing network organization modulated by dopamine capacity in PD have typically assumed temporal stability and, hence, time-averaged functional networks across the resting state data acquisition. However, functional networks dynamically fluctuate within scales of seconds and minutes (Chang & Glover, 2010). Incorporating the temporal features of spontaneous functional connectivity (FC) fluctuations in a dynamic FC analysis (dFC) aims to characterize these dynamics. How well the fluctuations in FC are aligned with actual brain dynamics is currently under debate. However, the note that dFC captures actual neural dynamics in the brain is supported by a growing body of literature (for review, see (Lurie et al., 2020). Thus, dFC has been suggested to index changes in macroscopic neural activity patterns underlying critical aspects of cognition and behavior (Calhoun et al., 2014;

Hutchison et al., 2013; Liégeois et al., 2019; Vidaurre et al., 2021). As dFC provides additional information about the temporal profile of brain function, it proposes the potential to improve our understanding of impaired brains and their changes in disorders. In fact, compared to the static approach, growing evidence suggests dFC to be a sensitive indicator for determining disability level (Tozlu et al., 2021) and distinguishing between individuals with pathological conditions and those without (Jin et al., 2017; Rashid et al., 2016). Concomitantly, altered network dynamics have been reported for various neuro-psychiatric conditions like schizophrenia (Damaraju et al., 2014; Fu et al., 2018; Sakoğlu et al., 2010; Yue et al., 2018), dementia (Córdova-Palomera et al., 2017; Jones et al., 2012; Schumacher et al., 2019), autism (de Lacy et al., 2017), major depression (Kaiser et al., 2015; Zhi et al., 2018), or epilepsy (Liu et al., 2017).

In PD, several recent whole-brain dFC accounts suggested the relevance of network dynamics in the clinical presentation of PD (Cao et al., 2023; Cordes et al., 2018; Díez-Cirarda et al., 2018; Fiorenzato et al., 2019; J. Kim et al., 2017). Importantly, these studies could show that PD-specific changes in dFC were linked to motor symptom severity (J. Kim et al., 2017), mild cognitive impairment (MCI) (Díez-Cirarda et al., 2018; Fiorenzato et al., 2019), PD dementia (Fiorenzato et al., 2019), and autonomic dysfunction (Cao et al., 2023). Together, these studies emphasize that motor and cognitive impairments in PD appear to be driven by spatial *and* temporal alterations of large-scale network dynamics. However, reports concerning dFC in PD are inconsistent. While some studies suggested PD to be associated with a higher occurrence of highly interconnected states (i.e., reoccurring patterns of functional connectivity across time) (Díez-Cirarda et al., 2018; Kim et al., 2017), others demonstrated PD (Fiorenzato et al., 2019) and PD progression (Cao et al., 2023) to be associated with a higher occurrence of sparsely connected states. These inconsistent findings, however, may be due to methodological differences in data analyses and study design. Moreover, the currently available studies employing dFC in PD are limited to correlations with behavior or clinical severity and do not use quantified information about the degree of dopaminergic terminal loss. Direct investigations of the modulatory role of dopamine on dynamic network fluctuations are currently missing.

To this end, we analyzed datasets of two age- and sex-matched cohorts. The PPMI data set (https://www.ppmi-info.org/study-design/study-cohorts) included rsfMRI for 63 PD patients and 16 controls and DaT-SPECT as a measure for presynaptic dopaminergic dysfunction. In comparison, the KFO dataset (https://gepris.dfg.de/gepris/projekt/101434521?language=en) comprised 52 PD patients and 17 controls, including ^{18}F-Dopa PET as the measure of presynaptic dopaminergic impairment. The objectives of our study were as follows: First, to probe the reproducibility of our dFC analysis in two different PD cohorts. Second, to investigate the relationship between dopamine deficiency and large-scale network dynamics. To achieve this, we obtained PD-specific dFC changes by comparing the dFC variables of a healthy control group with a PD group for each cohort separately. Consequently, we tested whether these PD-specific dFC changes were associated with clinical cognition, motor scores, and dopamine availability in the striatum. We suspected PD-specific changes in dFC to appear in both groups. According to the literature discussed above, we expected these to be associated with either motor or cognitive function and dopaminergic deficit in the striatum.

Materials and Methods:

Participants

Data used for this study included two different cohorts. The first cohort included subjects enrolled in the Clinical Research Group 219 (KFO219) in Cologne. For the KFO cohort, rsfMRI and structural MRI data of 52 PD patients and 17 healthy controls were available. A subset of 41 PD patients and 13 healthy control subjects additionally underwent ^{18}F-DOPA-PET imaging. The average time difference between MRI and ^{18}F-DOPA-PET imaging was 29 days (SEM 8.05 days). All PD patients fulfilled the UK Brain Bank Criteria for PD (Gibb & Lees, 1988). All participants gave informed consent. The study was approved by the local ethics committee (EK12-265).

The second cohort was matched to the KFO cohort regarding age and sex and was composed of individuals registered in the Parkinson's Progression Marker Initiative (PPMI). The PPMI dataset included 63 PD patients and 16 age- and sex-matched healthy controls. These subjects 1) had undergone a fixed rsfMRI protocol (see MRI acquisition), 2) were between fifty and eighty-five years old, and 3) had data of structural MRI, UPDRS-OFF, and DaT-SPECT imaging available. For PD individuals, the absolute time difference between the acquisition time points of these data and the rsfMRI acquisition date did not exceed 182 days. The PD group's average time difference between the DaT scan and rsfMRI acquisition was 12 days (SEM 2.29). For the control group, the difference was 728 days (SEM 165.22). All PD patients had a diagnosis of Parkinson's disease and exhibited bradykinesia and at least one of the following: resting tremor and/or rigidity.

Exclusion criteria for both cohorts included a history of other severe or neurological diseases and/or current medication that affects brain function, a clinical diagnosis of dementia, and MRI safety exclusion criteria. Any quality defects of the rsfMRI, like artifacts, phantoms, tilted planes, or cuts in the cortex, were excluded. The demographic characteristics of the two cohorts are summarized in Table 1.

Clinical assessment

In both cohorts, disease severity in PD patients was assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Goetz et al., 2008) in an unmedicated state (OFF). For the KFO dataset, this represented at least 12 hours of withdrawal of dopamine replacement therapy or 72 hours for extended release of dopamine agonists. In the PPMI cohort, 31 PD patients were taking medication. These subjects discontinued dopaminergic medication at least 6 hours (16 hours on average) before clinical examination (UPDRS-III). Furthermore, the Mini Mental State Examination (MMSE) in the KFO dataset and the Montreal Cognitive Assessment (MoCA) in the PPMI cohort were used as proxies for cognitive function. To establish comparability of these two tests, we converted the MoCA scores to MMSE scores according to a recently introduced table (Fasnacht et al., 2023).

Assessment of dopamine loss

Measures of presynaptic dopamine deficiency were used to assess the possible impact of striatal dopamine availability on large-scale network connectivity dynamics. In the KFO cohort, ^{18}F-DOPA-PET imaging was used, which was acquired for a subset of 56 subjects on a 24-detector ring scanner (ECAT EXACT HRRT, Siemens) at the Max-Planck-Institute for Metabolism Research in Cologne. ^{18}F-DOPA-PET was performed in the morning after overnight fasting and OFF dopaminergic medication. The image processing procedure was previously described elsewhere (Hammes et al., 2019). Briefly, dopamine metabolism was assessed using

a reference tissue model (Patlak plot) on dynamic scans comprising nine movement-corrected and spatially normalized frames. This data processing resulted in images exclusively representing the striatum's presynaptic dopamine synthesis capacity. Finally, the mean presynaptic dopamine synthesis capacity was extracted from four striatal volumes of interest (VOIs): the left and right putamen and caudate nucleus.
In the PPMI cohort, DaT-SPECT imaging was carried out in different imaging centers on different scanners. DaT-SPECT imaging was performed according to the PPMI standardized protocol to quantify dopamine transporters in the striatum. Each imaging center reconstructed SPECT images using a standard iterative reconstruction algorithm and then corrected them for attenuation. Detailed imaging protocols can be comprehended here: https://www.ppmi-info.org/study-design/research-documents-and-sops
Our analysis used mean putamen and caudate values for both cohorts.

MRI acquisition

An anatomical T1-weighted MRI and a rsfMRI series were acquired for each participant. In KFO, the structural T1-weighted images were obtained on a 3.0 T Siemens Magnetom Prisma scanner using multiband (SMS factor of 8) scanning combined with a 64 channel coil. The acquisition parameters were set as follows: repetition time (TR) = 2300 ms, echo time = 2.32 ms, flip angle = 8°, field of view =230 mm, slice thickness =0.90 mm, voxel size= 0.9 x 0.9 x 0.9 mm, number of slices = 192. The rsfMRI series included a gradient echo-planar imaging sequence with interleaved acquisition mode using the following parameters: TR = 0.776 ms, echo time = 37.4 ms, flip angle = 55°, field view =208 mm, voxel size = 2.0 x 2.0 x 2.0 mm, slice thickness = 2 mm. The acquisition time was 8 minutes and contained 617 time points comprised of 72 axial slices each.
In PPMI, the structural images were acquired on 3.0 T Siemens Magnetom scanners (Trio-A-Tim, Verio, or Prisma) using a slice thickness of 1 mm. The rsfMRI series used in the PPMI cohort was carried out in interleaved acquisition mode running the following protocol: TR = 2400 ms, echo time = 25.0 ms, voxel size = 3.3 x 3.3 x 3.3 mm, slice thickness 3.3 mm. The acquisition time was 8 minutes and 24 seconds, containing 210 time points composed of 40 axial slices each.
In both cohorts, subjects were asked to keep their eyes open and remain still.

Functional MRI data preprocessing and motion control

Preprocessing was carried out using the CONN toolbox v20.b (Whitfield-Gabrieli & Nieto-Castanon, 2012) implemented in Matlab (Matlab R2020b Update 4, MathWorks, Inc., Natick, Massachusetts, United States). A default preprocessing pipeline was used to normalize the images to the MNI (Montreal Neurological Institute) space (web.conn-toolbox.org/fmri-methods/preprocessing-pipeline). The pipeline includes spatial realignment, slice-timing correction, outlier identification, segmentation, normalization, and smoothing (Gaussian kernel 8mm full-width half maximum).
Using the artifact removal tool included in CONN potential outlier scans caused by subject motion were identified, yielding six-dimensional motion vectors composed of translational (x, y, z axes) and rotational (pitch, yaw, roll) displacement scores. These six displacement scores were each transformed into single framewise displacement (FD) values using a published formula (Power et al., 2012). Acquisitions were discarded if they showed a mean FD > ½ voxel size (1 mm in KFO and 1.65 mm in PPMI) and/or a maximum displacement of more than one voxel (2 mm in KFO and 3.3 mm in PPMI). According to these criteria, four PD patients and two

healthy controls were excluded from the KFO cohort, resulting in a global mean FD of 0.19 mm for the final cohort. Finally, two PD patients and two healthy controls were excluded from the PPMI cohort, which resulted in an average FD of 0.34 mm.

Identification of intrinsic connectivity networks

Dimensionality reduction and group component definition

Independent group components were identified in a data-driven approach by means of data reduction and a spatial independent component analysis (ICA) utilizing the Group ICA fMRI toolbox (GIFT) (v3.0c, https://trendscenter.org/software/gift/). To obtain comparable components between the two cohorts, the group component identification was conducted in a pooled approach on all subjects of the two cohorts, involving healthy controls and PD patients (see Fig 2 left). The applied data reduction and ICA protocol followed previous dFC analyses (Allen et al., 2014; Damaraju et al., 2014; Díez-Cirarda et al., 2018; Fiorenzato et al., 2019; J. Kim et al., 2017): On the subject level, a principal components analysis (PCA) reduced the data to 120 principal components (PCs). At the group level, the concatenated reduced data was condensed to 100 PCs using the expectation maximization algorithm for PCA (Roweis, 1998). Following the data reduction step, a Infomax ICA algorithm (Himberg et al., 2004) decomposed the group-level data into independent networks (A. J. Bell & Sejnowski, 1995), producing a single set of 100 group independent components (ICs). Reliability through process stability was ensured by repeating the Infomax algorithm 20 times using the ICASSO method. Only components with a stability index > 0.9 were selected, leaving 76 ICs for spatial characterization. Thereafter, a GICA-based back-reconstruction step was added to compute individual subject-specific spatial maps required for further analysis (Calhoun et al., 2001).

Feature identification and thresholding

Of the 76 stable ICs, we identified 57 independent network components (INCs) utilizing identification criteria previously described (Allen et al. 2014, 2011): 1) peak activations located primarily in the grey matter, 2) low spatial overlap with known vascular and ventricular spaces, 3) low susceptibility for artifacts. The resulting 57 INCs were subsequently grouped into 14 previously established resting state networks (RSNs) (Shirer et al. 2012; Allen et al. 2014): Using the Dice similarity coefficient (a measure of spatial overlap), the INCs were sorted according to their highest spatial overlap with one of the RSNs. In seven instances, a single INC had a similar spatial overlap with several RSNs. For these cases, one of the RSN options was chosen by the shared decision of two experts (M.H., T.v.E.). An overview of the component patterns and corresponding RSNs can be found in Figure 1. With the preceding steps, including data reduction, ICA, feature identification, and back-reconstruction, we defined RSNs that share comparable activation patterns and anatomical locations across each individual and both cohorts. This approach enabled us to assess changes in RSN connectivity and compare these changes between individuals, groups, and cohorts.

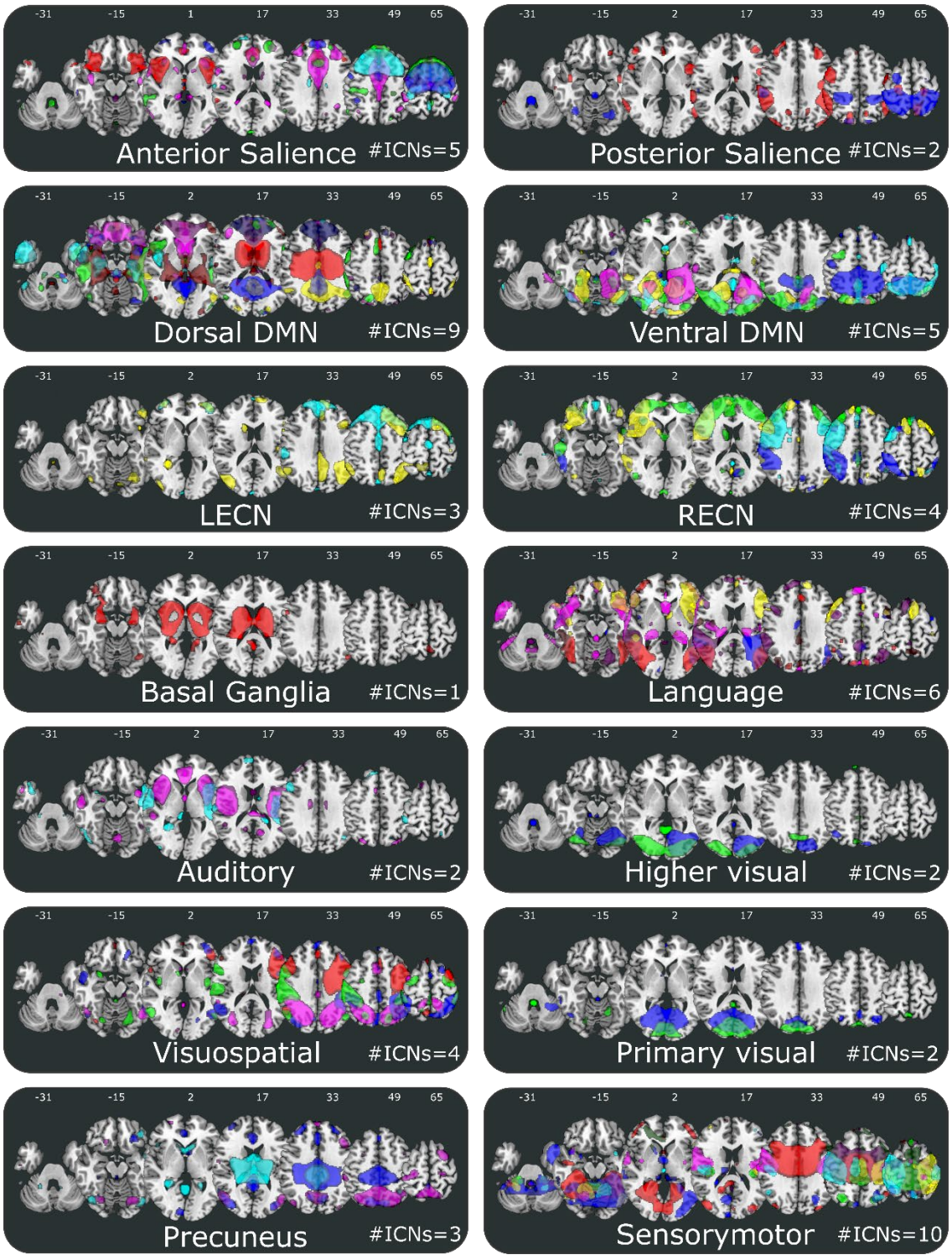

Figure 1: Composite maps of the 57 independent network components (INCs) identified by group ICA. Based on their anatomical and functional properties, 57 INCs were grouped into the 14 resting-state networks (RSNs) for functional connectivity previously established by Shirer et al., 2012. Each color in the composite maps corresponds to a single INC. The number of ICNs sorted into each RSN is stated in the bottom right corner of each panel. DMN = default mode network; LECN = left executive network; RECN = right executive network.

Dynamic functional connectivity analysis

The dynamic functional connectivity (dFC) analysis was conducted separately for each cohort. Using the temporal dFNC toolbox in GIFT, we combined two approaches: The sliding window approach, which determines changes in functional connectivity across time in single subjects, and the *k*-means clustering algorithm, which enables the extraction of reoccurring patterns of functional connectivity across time (see Figure 2 right).

Sliding window approach

The sliding window approach was applied on time courses of the back-reconstructed subject-specific spatial maps obtained from the ICA, including both cohorts. Therefore, the same subject-specific maps were used in both analyses. These time courses were analyzed in frames of a defined length, called windows. The first window was set at the beginning of a time course and was then moved along the data by a predefined number of data points, defined as step variable. For each window, a covariance matrix was calculated, portraying the connectivity as covariance (correlation) between all INCs at that particular time. Each covariance matrix was composed of (57 × (57-1))/2 = 1596) features. Following previously established methods (Allen et al. 2014), a tapered window of 44s (57 TRs in KFO and 18 TRs in PPMI) was used, which was convolved with a Gaussian kernel of 3 TR. The window was moved by 1TR steps along the 617 (KFO) and 210 (PPMI) -TR scan, resulting in 493 (KFO) and 174 (PPMI) consecutive windows and their corresponding functional connectivity (FC) estimates (covariance matrices). Prior to further analysis, the FC estimates were Fisher Z transformed to improve the normality of Pearson's r distribution. To investigate the potential effect of TR, we matched the TRs of the two samples by down-sampling the KFOs TR to 2.328 ms (average of three scans with a TR of 0.776 ms). The results were comparable for manipulated and unmanipulated TR. Hence, the TRs for the current analysis were not altered.

Clustering analysis

We applied the k-means clustering algorithm to all windowed FC estimates to assess reoccurring FC patterns. For each cohort, the clustering algorithm was initially performed on a defined subset of exemplary windows, chosen as the windows with local maxima in FC variance, and repeated 500 times on this set. The resulting centroids (cluster medians) were then used to initialize the clustering of all data on 69 subjects times 493 windows, equating to 35.496 instances in the case of KFO and 79 subjects times 174 windows, equating to 13,746 instances in the PPMI cohort. The similarity between each FC estimate and the cluster centers was determined using the L1 distance function (Aggarwal et al., 2001). The optimal number of clusters (k) was defined using the Elbow criterion, which independently yielded four valid clusters (*k*=4) in both cohorts. Hence, based on the similarity of each FC matrix with the four obtained cluster centroids, all respective FC matrices were then categorized into one of the given four clusters (states). Reproducibility of the estimated states has previously been validated, showing that k-means clustering results yielded reproducible cluster centroids from both analyses with bootstrap resamples and split-half samples of subjects (Allen et al., 2014).

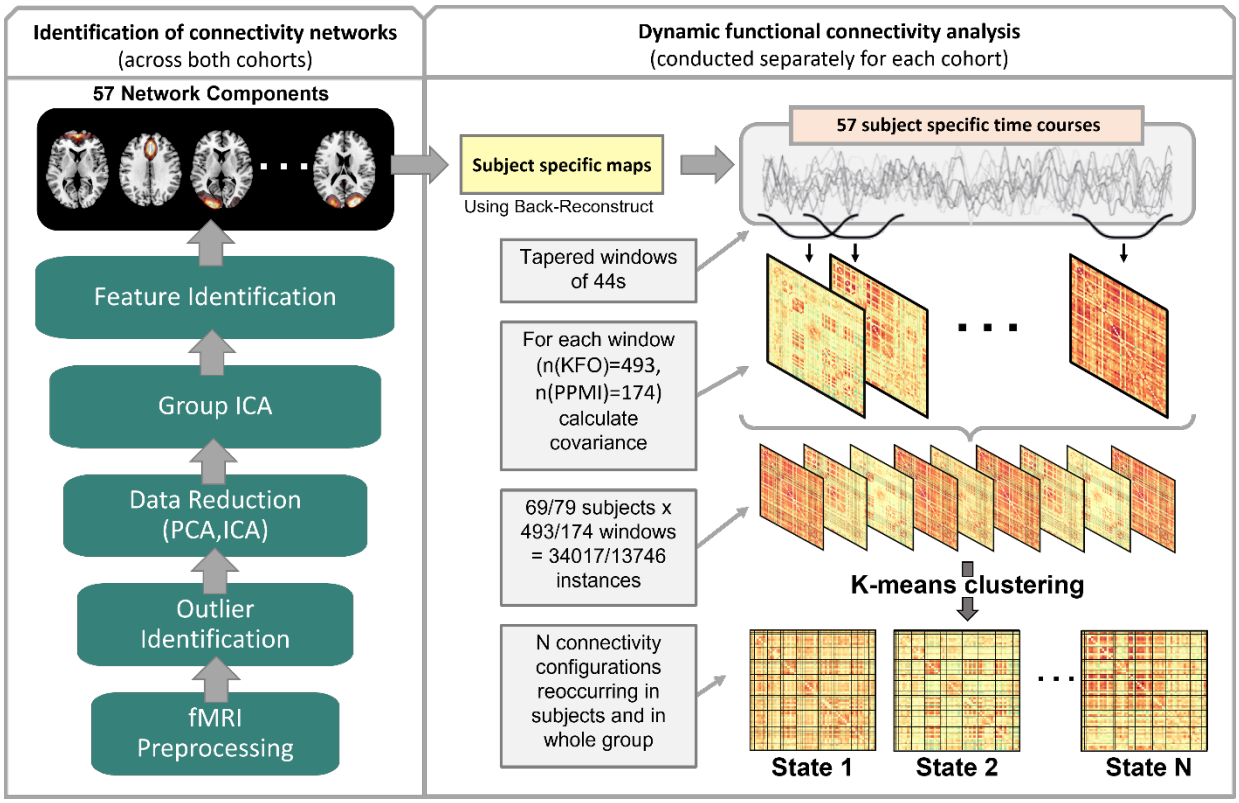

Figure 2: Schematic of the dynamic functional connectivity analysis pipeline: The green boxes represent the general steps to retrieve independent network components (INCs) from both cohorts. Afterward, a back reconstruction step resulted in subject-specific spatial maps and time courses for each INC. Via the sliding window approach utilizing tapered windows of 44s length, correlation matrices were obtained for each patient across the entire scan for each cohort. With the k-means clustering algorithm, the correlation matrices of the entire cohort were clustered according to similarity.

Global state characteristics

To derive and compare the connectivity pattern associated with a state, connectivity matrices were calculated using in-house Python scripts (Asendorf, 2024; Damaraju et al., 2014): First, a subject median was computed for each state based on the subject windows assigned to that state. Second, subject medians for each state were used to derive median connectivity matrices for each state per cohort (see Fig. 3). A state's connectivity strength was defined as the absolute sum of all correlation values in its median connectivity matrix. Notably, only correlation values higher or respectively lower than 10% of the highest and lowest correlation values were included to reduce the impact of noise on our measure. To define the proportionate similarity between two states, the Manhattan distance was calculated. According to the Manhattan distance, the most similar states were matched between cohorts. Next, to create state similarity profiles, we compared each individual tile (i.e. covariance of one INC with another) between the two matched states, respectively. For that purpose, we used Mann-Whitney U tests on all available subject medians for each tile (Asendorf, 2024; Damaraju et al., 2014). Hence, the comparison plots include the effect strength (r) of Mann-Whitney U tests for each tile. Only the effect strengths of results that were significant after FDR correction were reported. A state's occurrence was defined as the percentage of windows assigned to it. In an attempt to further characterize the connectivity pattern entailed in a state, we reported between-network correlations that stood out upon visual inspection.

Calculation of temporal properties

Temporal properties of the dFC analysis were extracted, analyzed, and plotted for each cohort separately using in-house Python scripts(Asendorf, 2024): Based on the categorized data obtained by the clustering analysis in GIFT, state transition vectors were created, representing the assigned state for each window for each participant. To examine the temporal properties, we assessed four variables: average dwell time, total number of transitions, bi-directional transitions, and state attendance. The average dwell time was defined as the mean time spent in a particular state. We also assessed the total number of transitions between any states and the number of bi-directional transitions between specific pairs of states. A state was considered as attended if at least one window of that participant was assigned to that particular state.

Statistical analyses

All statistical analyses were carried out using R (Rstudio ver. 2022.12.0) and Python (Spyder; Python ver. 3.10). Given that assumptions of normality and homoscedasticity were not met in terms of the dFC variables per cohort, non-parametric tests were applied. To minimize the influence of potential covariates, we corrected our statistical tests for age and sex. To this purpose, Whitney U tests were performed on the residuals of a linear model predicting the variable examined using age and sex. Further, Kendall's Tau correlations were corrected for age and sex using the ppcor package in R (S. Kim, 2015). Chi-squared tests can not be corrected for covariates. However, all variables labeled as significantly different between groups by the Chi-squared test also showed a significant effect of group on the variable examined in a logistic regression model correcting for age and sex. Since PPMI is a multi-center cohort study, we sought to estimate the effect of inter-scanner variability on our results. Therefore, these tests were repeated with additional corrections for scanner identifiers. However, inter-scanner variability did not appear to affect our results. Thus, they were not reported in the results. Considering states with generally low attendance are a potential cause for unreliable statistics, we only included states attended by more than 50% of the cohort's subjects. Hence, state four (23 %) of the KFO cohort and state two (23%) of the PPMI cohort were excluded from the statistical analyses. Corrections for multiple comparisons were carried out using the Dunn and Šidák criterion (Šidák, 1967).

Group comparisons of dFC measures

Mann-Whitney U tests were performed to compare the PD and control groups in terms of variables derived from dFC analysis (i.e., average dwell time, fraction time, and number of transitions). For categorical variables like state attendance, Chi-squared tests were utilized.

Correlation analyses – dFC measures, dopamine loss, and behavior

To assess whether dFC measures were associated with cognitive test scores and motor performance, MMSE and UPDRS-III scores were correlated with average dwell time and the number of total and bi-directional transitions using two-sided rank correlation tests (Kendall's Tau). Besides, to examine whether temporal properties of a distinct state were associated with striatal dopamine signal, rank correlations were carried out between the mean synthesis capacity of the putamen and caudate VOIs and the dFC measurements.

Results

Group characteristics

In both cohorts (see Table 1), we found no significant differences between the control group and the PD group in terms of sex, handedness, age and MMSE. In both cohorts, PD subjects had significantly fewer years of education and lower putaminal dopamine synthesis capacity or dopamine transporter availability, respectively.

Across cohorts, PD subjects did not show significant differences regarding sex, handedness, age and UPDRS-III OFF scores. The PD group included in the KFO study had fewer years of education, lower MMSE scores, a higher L-dopa equivalent daily dose (LEDD), and a longer disease duration compared to the PD group of the PPMI cohort. Across cohorts, the KFO control group also showed lower values on the MMSE compared to PPMI controls. Sex, handedness, age, and education did not differ between the KFO control and the PPMI control group.

Dynamic functional connectivity

Global state characteristics

In both cohorts, we identified three distinct connectivity states that reoccurred in individuals throughout a resting state scan and were present across subjects (see Figure 3).

For the KFO cohort, the two most frequently occurring states (a total of 64% of all windows) showed the most similar connectivity patterns (Manhattan distance of 119) across all state pairs (See Fig 3. top middle and top right pane). They mainly differed in overall connectivity strength. One state was clearly more interconnected with absolute correlation sums of 211.6 and 146.1, respectively. Hence, this state will be referred to as the more interconnected (MC) state, while the other state will be referred to as the lesser connected (LC) state of this state pair. Upon visual inspection, the pair can be characterized by strong correlations of the default mode network (DMN) with itself and parts of the left executive network (LECN) and the language network. The other state occurred less frequently (a total of 22% of all windows) and exhibited high correlations for the ventral DMN with the visual networks, the language network and parts of the SMN, the auditory network, and the salience networks (see Fig 3 top left pane). As this state showed high interconnectivity for all RSN despite the auditory network, the dorsal DMN, and parts of the SMN, we will refer to this state as the globally integrated (GI) state.

Among all states of the PPMI cohort, two states exhibited the highest similarity measured by Manhattan distance (Manhattan distance of 107) (see Fig 3. bottom middle and bottom right). These states occurred by far the most (total of 73 % of all windows) and primarily differed in connectivity strength (absolute correlation sum of 107.8 vs. 178.0). Hence, one state of the pair will be referred to as the more connected (MC) state, while the other will be termed the lesser connected (LC) state. The other state occurred least often (a total of 16% of all windows) and showed a very distinctive connectivity pattern (see Fig 3 bottom left pane). On visual assessment, this state presented relatively high connectivity between the DMN, the primary visual, and the somatomotor networks. Following the framework in the KFO data, it will be referred to as the globally integrated (GI) state.

The similarity between the sorted state profiles between both cohorts was described by Manhattan distance as follows: The highest similarity for the GI state and the LC state of the KFO cohort were the GI and the LC state of the PPMI cohort, respectively. For the MC state of the KFO, the LC state of the PPMI cohort was most similar. Further, upon visual inspection of the similarity matrices (See supplementary Fig 1), the LC states showed the highest similarity,

while the MC and the GI states showed less similarity. A thorough visual assessment of the supplementary figure suggests that the indifferences between the MC and GI states were especially driven by the presence of negative correlations.

Group differences in temporal properties

No significant group differences were found in terms of average dwell time in the KFO cohort and the PPMI cohort. (see Fig 4A).

We determined the number of subjects having at least once dwelled in a state during acquisition, to compare state attendance between the groups. In the KFO cohort, no group differences were observed for state attendance. For the PPMI cohort, this yielded a higher state attendance of the GI state for the control group in contrast to the PD group ($X^2(1, N=79) = 5.82$, $p= .016$) (see Fig 4B).

To determine further differences between groups, we compared the total number of transitions as well as the bi-directional transitions between pairs of states. For the KFO cohort, no group differences could be reported regarding total and bi-directional transitions. When assessing the distribution of the total number of transitions in the PPMI cohort, controls exhibited a higher number of transitions than PD patients in the ($U(N=79) = 331$, $z = -2.10$ $p= .035$) (See Figure 4D). In terms of bi-directional transitions, controls showed a higher number of transitions between the GI and the MC state ($U(N=79) = 276.5$, $z = -2.77$ $p= .006$) (see Figure 4C).

Correlation between striatal dopamine availability, dynamic functional connectivity measures, and clinical measures

dFC with clinical measures

We tested for an association between MMSE and UPDRS-III scores with the number of bi-directional transitions, average dwell times, and total number of transitions. In the KFO cohort, an association between UPDRS-III scores and the number of bi-directional transitions between the GI and the LC state ($\tau_b(N=52)= -.245$; $p =.012$) was observed in the PD group. For the MMSE scores, no associations with dFC were found in the KFO cohort. In the PPMI cohort, a correlation analysis revealed significant negative associations between UPDRS-III motor scores and average time spent in the GI state ($\tau_b(N=63) = -.276$; $p =.002$) and the MC state ($\tau_b(N=63) = -.201$; $p =.022$). Moreover, we found negative associations of the UPDRS-III and the total number of transitions ($\tau_b(N=63)= -.307$; $p < .001$) and number of bi-directional transitions between the GI and the LC state ($\tau_b(N=63)= -.227$; $p =.010$) and the MC and the LC state ($\tau_b(N=63)= -.213$; $p =.015$) in the PD group. In the PPMI cohort, no associations of dFC variables with MMSE were found.

Dopamine with clinical measures

In a subsequent step, we tested whether dopaminergic insufficiency of the two striatal VOIs was associated with either cognitive scores or motor function in the PD groups. The correlation analysis yielded a significant negative correlation between the mean putamen values and UPDRS-III OFF scores in the KFO cohort (τ_b $(N=41) = -.226$ $p= .043$) and the PPMI cohort (τ_b $(N=63) = -.180$ $p= .040$). Both results did not withstand correction for multiple comparisons (k=2: adj. $p= .025$). In both cohorts, we did not find an association between cognitive scores of the MMSE and mean dopamine scores in the putamen or the caudate.

Dopamine with dFC

As the average dwell time, the number of bi-directional transitions, and the number of total transitions correlated with UPDRS-III off scores in the PPMI cohort, we tested the association between striatal dopamine availability and the three dFC properties across the PD group in both cohorts. Inside the KFO PD group, no such associations between dFC variables and dopamine synthesis capacity could be reported. Inside the PPMI cohort, average time spent in the GI state correlated with the mean DaT availability in the putamen (τ_b(N=63)=.22, *p*= .012) and the caudate (τ_b(N=63)=.216, *p*= .014). The number of total transitions was also associated with mean DAT availability in the putamen (τ_b(N=63)=.341, *p*<.001) and the caudate (τ_b(N=63)=.24, *p*=.006). In terms of bi-directional transitions we observed an association of the number of transitions between the GI and MC state with mean DAT availability in the caudate (τ_b(N=63)=.225, *p*=.010) and the LC and MC with the DAT availability in the putamen (τ_b(N=63)=.225, *p*=.021). We further found an association of bi-directional transitions between the GI and MC (τ_b(N=63)=.183, *p*=.038) state and GI the LC (τ_b(N=63)=.182, *p*=.038) with the mean DAT availability in the putamen. These associations, however, did not survive correction for multiple comparisons (k=2: adj. p=0.025).

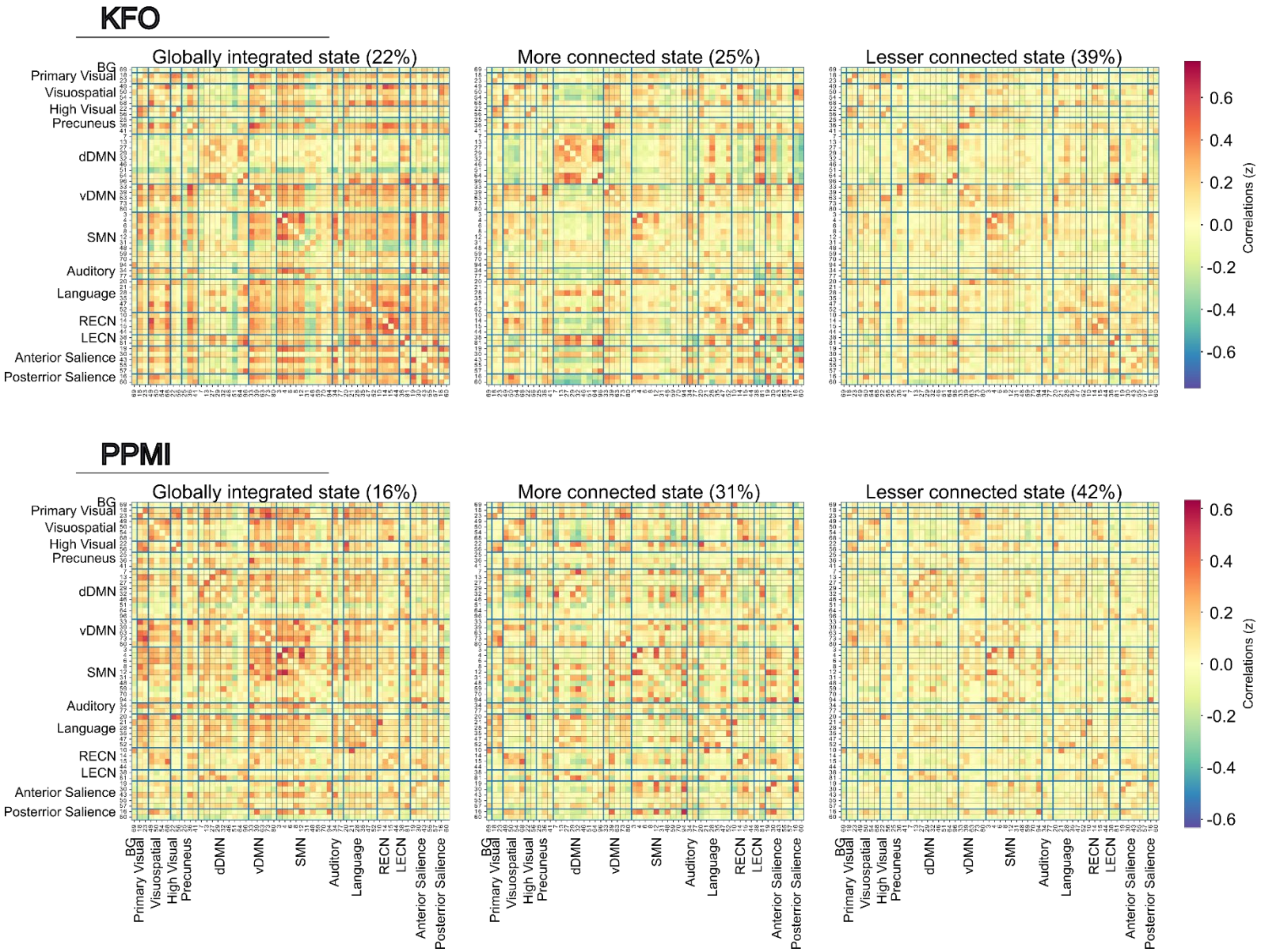

Figure 3: Dynamic Functional connectivity states along the whole sample (k =3) for each cohort. Each cluster is summarized in one functional connectivity (FC) map portraying FC within and between resting state networks (RSNs) (portioned by thick blue lines) in pairwise correlations. The correlations were Fisher z transformed and averaged across all subjects, then inverse z-transformed for display. The total percentage of windows assigned to the state is shown. The value of correlations is represented in the color bar; the red color represents positive and blue negative correlations. The diagonal represents the correlations of the subnetwork by itself and is thereby one.

Table 1: Demographic and clinical Data from both cohorts

	PPMI				KFO				*p*-values			
	PD n=63		**Controls n=16**		**PD n= 52**		**Controls n= 17**		**Controls vs. PD**		**PPMI vs. KFO**	
	Mean (SD)/ Median (IQR)	**Min-Max**	**Mean (SD)/ Median (IQR)**	**Min-Max**	**Mean (SD)/ Median (IQR)**	**Min-Max**	**Mean (SD)/ Median(IQR)**	**Min-Max**	**PPMI**	**KFO**	**PD**	**Controls**
Sex (m/f)	38/25 m=60%	-	13/3 m=81%	-	35/17 m=67%	-	9/8 m=47%	-	$X^2(1, N=79)=1.61$, *p*= .204	$X^2(1, N=69)=1.46$, *p*= .227	$X^2(1, N=115)=0.95$, *p*= .329	$X^2(1, N=33)=3.77$, *p*= .052
Handedness (r/l/b)	59/3/1 r=93%	-	14/1/1 r=87%	-	42/3 r=80%	-	15/1 r=88%	-	$X^2(2, N=79)=1.2$, *p*= .548	$X^2(1, N=61)=0.0$, *p*= 1.0	$X^2(2, N=108)=0.94$, *p*= .624	$X^2(2, N=32)=0.91$, *p*= .633
Age	63.6 (7.9)	50.5 - 78.3	66.3 (7.4)	54.6 - 83.0	66.8 (8.0)	51 - 83	65.1 (7.1)	50 - 75	U(N=79)= 583.0, z=-0.70, *p*= .338	U(N=69)= 393.5, z=-2.81, *p*= .503	U(N=115)= 1292.0, z=-13.27, *p*= 0.052	U(N=33)= 135.5, z=-4.92, *p*= 1.0
Education (years)	15.0 (2.9)	8 - 23	17.0 (2.2)	13 - 22	13.4 (4.1)	0.0 - 20.0	16.6 (4.6)	0.0 - 21.0	U(N=79)= 722.0, z=1.00, ***p*= .006***	U(N=69)= 682.0, z=1.21, ***p*= .001***	U(N=115)= 2038.5, z=-9.08, ***p*= .023***	U(N=33)= 115.0, z=-5.66, *p*= .452
MMSE	30 (1)	24 - 30	30 (1)	28 - 30	29 (2)	24 - 30	29 (1)	27 - 30	U(N=79)= 592.5, z=-0.58, *p*= .191	U(N=69)= 508.5, z=-1.21, *p*= .338	U(N=115)= 2234.5, z=-7.98, **p< .001***	U(N=33)= 199.5, z=-2.61, **p= .011***
UPDRS -III OFF	23(17)	7 - 51	-	-	25 (11.5)	8.0 - 56.0	-	-	-	-	U(N=115)= 1407.0, z=-12.63, *p*= .195	-
Disease duration (years)	2.0 (1.3)	0.1 - 6.2	-	-	5.0 (3.5)	0.0 - 14.0	-	-	-	-	U(N=115)= 768.0, z=-16.22, ***p*<.001***	-
DAT SPECT Putamen	0.7 (0.31)	0.29 - 2.31	1.91 (0.3)	1.53 - 2.81	-	-	-	-	U(N=79)= 991.0, z=4.28, ***p*< .001***	-	-	-
^{18}F-DOPA-PET Putamen	-	-	-	-	0.06 (0.02)	0.02 - 0.12	0.12 (0.01)	0.1 - 0.15	-	U(N=54)= 521.0, z=3.31, ***p*< .001***	-	-
LEDD	311.47 (416.35)	0 - 2200	-	-	468.52 (279.07)	50 - 1320	-	-	-	-	U(N=115)= 940.5, z=-15.25, **p< .001***	-

Deviation values are given in standard deviation (SD) and interquartile range (IQR) for ordinal values of UPDRS-III OFF and MMSE; MMSE = Mini Mental State Examination; UPDRS-III = Unified Parkinson's Disease Rating Scale-Part III, LEDD = L-dopa equivalent daily dose . P-values were obtained by a Mann-Whitney U-test. The Chi-square test was used to test for differences in categorical variables like gender and handedness; *p<.05. Not for all subjects in the KFO cohort, handedness was available.

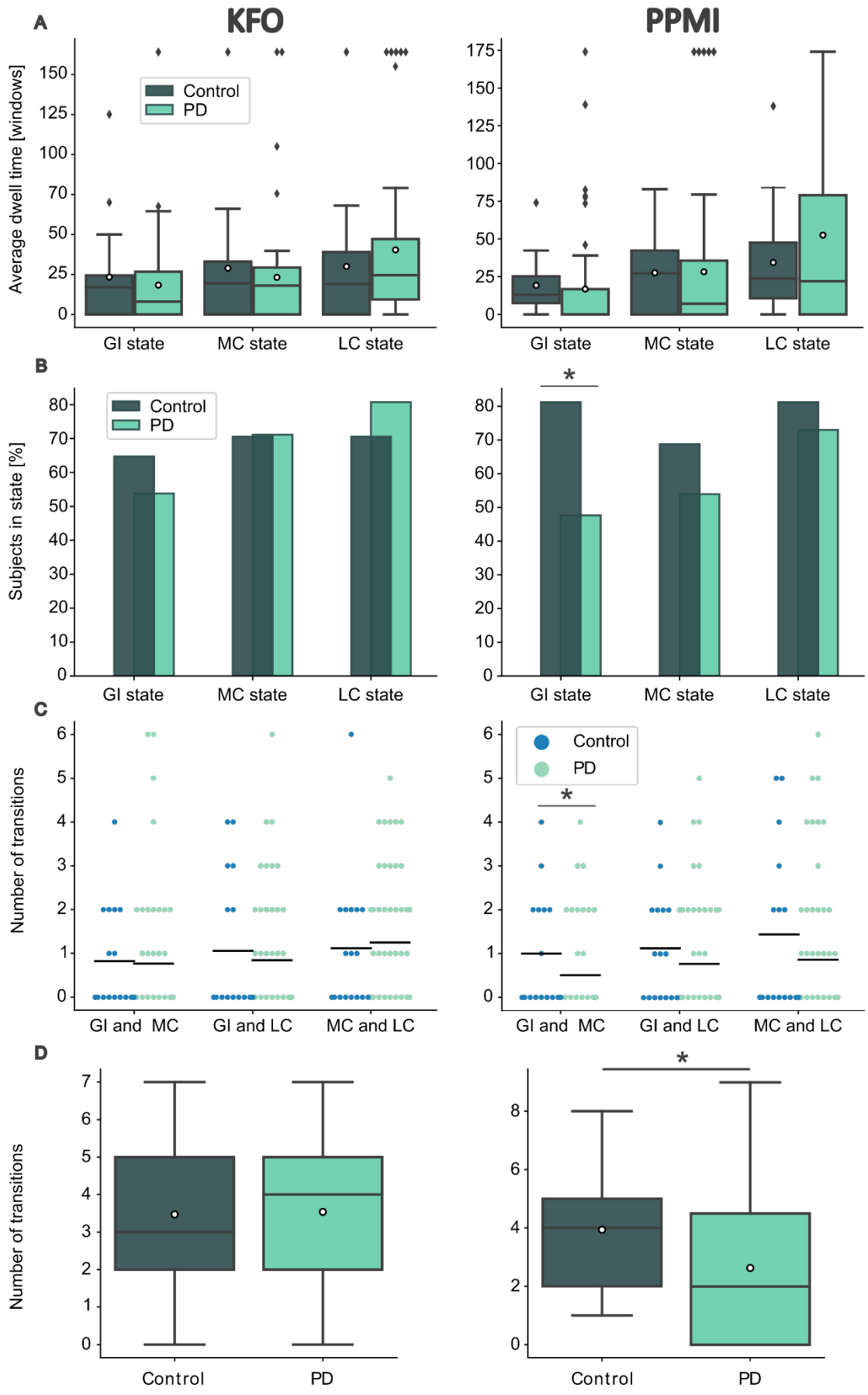
A
KFO
PPMI
Average dwell time [windows]
Control
PD
GI state
MC state
LC state
B
Subjects in state [%]
*
C
Number of transitions
GI and MC
GI and LC
MC and LC
D
Number of transitions
Control
PD

Figure 4: Temporal properties of dFC states for Parkinson's disease and healthy control groups. **(A)** Boxplot portraying the distribution of the average time spent in the globally integrated (GI), the more connected (MC), and the lesser connected (LC) state for each cohort. Each colored box represents the interquartile range (IQR), with the median plotted as a thin line and the mean represented by a white dot. The whiskers specify minimum and maximum. Outliers are shown in the form of diamonds. Time is specified in windows. **(B)** Percentual proportion of subjects having dwelled in the GI, the MC, and the LC state at least once during a scan. A Chi-squared test tested for between-group differences. **(C)** Group-specific number of transitions between the pairs of states GI and MC, GI and LC, and MC and LC. The black lines indicate the mean values. Within-group differences were tested via the Friedmann test. **(D)** Boxplot portraying the distribution of the total number of transitions between all states. Mann-Whitney U-tests tested for between-group differences; *p<0.05.

Discussion

The primary aim of this study was to elucidate dopamine's association with whole-brain network dynamics in PD. This study used two matched cohorts to assess the reproducibility of the dFC results. Ultimately, we found PD-specific network dynamics in the PPMI cohort: A decrease in the number of transitions and a lower overall presence of the GI state. Since these specific features of dFC were negatively associated with UPDRS-III scores (one also in KFO), we suspect a high transition frequency towards a GI state and an increased presence of a GI state to facilitate motor performance. As these have further been shown to be associated with striatal dopamine availability, dopamine appears to play an essential role in mediating those large-scale network dynamics in early PD patients. Notably, our results were not stable across cohorts, suggesting that the dFC alterations depended on cohort composition.

Employing dFC on two cohorts, we identified three connectivity states in both cohorts that followed the same pattern. In both cohorts, there were two states of high total occurrence, showing the highest similarity regarding connectivity patterns of all three states: One was highly connected, while the other was less connected. The last state, less frequent in both cohorts, was characterized by a more global, integrated connectivity pattern. Hence, using two independent k-means clustering approaches, we disentangled two similar connectivity cluster profiles for both cohorts, enabling us to compare inside group differences between cohorts. In the PPMI cohort, we found the overall expression of these states and the dynamic transition between states to be group-dependent. For the KFO cohort, however, we did not observe any differences between groups. Hence, if not explicitly stated, all the findings discussed below were found only inside the PPMI cohort.

First, PD individuals of the PPMI cohort showed overall decreased transitions between states. Indeed, most of the previous studies in whole-brain dFC in PD reported differences in the total number of transitions (Cordes et al., 2018; Díez-Cirarda et al., 2018; Fiorenzato et al., 2019). However, their results are conflicting. While one study reported a higher number of transitions in PD (Díez-Cirarda et al., 2018), two other studies showed a lower transitioning frequency in PD patients compared to controls (Cordes et al., 2018; Fiorenzato et al., 2019). Interestingly, in two of these studies, this trend solely depended on cognitive status (Díez-Cirarda et al., 2018; Fiorenzato et al., 2019). Although our findings suggest that PD patients exhibit limited dynamics in dwelling behavior, these results were not associated with deteriorating cognitive abilities, as reported by Fiorenzato and colleagues (Fiorenzato et al., 2019), or overall decreased cognitive flexibility, as suggested by Nomi and colleagues(Nomi et al., 2017). Against this body of studies, we found features of dFC in the PPMI and the KFO cohort to be associated with motor performance: In PPMI, PD patients who, in total, transitioned less between states showed higher motor impairments according to the UPDRS-III. This result contradicts previous observations linking better motor performance with reduced transition behavior (J. Kim et al., 2017).

Moreover, we observed the same relationship when comparing the specific transitioning patterns between groups. PD patients who specifically transitioned more often between the GI and the LC state showed better motor performance in both cohorts. In contrast, most of the studies mentioned above identified only two states in their study or did not investigate differences in transitioning patterns if more states were present. Hence, across two separate cohorts, we are the first to report associations of specific transitioning patterns with motor performance in PD. These associations suggest that overall high network dynamics and dynamics between particular connectivity configurations are relevant in motor control. Thus,

in PD, the underlying mechanisms facilitating these dynamic transitions between states of global integration and segregation seem to be impaired. Intriguingly, our results in PPMI further imply that this ability to generally transition between states and to specifically transition between globally segregated and integrated states depends on the integrity of the striatal dopaminergic system. This notion is based on two findings. First, we observed, trend significant, the well-known relationship between the decline in DaT signal and the increase in the UPDRS-III motor score (Benamer et al., 2001; Pirker, 2003; Seibyl et al., 1995) inside the PPMI PD group and the KFO cohort. Second, in PPMI PD patients, the ability to dynamically transition between all states, and the ability to transition specifically between the GI and LC state, were associated with caudal and putaminal DaT availability.

Further, fewer PD patients of the PPMI group visited the globally integrated state at least once during an 8-minute acquisition compared to controls. Hence, many PD individuals missed spending time in a state characterized by high interconnectivity between networks. Together with our previous results indicating that dynamic transitions between states of global integration and segregation are impaired in PD, these results extend the notion that PD patients may have problems transitioning specifically into a state of global integration. Interestingly, another study longitudinally investigating dFC changes in PPMI data revealed a decrease in dwell time in a state similar to the GI state and an increase in dwell time for a state corresponding to the lesser connected state (Cao et al., 2023). Their results suggest that hypocoupling worsens in the course of PD (Cao et al., 2023). We did not find a decrease in average dwell time in the GI state for PD. Yet, our other findings in the same cohort suggest this worsening of hypocoupling to be caused by an inability to transition into a state with high interconnectivity. Central to this, in our study, the average time spent in the GI state in the PPMI cohort and the number of bi-directional transitions between the GI and the LC state in both cohorts were positively associated with motor performance. This suggests the increased presence of hypocoupling and decreased dynamics between integrated and segregated connectivity configurations to be related to poor motor output. Similar associations were reported in whole-brain dFC before; however, again, the opposite effect was reported (Kim et al., 2017).

Nevertheless, another recent study showed levodopa intake to increase the dwell time in a state with the strongest functional coupling between the fronto-parietal network (FPN) and the SMN (Chen et al., 2021). OFF medication, this mean dwell time was reduced again in the same PD patients (Chen et al., 2021). Notably, this dopamine-associated change in mean dwell time was negatively associated with UPDRS-III scores, highlighting that altered dFC features are associated with motor performance and, particularly related to dopamine**.** In our PPMI cohort, we could reproduce these findings with a direct measure of dopaminergic impairment, as the mean dwell time in the globally integrated state was positively associated with the mean DaT signal in the putamen and the caudate. While Chen and colleagues' study was focused on dynamics between the SMN and networks involved in top-down motor control, our study assessed network dynamics on a whole-brain level. Hence, our results obtained in the PPMI cohort extend their view of SMN and FPN stability to be dopamine-dependent, pointing to the fact that global integration of the SMN with other non-motor associated networks is dopamine-dependent and relevant to sustaining proper motor output.

According to our results in both cohorts, we suspect that in early PD patients, network changes are affiliated with motor function. In particular, the overall presence of globally interconnected states and high dynamics towards a state of high interconnectivity seem to facilitate motor performance. As in PPMI, these have further been shown to be related to striatal dopamine availability, dopamine appears to play an essential role in mediating those

large-scale network dynamics in early PD patients. With these findings, we provide a novel mechanism for how dopamine might modulate motor control in PD and highlight the potential of investigating large-scale network dynamics in a disease context. In particular, investigating bi-directional transitions between connectivity states, which have never been assessed in PD, provided novel insights into how dopamine might contribute to motor functions.

Importantly, although the state profiles of both cohorts were very well matched, we did not observe any group differences in the KFO cohort. In this section, we will discuss potential reasons for that. First, we will assess how demographical differences and cohort composition might have fueled differences in dFC results across cohorts. Second, we will investigate whether the methodological approach itself might be the underlying cause of the varying results in both cohorts.

Comparing the demographics of both PD groups revealed two things:
First, the PD individuals of the KFO cohort were more advanced in the progression of the disease than the ones of the PPMI cohort. Accordingly, KFO PD patients presented a longer disease duration and a higher LEDD. In the course of the disease, the brain undergoes a functional reorganization of the RSNs, which may even occur before the onset of clinical symptoms (Tessitore et al., 2019). Accordingly, also PD-specific dFC alterations were shown to increase over time (Cao et al., 2023). Since the PD individuals of the KFO cohort showed a more advanced disease progression, we would expect these changes to be more profoundly expressed in the dFC metrics of the KFO PD group cohort compared to the PPMI PD group. However, contrary to our expectations, the KFO cohort did not show any group differences in dFC metrics to the healthy control group.
Second, KFO PD individuals showed lower levels of education and lower scores in cognitive tests despite inherently difficult comparisons between countries. In healthy subjects, cognitive performance (Cabral et al., 2017) and flexibility (Nomi et al., 2017) have been associated with the ability to switch dynamically between states. Further, also PD-specific alterations of dFC have been associated with increased cognitive impairment (Boon et al., 2020; Díez-Cirarda et al., 2018; Fiorenzato et al., 2019). Hence, contrary to the obtained results, we would expect the KFO cohort to be even more likely to show between-group differences than PPMI. This expectation is further supported by findings involving education, cognition, and functional connectivity in healthy aging. Age- and education-related changes in functional connectivity were associated with memory performance (Montemurro et al., 2023). Moreover, a cohort of healthy controls and multiple sclerosis with longer education showed higher dynamics and better cognitive performances.(Lin et al., 2018)

In summary, we could not identify any demographical feature that, in accordance with the current literature, explains why we obtained such imbalanced results between both cohorts. However, we assume that other unrecognized and untracked demographical differences might drive dynamic functional connectivity results. Assessing the cohort composition in more detail may lead to a clearer verdict as to why the group differences obtained in the PPMI cohort were not observed in the KFO cohort. Unfortunately, no more detailed and comparable cohort features were available.

Next, we will address how the methodological approach might have impacted the results. One could argue that due to the unconstrained nature of resting state experiments, the concept of rsfMRI itself may appear challenging when reproducing results in two cohorts. Nonetheless,

static RSNs were proven to have high levels of reproducibility across imaging sessions (Biswal et al., 2010; Shehzad et al., 2009) and different subjects (Damoiseaux et al., 2006; Shehzad et al., 2009). Through our data-driven approach that included both cohorts simultaneously, we established RSNs that were similarly expressed across all individuals of both cohorts. This enabled us to compare differences between groups inside the cohort and the obtained results across cohorts. By choosing comparatively similar sample sizes for controls and PD patients in both cohorts, we ensured that individuals of one particular cohort did not dominate the RSN composition. However, the clinical presentation of PD is heterogeneous. Previous reports indicate a difference in DMN and striatal connectivity in PD patients with tremor-predominant and primarily akinetic rigid symptoms (Karunanayaka et al., 2016; Zhang et al., 2015). Based on this, although PD groups were matched across cohorts, RSN connectivity might have varied in both PD groups due to different subtype ratios.

Furthermore, inside the cohorts, group sizes deviated highly from each other. Controls comprised 25.4% of the PPMI and 32.7% of the KFO cohort. Hence, overall RSN architecture could have been driven by PD RSN composition. Despite that argument, during our definition of meaningful components, the RSNs identified by the ICA considerably overlapped with RSNs previously established in groups of younger healthy controls (Shirer et al., 2012). Refining RSNs for each group in each cohort separately would resolve these two issues. However, they would critically dampen the between-group and especially the between-cohort comparability of our dFC results.

Likewise, the dFC approach might be susceptible to technical differences in data acquisition. Hence, although the same analysis pipelines were used, alterations in data acquisition may interfere differently with dFC results. The most notable alteration in data acquisition is the inter-scanner variability. In contrast to the KFO study, where all subjects were scanned on the same scanner, PPMI, as a multicenter study, includes individuals who were scanned on various scanners and scanner types. Importantly, to test the influence of inter-scanner variability on our results we additionally corrected our results in PPMI for scanner identifiers. The obtained results did not differ from our original results. Hence, we are confident that the variations among scanners in the PPMI dataset have a negligible effect on our findings. Further, it has been suggested that the duration of a dFC-appropriate resting state acquisition should be at least 10 min (Hindriks et al., 2016). Hence, the extended acquisition time in the PPMI resting-state protocol of 8.5 minutes might have been better suited to a dFC approach than the KFO's 8-minute acquisitions. Moreover, the cohort's acquisition paradigms varied drastically in TR. Hence, the analysis was carried out for the KFO cohort separately, once with a TR adjusted to the PPMI dataset and once with an unadjusted TR. Although these two approaches equally did not produce any sign group differences regarding dFC variables for the KFO cohort, we cannot rule out that the different TRs might affect dFC results. Nevertheless, as changing the KFO's TR by downsampling would entail a significant manipulation of the input data, we kept the data as they were. Interestingly, a preceding study provided evidence of the reproducibility of basic connectivity patterns amidst inter-regional connections over 7500 scans composing "probably" mixed independent resting-state datasets of healthy and diseased individuals (Abrol et al., 2017). However, all these scans followed the same acquisition protocol, and only 8 of these scans deviated in TR from the other scans. Vital to mention at this point is a recent study investigating the relationship of dFC alterations with non-motor symptoms of PD in a PPMI cohort. This study used the same analysis pipeline with slightly altered settings (50s windows, Yeo atlas). Intriguingly, this study found astonishingly similar state patterns to those we achieved for the PPMI cohort in our approach (Cao et al., 2023). This demonstrates the reproducibility of state patterns across different analysis

parameters and cohort composition in one of our cohorts. Further, this high similarity in sorted state patterns signifies that joining both cohorts in one ICA did not alter the state pattern composition of our PPMI cohort.

Considering all this, we can summarize that we identified differences in cohort composition and acquisition parameters that could have caused variation in the between-group differences observed in both cohorts. Yet, we did not identify one specific feature in methodology or cohort composition that we consider highly influential. We suspect these differences in the results to be driven by differences in cohort composition that were not assessed within the framework of this study, like disease subtype ratio or lifestyle factors. This again underlines the need for deep phenotyping in neuroimaging datasets, as a more detailed description of the cohorts and more significant group sizes would have been highly relevant to performing an effective group matching.

Conclusion:

Our findings in the PPMI cohort illustrate that PD patients exhibit altered network dynamics compared to healthy controls. These alterations are defined by a lower prevalence for integrated connectivity states and decreased transition frequency between a globally integrated and a lesser connected state. With these findings, we supply a potential mechanism for how dopaminergic neurodegeneration drives global changes in connectivity underlying motor dysfunction in PD. However, most of these results were obtained for only one of two cohorts. Therefore, it will be valuable to reassess these findings and their replicability in two bigger, effectively matched cohorts. Furthermore, it will be interesting to investigate whether the reported impairment of network dynamics is already observable in prodromal stages of PD, such as in patients with REM-sleep behavioural disorder.

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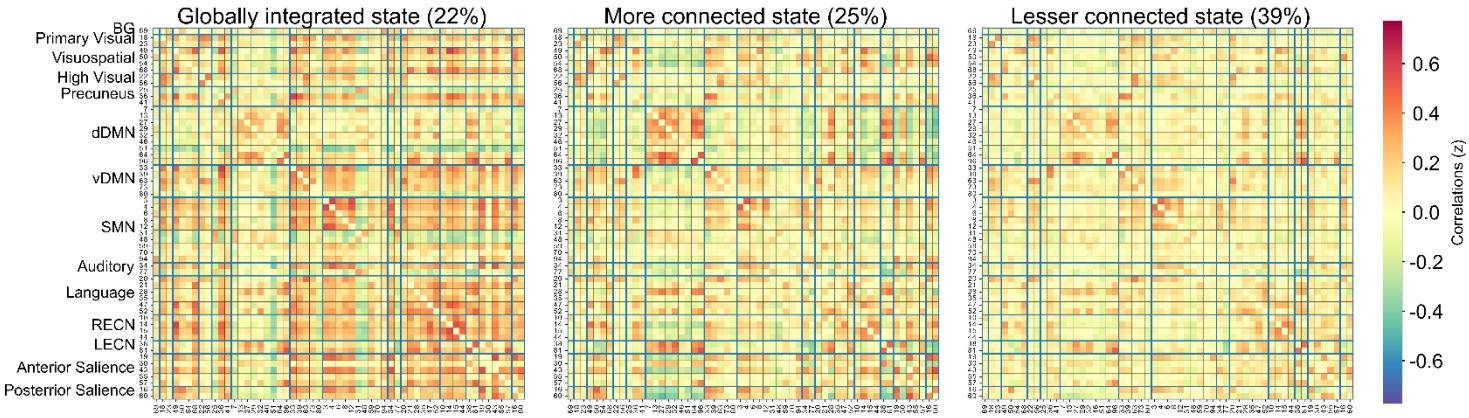
Supplementary Material:

KFO



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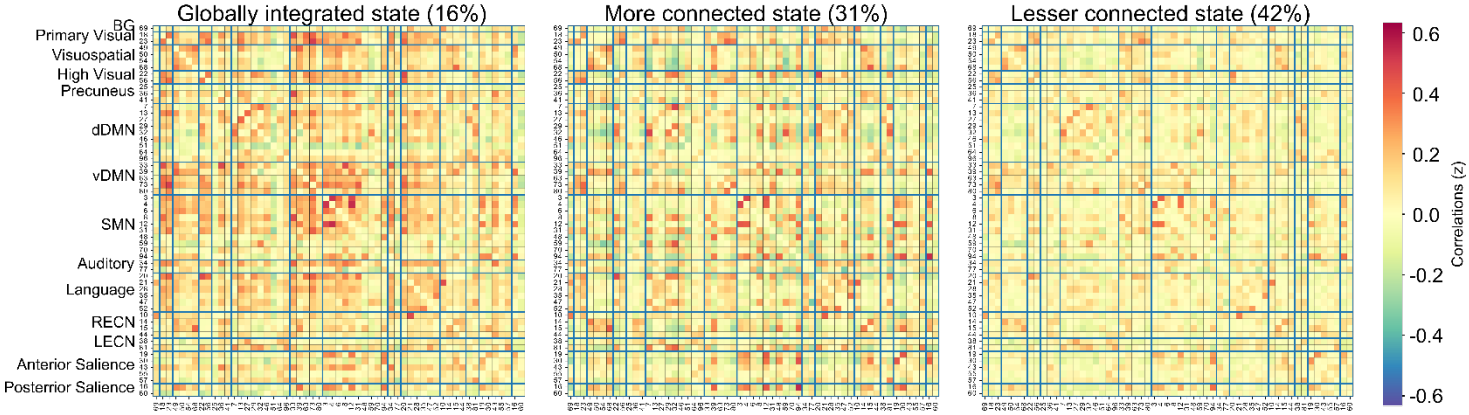
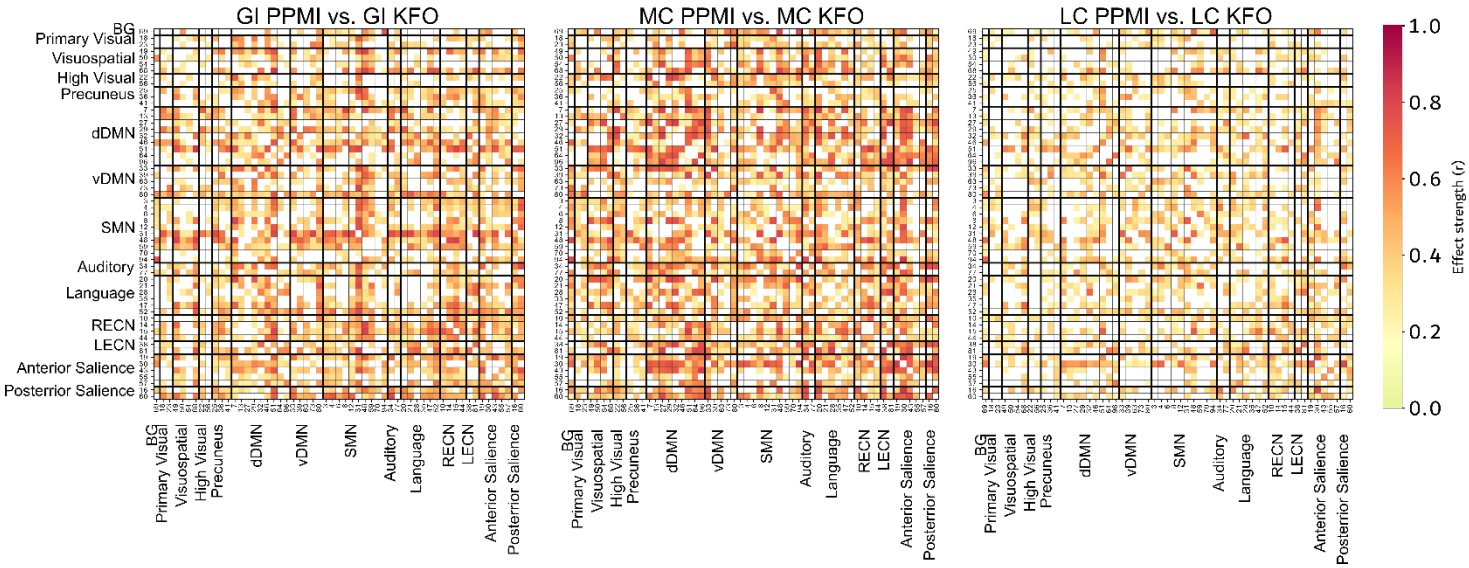


State comparison



Suppl. Fig.1: Dynamic Functional connectivity state comparison along the whole sample (k =3) for each cohort. Each cluster is summarized in one FC map portraying FC within and between resting state networks (RSNs) (portioned by thick blue lines) in pairwise correlations. The correlations were Fisher z transformed and averaged across all subjects, then inverse z-transformed for display. The total percentage of windows assigned to the state is shown. The value of correlations is represented in the color bar; the red color represents positive and blue negative correlations. The diagonal represents the correlations of the subnetwork by itself and is thereby one. For state similarity profiles, Mann-Whitney U tests were used to compare each tile (covariance for one INC with another INC) for each subject median between the cohorts. The comparison plots include the effect strength (r) of Mann-Whitney U tests for each tile. Only effect strengths of results significant after FDR correction were reported.

Publication Project 2:

Physical activity and network attack tolerance preserve motor function in Parkinson's disease: A pilot study

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Physical activity and network attack tolerance preserve motor function in Parkinson's disease: A pilot study

Check for updates

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We tested whether network resilience, quantified by network attack tolerance (NAT), is associated with dopamine terminal (DaT) integrity, motor function and lifestyle factors in Parkinson's disease (PD). Data from 22 individuals with PD and 39 healthy controls included information on lifetime physical activity (PA), cognitive/motor performance, putaminal DaT integrity, and resting-state fMRI. NAT was assessed at global and subnetwork level by calculating global efficiency upon iterative node removal. Linear-mixed-effects models were used to test the effects of PA, education, and dopamine integrity on NAT. Next, the moderating effect of lifestyle factors on the association between NAT and motor function were assessed, controlling for DaT integrity. Greater putaminal DaT integrity was linked to higher somatomotor NAT. Higher global and somatomotor NAT supported motor function, especially in patients with moderate lifetime PA. These preliminary results indicate that lifestyle factors serve network-specific attack tolerance, thereby aiding maintenance of motor function in early-stage PD.

PD is characterized by the progressive loss of striatal dopaminergic terminals (DaT), which is closely associated with the appearance of clinical features and can be quantified by single-photon emission computed tomography (SPECT). Importantly, the severity of cognitive and motor symptoms can vary significantly between individuals, despite similar levels of dopaminergic impairment. This points towards mechanisms that partially mitigate the effects of progressive loss of dopaminergic innervation and regional neurodegeneration on functional performance. These compensatory or coping mechanisms have been summarized under the umbrella term of *resilience* and can be facilitated by lifestyle factors such as lifetime physical activity (PA) or education. By definition, resilience can be divided into the concepts of motor reserve (MR) and cognitive reserve (CR). While MR is linked to the preservation of motor function, for instance, by the adaptation of motor-relevant networks, CR is associated with the relative maintenance of cognitive performance through the adaptation of cognitive-relevant networks[1,2]. To date, the neurobiological underpinnings of MR and CR in PD remain largely unknown.

Emerging evidence suggests improved efficiency, flexibility, and integration of functional networks to be associated with resilience in PD[3–6]. A metric that has recently been proposed to reflect CR in PD is network attack tolerance (NAT)[7]. NAT quantifies how well a network can maintain its structure and function when critical components of the network (i.e. nodes) are systematically removed[8]. Networks that continue to function well after these "attacks" are considered resilient. In the broader context of neurodegenerative diseases, NAT has more recently gained attention as a concept to characterize the brain's actual compensatory capacity towards progressive neurodegeneration. In AD, NAT was shown to be altered along disease stages and cognitive performance levels, and has been proposed as a marker for CR, aiding the compensation for structural loss and the maintenance of cognitive performance[9,10]. In PD, recent findings suggest that higher NAT in the frontoparietal network is associated with the absence of cognitive decline in individuals with PD[7], underscoring its relevance to CR in PD. However, it remains unknown whether NAT in PD is directly impacted by dopaminergic degeneration. Moreover, given that motor symptoms are among the most prominent clinical features of PD, it is yet to be determined whether greater NAT is also linked to the preservation of motor function (i.e., MR).

Notably, individual differences in resilience capacity, such as in MR or CR, have consistently been associated with certain lifestyle factors, such as education[11] and PA[12]. In PD, education has been positively associated with

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Parkinson's Foundation

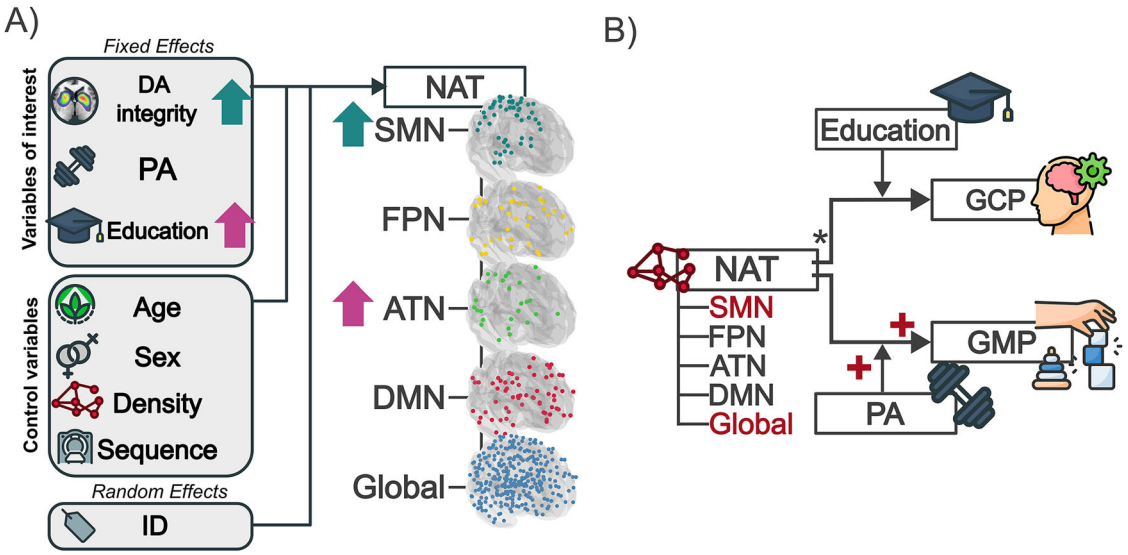

Fig. 1 | Model structure and key results. A Results of the generalized linear mixed models estimating the effect of biological (putamen dopamine terminal (DaT) integrity) and reserve factors (education and physical activity (PA)) on NAT. The arrows are color-coded and represent the direction of the association between NAT of the respective network and the covariate. The attention network (ATN) is shown in purple, and the somatomotor network (SMN) in turquoise. The surface projections depict the ROIs included for the somatomotor network (SMN, turquoise), the frontoparietal network (FPN, yellow), the attention network (ATN, green), the default mode network (DMN, red), and the global network (blue). **B** Results of the regression models. *Top:* Regression model predicting general cognitive performance (GCP) using education as a moderator. *Bottom:* Regression model predicting general motor performance (GMP) using PA as a moderator. The plus sign indicates a positive effect exerted by NAT (corresponding network also in red) and PA as a moderator on GMP. *Control variables for moderation analyses: age, sex, putaminal DaT, education or PA. For better visualization, effects of the control variables are not shown in both illustrations.

CR[11,13,14], while PA has traditionally been implicated as a proxy for MR. Both intense exercise interventions[15,16] and higher lifetime/habitual PA[12,17] have been demonstrated to attenuate motor decline and enhance dopamine availability[17,18] (for a recent review see ref. 19). However, whether these lifestyle factors (i.e., reserve proxies) contribute to greater NAT remains unknown.

In this pilot study, we therefore aimed to address two objectives: (1) to examine the impact of putaminal DaT integrity and lifestyle factors (i.e., PA and education) on global and subnetwork NAT; and (2) to subsequently investigate the moderating effects of the lifestyle factors on the association between NAT and general motor and cognitive performance. These objectives were tested using cross-sectional data of individuals with early PD, who were part of the "Dopamine and Motor Control" (DoMoCo) study that encompasses an extensive array of lifestyle questionnaires, DaT SPECT, MRI imaging, and a detailed battery of cognitive and motor function tests. We hypothesized that preserved integrity of the dopaminergic system has a positive effect on NAT, particularly in the somatomotor network. We further hypothesized that, despite differences in dopaminergic impairment, lifetime PA (MR proxy) would be linked to greater NAT in the somatomotor network, whereas education (CR proxy) would be associated with greater NAT in cognition-relevant networks, such as the frontoparietal or attention network. Finally, we hypothesized that lifetime PA and education would moderate the association between NAT and general motor and cognitive performance, respectively.

Results

Effect of DaT integrity and reserve proxies on NAT

The generalized linear mixed-effects models (GLMMs) assessing the contributions of DaT integrity and reserve proxies on NAT, while controlling for demographic, network density and interscan variability, yielded a positive effect of putaminal DaT integrity ($\beta = 0.079$; $p < 0.001$) on somatomotor network (SMN) NAT (see Fig. 1). In addition, one of our reserve proxies, namely education, presented a positive effect ($\beta = 0.013$; $p = 0.006$) on NAT in the attention network (ATN) (i.e., higher education was associated with increased NAT in the ATN). Remaining models did not result in significant findings in terms of DaT integrity or reserve proxies.

Regarding the control variables, we found a positive effect of age ($\beta = 0.001$; $p = 0.024$), network density ($\beta = 0.128$; $p < 0.001$) and interscan variability (1 < 2: $\beta = 0.035$; $p = 0.020$, 1 < 3: $\beta = 0.059$; $p = .026$) on global NAT. For the SMN, there was a positive effect of density ($\beta = 0.593$; $p < 0.001$) and interscan variability (1 < 2: $\beta = 0.109$; $p = 0.005$) on NAT. In terms of default mode network (DMN) NAT, a positive effect of sex ($f < m$: $\beta = 0.071$; $p = 0.043$) and network density ($\beta = 0.565$; $p < 0.001$) was observed. Regarding ATN NAT, the model yielded a negative effect of sex (f < m. $\beta = 0.071$; $p = 0.043$) and a positive effect of network density. Finally, frontoparietal network (FPN) NAT was positively affected by network density ($\beta = .671$; $p < .001$) and interscan variability (1 < 2: $\beta = 0.077$; $p = 0.014$, 1 < 3: $\beta = 0.198$; $p < 0.001$). All results have been summarized in Table 1.

No substantial differences in outcomes were observed when repeating the GLMMs in the smaller subgroup of patients only scanned with functional MRI (fMRI) sequence two. The results can be found in Supplementary Table 2. To further assess the potential influence of scanning sequence on our results, we calculated the temporal signal-to-noise ratio (tSNR) across all fMRI scans and sequences. The tSNRs were evenly distributed (See Supplementary Figure 2), indicating that our findings are unlikely confounded by systematic differences in signal quality across scanning sequences.

Effect of NAT on motor function and cognitive function

Given that we observed an effect of DaT integrity and one reserve proxy, we next aimed to test whether global and subnetwork NAT has an impact on behavior, namely motor performance (GMP) and cognitive performance (GCP), while considering a moderating effect of our respective reserve proxy (PA and education). The results are described below.

In terms of GMP, the linear moderation models yielded GMP to be positively affected by higher global NAT ($\beta = 279.127$; $p = .005$) and SMN NAT ($\beta = 117.415$; $p = .017$), respectively. Remaining models did not yield a significant effect of subnetwork NAT on GMP. Moreover, we did not find a significant moderation effect of PA on this association, for SMN NAT ($\beta = -1.418$; $p = .087$) and global NAT ($\beta = -2.536$; $p = .116$). We further elucidated the moderation effects of PA on the NAT-GMP association using

Table 1 | Results table of GLMMs assessing the factors contributing to network attack tolerance (NAT) in five different networks

Fixed effects	Global			SMN			DMN			ATN			FPN		
	β	*p*	CI	*β*	*p*	CI	*β*	*p*	CI	*β*	*p*	CI	*β*	*p*	CI
Biological factor															
Mean putamen	0.008	0.289	−0.007	.023	**0.079**	**<0.001***	**0.040**	**0.118**	−0.030	0.144	−0.069	0.010	−0.010	0.531	−0.042	.022	0.014	0.395	−0.018	0.046
Reserve proxies																				
Physical activity	0.000	0.968	0.000	0.000	0.000	0.823	0.000	0.000	0.000	0.419	0.000	0.000	0.000	0.641	0.000	0.000	0.000	0.137	0.000	0.000
Education	−0.001	0.503	−0.006	0.003	−0.009	0.140	−0.020	0.003	0.004	0.444	−0.007	0.016	**0.013**	**0.006***	**0.004**	**0.022**	0.001	0.815	−0.008	0.010
Control variables																				
Age	**0.001**	**0.024***	**0.000**	**0.003**	−0.003	0.165	−0.007	0.001	−0.001	0.738	−0.005	0.003	0.001	0.686	−0.003	0.004	0.003	0.113	−0.001	0.006
Sex(f < m)	0.024	0.066	−0.002	0.051	−0.003	0.528	−0.090	0.046	**0.071**	**0.043***	−0.002	**0.140**	−0.069	**0.015**	−0.125	−0.014	−0.025	0.373	−0.080	0.030
Network density	**0.128**	**<0.001***	**0.119**	**0.138**	**0.594**	**<0.001***	**0.570**	**0.618**	**0.565**	**<0.001***	**0.544**	**0.586**	**0.754**	**<0.001***	**0.722**	**0.786**	**0.671**	**<0.001***	**0.645**	**0.697**
Sequence (1 < 2)	**0.035**	**0.020***	**0.005**	**0.064**	**0.109**	**0.005***	**0.033**	**0.185**	0.076	0.051	0.000	0.153	−0.008	0.795	−0.070	0.054	**0.077**	**0.014***	**0.016**	**0.139**
Sequence (1 < 3)	**0.059**	**0.026***	**0.007**	**0.110**	0.072	0.295	−0.063	0.207	0.087	0.209	−0.049	0.223	0.064	0.252	−0.046	0.174	**0.198**	**<0.001***	**0.090**	**0.306**
Explained var.	R^2 = 0.81 N = 198			R^2 = 0.93 N = 198			R^2 = 0.94 N = 198			R^2 = 0.93 N = 198			R^2 = 0.94 N = 198							

Significant findings are highlighted in bold.
β unstandardized beta coefficients, *CI* represents the 95% confidence interval, *ATN* attention network, *DMN* default mode network, *FPN* frontoparietal network, *SMN* somatomotor network.
*$p < 0.05$.

the Johnson and Neymann technique. The test showed a significant moderating effect of PA, which was only present at PA levels below a weekly energy expenditure score (WEE) of 46.66 for global NAT and 29.35 for SMN NAT (see Supplementary Figure 3). Hence, at similar NAT levels, participants with PD, who engaged in moderate PA demonstrated better GMP compared to those with a highly sedentary lifestyle, suggesting that a moderately active lifestyle, in contrast to a more sedentary one, may enhance the positive impact of NAT on motor performance (see Fig. 1B). In terms of our covariates, we observed a significant effect of education on GMP in the ATN model ($\beta = -0.530$; $p = 0.033$). Across the five tested moderation analyses, a negative effect of age on GMP was found (Global: $\beta = -0.348$; $p < 0.001$; SMN: $\beta = -0.253$; $p = .002$; DMN: $\beta = -0.288$; $p = 0.002$, ATN: $\beta = -0.323$; $p < 0.001$, FPN: $\beta = -0.294$; $p = 0.003$). The model outputs are summarized in Table 2.

When repeating the linear regression models predicting GMP for individuals scanned with fMRI sequence two, the associations between global NAT ($\beta = 272.154$; $p = 0.053$) and SMN NAT ($\beta = 101.601$; $p = 0.078$) and GMP mentioned above did not reach significance. Interestingly, in the smaller group, ATN NAT had a significant, positive effect on GMP ($\beta = 141.639$; $p = 0.048$), which was moderated by lifetime physical activity (PA), particularly at lower PA levels (See Supplementary Table 3).

Concerning the association between GCP and NAT, none of the five linear moderation models demonstrated overall significance of the model test statistic, preventing interpretation of the individual effects of the moderation, and controlling variables.

Again, the same results were achieved when repeating the analysis in the smaller subgroup only including subjects scanned with fMRI sequence two.

Discussion

In this study, we applied a multimodal neuroimaging approach (DaT SPECT, fMRI) combined with a detailed characterization of lifestyle, cognitive, and motor performance in a relative small group of 22 individuals with early PD. The overarching aim was to elucidate the role of a graph theoretical metric, namely NAT, as a potential motor and cognitive reserve measure that is linked to distinct lifestyle features. In this context, our key results were: (1) Lower putaminal DaT integrity was directly associated with decreased SMN NAT; (2) Higher SMN and global NAT were associated with better motor performance, regardless of the underlying dopaminergic impairment; (3) The positive effect of SMN NAT on motor performance was less pronounced in individuals with a relatively sedentary lifestyle (i.e., lower PA levels) compared to moderately active individuals. (4) Educational attainment asserted a direct effect, but no moderating effect, on NAT of a cognition-relevant network, namely the ATN. Taken together, the results suggest that NAT may represent a relevant resilience mechanism, which may compensate for the progressive loss of dopaminergic terminals in PD. Notably, as these findings may not readily extrapolate to moderate or advanced stages of the disease, all subsequent references to PD in the discussion pertain specifically to early-stage PD.

Importantly, and in line with our hypothesis, diminished DaT integrity was associated with lower SMN NAT. This observation was solely confined to the SMN, which contained several subcortical regions, including four regions of interest (ROIs) located within the basal ganglia. These results suggest that a diminished dopaminergic innervation of the basal ganglia may trigger a denervation within cortico-subcortical circuits of the SMN. This denervation or disconnection may result in decreased tolerance of the SMN towards consecutive perturbations. Decreased SMN NAT may in turn induce the clinical motor features of PD. Indeed, lower SMN and global NAT were associated with decreased motor performance independent of the level of DaT integrity. Overall, these findings expand on previous studies reporting dysfunctional connections to be primarily present between the dopamine-depleted putamen and the SMN[20,21]. Further, the results overall support the notion that the dopamine-dependent disruption of functional connectivity between the putamen and the SMN primarily fuels motor impairments in PD, as previously suggested[21].

Table 2 | Results table of models assessing the interaction of network attack tolerance (NAT) and physical activity (PA) on motor performance (GMP) in five different networks

Effects on GMP	Global			SMN			DMN			ATN			FPN		
	β	*p*	CI	*β*	*p*	CI	*β*	*p*	CI	*β*	*p*	CI	*β*	*p*	CI
Direct effects															
NAT	**279.127**	**0.005***	**102.564**	**455.69**	**117.415**	**0.017***	**25.415**	**209.414**	43.665	0.417	−69.486	156.816	137.851	0.078	−18.204	293.907	68.816	.369	−91.791	229.423
PA	0.792	0.114	−0.219	1.802	0.345	0.083	−0.053	0.743	−0.017	0.901	−0.3	0.267	0.284	0.200	−0.1720	0.741	0.243	0.279	−0.224	0.709
Moderating effects																				
NAT × PA	−2.536	0.116	−5.793	0.721	−1.418	0.087	−3.075	0.238	0.105	0.864	−1.197	1.406	−1.335	0.208	−3.521	.851	−1.066	0.287	−3.153	1.02
Control variables																				
Education	−0.206	0.212	−0.545	0.134	−0.124	0.507	−0.517	0.27	−0.375	0.101	−0.836	0.086	**−0.53**	**0.033***	**−1.007**	**−.052**	−0.265	0.230	−0.722	0.192
Mean putamen	0.115	0.851	−1.194	1.424	−0.402	0.629	−2.172	1.367	0.282	0.709	−1.326	1.891	0.513	0.484	−1.032	2.057	0.455	0.595	−1.359	2.27
Age	**−0.343**	**<0.001***	**−0.481**	**−0.205**	**−0.253**	**0.002***	**−0.39**	**−0.116**	**−0.288**	**0.002***	**−0.449**	**−0.127**	**−0.323**	**0.001***	**−0.477**	**−0.17**	**−0.294**	**0.003***	**−0.463**	**−0.124**
Sex (*f* < *m*)	−0.700	0.483	−2.807	1.407	−0.335	0.773	−2.812	2.142	−0.239	0.86	−3.136	2.658	1.079	0.41	−1.675	3.834	0.315	0.803	−2.374	3.003
Sequence (1 < 2)	0.338	0.769	−2.115	2.791	0.748	0.577	−2.095	3.592	0.977	0.517	−2.211	4.166	1.751	0.184	−0.953	4.455	1.996	0.238	−1.502	5.493
Sequence (1 < 3)	−0.66	0.091	−8.003	0.683	−1.443	0.498	−5.945	3.059	−2.234	0.386	−7.643	3.175	−2.298	0.333	−7.257	2.662	−1.767	0.57	−8.357	4.823
Explained var.	$R^2 = 0.85$ $N = 22$			$R^2 = 0.82$ $N = 22$			$R^2 = 0.74$ $N = 22$			$R^2 = 0.78$ $N = 22$			$R^2 = 0.74$ $N = 22$							

Significant findings are highlighted in bold.
β unstandardized beta coefficients, *CI* represents the confidence interval, *ATN* attention network, *DMN* default mode network, *FPN* frontoparietal network, *SMN* somatomotor network.
*$p < 0.05$.

Notably, in the current study we focused on general motor performance rather than the severity of singular clinical features, such as tremor, rigidity, or akinesia. This is particular important concerning our investigations in terms of NAT being a potential MR mechanism. MR is defined as the relative preservation of motor function despite progressive neurodegeneration, through the functional adaptation of large-scale neural networks[2]. Here, we showed that independent of DaT loss, individuals with higher NAT in the global network and the SMN presented higher general motor performance. The current results expand on previous studies, which have mostly focused on regional structural[22] or functional[4,5,23,24] brain changes associated with MR. In contrast to these regional measures, NAT describes network properties that are more representative of the brain's global ability to compensate against neurodegeneration. Our findings highlight that the ability to preserve an efficient information flow within global and motor processing areas (i.e., SMN) despite DaT loss leads to a relative preservation of general motor performance. NAT may thus form the basis for underlying MR mechanisms and represent a quantitative measure of MR capacity in PD.

Interestingly, in terms of cognitive function, we did not observe an effect of NAT in cognition-relevant networks on general cognitive performance, which contrasts findings from a recent study on the association of NAT and cognitive decline in PD[7]. Yet, the lack of findings in our cohort may be due to the absence of cognitive impairment in our studied cohort and thus, less variation in general cognitive performance. Moreover, it has consistently been shown that likelihood for cognitive decline increases in later stages of the disease[25]. Given that we focused on early PD, more refined assessments concerning NAT and cognition are necessary in cohorts with more advanced disease stages.

Importantly, despite the observed lack of association of cognitive function with NAT, we found that higher educational attainment, traditionally considered a cognitive reserve proxy, was positively associated with NAT of the ATN. This is in line with previous findings indicating that higher levels of education are associated with greater functional connectivity of the dorsal attention network[26] and slower cognitive decline in healthy controls[27]. Interestingly, connectivity within the dorsal ATN appears to be crucial for cognitive performance as decreased connectivity in this network has been linked executive dysfunction in PD[28]. However, we neither found an association between ATN NAT and general cognitive performance nor a moderating effect of education in our PD cohort. Future assessments, in more advanced and clinically diverse PD stages may provide further insights into the role of educational attainment concerning a build-up of NAT and potential subsequent perseveration of cognitive performance. Moreover, education is a static, early lifetime factor, which may not entirely capture lifestyle-associated cognitive reserve mechanisms, as recently proposed[29]. More comprehensive measures, including composite lifestyle variables, may thus allow for more refined investigations of cognitive reserve aspects in PD.

While we observed a direct effect of education on NAT, we did not find any direct association of lifetime PA, our second lifestyle variable of interest with NAT. Importantly, lifetime PA and education were not correlated in our study cohort, suggesting an independent contribution of these factors to NAT and motor and cognitive reserve in PD. Indeed, we observed a positive moderating effect of PA on the association between 1) SMN NAT and general motor performance, and 2) global NAT and general motor performance. Specifically, at similar NAT levels, individuals with PD and highly sedentary lifestyles portrayed worse general motor performance compared to those with moderate PA levels. This suggests that a moderately active lifestyle, in contrast to a very sedentary one, may enhance the beneficial effects of NAT on motor performance. This is in line with other observations reporting a positive effect of premorbid PA on motor decline[12], and an association between dopamine depletion and motor impairment[30]. One potential mechanism underlying this association could be the protective effect PA exerts on the basal ganglia's structural integrity[31], and the beneficial effect of PA on the basal ganglia's dopaminergic innervation[17]. These effects may mitigate the severity of increasing striatocortical disconnection and thus aid the preservation of SMN NAT in the course of the disease[5,21].

Table 3 | Demographics of the study cohort

	Mean (SD) /Median (IQR)	
	PD (n = 22)	HC (n = 39)
Age	62.1 (8.0)	63.5 (6.5)
Sex (*m/f*)	15/7 *m* = 68%	26/13 *m* = 50%
Putaminal DaT integrity (z-scores)	−3.6 (0.7)	NA
Education (years)	15.8 (2.7)	16.7 (2.8)
PA	58.3 (82.8)	48.1 (34.0)
MoCA	27 (2)	28 (2)
GCP (z-scores)	−0.4 (2.4)	NA
GMP (z-scores)	−3.2 (3.1)	NA
MDS UPDRS III	14 (6)	0 (1)
LEDD	206.4 (113.2)	NA

Standard deviation (SD) is provided for continuous variables and interquartile range (IQR) for ordinal values (MDS UPDRS-III and MoCA scores). While the z-scores for DaT integrity were derived from an internal software cohort, the z-scores for GCP and GMP were based on the 39 HCs described in this table.

PD Parkinson's disease, *HC* healthy control, *DaT* dopamine transporter, *PA* lifetime physical activity, *MoCA* Montreal Cognitive Assessment, *GCP* general cognitive performance, *GMP* general motor performance, *MDS UPDRS-III* Movement Disorder Society Unified Parkinson's Disease Rating Scale-Part III, *LEDD* Levodopa equivalent daily dose.

Notably, in our study this protective effect was not observed for higher PA levels. This observation may be attributed to a recently reported U-shaped association of PA with motor performance in PD[30], which needs to be validated in a cohort including more advanced disease stages. While several studies have already indicated that immediate, high-intensity exercise interventions positively impact PD symptomatology[15,16,18,19], our results further demonstrate that also lifetime PA contributes to the build-up of MR-associated mechanisms, such as global and SMN NAT, that mitigate the effects of the disease later in life.

Several limitations need be considered when interpreting the current results. First, despite this well-characterized cohort, the sample was relatively small and replication in a larger sample is warranted. Nonetheless, the tested models explained a relatively high amount of variance. Moreover, given our repeated-measures design, 198 observations were included in the GLMMs that each estimated 8 coefficients, thereby increasing statistical power and reducing the risk of overfitting. Furthermore, the utilization of three different fMRI sequences may have potentially affected the results. To address this issue, we performed a sensitivity analysis in a subgroup of individuals scanned with the same sequence as well as a SNR assessment. Findings from these analyses suggested that scanner sequence had only a minimal influence on our findings. Aside from these statistical and technical drawbacks, we only considered physical activities between 20–49 years of age, thus potentially omitting contributions of early lifetime PA (12–19 years) to the build-up of reserve from that period. Finally, while our approach conceptualized education and lifetime PA as exclusive proxies for CR and MR, some studies show that these might be more inclusive. For example, PA has been shown to mediate the association between DaT integrity and cognition function[32], while education levels have been shown to be linked with motor performance[33–35]. This asserts a potential value to assessing lifestyle factors in a more integrated way across cognitive and motor domains. Thus, advancing our understanding of how lifestyle features affect resilience mechanisms in PD may require a shift from investigating isolated lifestyle factors towards assessing lifestyle as a cumulative, integrated construct, encompassing multiple behavioral features.

Given the cross-sectional nature of this study and the focus on early disease stages, longitudinal study designs including more diverse patient populations at different stages of the disease (i.e. early to advanced), different PD subtypes (e.g., tremor-dominant vs. akinetic-rigid) and also a focus on non-motor, autonomic features of the disease will be pivotal to gain more insights into resilience mechanisms of the brain, such as SMN NAT. Identification of these factors and understanding how NAT might add to resilience mechanisms may overall provide novel insights regarding prevention and intervention strategies in PD.

Taken together, the results of this pilot study suggest that the brain's compensatory capacity against neurodegenerative processes may be closely reflected by the degree of attack tolerance of distinct large-scale neural networks. Our findings underscore that lifelong behavioral factors, such as PA and education, affect the NAT of certain subnetworks, such as the somatomotor and attention network. Promoting these lifestyle factors may enhance the robustness of these networks, thereby contributing to the relative preservation of motor and cognitive performance despite the progressive loss of DaT in PD.

Materials and methods

Participants

This study comprised 22 individuals with early PD, who were recruited for the DoMoCo study during their clinical workup at the Department of Nuclear Medicine at the University Hospital Cologne, Germany. The DoMoCo study is conducted as part of the Collaborative Research Centre 1451 (CRC 1451) at the University Hospital Cologne. The inclusion criteria for this study were: 1) age between 49 and 80 years; 2) early-stage PD (clinical symptoms < 3 years); 3) available in-house DaT SPECT imaging; 4) right-handedness; 5) absence of severe cognitive deficits (Montreal Cognitive Assessment (MoCA) score ≥ 24); 6) absence of depressive symptoms (Geriatric Depression Scale score ≤ 5); 7) no current administration of selective serotonin reuptake inhibitors; 8) absence of significant other neurological disorders; 9) MRI safe (e.g. no pacemaker). Notably, all tests and imaging procedures in the DoMoCo study PD were performed in participants with PD, while they were off medication. As 13 of the 22 patients had already received dopaminergic medication, they were asked to discontinue their medication prior to study participation. This represented at least 12 h of withdrawal of dopamine replacement therapy or 72 h for extended release of dopamine agonists.

A group of 39 healthy controls, who underwent the study protocol of the DoMoCo study, except the DaT SPECT imaging, was used as reference for the cognitive and motor tests.

The study was approved by the ethics committee of the University Clinic of Cologne (reference: 20–1422) and was conducted according to the standards of the Declaration of Helsinki. All participants gave informed consent prior to enrollment and received monetary compensation for their participation. Demographic characteristics are summarized in Table 3.

Reserve proxies—lifetime physical activity and education

Lifetime PA was used as a proxy for MR and assessed using the Historical Leisure Activity Questionnaire (HLAQ)[36] and metabolic equivalents (METs)[37], which were assigned to account for the intensity of the respective activity. The HLAQ consists of four periods (12–19 years, 19–35 years, 35–50 years, above 50 years). For each period, the participant had to indicate which activity he or she performed more than 10 times and specify the number of hours per week, months per year, and years per period. Using the formula below (see Formula 1), we first calculated the average weekly number of hours each activity was carried out per period. Next, we obtained the weekly energy expenditure for each activity by multiplying the average weekly hours per activity by the corresponding MET score. Finally, a total weekly energy expenditure score (WEE_{period}) was calculated over all activities reported in that period. In this study, lifetime PA was defined as the mean of the WEE_{period} calculated for the periods 19–35 years and 35–50 years. We excluded the earliest period of the questionnaire (i.e., 12–19 years), given that a recall bias was noticed across participants. We also excluded the latest period (i.e., above 50 years) because all patients were only recently diagnosed with PD at around 50 years of age, which may have influenced their physical activity performance.

$$WEE_{period} = \sum_{i=1}^{n_{period}} \frac{years_i * month_i * weekly\ hours_i}{12 * years_{period}} * MET\ score_i \quad (1)$$

Aside from the lifetime PA variable, we further used educational attainment as proxy for CR. Educational attainment was defined as the total number of years spent in formal schooling, vocational training and/or university education.

Behavioral assessment—cognitive and motor function

All participants in the DoMoCo study underwent a detailed clinical, motor, and cognitive assessment. Clinically, disease severity was evaluated using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III[38]. To obtain more quantitative measures for cognitive and motor performance that go beyond clinical severity ratings, a battery of motor and cognitive tests was included in the current analysis. The test battery was conducted in the context of the Human Motor Assessment Centre (CRC 1451) and consisted of the following tests: Motor function was evaluated by measuring maximum grip strength and through the Finger Tapping Test, Purdue Pegboard Test, Jebsen-Taylor Hand Function Test, and Timed Up and Go Test. With exception of the Timed up and Go Test[39], a detailed description of the motor battery can be found elsewhere[40]. The cognitive battery consisted of the Cologne Neuropsychological Screening Tool for Stroke[41], DemTect Test[42] and Trail Making Test[43]. To obtain a measure for general motor performance (GMP) and general cognitive performance (GCP), the performance scores of the motor and the cognitive test battery were z-standardized using the sample of 39 age- and sex-matched healthy controls as reference. Subsequently, these z-scores were combined into two single composite scores, GMP and GCP, respectively. As longer durations in the Jebsen-Taylor, Timed Up and Go, and Trail Making Test represented poorer performance, these test scores were inverted prior to the composite score calculation.

Dopamine transporter SPECT acquisition and preprocessing

DaT SPECT images were acquired on a PRISM-3000 three-head SPECT system (Philips/Picker) located at the University Hospital of Cologne, following a standardized clinical procedure. The EARL-BRASS software (Hermes, Sweden[44]), was used for reconstruction and quantification of the DaT SPECTS, including attenuation correction[45] and spatial normalization to a reference sample of age-matched healthy controls, resulting in z-transformed deviation maps. Finally, for the current analysis, mean z-values of the bilateral putamen were extracted from these maps using EARL-BRASS. As the SPECT system used did not include additional CT or MRI imaging, correction for partial volume effects was not feasible. Nonetheless, this method has consistently been shown to capture dopaminergic integrity necessary for a reliable diagnosis of Parkinson's disease[46–48].

fMRI acquisition

All participants underwent a MRI session at the Research Centre Juelich. Anatomical T1-weighted MRI and resting state (rs) fMRI series were acquired on a 3 T Siemens Prisma scanner. The anatomical sequence followed a specific protocol: repetition time (TR) = 2300 ms, echo time (TE) = 2.32 ms, flip angle = 8°, slice thickness = 0.90 mm, voxel size = 0.9 × 0.9 × 0.9 mm, number of slices = 192. For each individual, one of three different fMRI sequences was available. Four individuals were scanned with sequence one: TR = 800 ms, TE = 37 ms, multiband SMS factor = 8, flip angle = 52°, slice thickness = 2 mm, voxel size = 2.0 × 2.0 × 2.0 mm, number of volumes 740, acquisition time = approx. 10 min. While 17 individuals were scanned with sequence two: TR = 980 ms, TE = 30 ms, multiband SMS factor = 4, flip angle = 70°, slice thickness = 2.2 mm, voxel size = 2.2 × 2.2 × 2.2 mm, number of volumes 500, acquisition time = ~8 min. Finally, one individual was scanned with sequence three: TR = 1120 ms, TE = 57 ms, multiband SMS factor = 8, flip angle = 52°, slice thickness = 2 mm, voxel size = 2.0 × 2.0 × 2.0 mm, number of volumes 740, acquisition time = ~13 min. The sequence changes were unintended, but necessary due to an unforeseen, minor update of the scanner's software during the study period.

fMRI preprocessing

Preprocessing of the fMRI data was carried out using the CONN toolbox v20.b (Whitfield-Gabrieli & Nieto-Castanon, 2012) implemented in Matlab (Matlab R2020b Update 4, MathWorks, Inc., Natick, Massachusetts, United States). CONN's default preprocessing pipeline was used to normalize the images to MNI (Montreal Neurological Institute) space (web.conn-toolbox.org/fmri-methods/preprocessing-pipeline). The pipeline included spatial realignment, slice-timing correction, outlier identification, segmentation, normalization, and smoothing (Gaussian kernel 8 mm full-width half maximum). The preprocessing was performed separately for each of the three sequences.

Graph theoretical network construction and network attack

In graph theory, the brain is conceptualized as a network of nodes (regions) connected by edges (functional connections). NAT is assessed by systematically deleting nodes (i.e., attacks) from this network and evaluating whether the network sustains efficient communication. Concomitantly, networks that maintain their efficiency despite successive attacks represent high NAT. How efficiently information is exchanged in a network can be estimated by global efficiency (GE), which assesses the shortest path length between all pairs of nodes in a network[49,50]. Importantly, unlike other graph theoretical metrics, GE can account for paths of disconnected nodes, rendering it especially suitable for disconnected networks[8,51] and hence, a robust measure of efficiency for NAT.

In a first step, we used a set of 300 predefined, spherical, non-overlapping ROIs[52] to compute individual ROI-to-ROI connectivity matrices in CONN. These 300 × 300 covariance matrices represent the functional connectivity between each ROI pair. Each element or tile of these covariance matrices contained the respective Fisher-transformed bivariate correlation coefficient between the Blood Oxygen Level-Dependent time series of two ROIs.

In a second step, we computed weighted, undirected, and unthresholded graphs based on the covariance matrices utilizing the Brain Connectivity Toolbox (brain-connectivity-toolbox.net)[8] and the Graph Analysis Toolbox (cbrain.stanford.edu/Tools.html)[53]. These graphs were computed on the whole-brain (global) level as well as the single subnetwork level. The single subnetworks of interest were the DMN (65 ROIs), the FPN (36 ROIs), the SMN (51 ROIs), and the ATN (27 ROIs), which are the major large-scale cognitive and motor networks defined by various resting state studies[54–56]. Importantly, none of these subnetworks included overlapping ROIs. The key regions for each network are visualized in Fig. 2 and listed in Supplementary Table 1. Subsequently, each of these graphs was proportionally thresholded, preserving only the strongest ten to fifty percent of the weighted edges in the graph, respectively. We chose this broad range as there is no consensus on appropriate thresholds for NAT analyses. Consequently, by using five percent increments, nine different network densities per network were examined. Each of these graphs was binarized, leaving nine differently thresholded, unweighted, undirected graphs per network and individual. Fig. 2 provides a graphic outline of the analysis and Supplementary Figure 1 portrays the approach as a detailed procedural map. In a final step, the constructed graphs were attacked using the same set of toolboxes. During the attack analysis, nodes were iteratively removed from the network in descending order of their degree (i.e., the number of edges connected to that node). Thus, nodes with the most connections were removed first. After each node removal, the network's GE was calculated (see Formula 2). GE was defined by the average inverse shortest path length between all pairs of nodes in the network, where N represented the number of nodes in the network and L_{ij} was the shortest path between nodes i and j[49]:

$$GE = \frac{1}{N(N-1)} \sum_{i,j,j \neq 1} \frac{1}{L_{ij}} \quad (2)$$

GE was then plotted on a graph for each attack iteration (see Fig. 2). The area under the curve (AUC) of each graph was used to obtain one single

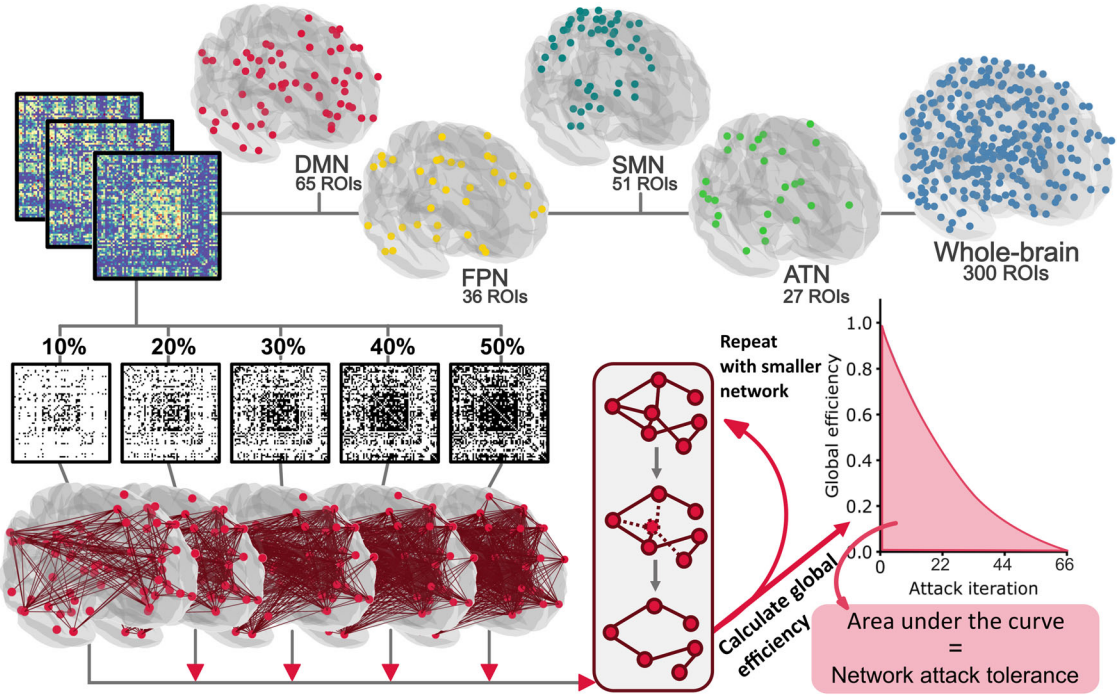

Fig. 2 | Illustration of the analysis pipeline. Top: Individual resting-state connectivity matrices were computed using a Region of interest (ROI) based functional atlas. ROIs of the attention network (ATN, green), the default mode network (DMN, red), the frontoparietal network (FPN, yellow), the somatomotor network (SMN, turquoise) and the whole-brain network (blue) were analyzed separately. The analysis steps are illustrated using the DMN as an example. Bottom left: Connectivity matrices were thresholded at nine different densities from 10% to 50% (for clarity only five out of nine densities are depicted above), then binarized, and finally used for network construction. Bottom right: During the attack analysis, the network's nodes were iteratively removed in descending order of their connectedness. For each removed node, the network's global efficiency was computed. The ability to sustain its global efficiency to successive attacks (area under the curve) defined the attack tolerance of the respective network. All renderings and covariance matrices were plotted using nilearn[64].

measure of individual NAT. Next, the AUC was normalized according to the number of attacks performed (i.e., the number of nodes in the respective network). After normalization, NAT described how many percent of the maximum possible GE was retained during attacks.

Statistical analysis: generalized linear mixed-effects models and moderation analysis

In a first step, we wanted to examine the direct effects of two reserve proxies, specifically lifetime PA and education, as well as the effects of dopaminergic impairment, namely putaminal DaT integrity, on NAT, while accounting for individual variances in demographics. To account for the repeated measure design due to the different network densities, we performed GLMMs[57], allowing individual intercepts for each participant. Fixed effects included lifetime PA, education, and putaminal DaT-integrity, while controlling for network density, fMRI sequence (interscan variability), age, and sex. Since NAT is a fraction and by design never one or zero, a beta regression model was used[58], i.e., a GLMM with a beta response distribution utilizing a logit link function. R-squared estimates of the GLMMs were derived from the 'mgcv' R package[59]. The significance level was set to $p = 0.05$.

Next, we assessed the potential moderating effects of lifetime PA and education on the association between NAT and motor/cognitive performance. To do this, we ran two linear moderation models estimating either general motor or cognitive performance based on the respective network's NAT, the reserve proxies (education and PA) as well as their interaction. Since NAT was originally a repeated measurement (due to the nine different network densities), we used the mean NAT value across all densities for each network as input variable. More specifically, in the first model we estimated motor performance (GMP) using putaminal DaT integrity, age, sex, fMRI sequence, education, and NAT, introducing PA as moderating variable. The second model estimated cognitive function (GCP) using putamen DaT integrity, age, sex, fMRI sequence, PA, and NAT as covariates and education as a moderating variable. Since GCP was missing for one individual this model was run on data of 21 individuals. Finally, the Johnson-Neyman technique[60] was used to identify ranges of significance and visualize interaction effects in the data.

All statistical models listed above were run separately for global and subnetwork NAT (5 runs) using R (Rstudio ver. 2022.12.0) and the following packages: 'mgcv'[59], 'ggplot2'[61], 'interactions'[62], 'broom'[63]. To evaluate the impact of fMRI sequence variability on our results, we re-ran all statistical analyses in a subgroup of 17 individuals with PD, who were exclusively scanned with fMRI sequence two.

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.

Code availability

The underlying inhouse code for this analysis is available on GitHub and can be accessed via this link https://github.com/Asendorfa/NAT. We provide a procedural map in the supplements that depicts which script was used for which analysis step (See Supplementary Figure 1).

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Author contributions

M.H. and A.A. were involved in outlining the research, planning the project, writing the manuscript, and making key decisions throughout the study. A.A. carried out all aspects of the data review, preprocessing and analysis, wrote the inhouse scripts utilized, carried out the statistical analysis, and created all figures and tables included. The data used was taken from the DoMoCo study. A.A., M.H., M.B., V.D., H.T. and Tv.E. were highly involved in the execution of this study (e.g., data acquisition, patient recruitment, study design, data management). N.H. and K.M. contributed by guiding and overseeing the statistical approach. E.G. established the analytical framework for calculating the lifetime physical activity score. Finally, all authors reviewed the final manuscript.

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Additional information

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Publication Project 3:

Dopamine-Deficiency-Related Reorganization of the Somatomotor Network in Prodromal and Early Parkinson's Disease

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Dopamine-Deficiency-Related Reorganization of the Somatomotor Network in Prodromal and Early Parkinson's Disease

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Abstract

Introduction: Network attack tolerance (NAT) measures the brain's ability to sustain information flow despite the loss of critical brain regions. In PD, NAT has been linked to cognitive and motor function. However, it remains unclear how dopaminergic degeneration shapes NAT, and whether it relates to motor symptom progression.

Objective: To examine dopamine-deficiency-related changes in NAT across the early PD disease continuum and its association with longitudinal motor outcomes.

Methods: We used cross-sectional resting-state functional MRI of 28 healthy controls, 60 prodromal and 94 clinical PD patients to create graph-theoretical networks. NAT was assessed at global and subnetwork level by calculating the global efficiency upon iterative node removal at different network densities. Using linear mixed-effects models, we assessed how putaminal dopamine terminal (DaT) binding, or disease status affected NAT, controlling for network density, age, sex and education. Baseline somatomotor (SMN) NAT was examined as a predictor of motor symptom progression in 145 patients.

Results: Lower putaminal DaT signal was associated with higher SMN NAT across groups. PD patients exhibited elevated SMN NAT relative to controls. Neither global nor other subnetworks showed effects. While the effect of baseline SMN NAT on motor progression was not significant, an exploratory analysis (Johnson-Neyman) suggested that higher SMN NAT may associate with slower motor decline across most of the observed NAT range.

Conclusions:

Dopaminergic depletion is associated with a targeted SMN reorganization, potentially maintaining network information flow despite progressive hub loss. Whether this reorganization represents compensation or a consequence of progressive pathology requires further longitudinal assessment.

Introduction

Parkinson's disease (PD) exhibits a notable capacity to buffer the functional consequences of progressive neurodegeneration. Motor symptoms typically emerge only after substantial dopaminergic cell loss in the substantia nigra, estimated at approximately 30–70%, and clinical presentation varies considerably across individuals[1–3]. Together, these observations point to the presence of neurobiological mechanisms that temporarily preserve function despite ongoing pathology. Such mechanisms are likely reflected in measurable changes in brain structure and connectivity, which are considered compensatory when they support the preservation of motor or cognitive performance. While a growing body of evidence demonstrates that PD is associated with widespread structural and functional alterations in brain connectivity [4,5], some of these brain alterations have been linked to the compensation of cognitive and motor function, thereby counteracting the detrimental effects of dopaminergic dysfunction [6,7]. Interestingly, it has been suggested that structural network changes associated with compensation differ between prodromal and clinical PD, indicating stage-specific patterns of compensation [8]. Yet, it remains largely unclear how compensatory mechanisms on the functional network level evolve across clinical progression, from prodromal to clinical stages, and in relation to dopaminergic terminal loss.

Among the various neuroimaging approaches used to study compensation in PD, one promising method that has recently been linked to mechanisms supporting the maintenance of cognitive [9] and motor function [10] in clinical PD, is the graph-theoretical concept of network attack tolerance (NAT) [9]. This method captures how well a brain network can maintain effective information flow when crucial nodes of the network are iteratively removed [11]. Consistent with a potential compensatory role, we recently demonstrated that NAT of the somatomotor network (SMN) was positively associated with motor function in a group of PD patients, independent of the degree of dopamine transporter terminal (DaT) loss [10]. However, while this study provides first indications that SMN NAT may actively serve as compensatory mechanism in clinical PD, it remains unknown whether NAT of the SMN or other subnetworks is also involved in the prodromal stage of PD, when significant dopaminergic loss is already present, but motor symptoms have not yet emerged.

To examine changes in NAT in different brain networks across the PD continuum and as a function of dopaminergic terminal loss, we utilized resting-state functional MRI (fMRI) and DaT imaging of a large, well-characterized cohort of 182 participants, including healthy controls (HC) and patients with prodromal (PM) and clinical PD in the de novo stage. Across this sample, we tested whether NAT of various large-scale networks, such as the SMN, is associated with DaT integrity and scales across clinical disease stages. Furthermore, we investigated whether NAT was linked to longitudinal motor symptom stability. Building on our previous findings in a relatively small partially medicated early-stage PD sample, we sought to further examine whether NAT reflects a compensatory mechanism. If NAT is indeed compensatory, higher baseline NAT would be associated with a slower decline in motor function over time. In this compensatory context two roles of NAT may be hypothesized: 1) NAT as a mechanism that is actively increased in response to progressive dopaminergic decline; a process that likely begins during the PM stage of the disease. 2) NAT as an inherent trait of the healthy brain that fades with increasing dopamine loss, with clinical symptoms manifesting once its compensatory function is exhausted. With additional evidence of increased prefrontal connectivity in prodromal PD and altered connectivity within the sensorimotor network (SMN) in clinical PD compared to healthy controls [8], we hypothesized NAT levels in different networks may relate to dopamine-driven reorganization processes in a stage-specific manner (i.e. prodromal vs. clinical PD), potentially reflecting compensation.

Materials and Methods

Participants

This analysis included 182 participants, aged between 50 and 80 years, retrieved from the Parkinson's Progression Markers Initiative (PPMI) in June 2025. According to the Declaration of Helsinki all participants gave written consent, and each PPMI site obtained ethical approval for the study. Key inclusion criteria for the current study were: 1) available resting-state (rs) functional MRI (fMRI), structural MRI, and DaT single-photon emission computed tomography (DaT-SPECT), acquired within a time window of six months; 2) right-handedness; 3) no cognitive impairment (Montreal Cognitive Assessment ≥ 25); 4) no depressive symptoms

(Geriatric Depression Scale ≤ 5), 5) no other neurological disorder; 6) availability of curated demographic data. All PD patients had an idiopathic PD diagnosis, a disease duration of less than three years, and had no dopaminergic therapy initiated (Levodopa equivalent daily dose (LEDD) = 0, de novo). The PM group consisted of participants enrolled in the PPMI prodromal cohort (Clinical Protocol 002 v3.0), all of whom were unmedicated (LEDD = 0). Within this sample, 41 individuals were classified based on the presence of hyposmia, 17 on probable REM sleep behavior disorder (RBD), one carried a PRKN mutation with concomitant RBD, and one was a LRRK2 mutation carrier. No polysomnography information was available for this cohort. Healthy controls (HCs) were solely selected based on the general inclusion criteria listed above. These selection criteria resulted in 28 HCs, 60 prodromal and 94 clinical PD patients. Group demographics are provided in Table 1, while additional details on selection procedures and a summary on inclusion criteria can be found in the supplements.

fMRI acquisition and preprocessing

Since PPMI is a multi-center study, anatomical T1-weighted MRI and rs-fMRI series were acquired on 32 different 3T Siemens scanners, comprising six models of the types: Prisma (34 subject IDs), Prisma fit (81 subject IDs), Verio (15 subject IDs), Skyra (41 subject IDs), Vida (10 subject IDs) and TrioTim (1 subject ID). The anatomical and rs-fMRI sequences followed the same specific protocol: Structural MRI: repetition time (TR) = 2300 ms, echo time (TE) = 1.9 -3 ms, flip angle = 9°, slice thickness = 1 mm, voxel size = 1x1x1 mm, number of slices = 256; Functional MRI: TR = 2500 ms, TE = 30 ms, flip angle = 80°, slice thickness = 3.5 mm, voxel size = 3.5x3.5x3.5 mm, number of volumes 240, acquisition time = approx. 10 min. Preprocessing of the fMRI data was carried out using CONN's [12] default preprocessing pipeline (https://web.conn-toolbox.org/fmri-methods/preprocessing-pipeline), including spatial realignment, slice-timing correction, outlier identification, segmentation, normalization, and smoothing (Gaussian kernel, 7mm full-width half maximum). After preprocessing, fMRI data were denoised using CONN's default denoising pipeline, comprising regression of the six realignment parameters and their first order derivatives, white matter and CSF signal components, and ART-based scrubbing of BOLD and motion outlier volumes (https://web.conn-toolbox.org/fmri-methods/denoising-pipeline). Finally, individuals with extensive head motion and signal drift according to scrubbing were excluded from the final dataset (n=21).

DaT-SPECT acquisition and preprocessing

As neurodegeneration in early PD is expected to mainly affect putaminal regions [13,14], only mean putamen values were retrieved from PPMI. DaT-SPECT ([^{123}I]Ioflupane) imaging followed PPMI's standard operating procedures (https://www.ppmi-info.org/study-design/research-documents-and-sops). Preprocessing involved raw projection reconstruction (HOSEM, HERMES), attenuation correction [15], 6 mm Gaussian filtering, and normalization to Montreal Neurological Institute space. Striatal binding ratios (SBRs) were calculated for the bilateral putamen using the occipital cortex as reference and average across left and right hemisphere. The more affected hemisphere (MAH) and lesser affected hemisphere (LAH) were defined based on left and right putaminal SBRs respectively.

Graph theoretical network construction and network attack

Graph theory offers a powerful framework for modeling the brain as a network, where brain regions are represented as nodes and their functional connections as edges. Subsequently, a NAT analysis quantifies how efficiently a network continues to exchange information as its most connected and critical nodes are systematically removed.

In this analysis a set of 300 predefined functional regions of interest (ROIs) [16] were used to generate individual ROI-to-ROI connectivity matrices from the rs-fMRI data. These matrices served as the basis for constructing networks, which were then subjected to a targeted attack analysis. For each subject, this analysis estimated how well a network preserved its efficiency as nodes were removed. Nodes were removed iteratively in descending order of their degree of connectedness (i.e. the number of edges connected to this node). After each node removal the global efficiency of the network was calculated and plotted. Upon final node removal, the AUC of the resulting plot served as measure for NAT. Each subject received a NAT value, reflecting the percentage of maximum efficiency maintained during attacks. The procedure was repeated across nine network thresholds (densities), retaining 10–50% of the strongest connections (see Fig. 1A). This was done at the whole-brain (global) level as well as the single subnetwork level. The single subnetworks of interest comprised the default mode network (DMN, 65 ROIs), the frontoparietal network (FPN, 36 ROIs), the SMN (51 ROIs), and the attention network (ATN, 27 ROIs). For more detailed information on network construction and attack analysis, see Asendorf et al., (2025).

Longitudinal MDS-UPDRS III data:

Longitudinal MDS-UPDRS III and LEDD data for prodromal and PD participants were obtained from the PPMI database (February 2026), with analyses restricted to the OFF-state or unmedicated assessments occurring after the imaging visit assessments, which were defined as time point zero. After quality control and exclusions, 145 participants (86 PD, 59 PM) contributed a total of 603 observations with follow-up durations of up to five years. More detailed preprocessing steps are provided in the Supplementary Methods.

Statistical analyses

To address our research goals, we first assessed the association between putaminal DaT integrity and global/subnetwork NAT across all individuals. Next, we compared NAT between the three groups. All models were controlled for network density, age, sex, and education. To account for the repeated measure design due to the different network densities, we performed two generalized linear mixed-effects models (GLMMs) [17], allowing crossed individual intercepts for each participant and MRI scanner. Fixed effects included: putaminal DaT-integrity or disease status, network density, age, sex and education. As disease status and putaminal DaT integrity were highly correlated, they were not included simultaneously in any model.

Since NAT is a fraction and by design never one or zero, a beta regression model was used [18], i.e., a GLMM with a beta response distribution utilizing a logit link function. Both statistical models were run separately for global and subnetwork NAT (5 runs = total of 10 models) using the 'mgcv' package in R (Rstudio ver. 2022.12.0). Significance was set to $p = 0.05$; no correction for multiple comparisons was applied, as networks were tested independently.

As sensitivity analysis, we further examined the DaT-SMN NAT associations in each clinical group separately. Further, we tested whether MAH and LAH putaminal SBRs showed different effects on NAT, employing the same GLMM approach.

Finally, to assess whether SMN NAT was associated with longitudinal motor symptom stability, a GLMM was computed. The model included fixed effects for time (years since imaging date for NAT assessment), SMN attack tolerance, and their interaction to test whether baseline NAT was associated with differential rates of motor symptom progression (assessed by MDS-

UPDRS III total score). Additional covariates included mean putaminal DaT integrity, age, sex, years of education, and LEDD. To account for within-subject dependency of repeated measurements, patients specific intercepts and slopes (i.e. time) were included. This structure allowed individuals to differ both in baseline motor severity and in their rate of change over time. As no meaningful longitudinal change was expected in healthy controls, the model was restricted to participants with prodromal or clinical PD.

Assessment of SMN node degree distribution

Given that the NAT analysis does not provide insights into the structural network alterations that underly shifts in NAT, we visualized the changes of SMN functional architecture across groups by using mean nodal degree maps. Mean nodal degree maps depict the average number of connections each of the 51 SMN ROIs had for each participant and were obtained by averaging the nodal degree for each ROI across the nine densities. To visualize general SMN network topology, these maps were averaged over all participants, mean centered and plotted. Next, to explore how functional architecture might change across groups, groupwise degree maps were averaged and used to plot pairwise group contrasts (e.g., PD–HC = mean PD – mean HC). Finally, to illustrate group differences in node degree distribution, frequency counts of node degrees for each group were smoothed into continuous probability distributions, using kernel density estimation.

Results

Effect of putaminal DaT integrity on NAT

GLMMs assessing the effect of putaminal DaT integrity on global/subnetwork NAT across all groups revealed a negative effect of mean putaminal DaT integrity on SMN NAT (β = -.030; p = .029). No significant associations were found for global NAT or the remaining subnetworks (Fig. 1B). For visualization purposes the raw SMN NAT was grouped by high and low (median split, 1,52 SBR) putaminal DaT integrity in Fig. 1C and the model effects are plotted in Supp. Fig 1A.

Regarding the covariates, network density displayed a robust positive relationship with NAT of every network. Further, higher age was linked to increased global, DMN and ATN NAT. Sex and education remained non-significant. Full model outputs are provided in Table 2.

Sensitivity analyses showed no significant within-group associations (PM: β = 0.012, p = 0.671; PD: β = 0.022, p = 0.535) and consistent results across MAH, LAH, and mean SBR models (MAH: β = −0.029, p = 0.027; LAH: β = −0.029, p = 0.037; mean: β = −0.030, p = 0.029). For detailed information see Supplementary Material.

Effect of disease status on NAT

The GLMMs testing the effect of disease status on global/subnetwork NAT, while controlling for demographic variables and network density, showed that patients with PD exhibited higher NAT within the SMN compared to HC (β = .059; p = .016; Fig. 1B). SMN NAT in the PM was intermediate between HC and PD groups, showing higher values than the HC group and lower values than the PD group. However, neither comparison reached significance (PM>HC: β = .034; p = .199, PD>PM: β = .025; p = .218). None of the other tested models resulted in significant group differences. Raw SMN NAT data plotted for each disease group can be found in Fig. 1C and the model effects are plotted in Supp. Fig 1B.

The covariates showed the same effects and directions as reported for the model assessing the effect putaminal DaT integrity on NAT. Importantly, in this model age was not linked to DMN NAT. All results are summarized in Table 3.

Longitudinal effects of baseline SMN NAT on motor progression

Finally, we assessed the effect of baseline SMN NAT on motor symptom progression in a subset of patients with longitudinal information on clinical motor symptom severity. While mean putamen DaT signal (β = -14.813; p < .001), LEDD (β = -.004; p = .017), and education (β = -.875; p = .025) showed a negative effect on MDS-UPDRS III scores, the introduced interaction term of SMN NAT and time since imaging on MDS-UPDRS III scores (β = -.150; p = .394) was not significant (Table 4). Given the non-significant primary interaction term, and an observed negative slope of SMN NAT x time on MDS-UPDRS III, we conducted an exploratory Johnson and Neyman analysis, to identify potential ranges of significant moderation. The analysis indicated a moderating effect of SMN NAT, across most individuals, excluding three cases with SMN NAT levels > 26% (see Figure 2).

Qualitative comparison of SMN node degree distribution across groups

SMN nodes showed a clear topographical organization across the cohort: nodes with above-mean degree were predominantly located in cortical regions, whereas all subcortical and cerebellar nodes exhibited below-mean degree (Fig. 3A). Conversely, upon visual inspection, all subcortical and cerebellar nodes showed higher node degree values in the PD group in comparison to HCs. In PM patients, a high proportion of cerebellar and subcortical nodes had higher node degrees relative to HCs (Fig. 3B). In PD, nodes with extremely low and extremely high degrees occurred less, effectively increasing the probability of intermediate degree values (Fig. 3C).

Discussion:

In the current study, we investigated whether network attack tolerance (NAT) may potentially reflect a compensatory mechanism, as a function of dopaminergic terminal loss and clinical stage. To this end, we used a large, well-characterized cohort including healthy controls and prodromal and clinical PD patients from the PPMI database with available multimodal neuroimaging data. Our primary findings were that SMN NAT increased with lower dopaminergic terminal availability and was highest in clinical PD. More specifically, SMN NAT appeared to scale with progressive DaT loss, suggesting an increasing degree of network reorganization towards a more robust architecture in response to advancing dopaminergic degeneration. This was also reflected in a graded pattern across disease stages, with SMN NAT being highest in early clinical PD and slightly, albeit non-significantly, elevated in prodromal individuals compared to healthy controls. Finally, the overall effect of baseline SMN NAT on motor symptom progression over time did not reach significance. Yet, an exploratory analysis provided a tendency towards higher SMN NAT being associated with slower motor decline across most of the observed NAT ranges. Given the exploratory nature of this finding, future longitudinal studies are required to assess whether the observed increase in NAT reflects a compensatory mechanism or whether it is actually represents a more general pathophysiological process in PD, as will be discussed in the following.

Across all analyses, the pattern of findings suggests that alterations in SMN NAT are closely linked to the underlying disease process in PD. Although we tested NAT in several subnetworks, only the SMN showed a disease-related effect, while other networks (i.e. DMN, FPN, ATN and whole brain) remained unaffected. This selectivity is consistent with the current understanding of early PD pathophysiology, in which nigrostriatal degeneration primarily disrupts basal ganglia and, subsequently, cortical motor circuits [19]. Prior PD imaging studies reported that especially the SMN and the basal ganglia together with the DMN appeared to be affected by functional changes associated with disease progression [20]. Importantly, various studies specifically suggested functional changes related to dopamine medication intake [21,22] or striatal dopamine availability [23–25] in regions involving key nodes of our SMN network. Our findings align with these reports indicating that the architecture of the SMN changes as DaT availability declines.

Indeed, in the current study, visual inspection of the network architecture (i.e. degree distribution) within the SMN revealed that subcortical and cerebellar nodes, which typically show lesser connections, showed increased connectivity in PM and PD patients, while the number of connections in cortical nodes slightly decreased. This is consistent with recent reports of additional subcortical and motor region recruitment in motor compensation [26,27]. These findings overall suggest that when striatocortical input is disrupted, the SMN may reroute information through alternative, lesser involved pathways to preserve its function. In line with our visual assessments the reorganization of the SMN may thereby be partly orchestrated through the increasing involvement of lesser-connected regions, particularly subcortical nodes, potentially shifting the network towards a more distributed and robust architecture. Importantly, these network changes may already emerge in the prodromal stage. While no significant differences in SMN NAT were observed between PM and HC, a small positive effect was evident across SMN network densities, alongside shifts in SMN degree distribution.

While these observations may indicate early adaptive changes that intensify with progressive DaT loss and increasing compensatory demand, they may also reflect more general network deterioration associated with neurodegeneration. As critical hubs are progressively lost, the network may shift from a highly segregated, hub-dominated architecture toward a more distributed and integrated configuration. Such reorganization could inherently increase attack tolerance even in the absence of a truly compensatory process. Given that we only observed a tendency of a moderating effect of NAT on motor decline and no association of NAT with baseline motor symptom severity, further studies are required to disentangle the role of NAT in PD. This will require future studies extending follow-up beyond five years, more detailed motor assessments and including more advanced disease stages, to capture sufficient variance in both NAT and motor decline.

Importantly, the current results on the relationship between DaT loss and NAT expand on previous findings of our group, examining SMN NAT in relation to general motor function in a smaller cohort [10]. Within that cohort, higher SMN NAT was associated with greater DaT integrity. This finding appears to contrast with the present results, where higher SMN NAT was observed alongside lower dopaminergic terminal integrity. One possible framework that could reconcile the opposing relationships is the inverse U-shaped trajectory of compensation,

whereby adaptive mechanisms emerge and peak before rapidly declining as pathology advances and symptoms become overt [29]. Since our current dataset comprised only de novo patients, it might thereby merely capture the ascending portion of this compensation curve. In contrast, the preceding study, which included medicated patients with disease durations of up to three years, may rather reflect the descending part of the slope, resulting in opposing NAT-DAT relationships. However, this interpretation remains speculative in the absence of data spanning the full disease trajectory, and alternative explanations, including progressive network deterioration, cannot be excluded.

Notably, what both studies do converge on is an association between higher SMN NAT and more favorable motor outcomes. While our exploratory longitudinal findings provide initial evidence that higher SMN NAT may be associated with more favorable motor trajectories, the previous study showed a mitigating effect of higher NAT on general motor function [10]. However, given that the overall interaction term of the current study did not reach significance and the sample size of the previous study was relatively small, these findings need to be handled cautiously.

Moreover, further limitations need to be considered when interpreting the current findings. First, the NAT-DaT assessments were limited by scanner type variability and their cross-sectional nature. Since DaT-SPECT has only recently been proposed as marker of PD progression [30], validation in longitudinal designs, including longitudinal DAT imaging, is warranted. Additionally, more refined motor tests, which are sensible to subtle motor changes even in PM patients, could aid to determine whether NAT plays a role in the phenoconversion from prodromal to manifest PD. Lastly, examining a broader patient spectrum encompassing prodromal, early, and more advanced clinical stages may provide further insight into the dynamic trajectories underlying SMN reorganization in PD.

Taken together, our findings indicate that NAT reflects a network property that is specifically modulated in the SMN as response to increasing pathological load and clinical progression. In this regard, striatal DaT loss may drive a reorganization of the SMN, enabling it to sustain efficient information flow despite the loss of critical hubs. However, longitudinal studies across broader disease stages are required to determine whether these alterations represent transient compensation or progressive network deterioration over the course of PD.

Data availability statement:

Data used in the preparation of this article was obtained in June 2025 from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/access-dataspecimens/download-data), RRID:SCR_006431. For up-to-date information on the study, visit www.ppmi-info.org.

Author contributions

M.H. and A.A. were involved in outlining the research, planning the project, writing the manuscript, and making key decisions throughout the study. A.A. carried out all aspects of the data extraction, curation, preprocessing and analysis, wrote the in-house scripts utilized, carried out the statistical analysis, and created all figures and tables. V.D. and M.H. guided the statistical analysis. TvE provided critical feedback and overall guidance throughout the project. Finally, all authors reviewed the final manuscript.

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Table 1: Demographics of the study cohort.

	HC (n=28)		PM (n=60)		PD (n=94)		
	Mean (SD)	MIN/MAX	Mean (SD)	MIN/MAX	Mean (SD)	MIN/MAX	*p*-value
Sex (m/f)	16/12	m=57%	35/25	m= 58%	65/29	m= 69%	.290
Age	66.7 (6.2)	52.2 - 77.7	69.1 (5.6)	52.9- 80.0	65.7 (7.1)	50.4 - 79.8	.013*
Education	16 (2.5)	7 - 20	17 (2)	12 - 20	17(2)	10 - 20	.524
MoCA	28 (2)	25- 30	28 (2)	25 - 30	28 (3)	25 - 30	.686
MDS-UPDRS III	1.5 (2.2)	0 - 7	3 (5)	0 - 14	24 (16)	8 - 57	<.001*
Mean DaT (putamen)	2.5 (0.4)	1.88 - 3.46	1.7 (0.5)	0.49 - 3.21	1.2 (0.4)	0.16 - 2.07	<.001*

Standard deviation (SD) is provided for continuous variables and interquartile range (IQR) for ordinal values (MDS-UPDRS III, Education and MoCA scores). PD = Parkinson's disease, PM= prodromal PD, HC = healthy control, DaT = dopamine transporter, MoCA = Montreal Cognitive Assessment, UPDRS-III = Movement Disorder Society Unified Parkinson's Disease Rating Scale-Part III, *: p<.05

Table 2: Results table of GLMMs assessing contribution of DaT integrity in the putamen to network attack tolerance (NAT) in five different networks.

Fixed effects	Global				SMN				DMN				ATN				FPN			
	ß	*p*	CI		β	*p*	CI		β	*p*	CI		β	*p*	CI		β	*p*	CI	
Biological factor																				
Mean putamen	-.001	.807	*-.005*	*.004*	**-.030**	**.029***	***-.057***	***-.003***	.013	.276	*-.010*	*.035*	.008	.457	*-.013*	*.028*	-.009	.375	*-.028*	*.011*
Control variables																				
Age	**.001**	**.009***	***.000***	***.001***	-.001	.679	*-.002*	*.003*	**.002**	**.034***	***.000***	***.004***	**.002**	**.025***	***.000***	***.004***	.001	.532	*-.001*	*.002*
Sex(f<m)	.003	.278	*-.002*	*.009*	-.015	.401	*-.050*	*.020*	.025	.106	*-.005*	*.055*	.017	.226	*-.010*	*.043*	.005	.725	*-.021*	*.030*
Education	.000	.729	*-.001*	*.001*	.002	.566	*-.009*	*.005*	-.001	.712	*-.007*	*.005*	.001	.599	*-.004*	*.007*	.000	.800	*-.006*	*.004*
Network density	**.106**	**<.001***	***.104***	***.109***	**.616**	**<.001***	***.606***	***.625***	**.542**	**<.001***	***.0533***	***.550***	**.747**	**<.001***	***.735***	***.760***	**.676**	**<.001***	***.666***	***.685***
Explained var.	R^2=.81 N=198				R^2=.93 N=198				R^2=.91 N=198				R^2=.91 N=198				R^2=.94 N=198			

Significant findings are highlighted in bold. ß = unstandardized beta coefficients, *: p<.05, CI represents the 95% confidence interval, ATN = attention network, DMN = default mode network, FPN = frontoparietal network, SMN =somatomotor network.

Table 3: Results table of GLMMs assessing contribution of disease status to network attack tolerance (NAT) in five different networks.

Fixed effects	Global				SMN				DMN				ATN				FPN			
	ß	*p*	CI		β	*p*	CI		β	*p*	CI		β	*p*	CI		β	*p*	CI	
Variable of Interest																				
Status (PD > HC)	.002	.619	*-.006*	*.010*	**.059**	**.016***	***-.018***	***.087***	.015	.488	*-.027*	*.056*	-.008	.667	*-.045*	*.029*	.014	.344	*-.021*	*.049*
Status (PM > HC)	.001	.791	*-.007*	*.009*	.034	.199	*.011*	*.107*	.035	.135	*-.011*	*.080*	-.018	.361	*-.057*	*.021*	.018	.425	*-.019*	*.056*
Status (PD > PM)	.001	.802	*-.005*	*.007*	.025	.218	*-.015*	*.064*	-.020	.250	*.-.054*	*.014*	.010	.489	*-.019*	*.039*	-.004	.789	*-.031*	*.024*
Control variables																				
Age	**.001**	**.009***	***.000***	***.001***	.001	.400	*-.001*	*.004*	.002	.087	*.000*	*.004*	**.002**	**.020***	***.000***	***.004***	.001	.558	*-.001*	*.002*
Sex(f<m)	.003	.267	*-.002*	*.009*	-.011	.540	*-.045*	*.024*	.021	.154	*-.008*	*.051*	.014	.302	*-.012*	*.040*	.007	.598	*-.018*	*.032*
Education	.000	.732	*-.001*	*.001*	-.002	.637	*-.009*	*.005*	-.002	.548	*.-.008*	*.004*	.001	.623	*-.004*	*.007*	-.001	.830	*-.006*	*.004*
Density	**.107**	**<.001***	***.104***	***.109***	**.616**	**<.001***	***.606***	***.625***	**.542**	**<.001***	***.533***	***.550***	**.747**	**<.001***	***.735***	***.760***	**.676**	**<.001***	***.666***	***.685***
Explained var.	R^2=.81. N=1638				R^2=.92. N=1638				R^2=.92. N=1638				R^2=.91 N=1638				R^2=.94 N=1638			

Significant findings are highlighted in bold. ß = unstandardized beta coefficients, *: p<.05, CI represents the 95% confidence interval, PD= Parkinsons disease, HC = healthy control, PM prodromal, ATN = attention network, DMN = default mode network, FPN = frontoparietal network, SMN =somatomotor network

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Table 4: Results table of the LMM assessing contribution of network attack tolerance (NAT) in the SMN on MDS-UPDRS III change over time.

Fixed effects	MDS-UPDRS III			
	β	*p*	CI	
Term of interest				
SMN NAT x Time	-0.150	0.394	*-0.495*	*0.194*
Control variables				
Time delta (years)	5.312	.190	*-2.579*	*13.203*
SMN NAT (percent)	0.370	.488	*-0.563*	*1.303*
Mean putamen	**14.183**	**<.001***	***-18.325***	***-11.301***
Age	-0.243	.060	*-0.495*	*0.009*
Sex	-1.878	.311	*-5.498*	*1.742*
Education	**-0.876**	**.025***	***-1.634***	***-0.115***
LEDD	-0.004	**.017***	*-0.007*	*-0.001*
Explained var.	R^2= .87 N=600			

Significant findings are highlighted in bold. ß = unstandardized beta coefficients, *: p<.05, CI represents the 95% confidence interval, SMN =somatomotor network, NAT = Network attack tolerance, LEDD = Levodopa equivalent daily dose

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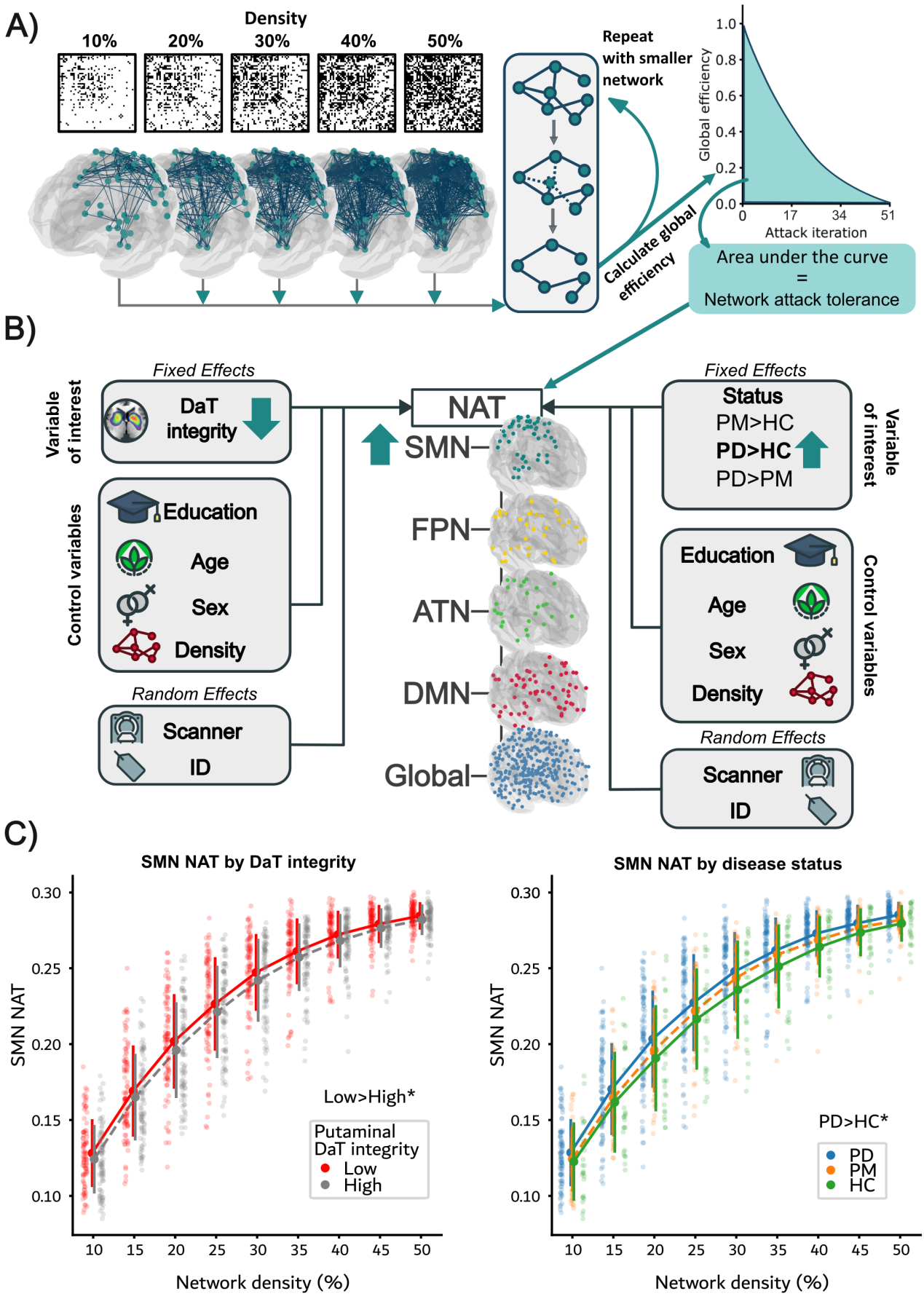

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Figure 1: A) Illustration of analysis pipeline: Left: Region of interest (ROI) to ROI connectivity matrices were thresholded at nine different densities from 10% to 50% (for clarity only five out of nine densities are depicted), then binarized, and finally used for network construction. Right: During the attack analysis, the network's nodes were iteratively removed in descending order of their connectedness. For each removed node, the network's global efficiency was computed. The ability to sustain its global efficiency to successive attacks (area under the curve) defined the attack tolerance of the respective network. All analyses steps are illustrated using the SMN as an example. **B)** Model structure and key results: Left panel shows the effect of putamen dopamine terminal (DaT) integrity on NAT; right panel shows the effect of group status (Prodromal (PM), Parkinson's disease (PD), and healthy controls (HC)) on NAT. The arrows are color-coded and represent the direction of the association between NAT of the respective network and the fixed effects. The surface projections depict the ROIs of the somatomotor network (SMN, turquoise), the frontoparietal network (FPN, yellow), the attention network (ATN, green), the default mode network (DMN, red), and the global network (blue). **C)** SMN NAT plotted for each network density and grouped by high and low (median split) putaminal DaT integrity (left) and disease status (right). Illustrations were plotted using nilearn 31 , *:sign. Difference ($p<.05$) in linear mixed model

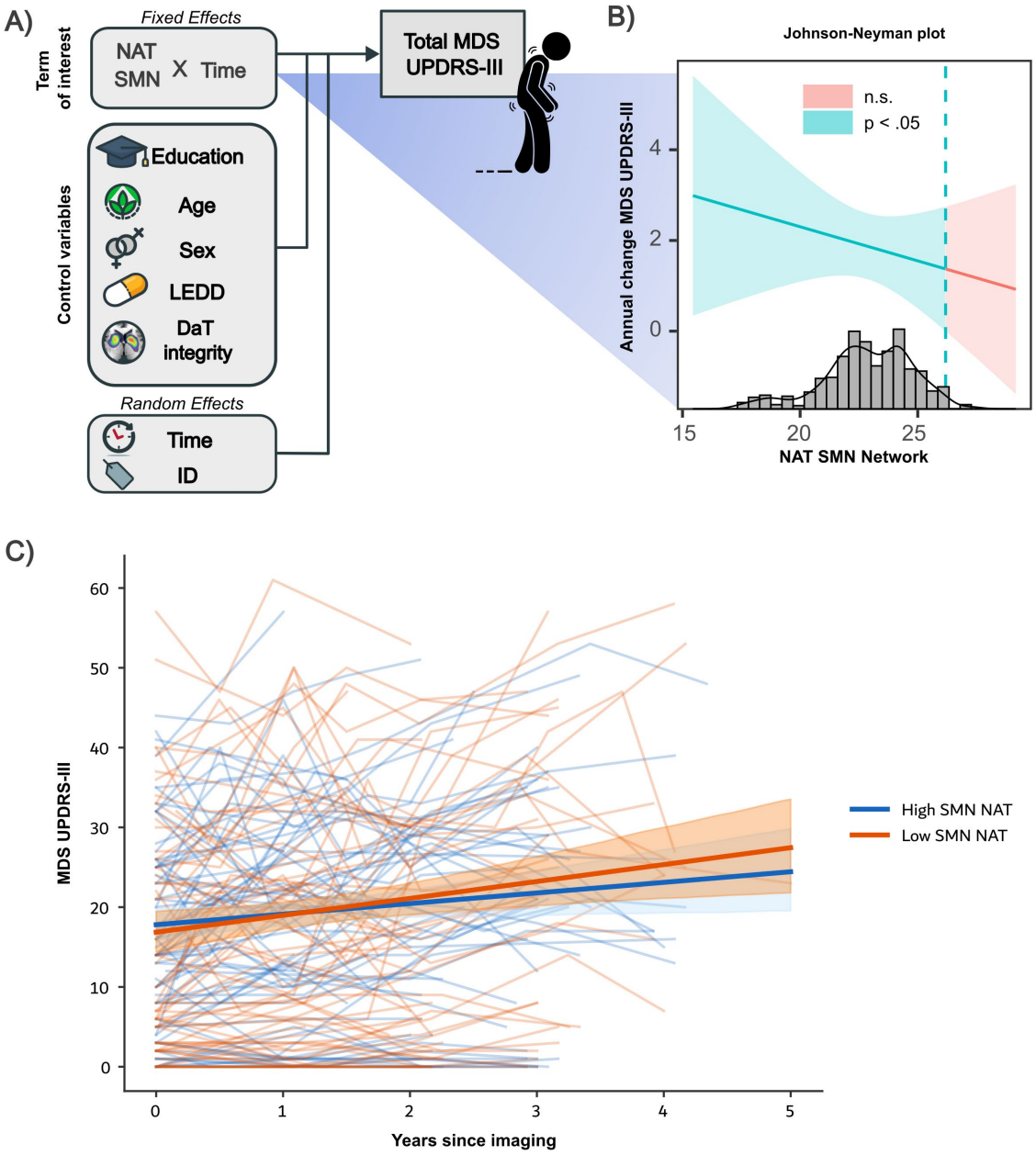

Figure 2. Longitudinal model structure and key results: A) Illustration of the longitudinal analysis pipeline. The model assessed the effect of somatomotor (SMN) network attack tolerance (NAT) on the association of motor impairments (MDS-UPDRS III scores) and time, correcting for putamen dopamine terminal (DaT) integrity, education, age, sex and levodopa equivalent daily dose (LEDD), and allowing random intercept and slope for Time and ID. **B)** Johnson and Neyman plots assessing the moderating effect of SMN NAT on the association between and total MDS-UPDRS III scores and time. Ranges where SMN NAT significantly moderated the effect on the association between UPRS-III scores and time are shown in light blue. Ranges of non-significance are depicted in red. On the x axis a 'densigram' (density grey line and histogram as grey bars) shows the distribution of observed SMN NAT levels, providing context for the applicability of the identified ranges of significance. Significance threshold: $p < .05$ **C)** Individual longitudinal MDS-UPDRS III trajectories for prodromal and clinical Parkinson's disease participants (n = 145), stratified by a median split of baseline SMN NAT (median = 23.0 %). Participants with high baseline SMN NAT (≥ median) are shown in blue; participants with low baseline SMN NAT (<

median) are shown in orange. Thin lines represent individual trajectories. Bold lines indicate group-level unadjusted linear regression fits; shaded areas denote 95% confidence intervals.

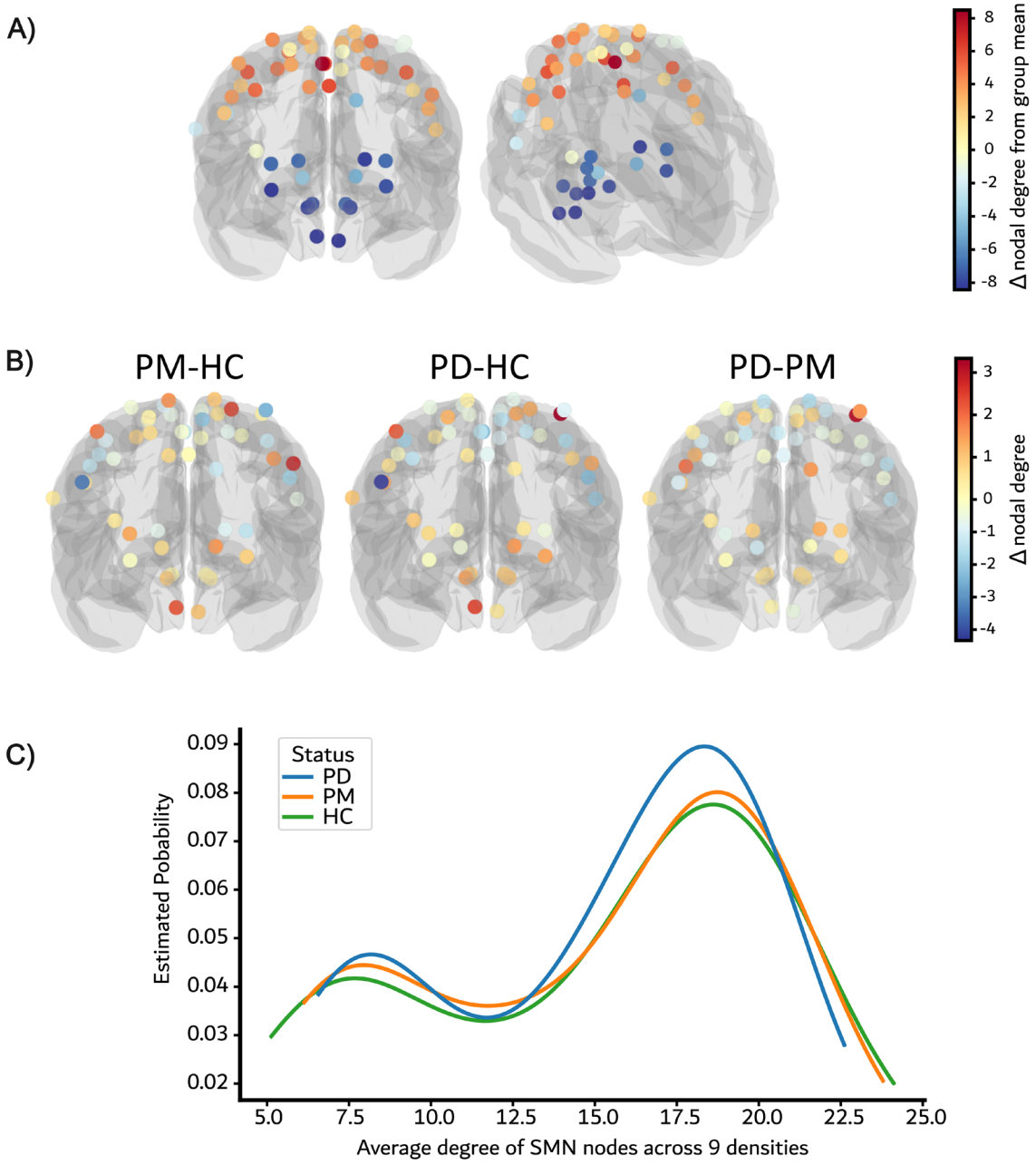

Figure 3: (A) Average SMN node degree profile. Surface renderings of the SMN (frontal, left; lateral, right). Node colors indicate mean-centered degree (node degree minus the SMN-wide mean), averaged across the entire cohort. Warm colors mark above-average degree; cool colors mark below-average degree. **(B)** Grouplevel SMN node degree contrasts (PM, PD, HC). Frontal surface renderings of the SMN. Colors encode the difference for each node for the specified contrast (e.g., PD minus HC): warm = higher in the first group; cool = lower in the first group. **(C)** Distributions of node degree across SMN by group (kernel density estimates). The y-axis reflects the estimated probability, with each group normalized independently to enable direct comparison of distribution shape. Each degree value represents the average across the nine density thresholds. Surface renderings were plotted using nilearn 31

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Supplements:

1 PPMI data extraction and curation

1.1 Crosssectional data:

Data were obtained from the Parkinson's Progression Markers Initiative (PPMI) in June 2025 via the Image and Data Archive (IDA), selecting participants aged between 50–80 years from the three respective groups: PD, PM, and HC groups. We included the following visits: Screening, Baseline, and Months 3, 6, 9, 12, 18, and 24. Filters were applied for radiopharmaceutical use (DAT) and MRI/fMRI data acquired on Siemens scanners. This yielded metadata for 2078 subjects. The resulting CSV file was cleaned to correct modality labels, reformat date-time fields, and replace SPECT entries with higher-resolution DaT-SPECT metadata from PPMI spreadsheets (September 2024; PM subset July 2023). Only SPECT sessions within ±6 months of MRI scans were retained. Demographic data was added using the "curated data set" (March 2025). Next, filtering criteria outlined in Supp. Table 1 were applied globally and at the group level (see Supp. Table 1), resulting in 399 subjects: 131 PM, 223 PD, and 45 HC. Respective imaging data was downloaded via IDA and converted from DICOM to NIfTI using dcm2niix (v1.0.20211006). Using the ".json" files we assured that all MRI and fMRI sessions followed one identical sequence, reducing the sample to 213 subjects. Visual inspection excluded 10 cases (ghosting, structural lesions). Following preprocessing, automated quality control excluded 21 more (signal drift, motion artifacts), resulting in a final analytical sample of 182 participants.

Whole group:	✓ MRI + fMRI + DaT SPECT available ✓ Time delta between fMRI and DaT SPECT ≤ 6 months ✓ Curated data available ✓ Absence of cognitive impairment: MoCA ≥ 25 ✓ Age between: 50 -80 ✓ Absence of depressive symptoms: GDS ≤ 5 ✓ Only right-handed participants ✓ Absence of any other neurological condition
PD group	✓ Disease duration < 3 Years ✓ Unmedicated (LEDD = 0mg) ✓ Primary diagnosis of 'idiopathic PD'
PM group	✓ Only Baseline scans ✓ Unmedicated (LEDD = 0mg) ✓ Primary diagnosis of 'Prodromal Synucleinopathy'
Control group	✓ Primary diagnosis of 'Healthy Control'

Supp. Table 1. Inclusion criteria applied to the IDA advanced search result: Whole-group criteria were applied first, ensuring that every participant (PD, PM, HC) had complete multimodal imaging (MRI, resting-state fMRI, and DaT SPECT) acquired within six months of each other, met basic demographic and health requirements (age 50–80 y, right-handed, MoCA ≥26, GDS ≤5, no other neurological disorders), and had fully curated clinical records at PPMI. Group-specific criteria were then layered on: idiopathic Parkinson's disease (PD) within three years of diagnosis and unmedicated (LEDD = 0 mg); prodromal synucleinopathy (PM) at baseline, also unmedicated; and healthy controls (HC) without neurological or psychiatric diagnoses. DaT = dopamine transporter, GDS = Geriatric Depression Scale, MoCA = Montreal Cognitive Assessment, LEDD = Levodopa equivalent daily dose

1.2. Longitudinal motor assessment and Levodopa equivalence dose data:

To obtain information about the longitudinal change in MDS-UPDRS III scores across participants (PD,PM) longitudinal data regarding the LEDD and the MDS-UPDRS III was obtained from PPMI on Feb 2026. The MDS-UPDRS III was filtered for entries that were either in the OFF state or did not receive any medication at the timepoint being. Cases where the total MDS-UPDRS III was empty were dropped. Then only cases where the assessment date of the MDS-UPDRS III was equal to or higher than the imaging date were kept. Next, a time delta to the imaging date was calculated with 0 regarding to the time of the imaging. Since in some instances imaging data was chosen from later visits (Still medication = 0) time point zero did not always align with BL in PPMI. More and lesser affected bodyside were defined based on mean putaminal SBRs. For each case where the assessment was noted to be done in the OFF state with active treatment, all active medication during the assessment date were extracted from the LEDD list and total LEDD was calculated according to PPMI standards. In three cases, no LEDD was annotated despite documented medication use. These three assessments were dropped. As imaging data used was in some cases acquired very recently, for seven participants (6 PD and one PM), no longitudinal MDS-UPDRS III assessments were available, which led to the exclusion. Further, two PD patients showed an annual decrease in MDS-UPDRS III scores of over 30 points and were therefore classified as outlier and excluded, as such large improvements are not clinically plausible and likely reflect measurement or data inconsistencies. This led to a PD-PM cohort of 86 PD and 59 PM individuals. Finally, a total of 145 participants contributed longitudinal data with a total of 603 data points. The number of available assessments per participant ranged from two to eight. Specifically, two assessments were available for 19 participants (13.1%), three assessments for 33 participants (22.8%), four assessments for 40 participants (27.6%), five assessments for 23 participants (15.9%), six assessments for 21 participants (14.5%), seven assessments for 8 participants (5.5%), and eight assessments for 1 participant (0.7%). The follow-up duration ranged from baseline to up to five years. Change of MDS-UPDRS III across time can be assessed in Supp. Figure 1.

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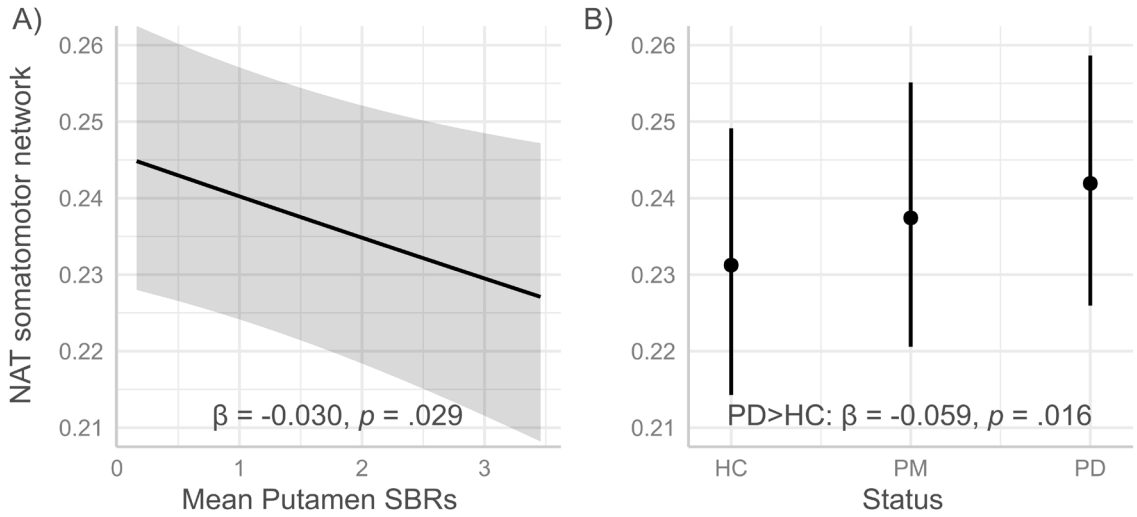
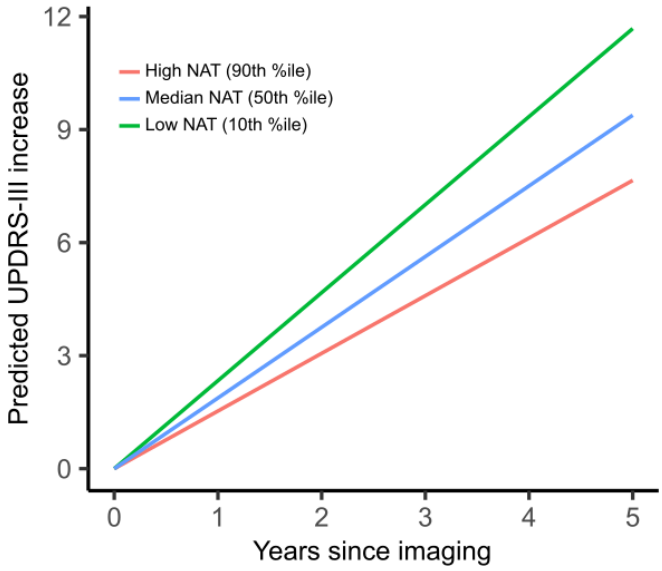


Supp. Figure 1. Model-estimated somatomotor network (SMN) attack tolerance (NAT) across disease stages and dopaminergic terminal availability. A): Predicted relationship between mean putaminal dopamine transporter availability (specific binding rations, SBRs) and somatomotor network (SMN) attack tolerance (NAT) derived from the generalized linear mixed effects model. The solid line represents model predictions with covariates held constant. The shaded area denotes the 95% confidence interval**. B)** Model-estimated SMN NAT across groups, including healthy controls (HC), prodromal participants (PM), and Parkinson's disease (PD). Points indicate estimated marginal means from the model and error bars represent 95% confidence intervals.



Supp Figure 2: Model-estimated interaction between somatomotor network (SMN) network attack tolerance (NAT) and time on longitudinal motor symptom progression. Y-axis represents years that passed since baseline NAT assessments, while X-axis represents the predicted increase of UPDRS-3 scores. Lines represent predicted changes in MDS-UPDRS Part III scores over time derived from the linear mixed-effects model. Trajectories are shown for three representative NAT levels: low NAT (10th percentile, green), median NAT (50th percentile, blue), and high NAT (90th percentile, red). Predictions reflect fixed-effect estimates from the model while holding covariates constant.

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Supplementary Table 2: Results of the GLMMs assessing contribution of DaT integrity in the putamen to network attack tolerance (NAT) in the SMN repeated in the PD and PM only

Fixed effects	SMN PD Group only				SMN PM Group only			
	β	*p*	CI		β	*p*	CI	
Biological factor								
Mean putamen	.021	.535	*-.047*	*.091*	.012	.671	*-.042*	*.066*
Control variables								
Age	.002	.164	*-.001*	*.006*	.004	.116	*-.001*	*.008*
Sex(f<m)	.023	.375	*-.028*	*.073*	**-.054**	**.035***	***-.140***	***-.004***
Education	-.003	.610	*-.012*	*.007*	.008	.187	*-.004*	*.020*
Network density	**.606**	**<.001***	***.592***	***.619***	**.626**	**<.001***	***.610***	***.641***
Explained var.	R^2=.93 N=846				R^2=.94 N=540			

Significant findings are highlighted in bold. ß = unstandardized beta coefficients, *: p<.05, CI represents the 95% confidence interval, SMN =somatomotor network.

Overview on Funding

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Asendorf, A. L., Theis, H., Tittgemeyer, M., Timmermann, L., Fink, G. R., Drzezga, A., Eggers,C., Ruppert-Junck, M. C., Pedrosa, D. J., Hoenig, M. C., & van Eimeren, T. (2024). Dynamic properties in functional connectivity changes and striatal dopamine deficiency in Parkinson's disease. Human Brain Mapping, 45(10), e26776. https://doi.org/10.1002/HBM.26776

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