Heinrich Heine Universität Düsseldorf

Structural and Microstructural Markers of PSP-specific Network Disruption

Inaugural-Dissertation

zur Erlangung des Doktorgrades
der Mathematisch-Naturwissenschaftlichen Fakultät
der Heinrich-Heine-Universität Düsseldorf

vorgelegt von
Silja Querbach (geb. Kannenberg)
aus Lüneburg

Düsseldorf, Juni 2025

Aus dem Institut für Klinische Neurowissenschaften und Medizinische Psychologie der Heinrich-Heine-Universität Düsseldorf

Gedruckt mit der Genehmigung der

Mathematisch-Naturwissenschaftlichen Fakultät der

Heinrich-Heine-Universität Düsseldorf

Berichterstatter:

1. **Prof. Dr. Dipl.-Inform. Julian Caspers**, Institut für Diagnostische und Interventionelle Radiologie, Universitätsklinikum Düsseldorf
2. **Prof. Dr. Christian Bellebaum**, Institut für Biologische Psychologie, Heinrich-Heine-Universität Düsseldorf

Tag der mündlichen Prüfung: 07.10.2025

"Acceptance doesn't mean resignation; it means understanding that something is what it is and that there's got to be a way through it."

Michael J. Fox

Dedicated to my mother, who taught me that I can achieve anything, no matter where I start, no matter how long it takes

—yet reminded me, that I'm never obligated to chase the dreams others choose for me.

Table of Contents

List of abbreviations (articles excluded)

AD	axial diffusivity
ALE	Anatomic Likelihood Estimation
APD	atypical parkinsonian disorders
AUC	area under the curve
CBD	corticobasal degeneration
CST	corticospinal tract
DTI	diffusion tensor imaging
FA	fractional anisotropy
fMRI	functional MRI
FSL	FMRIB software library
GM	gray matter
HC	healthy control subjects
HCP-A	Lifespan Human Connectome Project Aging
HT	hyperphosphorylated tau
ILF	inferior longitudinal fasciculus
IPD	idiopathic Parkinson's disease
MA	midbrain area
MACM	Meta-Analytic Connectivity Modelling
MCP	middle cerebellar peduncles
MD	mean diffusivity
MDRS	Mattis dementia rating scale
MLF	medial longitudinal fasciculus
MoCA	Montreal Cognitive Assessment

MPAR	Midbrain-to-Pons-Area Ratio
MRI	magnetic resonance imaging
MRPI	Magnetic Resonance Parkinsonism Index
MSA	multiple system atrophy
MTPR	midbrain-to-pons ratio
MW	midbrain width
NDH	network degeneration hypothesis
PA	pons area
PET	positron emission tomography
PS	parkinsonian syndromes
PSP	progressive supranuclear palsy
PSPRS	PSP-Rating Scale
PSP-RS	PSP-Richardson syndrome
PSP-S	PSP-syndrome
PW	pons width
RD	radial diffusivity
ROC	Receiver Operating Characteristic
SCP	superior cerebellar peduncles
SLF	superior longitudinal fasciculus
SNc	substantia nigra pars compacta
TBSS	tract-based spatial statistics
UPDRS	Unified PD Rating Scale
VBM	voxel-based morphometry
WM	white matter

Abstract

Although recent progress in research has improved our understanding of the underlying mechanisms of progressive supranuclear palsy (PSP), an integrated model of the disease remains elusive. Large-scale brain network approaches have gained attention in accounting for the complex symptomatology of PSP; however, region-specific structural alterations continue to play a significant and complementary role.

This thesis investigated neuroanatomical atrophy patterns in PSP to extend the understanding of the structural substrates underlying its heterogeneous clinical presentation. Three studies were conducted to characterize PSP-specific gray matter (GM) and white matter (WM) degeneration and to explore their associations with clinical manifestation. The overarching aim was to integrate focal atrophy patterns with large-scale brain network disruptions, thereby providing insight into the complex interplay between structural degeneration and symptom development in PSP. **STUDY 1** utilized an activation likelihood estimation meta-analysis to identify consistent GM atrophy across PSP cohorts relative to clinical differential diagnoses. Four convergent clusters were identified in the thalamus and midbrain, bilateral caudate nuclei, and insula. Notably, these regions are embedded within distributed large-scale networks, thereby supporting the hypothesis that PSP reflects a systems-based disorder rather than isolated regional damage. **STUDY 2** assessed the diagnostic utility of the midbrain-to-pons ratio (MTPR), confirming its effectiveness as a structural biomarker for PSP. The findings further underscored the midbrain's central role in the PSP pathology and suggested the potential utility of the MTPR as a longitudinal marker for disease monitoring. **STUDY 3** identified extensive WM disconnections associated with core symptoms of PSP, encompassing both motor and cognitive domains, thereby providing evidence for widespread network-level disintegration. Additionally, a relation between the MTPR and WM pathology could be established.

The presented studies underscore the critical role of both localized and network-level structural changes in PSP. The results reinforce the centrality of the midbrain as a pathological node for network-based models in the characterization of PSP pathogenesis. Taken together, this work contributes compelling evidence towards a more integrated understanding of the disease, thereby supporting the development of improved diagnostic strategies.

1. Introduction

Progressive supranuclear palsy (PSP) is a complex neurodegenerative disorder that states significant diagnostic challenges due to its clinical overlap with certain movement disorders (Rowe et al., 2021; Stamelou et al., 2021):

Parkinsonian syndromes (PS) encompass a diverse spectrum of heterogeneous neurological disorders characterized by the manifestation of parkinsonism—a clinical syndrome marked by bradykinesia (slowness of movement), rigidity (stiffness), resting tremor, and postural instability (McFarland, 2016; Williams & Litvan, 2013). These conditions involve progressive neuronal loss; however, they differ in their underlying pathologies and patterns of brain atrophy. This results in distinct clinical and cognitive profiles. Consequently, PS can be classified based on their etiology, clinical features, and neuropathological characteristics. The most common form is idiopathic Parkinson's disease (IPD). However, the spectrum also includes atypical parkinsonian disorders (APD), such as PSP, multiple system atrophy (MSA), and corticobasal degeneration (CBD), as well as secondary parkinsonism. Differentiating between PS is crucial, as APD generally exhibit a more rapid progression, a limited response to levodopa, and more complex symptomatology. Despite distinct pathological hallmarks, APD are frequently misdiagnosed, based on the common representation of parkinsonism. This leads to unnecessary procedures and wrong prognostic expectations (Höglinger et al., 2017; Hughes et al., 2002).

This thesis focuses on PSP, the most common APD, to allow for a detailed investigation of disease-specific structural brain alterations. A focused approach enables precise characterization of the changes uniquely associated with PSP, which would be more difficult in studies including multiple APD due to their clinical and pathological heterogeneity. While many of the mechanisms explored in this thesis—such as the role of gray matter (GM) and white matter (WM) atrophy within large-scale brain networks—are relevant across all APD, PSP serves as a traceable model system due to its relative pathological and diagnostic specificity.

The following chapters will introduce relevant pathophysiological and clinical aspects of PSP. Moreover, information regarding differential diagnoses and relevant neuroimaging methods will be provided. Then, three original research articles will be presented. Finally, the results obtained will be discussed and integrated into a disease-specific network approach.

1.1. Progressive Supranuclear Palsy

PSP was first described by John C. Steele, J. Clifford Richardson, and Jerzy Olszewski in 1964 as a combination of supranuclear gaze palsy, axial rigidity, pseudobulbar palsy, and mild dementia (Steele et al., 1964). Today, its clinical spectrum is known to be more variable than originally described, with various phenotypes, such as PSP-Richardson syndrome (PSP-RS). The resemblance to other PS leads to frequent misdiagnoses (Respondek et al., 2014).

PSP is characterized by the accumulation of abnormal tau protein aggregates in the brain, particularly affecting the brainstem, resulting in various motor impairments, including parkinsonism. PSP develops defining features such as frequent backward falls, supranuclear, mostly vertical, gaze palsy, and cognitive dysfunction (Boxer et al., 2017; Litvan et al., 1996; Litvan, 2003; Pantelyat, 2022). Diagnosis remains based on clinical criteria (Höglinger et al., 2017; Whitwell et al., 2017). However, the complex clinicopathologic nature of the disease can only be definitively confirmed at autopsy, and precise diagnosis remains a challenge (Williams & Lees, 2010). So far, there is no curing therapy for PSP; multiple neuroprotective medications (e.g., levodopa) have proven ineffective, which represents a major distinguishing criterion from IPD. Thus, treatment options focus on providing supportive care for now (Jackson et al., 1983; Litvan, 2003; Stamelou & Höglinger, 2016). As PSP is rapidly progressive and clinical presentation varies individually, it is impossible to establish reliable prognoses. Typically, PSP rapidly leads to severe disability of or ends fatal, within a few years from onset (Litvan & Kong, 2014).

1.1.1. Epidemiology

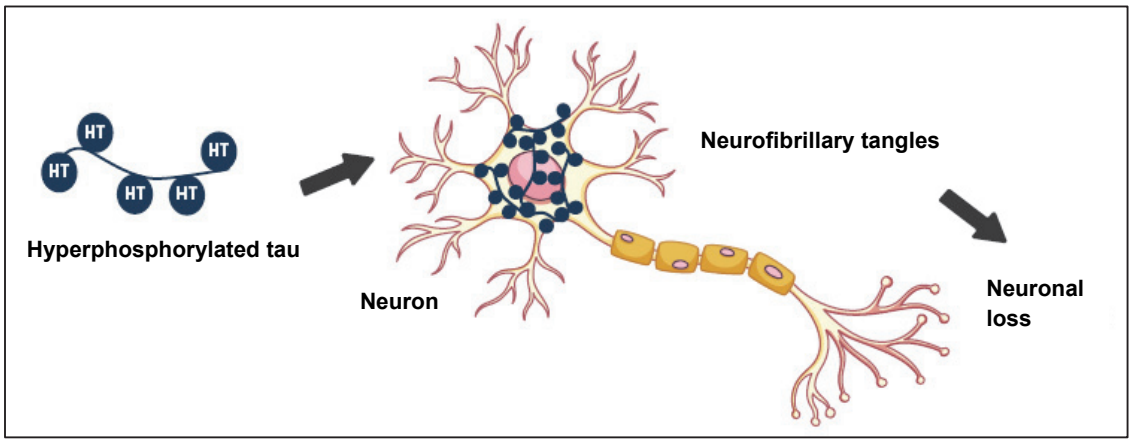
With approximately 1–7 cases per 100,000 individuals, PSP is less common than other neurodegenerative diseases (Golbe, 2008; Lyons et al., 2023). However, prevalence rates can vary considerably depending on geographic region and population characteristics, and a consistent epidemiological description remains elusive (Lyons et al., 2023; Swallow et al., 2022). Frequent misdiagnoses contribute to the underestimation of PSP cases. PSP is considered a late-onset neurodegenerative disorder, typically developing in the sixth decade of life, with a mean age of onset at around 63 years (Boxer et al., 2017; Golbe, 2014). Importantly, the initial appearance of symptoms is variable: some individuals may present in their 50s, while others may not develop symptoms until their 70s or later (Golbe, 2014; Höglinger et al., 2017). The median interval between symptom onset and diagnosis is approximately 3 years, ranging from 6 months to 9 years, reflecting the diagnostic challenges associated with the disease. The estimated median survival from symptom onset is around 7 years (Golbe, 2008). PSP appears

to affect both, males and females equally, but some studies have suggested a slight male predominance (Mahale et al., 2022). While the majority of PSP cases are sporadic (i.e., occur without a family history), a small percentage represents familial PSP, which is linked to specific genetic mutations (Fujioka et al., 2014).

1.1.2. Underlying Pathology

When first described, Steele et al. (1964) suspected a neurodegenerative origin of PSP. A central neuropathological feature of PSP is the abnormal accumulation of tau protein in the brain (Zhang et al., 2024). Tau is a microtubule-associated protein essential for stabilizing microtubules, which support intracellular transport, cell morphology, and synaptic integrity. In PSP, tau becomes hyperphosphorylated, detaches from microtubules, and aggregates into insoluble neurofibrillary tangles (see Figure 1). These tangles are distributed across several brain regions, including the basal ganglia, brainstem, and cerebral cortex, disrupting neural circuitry and contributing to progressive neuronal loss (Kovacs et al., 2020). The severity and distribution of tau pathology in PSP correlate with the clinical presentation and disease progression (Robinson et al., 2020).

Figure 1. Pathophysiological Mechanism of PSP.

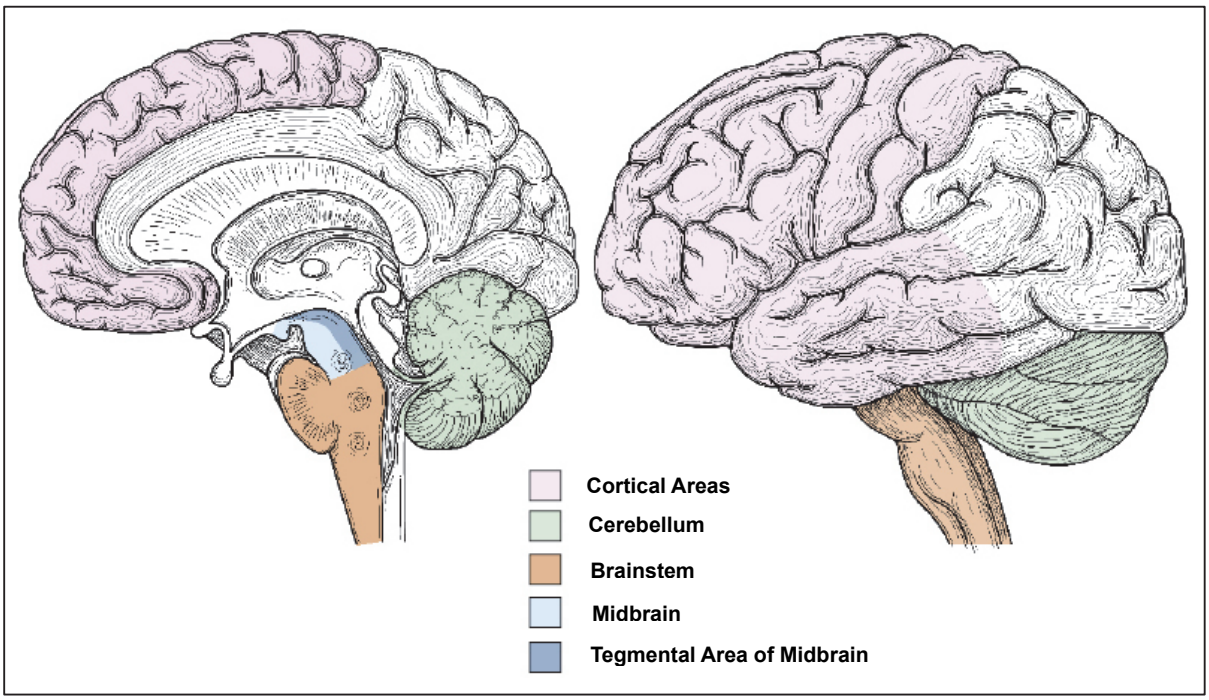


Note. In PSP, hyperphosphorylated tau protein with an altered repeat ratio leads to tau depositions in neurons, which ultimately results in neuronal loss. HT = hyperphosphorylated tau. Adapted from (Ichikawa-Escamilla et al., 2024).

1.1.3. Clinical Manifestations

Though PSP is often diagnosed based on a combination of clinical assessment, neuroimaging, and exclusion of other diseases, the clinical manifestation is crucial to the diagnostic process (Boxer et al., 2017; Tolosa et al., 1994). As PSP affects multiple brain regions (see Figure 2), it can lead to a wide range of motor, cognitive, and behavioral symptoms. Its overlap with other neurodegenerative disorders is a major diagnostic challenge; however, distinct features help to clearly define PSP (Höglinger et al., 2017). The following passages will discuss the major symptoms commonly associated with PSP.

Figure 2. Brain regions, commonly affected in PSP.



Note. In PSP, multiple brain areas are affected to varying extents. Adapted from (Ichikawa-Escamilla et al., 2024).

1.1.3.1. Parkinsonism and other Motor Symptoms

PSP initially presents with motor symptoms resembling those seen in IPD, including the aforementioned hallmark features of parkinsonism: bradykinesia, rigidity, and postural instability (Levin et al., 2016). However, in PSP, these symptoms tend to be more symmetric and less responsive to dopaminergic treatment (Chunowski et al., 2024; Levin et al., 2016).

Bradykinesia, or the slowness in initiating and executing voluntary movements, can affect limb movement, facial expression, and speech. While both patients with PSP and those with IPD exhibit bradykinesia, PSP is less commonly associated with the characteristic resting tremor that is more often observed in IPD. Furthermore, PSP more frequently involves axial muscles, leading to a characteristic facial stiffness resulting in a fixed stare, known as hypomimia (Romano & Colosimo, 2001). Also, PSP-characteristic axial rigidity primarily affects the neck and upper body, in contrast to the limb-predominant rigidity seen in IPD (Respondek et al., 2014). In addition, dystonia may manifest, especially affecting the trunk and neck, leading to abnormal, involuntary muscle contractions, which may cause postural deformities, such as camptocormia or opisthotonus (Godeiro-Junior et al., 2008). Speech is commonly affected due to dysarthria, resulting in slurred, slow, or monotonous speech patterns stemming from impaired motor control of speech musculature. Alterations in voice quality, including reduced loudness and monotonicity, further compromise communication (Kim & McCann, 2015).

Patients commonly exhibit freezing of gait, where their feet appear “glued” to the ground, especially when initiating movement or turning. This may be misattributed to IPD but tends to be more resistant to treatment in PSP (Osaki et al., 2017; Williams & Lees, 2009). Further gait disturbances in PSP are characterized by slow, shuffling movements and a propensity for sudden backward falls. In contrast to IPD, these falls often occur early in the disease course and are typically unaccompanied by protective reflexes (Bluett et al., 2017; Brown et al., 2020). Hence, frequent early falls have been shown to be a key diagnostic indicator of PSP. Most notably, supranuclear gaze palsy is another defining symptom, characterized by impaired voluntary vertical eye movements, especially downward gaze, and slow saccades. This gaze abnormality is highly specific to PSP and often serves as a key clinical differentiator from other PS (Golbe, 2014; Armstrong, 2018). The critical combination of postural instability, reduced gaze control, and difficulty initiating or executing complex movements substantially increases the risk of severe injuries in individuals with PSP.

1.1.3.2. Cognitive, Behavioral, and Non-Motor Symptoms

Cognitive impairment, often overshadowed by the prominent motor symptoms of PSP, is a common and frequently early feature of the disease. Although both PSP and IPD present with cognitive deficits, there are notable differences in the timing, severity, and specific cognitive profiles of these disorders (Stamelou & Höglinger, 2013, 2016).

In PSP, cognitive impairment typically reflects a frontal-subcortical dysfunction, with deficits in attention, executive function, and processing speed (Bak et al., 2005; Boxer et al., 2017; Donker Kaat et al., 2007; Gerstenecker et al., 2013). This ends in difficulties with multitasking, planning, and inhibitory control. In this context, a notable clinical sign, attributed to PSP, is the applause sign, characterized by an involuntary tendency to clap the hands together after being instructed to stop after three times (Höglinger et al., 2017; Williams & Lees, 2009). Further deficits have been reported in verbal fluency (Bak et al., 2005; Donker Kaat et al., 2007), naming (Cotelli et al., 2006), and memory (Macedo et al., 2022).

Beyond cognitive deficits, PSP is frequently associated with significant behavioral alterations, including emotional lability, apathy, disinhibition, and personality changes. These symptoms often resemble the behavioral variant of frontotemporal dementia (Gerstenecker et al., 2013; Han et al., 2010). Impulsivity and disinhibition present as inappropriate social behavior or comments, creating interpersonal challenges. Personality changes—such as diminished empathy—are particularly distressing for caregivers, as they can fundamentally change interpersonal dynamics and complicate social relationships (Millar et al., 2006).

Additionally, visual disturbances are another hallmark of PSP and include impaired smooth pursuit, slowed or restricted saccades, and diplopia, blurred vision, and photophobia (Armstrong, 2011; Chen et al., 2010). Although core language abilities, such as vocabulary and comprehension, are often preserved, some individuals develop features of aphasia, impairing their expressive language (Burrell et al., 2018).

Dysphagia, or difficulty swallowing, is also prevalent in PSP and tends to worsen rapidly with disease progression. It may result in coughing or choking, increasing the risk of aspiration. In advanced stages, dysphagia requires careful monitoring and intervention to prevent life-threatening complications, such as aspiration pneumonia (Clark et al., 2020; Flynn et al., 2024).

1.1.4. Structural Brain Changes in PSP

In order to fully understand the pathology underlying the symptoms described above, it is of particular interest to consider the brain changes that may influence the development of these manifestations. To this end, structural magnetic resonance imaging (MRI) is a central part of the diagnostic workup in PSP, as it enables the identification of key brain alterations that are essential for accurate diagnosis and differentiating PSP from other neurodegenerative disorders (Stamelou et al., 2011).

1.1.4.1. Gray Matter Changes

GM consists of neuronal cell bodies and dendrites and plays a critical role in processing and integrating information within the central nervous system. Tau protein aggregation has been demonstrated to induce neuronal loss in affected brain regions, thereby contributing to the progressive deterioration of motor and cognitive functions observed in PSP (Kovacs et al., 2020). Neuroimaging studies have consistently shown widespread GM atrophy in PSP, particularly affecting the midbrain, thalamic regions, frontal cortex, and basal ganglia (Pan et al., 2017; Piattella et al., 2015a,b; Stezin et al., 2017). This atrophy has been found to correlate with the severity of the hallmark symptoms of PSP (Giordano et al., 2013; Pan et al., 2017; Paviour et al., 2006).

One of the most striking features of PSP is significant atrophy in the midbrain, particularly affecting the tegmental area, which contributes to the characteristic vertical supranuclear gaze palsy, impairing voluntary eye movements (Buch et al., 2022; Massey et al., 2013). Atrophy of other subcortical structures, such as the caudate nuclei, putamen, and thalamus, has been linked to bradykinesia, rigidity, and postural instability (Cordato et al., 2005; Paviour et al., 2006). Additional atrophy in the cerebellum exacerbates motor symptoms, impairing coordination and balance (Rajput et al., 1990, 2001).

While PSP predominantly targets subcortical structures, there is also evidence of cortical involvement, including the frontal, parietal, and temporal cortices. This cortical involvement is especially associated with cognitive and behavioral changes, including executive dysfunction, language difficulties, and personality changes (Rittman et al., 2016). Frontal regions have been linked to impairments in planning, emotional regulation and decision-making, as well as visuospatial interpretation and language difficulties, frequently observed in PSP (Gerstenecker et al., 2013).

Overall, GM atrophy in PSP has been shown to correlate closely with the severity of clinical symptoms and disease progression (Whitwell et al., 2012a; Whitwell et al., 2012b), thus, serving as a critical source to the underlying pathophysiology. Several regions have been observed to be linked to symptoms characteristic of PSP, raising important questions about their connectivity and the underlying trajectory of disease progression. There is an idea of the brain regions that must be involved in the disease, but it remains to be investigated to what extent they are connected and which exact roles they play.

1.1.4.2. White Matter Changes

Tau pathology in PSP also affects WM (Coughlin et al., 2022), which is responsible for transmitting signals between brain regions and facilitating communication between neurons (Bennett & Madden, 2014). While WM atrophy in PSP is less characterized compared to GM changes, recent research has provided valuable insights linking changes in WM tracts, (indicating disruptions in connectivity between brain regions) to the variable symptom complex in PSP (Agosta et al., 2014; Agosta et al., 2011; Knake et al., 2010; Piattella et al., 2015 a,b; Saini et al., 2012; Whitwell et al., 2011; Worker et al., 2014).

Notable abnormalities could be observed in the superior cerebellar peduncles (SCP), inferior and superior longitudinal fasciculus (ILF; SLF), and corpus callosum of PSP patients. These structural WM changes have been shown to correlate with clinical measures: degeneration of the SCP has been associated with overall disease severity, the ILF with motor dysfunction, and the SLF with saccadic eye movement impairments (Agosta et al., 2014; Tessitore et al., 2014; Whitwell et al., 2014). The transhemispheric fibers forming the corpus callosum, potentially contribute to both cognitive and motor coordination deficits (Whitwell et al., 2011). Similarly, the corticospinal tract, which is crucial for motor control, are often affected in PSP and could potentially account for the motor symptoms observed in the disease, including typical parkinsonian features. Additionally, damage to the medial longitudinal fasciculus (MLF), responsible for coordinating eye movements, may contribute to supranuclear vertical gaze palsy (Chen et al., 2010).

Regarding cognitive decline, PSP often involves WM changes in the frontal lobe, affecting areas responsible for higher-order cognitive functions, such as planning, executive function, and decision-making. Degeneration of the uncinate fasciculus, which connects the frontal and temporal lobes, may also contribute to memory and emotional disturbances (Agosta

et al., 2014; Heide et al., 2013). In conclusion, evidently both cortical and subcortical WM alterations shape the clinical profile of PSP together with GM loss.

1.1.4.3. Functional Brain Changes in PSP

Functional changes in PSP refer to alterations in brain activity and connectivity that impact how different regions communicate and process information. Functional imaging studies have consistently demonstrated widespread network dysfunction, particularly affecting frontal and subcortical regions (Black et al., 2024).

One of the earliest and most prominent functional alterations in PSP occurs in the brainstem, especially the midbrain and superior colliculus. Dysfunction in these areas can lead to vertical supranuclear gaze palsy as well as falls and postural instability (Litvan et al., 1996). The disrupted connectivity between cortical and subcortical structures compromises the coordination of complex motor tasks, further contributing to gait disturbances and balance problems (Boxer et al., 2006; Gardner et al., 2013).

Beyond motor symptoms, functional disruption in the lateral and prefrontal cortices has been associated with impairments in executive functions, including attention, memory, and decision-making (Coyle-Gilchrist et al., 2016; Friedman & Robbins, 2022; Hertrich et al., 2021). Compared to IPD, which exhibits more localized basal ganglia dysfunction, PSP presents with broader frontoparietal disconnections, affecting higher-order cognitive processes. In addition, some individuals with PSP exhibit psychiatric symptoms such as apathy, depression, and disinhibition. These are thought to arise from functional abnormalities in regions involved in emotion regulation and social behavior, particularly the anterior cingulate cortex (Rampello et al., 2005).

Taken together, these findings support the notion that PSP is characterized by widespread functional network dysfunction encompassing the frontal lobes, subcortical circuits, and brainstem structures—also forming the variable symptom complex of PSP.

1.1.5. Network Degeneration in PSP?

PSP has long been considered as a disorder driven by degeneration in localized brain structures, particularly the midbrain. However, emerging evidence suggests PSP is better characterized as a network degeneration disorder with widespread disruptions in brain connectivity rather than isolated focal lesions (Gardner et al., 2013; Whiteside et al., 2021, 2023).

According to the network degeneration hypothesis (NDH), neurodegenerative disorders exhibit characteristic atrophy patterns that align with intrinsic connectivity networks in healthy individuals (Seeley et al., 2009; Zuo et al., 2012). This overlap suggests that neurodegeneration originates in focal points, or disease epicenters, and spreads through interconnected neural circuits (Whiteside et al., 2021). Later-affected regions are anatomically connected to earlier-impaired areas, highlighting a process driven by progressive dysfunction of neural networks rather than isolated brain regions (DeTure & Dickson, 2019). As pathology accumulates, affected regions deteriorate while remaining partially functional, interacting with intact brain areas. This supports staged disease progression, where dysfunction spreads through network interactions between impaired and healthy regions.

The structural changes observed in PSP—i.e. in the midbrain, basal ganglia, thalamus, and frontal cortex—tend to co-occur in anatomically and functionally interconnected regions. These alterations suggest the breakdown of large-scale neural circuits and first studies suggested that the NDH may also be applicable to PSP (Gardner et al., 2013; Pandya et al., 2017; Spinelli et al., 2024). Still, it remains uncertain whether the NDH fully applies to PSP, as the disease's pathological distribution does not consistently follow functional or structural brain networks. PSP exhibits both focal and widespread degeneration patterns, making it challenging to attribute symptomatology solely to either of both mechanisms.

1.2. Differential Diagnosis of PSP

The clinical overlap between PSP and other PS underscores the importance of accurate differential diagnosis. Proper identification is essential for guiding treatment, prognosis, patient quality of life, and ensuring valid research. Differentiating PSP from IPD enables tailored therapies, informed decision-making, and better support for both patients and caregivers, ultimately leading to improved outcomes (Respondek et al., 2023; Whiting et al., 2006).

1.2.1. Neuroimaging in the Differential Diagnosis

In the absence of a definite diagnostic test, neuroimaging plays a crucial role to support clinical diagnosis (Rowe et al., 2021). Neuroimaging techniques, such as structural MRI, functional MRI (fMRI), and diffusion tensor imaging (DTI), help to detect structural and functional brain changes, thereby supporting the identification of disease-specific alterations (Boxer et al., 2017; Peralta et al., 2022).

Structural MRI, including T1- and T2-weighted imaging, reveals GM atrophy, WM changes, and ventricular enlargement. Voxel-based morphometry (VBM) is a technique that

quantifies structural changes and brain atrophy based on structural MRI data (Ashburner & Friston, 2000) DTI assesses WM integrity by analyzing water diffusion patterns in MRI, with metrics like fractional anisotropy (FA) providing insights into structural connectivity (Basser et al., 1994). Functional neuroimaging, such as resting-state fMRI, helps to assess brain activity and connectivity. As imaging technology advances, MRI's role in early diagnosis and treatment of PSP continues to expand, improving patient care and research. This work focuses on structural MRI, particularly T1-weighted imaging and DTI, which are explored further in the following sections.

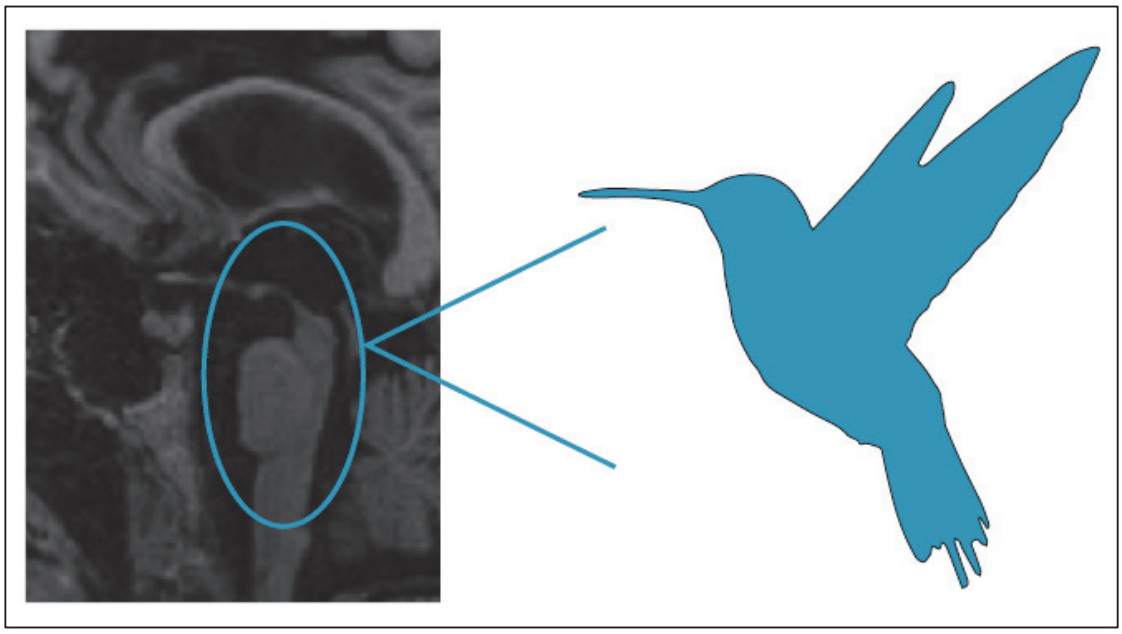
Conclusively, MRI offers a non-invasive window into both structural and functional brain alterations, making it a powerful candidate for biomarker development. To move towards earlier diagnosis and better disease monitoring, it is essential to find MRI markers that are sensitive, specific, and reproducible across patient cohorts.

1.2.2. Structural Biomarkers in PSP

1.2.2.1. Gray Matter Biomarker: The Hummingbird Sign in PSP

Midbrain atrophy is the hallmark feature of PSP**,** consequently playing a critical role in its diagnosis. Thus, one of the most reliable structural biomarkers in PSP is the so-called hummingbird sign (Graber & Staudinger, 2009; Gröschel et al., 2006; Mueller et al., 2018). This MRI finding refers to midbrain atrophy that appears as a narrowing of the midbrain. It's called the hummingbird sign because the shape of the brainstem resembles the outstretched wings and body of a hummingbird when viewed from the side. The hummingbird sign in PSP is most evident on midsagittal brain MRI and is characterized by several key features: pronounced midbrain atrophy with a "tucking" appearance and atrophy of the midbrain tegmentum (the ventral part of the midbrain) with relative pons preservation (see Figure 3).

Figure 3. The hummingbird sign.



Note. The hummingbird sign is characterized by a thinned-out midbrain (resembling the bird's head and beak) and a preserved pons (like the bird's body).

Since it was initially quantified by Oba et al. (2005), several approaches have been established to reliably quantify midbrain atrophy, such as the midbrain-to-pons-area ratio (MPAR), or the midbrain-to-pons ratio (MTPR):

Oba et al. (2005) used the cross-sectional areas of midbrain (MA) and pons (PA) to provide a robust measure against anatomical variation. The measures were divided following this formula, where a value ≤ 0.18 is considered highly specific for PSP:

$$MPAR = \frac{MA\,(mm^2)}{PA\,(mm^2)}.$$

Massey et al. (2013) used a simplified version of the initial measures and measured the linear width of midbrain (MW) and pons (PW) on midsagittal T1-weigthed images. To calculate the MTPR, the two measures were divided following this formula, where a value ≤ 0.52 is considered highly specific for PSP:

$$MTPR = \frac{MW\,(mm)}{PW\,(mm)}.$$

Though the hummingbird sign is often associated with PSP, its presence and diagnostic specificity can vary, and further investigation is needed to clarify its role in early differential diagnosis and monitoring disease progression (Mueller et al., 2018; Virhammar et al., 2022).

1.2.2.2. White Matter Biomarkers

With regard to connectivity between involved areas, potential WM biomarkers have gained considerable attention for their role in understanding the disease's symptom complex. WM changes have been reported to be of particular significance in assessing non-motor and cognitive alterations in PSP (Prodoehl et al., 2013).

DTI studies consistently revealed widespread WM disruption in PSP, with reduced FA in tracts and regions such as the corpus callosum, cingulum, SLF, and cerebellar pathways (Zhang & Burock, 2020). These findings were clinically meaningful, as they were correlated with cognitive deficits and, thus, may serve as early biomarkers in cases with prominent non-motor features (Caso et al., 2016). Besides the midbrain, the SCP belong to the most affected structures in PSP (Whitwell et al., 2017). Taken together, these WM changes reflect the breakdown of long-range connectivity within motor and cognitive control networks, reinforcing the utility of a WM-based biomarker for PSP.

To improve diagnostic specificity, Quattrone et al. (2008) introduced the Magnetic Resonance Parkinsonism Index (MRPI), which extends conventional morphometric biomarkers by incorporating measurements of SCP and the middle cerebellar peduncle (MCP). As the SCP primarily consists of WM, its inclusion is thought to enhance the sensitivity to PSP-specific changes. The MRPI is calculated as follows, with values ≥ 13.55 highly indicative of PSP:

$$MRPI = \left(\frac{PA\ (mm^2)}{MA\ (mm^2)}\right)\frac{MCPW\ (mm)}{SCPW\ (mm)}.$$

This index significantly increases in PSP due to midbrain and SCP atrophy and has demonstrated high diagnostic accuracy (Quattrone et al., 2018; Quattrone et al., 2016). Nonetheless, it remains an open question whether WM-based biomarkers serve as direct indicators of disease pathology or rather as correlates of symptomatic progression.

1.3. Aims of this Thesis

As outlined, research on PSP has gradually shifted from focusing on isolated structural atrophy of certain brain regions to embracing the possibility of a network-based model of neurodegeneration. However, to date, there is still limited evidence supporting this hypothesis or clarifying the extent to which it holds true for PSP. By integrating region-specific findings with network-based interpretations, this work seeks to clarify the complex interplay between brain atrophy, WM degeneration, and overall impairment in PSP. To this end, three studies were conducted:

STUDY 1 presents a comprehensive meta-analysis of VBM studies to identify consistent patterns of brain atrophy across PSP patients, highlighting key regions and networks of structural vulnerability as well as connectivity amongst each other.

STUDY 2 investigated the utility of the MTPR as an imaging biomarker for PSP by assessing its sensitivity to disease progression over a one-year period, thereby emphasizing the central role of the midbrain in PSP.

STUDY 3 explores WM abnormalities associated with PSP and their relationship to cognitive, motor, and behavioral symptomatology, providing insights into network-level disruptions.

Together, these studies aim to (1) characterize PSP-specific structural features, (2) evaluate imaging biomarkers with prognostic potential, and (3) link neuroanatomical changes to clinical outcomes. Ultimately, this thesis aspires to refine diagnostic approaches and contribute to a more nuanced understanding of PSP as a complex, network-based neurodegenerative disorder.

2. Studies included in this Thesis

This thesis is based on the following original research articles:

STUDY 1: **Querbach, S. K.**, Eickhoff, S. B., Hausmann, A.C., Schnitzler, A., Caspers, J., & Eickhoff, C.R. (2025). Consistent PSP Atrophy involves Regions connecting the Salience Network to Subcortical Circuits [Manuscript submitted for publication].

STUDY 2: **Kannenberg, S.**, Caspers, J., Dinkelbach, L., Moldovan, A.S., Ferrea, S., Butz, M., Schnitzler, A., & Hartmann, C.J. (2021). Investigating the 1-year Decline in Midbrain-to-Pons Ratio in the Differential Diagnosis of PSP and IPD. *Journal of Neurology, 268*, 1526–1532. https://doi.org/10.1007/s00415-020-10327-2.

STUDY 3: **Querbach, S. K.**, Hausmann, A.C., Schnitzler, A., Hartmann, C.J., Rubbert, C., & Caspers, J. (2025). Tract-specific DTI Scalars and Clinical Correlates in Progressive Supranuclear Palsy [Manuscript submitted for publication].

3. STUDY 1:

Consistent PSP-atrophy involves Regions connecting the Salience Network to Subcortical Circuits

STUDY 1 (Appendix 1) investigated regions of notable GM atrophy in PSP patients relative to other PS and healthy control subjects (HC). The primary objective was to identify specific regions exhibiting distinct atrophy patterns. Furthermore, it was of interest to make inferences about potential implications for regional connectivity and functionality, influenced by disease-specific neurodegenerative processes.

3.1. Introduction

A major challenge in studying a rare condition like PSP is the limited patient sample size, which often results in inconsistent and non-replicable findings across structural studies (Focke et al., 2011; Stamelou & Hoeglinger, 2013). This limitation can be addressed by meta-analytic approaches, which identify convergent findings across studies (Eickhoff et al., 2012; Eickhoff et al., 2009; Turkeltaub et al., 2002). In the present work, a meta-analysis was employed to yield convergence across the existing literature on PSP-related atrophy. In contrast to previous meta-analytic reports, we went beyond the structural approach: after identifying the consistent atrophy patterns, the delineated regions were then characterized with respect to their functions, connectivity, and neurotransmitter receptor profiles to provide a comprehensive assessment of potential network disruption.

3.2. Methods

To identify consistent regions of atrophy in PSP, an Anatomic Likelihood Estimation (ALE) meta-analysis was conducted on 27 whole-brain morphometry studies. Significant GM coordinates were extracted and modeled using 3D Gaussian distributions to account for spatial uncertainty (Eickhoff et al., 2016). These were aggregated into probability maps indicating consistent GM atrophy (Eickhoff et al., 2012; Turkeltaub et al., 2012). Functional decoding was employed to link these regions to cognitive functions using task-based fMRI meta-data (Genon et al., 2018; Rottschy et al., 2013). In addition, Meta-Analytic Connectivity Modeling (MACM) was utilized to reveal co-activation networks (Reid et al., 2017). Finally, PSP-related atrophy was correlated with positron emission tomography (PET)-derived maps of neurotransmitter systems to explore molecular underpinnings (e.g., dopamine, serotonin,

cannabinoid, noradrenaline, acetylcholine, μ-opioid, GABA, and glutamate) (Dukart et al., 2020).

3.3. Results

Four clusters exhibited significant GM atrophy in PSP compared to HC and other PS: (1) bilateral thalamus and midbrain, (2) left insula extending to the frontal operculum, (3) left caudate nucleus, and (4) right caudate nucleus. Regions consistently affected across all four clusters were primarily linked to language, interoception, somatosensation, cognition, and emotion. MACM revealed functional connectivity between atrophied areas and the frontal cortex, bilateral insula, caudate nuclei, thalamus, midbrain, putamen, globus pallidus, and claustrum. GM alterations in PSP showed positive spatial correlations with the distribution of most dopaminergic, serotonergic, cholinergic, opioid, and GABAergic systems in healthy individuals. Notably, GABAa and 5-HT2a exhibited negative correlations, suggesting that regions with lower receptor availability in healthy subjects were less likely to show PSP-related atrophy.

3.4. Discussion

In summary, the findings of **STUDY 1** highlight consistent PSP-specific atrophy in the bilateral thalamus, midbrain, caudate nuclei, and left insular cortex. These regions are functionally connected to networks such as the salience network, likely contributing to both motor and non-motor symptoms, including impairments in executive function, emotion, and cognition. Additionally, PSP-related atrophy was associated with alterations in serotonergic and cholinergic systems, extending beyond dopaminergic dysfunction. Overall, the results emphasize widespread network disruption in PSP, with a central role for insular cortex involvement.

Besides prominent midbrain atrophy, **STUDY 1** identified significant atrophy in the insula, a region closely connected to other clusters from our meta-analysis and central to multiple functional domains (Kurth et al., 2010). This suggests that disruption of the insular "hub-zone" within the salience network—known for its widespread cortical and subcortical connectivity (Mazzola et al., 2019; Namkung et al., 2017; Uddin et al., 2017)—might be a key feature of PSP. Strong co-activation patterns in the anterior insula support its involvement in PSP-related network dysfunction. We propose that salience network disruption, particularly in the insula, plays a more prominent role in PSP pathophysiology than previously recognized, aligning with both neuroanatomical findings and clinical symptomatology.

Significant atrophy was additionally observed in the bilateral caudate nucleus, implicating disruptions in motor control and goal-directed cognitive functions. While parkinsonian symptoms respond to dopaminergic treatments, PSP shows a poor response despite reduced dopamine transporters, indicating distinct underlying mechanisms. We suggest that PSP's symptoms may stem from disruptions in serotonin and acetylcholine circuits, which are linked to mood, emotional, and sleep disturbances. Thus, PSP symptoms likely involve dopaminergic, serotonergic, and cholinergic system dysfunctions.

3.5. Conclusion

STUDY 1 provides strong evidence of atrophy in key regions implicated in PSP, including the thalamus, midbrain, caudate nuclei, and insular cortex. Their activation and connectivity patterns may explain the diverse motor and non-motor symptoms, including impairments in control functions, emotion, and cognition. Additionally, PSP-related atrophy appears to impact not just dopaminergic but also serotonergic and cholinergic networks. Overall, **STUDY 1** highlights widespread brain network disruption in PSP, with a key role for the insula.

4. STUDY 2:
Investigating the 1-year Decline in Midbrain-to-Pons Ratio in the Differential Diagnosis of PSP and IPD

STUDY 2 (Appendix 2) evaluated the diagnostic value of the MTPR and its change over one year in PSP, IPD, and HC. While the MTPR is known to reliably measure PSP-specific midbrain atrophy, longitudinal analyses were previously lacking. This study aimed to determine if changes in MTPR could enhance diagnostic accuracy and provide insights into the pathophysiology of PSP's diverse progression.

4.1. Introduction

The MTPR, as a reliable biomarker for PSP-related midbrain atrophy, can support the differential diagnosis of PSP and IPD (Massey et al., 2013). PSP progresses considerably faster than IPD (Höglinger et al., 2017), and PSP-specific rates of atrophy could potentially serve as biomarkers of the disease and support differential diagnosis. Since longitudinal analyses were lacking so far, the present study aimed to evaluate the diagnostic value of the relative change of MTPR over a 1-year period in patients with PSP, IPD, and HC.

4.2. Methods

The study included 15 PSP-RS patients, 15 IPD patients, and 15 HC, with diagnoses confirmed by movement disorder specialists. Participants underwent two MRI scans, one at baseline and another after one year. Midbrain and pons measurements were assessed on T1-weighted midsagittal MRIs by two independent raters. The MTPR was calculated as the midbrain width divided by the pons width, and its relative change was defined as the difference between baseline and one-year MTPR. The diagnostic accuracy for differentiating PSP, IPD, and HC was evaluated using Receiver Operating Characteristic (ROC) curve analysis, with the optimal cutoff value determined by Youden's Index and 95% confidence intervals.

4.3. Results

Midbrain MRI measures showed significant differences between PSP and non-PSP groups. PSP patients had a lower baseline MTPR compared to IPD and HC groups, with MTPR demonstrating excellent diagnostic accuracy for distinguishing PSP from IPD (sensitivity 93.33%, specificity 93.33%). PSP patients also exhibited a greater one-year MTPR decline than IPD. While the MTPR change effectively distinguished PSP from IPD, it was less effective for differentiating PSP from both non-PSP groups. Combining baseline MTPR with its one-year change improved specificity to 100%, but did not significantly enhance diagnostic accuracy.

4.4. Discussion

STUDY 2 evaluated the diagnostic value of MTPR change over one year. Longitudinal data showed a distinct decline in MTPR in PSP patients, indicating faster midbrain atrophy compared to IPD and HC. Combining baseline MTPR with its change rate slightly improved diagnostic accuracy and specificity, but not significantly. The findings confirm that an MTPR of 0.52 or less is highly specific for PSP (Massey et al., 2013). While the change in MTPR alone could not differentiate PSP from non-PSP groups, it effectively distinguished PSP from IPD. This was attributed to a significant decrease of midbrain width in HC, as reported in literature before (Lambert et al., 2013). The study suggests that midbrain atrophy may also serve as a preclinical marker in the early stages of PSP. Limitations include the lack of disease severity measures, post-mortem verification, and differentiation between PSP subtypes. Nevertheless, the study supports using the MTPR to improve PSP diagnosis and monitoring, with larger studies needed to explore its full potential.

4.5. Conclusion

STUDY 2 confirms that the MTPR is a valuable biomarker for distinguishing PSP from IPD. The relative change in MTPR, particularly in early-stage PSP, can further aid diagnosis. While baseline MTPR already offers high specificity, combining it with its change over time may enhance diagnosis in follow-up exams and serve as a marker for disease progression, crucial for evaluating disease-modifying treatments.

5. STUDY 3:

Tract-specific DTI Scalars and Clinical Correlates in Progressive Supranuclear Palsy

STUDY 1 revealed PSP-specific degeneration in widespread brain networks. Building on this, **STUDY 3** (Appendix 3) aimed to investigate PSP-related WM pathology and how network connectivity alterations contribute to typical symptoms. DTI and tract-based spatial statistics (TBSS) were used to link microstructural changes to clinical symptoms, while also exploring the relationship between GM biomarkers and corresponding WM tracts.

5.1. Introduction

A key challenge in diagnosing and predicting PSP is its heterogeneous symptom presentation (Horta-Barba et al., 2021; Lopez et al., 2016). While specific brain regions like the midbrain are known to degenerate, the role of WM pathology in the overall degeneration and symptom variability remains unclear (Boxer et al., 2006). By examining associations between DTI scalars and clinical symptoms, the study aimed to clarify the neuroanatomical basis of PSP's cognitive and motor impairments.

5.2. Methods

STUDY 3 included 15 PSP-Richardson syndrome (PSP-RS) patients diagnosed using established criteria. Participants underwent T1-weighted and multi-shell diffusion MRI (3T Siemens Prisma), following protocols adapted from the Lifespan Human Connectome Project in Aging (HCP-A). The Mattis Dementia Rating Scale (MDRS) and the Montreal Cognitive Assessment (MoCA) were used to assess cognitive function. Motor impairments were evaluated using the PSP Rating Scale (PSPRS) and the Unified Parkinson's Disease Rating Scale (UPDDRS), with the PSPRS also indicating disease severity. Midsagittal T1 slices were used for morphometric measurements of the SCP, midbrain and pons, and the MTPR was calculated as a PSP biomarker. The DTI scalars FA, mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were analyzed with the FMRIB Software Library (FSL) and TBSS. Statistical analyses with permutation testing identified WM tracts with significant correlations between DTI scalars and clinical scores, with results visualized on the study-specific WM skeleton.

5.3. Results

The results show significant correlations between WM integrity measures and clinical assessments, particularly in regions linked to cognition, emotion, motor control, and interhemispheric communication. For both motor scores, FA was negatively correlated in WM

tracts like the thalamic radiation, corticospinal tracts, corpus callosum, fronto-occipital fasciculus, and cerebellar peduncles. MD and RD were positively correlated with the PSPRS scores in these regions, additionally including the SLF. The PSPRS gait subscore showed positive correlations with MD mainly in the corticospinal tract, SLF, and splenium of the corpus callosum. FA was positively correlated with the MoCA score in tracts like the thalamic radiation and fronto-occipital fasciculus, while RD and AD were negatively correlated with both MoCA and MDRS scores in tracts such as the thalamic radiation and corpus callosum. The midbrain width and MTPR were below established PSP cutoffs, while SCP measurements were not. FA and the MTPR were positively correlated in several tracts, including corticospinal tracts and the cingulum.

5.4. Discussion

STUDY 3 employed DTI to investigate the relationship between WM microstructural alterations and clinical symptoms in PSP. The results demonstrate that widespread WM disruption correlates with both cognitive and motor impairments, underscoring the critical role of WM network integrity in PSP symptomatology. Most affected tracts were situated within key brain networks—including the limbic, sensorimotor, default mode, frontoparietal, and executive control networks—which are essential for motor coordination, cognitive processing, emotional regulation, and interhemispheric communication. Alterations in these tracts were associated with hallmark PSP symptoms, such as motor dysfunction, disease severity, and cognitive decline. These findings are consistent with prior research (Agosta et al., 2014; Whitwell et al., 2011) and further support the conceptualization of PSP as a network-based neurodegenerative disorder. By highlighting disease-specific, symptom-related WM changes, this study contributes to a more nuanced understanding of the complex and heterogeneous clinical presentation of PSP.

5.5. Conclusion

STUDY 3 suggests that microstructural changes in interconnected brain regions are linked to both cognitive and motor impairments in PSP. Despite limitations such as a small sample size and the absence of a control group, the findings provide valuable insights into the PSP pathology, indicating that WM degeneration affects both symptom domains through neural network disruption. Overall, these results support the notion of a PSP-specific connectivity network, advancing our understanding of the disease.

6. General Discussion

The present thesis aimed at investigating structural brain alterations in PSP and their relation to symptom manifestations at the level of large-scale networks by means of MRI-based neuroimaging. The overarching goal was to enhance the understanding of disease-specific structural changes, thereby shedding light on aspects relevant to earlier and more accurate differential diagnosis and underlying pathological mechanisms. In the following sections, the main findings of the three studies included in this thesis will be summarized and contextualized within existing literature. Particular emphasis will be placed on integrating the results obtained into the concept of a larger disease-specific network, moving beyond the focus on isolated structures to better explain the complex symptomatology that defines this heterogeneous disease.

6.1. Summary and Interpretation of Overall Results

The overall findings underscore the importance of incorporating broader disease-associated atrophy patterns in conjunction with individual neuroimaging biomarkers for the accurate differential diagnosis of PSP.

First, **STUDY 1** identified consistent patterns of significant network degeneration in PSP across 27 whole-brain morphometry studies, highlighting the critical involvement of key brain structures, including the midbrain, thalamus, caudate nuclei, and insular cortex, along with their respective connections to other brain regions. These findings are consistent with previous research, demonstrating PSP-related atrophy in these core regions compared to non-PSP groups (Erlinger et al., 2023; Gellersen et al., 2017; Heim et al., 2021). Given our meta-analytic findings of robust midbrain, thalamic, and caudate atrophy, these structures likely play a pivotal role within a PSP-specific pathological network.

An important key finding in **STUDY 1** is the robust atrophy of the insula, which likely contributes to the variability in atrophy patterns of PSP, as it is commonly observed in this context as well as in other neurodegenerative diseases (Pan et al., 2013; Pan et al., 2017; Scotton et al., 2023). Although the insula's involvement is predominantly evident in PSP (Yu et al., 2015), it has also been linked to cognitive decline and behavioral abnormalities in patients with IPD (Christopher et al., 2014), Therefore, it seems plausible that impairment of the insula in PSP causes similar symptoms, albeit to a greater or earlier extent.

In contrast to former research, this study did not identify consistent cerebellar atrophy, highlighting the importance of the possible variability across PSP subtypes and disease stages

(Ichikawa-Escamilla et al., 2024). While some studies have reported GM atrophy in the cerebellum in PSP (Giordano et al., 2013; Pan et al., 2017), atrophy of the SCP—primarily affecting WM—has been more consistently observed (Albrecht et al., 2019; Costa et al., 2025; Koizumi et al., 2023; Paviour et al., 2006). This aligns with evidence suggesting a role for cerebellar dysfunction in PSP-related cognitive impairment (Caso et al., 2016; Tse et al., 2020). However, distinct cerebellar changes appear to correspond to concurrent cortical or subcortical degeneration (Gellersen et al., 2017), which might explain the missing finding.

In light of existing literature, the findings highlight the involvement of an extensive network of interconnected brain regions, as reflected in the functional connectivity patterns observed in **STUDY 1**. Significant co-activation patterns were identified, indicating strong functional coupling between the discussed core structures and frontal regions. Core regions could be allocated to certain networks such as the salience network, attention network, and default mode network, further reinforcing the network-based nature of PSP-related neurodegeneration. The connectivity among the given structures along with additional frontal and cingulate regions strongly supports the conceptualization of a midbrain-centered neural network in PSP (Spinelli et al., 2024; Uddin et al., 2017).

Additional findings of **STUDY 1** suggest that PSP-related atrophy predominantly affects the serotonergic and cholinergic networks rather than being confined to the dopaminergic system (as observed in IPD), confirming a more extensive neurodegenerative process. This corresponds well with the observation that dopaminergic treatment remains insufficiently effective in managing PSP (Rowe et al., 2021; Stamelou & Höglinger, 2016). The presence of multiple neurotransmitter abnormalities—including disruptions in cholinergic, γ-aminobutyric acid, and noradrenergic systems—complicates pharmacological treatment strategies for PSP (Rajput & Rajput, 2001; Rajput et al., 1990) and gives another indication of multiple areas and networks involved.

STUDY 2 expanded on previous research confirming midbrain atrophy as the hallmark feature of PSP, particularly when assessed using the MTPR. Prior studies have demonstrated that a MTPR around 0.52 exhibits high specificity for PSP, effectively distinguishing it from other PS (Kaasinen et al., 2015; Massey et al., 2013). However, most of these studies employed cross-sectional designs, leaving uncertainty regarding the potential diagnostic value of longitudinal MTPR changes. To address this gap, **STUDY 2** was the first to investigate whether assessing the MTPR decline over one year could enhance diagnostic accuracy. The results

demonstrated that PSP patients exhibit a significantly steeper midbrain atrophy rate compared to individuals with IPD, further supporting the evidence of PSP's more rapid neurodegenerative progression (Boxer et al., 2017; Andrea Quattrone, Franzmeier, et al., 2024; J. L. Whitwell, Duffy, et al., 2013a).

Most importantly, our findings underscore the clinical utility of the MTPR as a stable and highly specific biomarker for PSP (Massey et al., 2013; Oba et al., 2005). The combination of baseline MTPR and its longitudinal decline improved specificity but did not significantly enhance overall diagnostic accuracy when compared to a single cross-sectional MTPR measurement. Still, the longitudinal findings reinforce the notion that PSP is not merely a disorder of static structural atrophy, but rather a condition characterized by progressive degeneration around the midbrain.

Former evidence suggests that midbrain atrophy serves as a robust biomarker for the PSP syndrome, but it does not necessarily reflect the underlying pathology itself (Whitwell et al., 2013a; J. L. Whitwell et al., 2013b). This underscores the clinicopathological heterogeneity of the disease and leaves the question whether different subtypes progress to different extents. Notably, all patients in **STUDY 2** were diagnosed with PSP-RS, which may account for the observed significant results. However, in the absence of post-mortem confirmation, definitive conclusions regarding the underlying pathology cannot be drawn. If midbrain atrophy is solely characteristic of the PSP syndrome, this implies that distinct pathological processes contribute to different phenotypic variants, further supporting the notion of a network-based disease mechanism (Hong et al., 2023).

Complementing the discussed findings, **STUDY 3** also supported the idea that widespread brain networks undergo a PSP-specific pattern of degeneration. Microstructural alterations in interconnected brain regions were shown to be associated with both cognitive decline and motor impairment. These results provide strong evidence that disease-specific patterns of WM alterations, implicated in the connectivity in large-scale networks, account for the distinct symptom complexes in PSP: **STUDY 3** showed altered WM connections in PSP that include the brainstem, cerebellar, and thalamic projections, as well as associative fibers, which aligns with findings from previous studies (Agosta et al., 2018; Nguyen et al., 2021). Our findings support the hypothesis that PSP causes progressive, incapacitating cognitive, behavioral, and motor dysfunction to varying extents, which can be related to the WM tracts found (Agosta et al., 2014):

Key motor-related regions in **STUDY 3**—the corticospinal tract, SLF, and corpus callosum—have proven to be crucial for motor control and coordination, with well-established roles in movement disorders (Bosch et al., 2012; van der Knaap & van der Ham, 2011; J. Zhang et al., 2014). This is especially plausible regarding the corticospinal tract, passing through the midbrain, which was proven to be involved in motor dysfunction in PSP (Cui et al., 2020; Quattrone et al., 2016; Wen et al., 2023).

Tracts in which diffusion metrics were associated with lower cognitive scores include the SLF and ILF, corona radiata, cingulum bundle, and thalamocortical radiation, supporting the attention network's and salience network's role in PSP-related cognitive impairment (Bharti et al., 2017). This is consistent with prior findings (Gerstenecker et al., 2013). Especially the SLF is crucial for higher-order functioning (Janelle et al., 2022), such as executive control, often impaired in PSP (Gerstenecker et al., 2013). The observed correlations suggest that WM integrity changes are key contributors to specific cognitive symptoms in this disease.

Also, the analysis of diffusion metrics in relation to the MTPR showed widespread correlations in midbrain and frontal tracts, particularly the SLF and cingulum, which are central to the executive network. Previous studies have linked these regions to motor symptoms and PSP progression (Giordano et al., 2013; Padovani et al., 2006; Tessitore et al., 2014), reinforcing the potential role of the MTPR as a biomarker of PSP-related disease spread.

Many of the identified tracts are related to the midbrain, serving as pathways to other regions that also exhibit impairments in PSP (Gardner et al., 2013; Gatto et al., 2022; Sakai et al., 2014). Overall, **STUDY 3** strongly supports the concept of PSP as a disorder of functional network degeneration, where interconnected regions and tracts contribute to distinct symptom complexes. Besides GM, WM appears to play a key role in the disease's heterogeneity, and cognitive and motor impairment in PSP likely arises from multiple pathological processes. As neurodegeneration may stem from neural network dysfunction (Gardner et al., 2013; Palop & Mucke, 2016), PSP may similarly involve a progressive spread along vulnerable neural circuits.

6.2. From Regional Degeneration to Network Disruption in PSP

Brain regions involved in motor control, executive function, and behavioral regulation appear particularly vulnerable to PSP-related degeneration: It is primarily characterized by selective subcortical degeneration—most notably in the midbrain, thalamus, and parts of the basal ganglia—which corresponds to the distribution of tau pathology (Boxer et al., 2006; Kovacs et al., 2020; Whiteside et al., 2021). Strong evidence of coupling between structural

and functional network deterioration (Qu et al., 2024, 2025) further supports the NDH for PSP. Furthermore, the overlapping but distinct patterns of regional involvement seen in PSP subtypes and related PS imply that differences in network vulnerability may underlie the clinical variability (Whiteside et al., 2021). This convergence of network-based pathology and symptom heterogeneity reinforces the view of PSP and related APD as disorders of progressive network disintegration (Whiteside et al., 2023).

In the following sections, the results of **STUDY 1**, **2**, and **3** are integrated to discuss the observed structural brain alterations within the framework of a PSP-specific network model.

6.2.1. The Midbrain as the Epicenter of PSP Network Degeneration

STUDY 1 and **2** both confirmed the well-documented midbrain atrophy usually found as a defining feature of PSP, effectively distinguishing it from other disorders with overlapping symptoms (Gröschel et al., 2006; Höglinger et al., 2017; Oba et al., 2005; Quattrone et al., 2024; Quattrone, Zappia, & Quattrone, 2024). Notably**,** midbrain atrophy in PSP predominantly affects the tegmentum (Jalal & Menon, 2017; Kawabata et al., 2025), which gives rise to the characteristic hummingbird sign on midsagittal MRI scans. In contrast, midbrain degeneration in IPD is primarily confined to the substantia nigra pars compacta (SNc) located outside the tegmental area. In the context of network connectivity, this is of particular interest when regarding that most midbrain WM tracts pass through the tegmental area (Basinger & Hogg, 2025; Bullock et al., 2022; Hosp et al., 2019). This differential pattern in PSP compared to IPD underscores the diagnostic value of midbrain-related biomarkers and might explain the more heterogeneous variants of PSP.

As PSP can be characterized by network disruption where midbrain degeneration is the key node (Gardner et al., 2013; Hori et al., 2025; Whiteside et al., 2021), it seems that accelerated midbrain atrophy also plays a key role in the broader understanding of PSP's network-level degeneration. Advanced neuroimaging techniques have demonstrated that midbrain atrophy represents the most prominent and the earliest structural alteration in PSP that precedes cortical involvement, suggesting that the disease's pathology may originate in the midbrain and, subsequently, propagate (Kovacs et al., 2020; Lupascu et al., 2023). The MTPR has demonstrated a strong predictive value for disease progression. Concurrently, studies have shown that midbrain atrophy in PSP is not only more pronounced but also progresses more rapidly than in IPD (Dutt et al., 2016; Wen et al., 2023), highlighting midbrain atrophy as a critical marker for tracking disease evolution and assessing the severity of neurodegeneration.

Furthermore, findings from **STUDY 3**, which identified correlations between the MTPR and PSP symptomatologies involving midbrain and frontal WM tracts, raise the question of whether the MTPR may serve as a biomarker of network-level dysfunction, potentially reflecting the spatial spread of disease pathology.

Tau pathology in PSP is especially pronounced in specific midbrain regions (Kovacs et al., 2020), and distinct PSP subtypes demonstrate varying levels of tau burden across different areas (Sánchez-Ruiz de Gordoa et al., 2022; Williams et al., 2007). Since the patients included in **STUDY 2** were at more advanced disease stages, the relative decline in MTPR may be more sensitive in earlier stages of PSP. This supports the idea that the PSP pathology progresses in a stepwise manner, beginning in the midbrain and subsequently spreading to other regions (Kovacs et al., 2020). This aligns with findings by Albrecht et al. (2019), who reported that midbrain atrophy in PSP reflects degeneration of both GM and WM. Given the midbrain's involvement in multiple symptom domains our findings reinforce the view that the combined deterioration of GM and WM contributes to the disease's diverse clinical manifestations.

In summary, midbrain atrophy, as measured using the MTPR, plays a critical role in both diagnosis and pathophysiological understanding of the disease as well as its variants. It serves as a key marker that helps to differentiate PSP from other PS, and is able to quantify the rapid neurodegeneration characteristic for PSP. Since network degeneration models suggest that PSP-related neurodegeneration spreads through interconnected brain regions beyond the midbrain (Höglinger et al., 2017; Whitwell et al., 2021), the MTPR could serve as an indicator of progressive disruption within a midbrain-centered network (Spinelli et al., 2024).

6.2.2. PSP-specific Gray and White Matter Network Degeneration

A supplementary analysis from **STUDY 1**, in which PSP was contrasted solely with HC, revealed an additional cluster of GM atrophy in the precentral gyrus. This cluster has not reached significance in the full comparison across all non-PSP groups as it most likely represents a shared substrate across Parkinsonian conditions—each of which involves motor dysfunction. The precentral gyrus encompasses the primary motor cortex, responsible for initiating voluntary motor commands, a function that is notably impaired across the spectrum of PS (Pan et al., 2017; Zwergal et al., 2011). This finding potentially reflects early or shared network-level degeneration across PS.

In PSP specifically, the progressive accumulation of tau has been mapped into a staging system that reflects its sequential spread. Tau pathology—and, consequently,

neurodegeneration—is thought to advance from the midbrain to the striatum and, eventually, the frontal lobe, contributing to the disorder's complex clinical profile (Jellinger, 2023; Kovacs et al., 2020; Price et al., 2004; Robinson et al., 2020; Surova et al., 2015). Findings from **STUDY 1** support this proposed trajectory, with the most prominent atrophy cluster located in the midbrain and thalamus, accompanied by smaller clusters in the insular region as well as the caudate nuclei. Moreover, **STUDY 3** identified symptom-related alterations in WM tracts in PSP that connect these regions, further supporting the notion of a network-based spread of pathology. Distinct PSP phenotypes have been identified based on patterns of brain atrophy, supporting the notion that symptom heterogeneity reflects differential neuroanatomical involvement (Ichikawa-Escamilla et al., 2024).

The thalamus and caudate nuclei are critically involved in the pathophysiology and progression of PSP. These structures are essential for emotional regulation, executive functioning, and goal-directed behavior (Alexander et al., 1986; Cordato et al., 2005; Palmisano et al., 2020; Rosenberg-Katz et al., 2013). Thalamic involvement in PSP includes not only structural atrophy but also disrupted connectivity and functional deficits (Brown et al., 2017; Whitwell et al., 2011; Zwergal et al., 2011). PSP typically features symmetrical caudate atrophy, in contrast to the asymmetrical degeneration observed in IPD, which aligns with the latter's commonly unilateral onset of motor symptoms (Cordato et al., 2005; Dickson, 2008). This distinction is supported by the consistent bilateral atrophy clusters observed in **STUDY 1**. However, previous findings on caudate involvement in PSP remain somewhat inconsistent—while some studies have reported varying degrees of atrophy, others have not found significant caudate volume reduction (Cordato et al., 2002; Erlinger et al., 2023). This variability suggests that caudate degeneration in PSP may be influenced by individual disease progression or subtype-specific factors.

The connectivity analysis in **STUDY 1** showed that the core structures are functionally interconnected and linked to higher-order cortical regions. These connections appear to be mediated by midbrain WM tracts (Ruchalski & Hathout, 2012). Among the major WM regions affected in PSP, the SCP is essential for motor control, transmitting cerebellar output to the red nucleus and thalamus (D'Angelo & Casali, 2012; Palesi et al., 2015). Albrecht et al. (2019) proposed that cerebellar atrophy in PSP is largely confined to WM structures such as the cerebellar peduncles. This is supported by **STUDY 3**, which found multiple correlations between DTI parameters and clinical symptoms in the corticospinal tract, closely linked to the SCP. The absence of cerebellar atrophy in **STUDY 1** along with the lack of structural SCP

decline in **STUDY 3** may point toward a network-level interpretation. Although the SCP may not be structurally impaired, related pathways such as the corticospinal tract show alterations, suggesting broader network involvement. This aligns with findings that WM disruption may precede GM degeneration (Rektor et al., 2018; Sarasso et al., 2021)

Beyond motor and sensory integration, PSP pathology extends to higher-order cognitive and emotional domains. WM degeneration in associative tracts disrupts cortico-subcortical communication, contributing to deficits in cognition and emotion (Bullock et al., 2022; Wycoco et al., 2013). Neurotransmitter depletion and loss of cholinergic function further exacerbate cortical involvement and cognitive decline, in line with the progressive tau pathology and symptom escalation (Pansuwan et al., 2023; Ruberg et al., 1985). Moreover, the observed correlations between WM alterations and cognitive impairment point to a significant involvement of the attention and the salience network in PSP. This network includes key tracts such as the SLF, corona radiata, cingulum bundle, ILF, and thalamocortical radiation (Bharti et al., 2017). The salience network is essential for filtering environmental stimuli and allocating attention to behaviorally relevant information, while the broader attention network encompasses multiple subsystems responsible for sustained attention, selective attention, and executive control.

The extensive involvement of white matter tracts in PSP underscores the disorder's widespread effects on motor, sensory, and cognitive systems, supporting the idea that it's a network-level neurodegenerative disease (Boxer et al., 2017). Its core symptoms—including movement difficulties, cognitive decline, and emotional changes—reflect a complex interplay of distinct yet interconnected pathological processes (Whitwell et al., 2013a). The typical sequence of symptom onset, with motor dysfunction often preceding cognitive decline, further suggests that PSP pathology spreads along functionally connected brain regions, particularly those adjacent to and connected with the midbrain.

6.2.3. Does the Insula play a Role?

Anterior insular atrophy has been identified as a consistent yet underrecognized feature of PSP (Mueller et al., 2017; Scotton et al., 2023). As a central hub integrating sensorimotor, autonomic, and cognitive-emotional functions, the insula is well-positioned to influence the broad clinical spectrum of PSP (Gasquoine, 2014; Molnar-Szakacs & Uddin, 2022). Despite this, its role has received limited attention in the existing literature.

Structural and functional alterations of the insula have been consistently reported in patients with PSP (Piattella et al., 2015b; Piattella et al., 2015a; Sintini et al., 2025; Stezin et al., 2017), frequently accompanied by frontal and subcortical degeneration (Höglinger et al., 2017; Stamelou & Höglinger, 2016). The insula maintains dense reciprocal connections with the midbrain, basal ganglia, and salience network—regions prominently affected in PSP—suggesting that insular degeneration may reflect a broader network disruption rather than an isolated phenomenon. It is integrated into thee cortico–basal ganglia–thalamo–cortical circuits involved in motor planning and coordination (Haber & Calzavara, 2009; Ji et al., 2018; Uddin et al., 2017). Degeneration of midbrain structures in PSP have been demonstrated to disrupt these loops, thereby impairing basal ganglia output and contributing to motor symptoms such as rigidity and postural instability at a higher level.

Importantly, the insula is anatomically connected to the periaqueductal gray, a midbrain region involved during the early stages of PSP (Dickson et al., 2007; Liang & Labrakakis, 2024; Rajput & Rajput, 2001), further supporting a mechanistic link between brainstem and insular dysfunction. This disconnection may contribute to the early onset of cognitive and emotional symptoms. Comparative studies show that PSP features early and widespread atrophy of both anterior and posterior insular regions, whereas insular changes in IPD are typically milder, more posterior, and occur primarily in patients with cognitive decline—highlighting the greater functional relevance of the insula in PSP's cognitive symptoms (Fathy et al., 2020; Scotton et al., 2023). **STUDY 1** supports this perspective by identifying affected regions associated with attention, interoception, and emotional regulation—key domains of insular function. The disruption of midbrain–thalamus–insula pathways may be the underlying cause of these symptoms, with the anterior insula acting as a central hub in the pathology of PSP, linking motor, cognitive, and emotional dysfunction.

PSP-related degeneration originates in the midbrain and progressively disrupts its connections to the insular cortex. This disconnection likely impairs insular function, compromising its integrative role in cognitive and emotional processing (Molnar-Szakacs & Uddin, 2022). The insula may therefore serve as a critical node in the network underlying the emergence of cognitive symptoms in PSP.

6.3. Limitations

Several limitations must be acknowledged when interpreting the findings of this research. One of the fundamental challenges in PSP studies is the limited sample size. Due to the rarity

and rapid progression of the disease, recruiting large and homogeneous patient cohorts in a prospective manner remains difficult. Small sample sizes reduce statistical power and may limit the generalizability of results. While meta-analytic approaches can mitigate this issue by synthesizing data across studies (Eickhoff et al., 2012), individual investigations—such as **STUDY 2** and **STUDY 3**—are constrained by their relatively small cohorts. This limitation is of particular importance given the phenotypic and clinical heterogeneity of PSP.

The validity of meta-analytic conclusions is constrained by the quality and diagnostic accuracy of the underlying studies (Willis & Quigley, 2011). In **STUDY 2**, diagnoses were based on expert clinical assessments conducted by movement disorder specialists. However, differentiating between PSP and IPD, as well as other APD, remains inherently challenging, (McFarland, 2016; Tolosa et al., 2021) and the possibility of misdiagnosis cannot be fully excluded. Moreover, disease heterogeneity—including different PSP subtypes and stage-dependent patterns of atrophy—was not explicitly addressed in our analyses, which could have influenced the results (Saito et al., 2022). Nonetheless, the implementation of standardized diagnostic criteria across patients provides a degree of consistency and reduces the probabilty of systematic misclassification.

STUDY 1 employed supplementary analyses that lent further support to its core findings. However, caution is warranted when interpreting the specificity or diagnostic relevance of all brain regions identified by the meta-analysis, as these factors were not explicitly analyzed. Only in **STUDY 2**, where ROC analyses were conducted, the diagnostic potential can be evaluated with greater confidence (Polo & Miot, 2020). Broader literature continues to debate the utility of PSP-specific brain regions as biomarkers, a challenge likely stemming from the complex, stage- and subtype-dependent spread of tau pathology.

STUDY 3 presents additional interpretive constraints due to the absence of a control cohort (Paulus et al., 2014). While it revealed correlations between DTI metrics and clinical symptoms, these associations do not establish causality, nor can they confirm the pathological nature of the observed changes. Nevertheless, the consistency of these findings with prior research supports the involvement of the identified WM tracts in the pathophysiology of PSP.

A further consideration in **STUDY 2** is the predominantly advanced disease stage of the participants. Since both atrophy patterns and biomarker performance may vary across different disease stages (Boxer et al., 2017; Ossenkoppele et al., 2015), it remains unclear whether the observed markers would demonstrate similar diagnostic utility in early-stage PSP.

6.4. Implications for Future Research

Despite the limitations outlined above, this thesis provides important insights into the underlying pathophysiological mechanisms of PSP. The findings highlight that distinct atrophy patterns—particularly midbrain degeneration—are central contributors to the syndrome's core symptoms and phenotypic variability. While prior studies have primarily focused on isolated regional atrophy (Massey et al., 2013; Oba et al., 2005), this work supports a shift in perspective by positing the midbrain as a central node within a more extensive and interconnected network of neurodegeneration, rather than viewing it as a static anatomical marker.

The interaction between WM and GM degeneration remains an underexplored yet critical area. While GM atrophy has traditionally received more attention, WM changes are increasingly recognized as pivotal drivers of clinical symptoms and disease progression. Clarifying the interplay between these two domains may offer a more comprehensive understanding of PSP pathology. Thus, future research should aim to integrate the MTPR with advanced neuroimaging techniques to yield more comprehensive insights into its relationship with underlying disease mechanisms. In particular, DTI could be employed to investigate the integrity of relevant WM tracts—such as the SCP and frontostriatal pathways—in relation to the MTPR, potentially establishing it as a surrogate marker of structural disconnection (Madden et al., 2012). Multimodal imaging approaches are needed to establish a connection between structural abnormalities and disruptions in functional connectivity. A key objective of future research will be to determine whether lower MTPR values correspond to dysfunction in pivotal networks for PSP, including the midbrain-frontal, cortico–basal ganglia–thalamo–cortical, salience, attention, and default mode networks. Functional MRI may offer additional insight by assessing whether MTPR reductions can serve as a predictor of network-level breakdown. Overall, combining the MTPR with complementary biomarkers may further enhance diagnostic and prognostic precision, particularly across different PSP subtypes.

Building on the encouraging results observed in **STUDY 2**, we suggest that longitudinal studies to be essential to validate the efficacy of the MTPR as an indicator of disease progression. Investigating whether a decline in MTPR correlates with clinical deterioration and expanding atrophy could yield insights that would be valuable for both disease monitoring and therapeutic decision-making. Also, investigating biomarker sensitivity at earlier stages—before MTPR declines reach PSP-specific thresholds—represents a crucial avenue for future research. Larger, multicenter studies incorporating a broader range of demographic variation (e.g., in age, sex, disease duration, and PSP subtypes) are essential to validate and extend these

findings. Furthermore, integrating standardized measures of clinical severity, such as the PSPRS, as we implemented in **STUDY 3,** has the potential to enhance insight into disease progression and the clinical relevance of biomarkers.

Addressing the persistent challenge of small sample sizes is imperative (Ziegler & Fiedler, 2024). Larger, multicenter studies will be necessary to improve statistical power, external validity, and representativeness across PSP subtypes (Das, 2022). Collaborative research networks and data-sharing initiatives represent promising strategies to accelerate biomarker discovery, refine diagnostic frameworks, and inform the development of more targeted interventions.

In conclusion, further exploration of these mechanisms—midbrain network disintegration, WM-GM interactions, and multimodal biomarker development—will be essential to improving diagnostic accuracy, prognostic assessment, and, ultimately, clinical outcomes for individuals living with PSP.

7. Conclusion

Overall, this thesis presents a comprehensive investigation of the pathological mechanisms underlying PSP. By integrating findings from three complementary studies, it reinforces the critical diagnostic value of the MTPR and repositions the midbrain from a static site of atrophy to the epicenter of a progressively degenerating, functional network. Additionally, the present work highlights a disease-specific atrophy process, involving the insula as a key contributor to the multifaceted PSP symptom complex. This perspective supports a necessary paradigm shift in our understanding of PSP pathophysiology.

Taken together, the findings of the present thesis support a reconceptualization of PSP as a disorder of large-scale network degeneration. This framework provides a compelling explanation for the clinical heterogeneity observed across patients with PSP and underscores the importance of network-based approaches in future research and clinical practice.

References

Agosta, F., Caso, F., Ječmenica-Lukić, M., Petrović, I. N., Valsasina, P., Meani, A., Copetti, M., Kostić, V. S., & Filippi, M. (2018). Tracking brain damage in progressive supranuclear palsy: A longitudinal MRI study. *Journal of Neurology, Neurosurgery & Psychiatry*, *89*(7), 696–701. https://doi.org/10.1136/jnnp-2017-317443

Agosta, F., Galantucci, S., Svetel, M., Lukić, M. J., Copetti, M., Davidovic, K., Tomić, A., Spinelli, E. G., Kostić, V. S., & Filippi, M. (2014). Clinical, cognitive, and behavioural correlates of white matter damage in progressive supranuclear palsy. *Journal of Neurology*, *261*(5), 913–924. https://doi.org/10.1007/s00415-014-7301-3

Agosta, F., Pievani, M., Sala, S., Geroldi, C., Galluzzi, S., Frisoni, G. B., & Filippi, M. (2011). White matter damage in Alzheimer disease and its relationship to gray matter atrophy. *Radiology*, *258*(3), 853–863. https://doi.org/10.1148/radiol.10101284

Albrecht, F., Bisenius, S., Neumann, J., Whitwell, J., & Schroeter, M. L. (2019). Atrophy in midbrain & cerebral/cerebellar pedunculi is characteristic for progressive supranuclear palsy - A double-validation whole-brain meta-analysis. *NeuroImage: Clinical*, *22*, 101722. https://doi.org/10.1016/j.nicl.2019.101722

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, *9*(1), 357–381. https://doi.org/10.1146/annurev.ne.09.030186.002041

Armstrong, R. A. (2011). Visual signs and symptoms of progressive supranuclear palsy. *Clinical & Experimental Optometry*, *94*(2), 150–160. https://doi.org/10.1111/j.1444-0938.2010.00504.x

Armstrong, R.A. (2018). A comparison of visual problems in the parkinsonian syndromes. *Internal Medicine Review*, *4*(3). https://doi.org/10.18103/imr.v4i3.679

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry--the methods. *NeuroImage*, *11*(6 Pt 1), 805–821. https://doi.org/10.1006/nimg.2000.0582

Bak, T. H., Crawford, L. M., Hearn, V. C., Mathuranath, P. S., & Hodges, J. R. (2005). Subcortical dementia revisited: Similarities and differences in cognitive function between progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA). *Neurocase*, *11*(4), 268–273. https://doi.org/10.1080/13554790590962997

Basinger, H., & Hogg, J. P. (2025). StatPearls: Neuroanatomy, Brainstem. https://pubmed.ncbi.nlm.nih.gov/31335017/

Basser, P. J., Mattiello, J., & LeBihan, D. (1994). Mr diffusion tensor spectroscopy and imaging. *Biophysical Journal*, *66*(1), 259–267. https://doi.org/10.1016/s0006-3495(94)80775-1

Bennett, I. J., & Madden, D. J. (2014). Disconnected aging: Cerebral white matter integrity and age-related differences in cognition. *Neuroscience*, *276*, 187–205. https://doi.org/10.1016/j.neuroscience.2013.11.026

Bharti, K., Bologna, M., Upadhyay, N., Piattella, M. C., Suppa, A., Petsas, N., Giannì, C., Tona, F., Berardelli, A., & Pantano, P. (2017). Abnormal Resting-State Functional Connectivity in Progressive Supranuclear Palsy and Corticobasal Syndrome. *Frontiers in Neurology*, *8*, 248. https://doi.org/10.3389/fneur.2017.00248

Black, J. A., Pham, N. T. T., Ali, F., Machulda, M. M., Lowe, V. J., Josephs, K. A., & Whitwell, J. L. (2024). Frontal hypometabolism in the diagnosis of progressive supranuclear palsy clinical variants. *Journal of Neurology*, *271*(7), 4267–4280. https://doi.org/10.1007/s00415-024-12350-z

Bluett, B., Litvan, I [I.], Cheng, S., Juncos, J., de Riley, Standaert, D. G., Reich, S. G., Da Hall, Kluger, B., Shprecher, D., Marras, C., & Jankovic, J. (2017). Understanding falls in progressive supranuclear palsy. *Parkinsonism & Related Disorders*, *35.* https://doi.org/10.1016/j.parkreldis.2016.12.009

Bosch, B., Arenaza-Urquijo, E. M., Rami, L., Sala-Llonch, R., Junqué, C., Solé-Padullés, C., Peña-Gómez, C., Bargalló, N., Molinuevo, J. L., & Bartrés-Faz, D. (2012). Multiple DTI index analysis in normal aging, amnestic MCI and AD. Relationship with neuropsychological performance. *Neurobiology of Aging*, *33*(1), 61–74. https://doi.org/10.1016/j.neurobiolaging.2010.02.004

Boxer, A. L., Geschwind, M. D., Belfor, N., Gorno-Tempini, M. L [Maria Luisa], Schauer, G. F., Miller, B. L., Weiner, M. W., & Rosen, H. J. (2006). Patterns of brain atrophy that differentiate corticobasal degeneration syndrome from progressive supranuclear palsy. *Archives of Neurology*, *63*(1), 81–86. https://doi.org/10.1001/archneur.63.1.81

Boxer, A. L., Yu, J.-T., Golbe, L. I., Litvan, I., Lang, A. E., & Höglinger, G. U. (2017). Advances in progressive supranuclear palsy: New diagnostic criteria, biomarkers, and therapeutic approaches. *The Lancet Neurology*, *16*(7), 552–563. https://doi.org/10.1016/S1474-4422(17)30157-6

Brown, F. S., Rowe, J. B., Passamonti, L., & Rittman, T. (2020). Falls in Progressive Supranuclear Palsy. *Movement Disorders Clinical Practice*, *7*(1), 16–24. https://doi.org/10.1002/mdc3.12879

Brown, J. A., Hua, A. Y., Trujllo, A., Attygalle, S., Binney, R. J., Spina, S., Lee, S. E., Kramer, J. H., Miller, B. L., Rosen, H. J., Boxer, A. L., & Seeley, W. W. (2017). Advancing functional dysconnectivity and atrophy in progressive supranuclear palsy. *NeuroImage: Clinical*, *16*, 564–574. https://doi.org/10.1016/j.nicl.2017.09.008

Buch, K. A., Bouffard, M. A., Kardon, R. H., Wills, A.-M. A., Privitera, C. M., Sharma, M., & Wray, S. H. (2022). *Clinical Correlation Between Vertical Gaze Palsy and Midbrain Volume in Progressive Supranuclear Palsy* (Vol. 42). Wolters Kluwer. https://www.ingentaconnect.com/content/wk/jno/2022/00000042/00000002/art00018 https://doi.org/10.1097/WNO.0000000000001393

Bullock, D. N., Hayday, E. A., Grier, M. D., Tang, W., Pestilli, F., & Heilbronner, S. R. (2022). A taxonomy of the brain's white matter: Twenty-one major tracts for the 21st century. *Cerebral Cortex (New York, N.Y. : 1991)*, *32*(20), 4524–4548. https://doi.org/10.1093/cercor/bhab500

Burrell, J. R., Ballard, K. J., Halliday, G. M., & Hodges, J. R. (2018). Aphasia in Progressive Supranuclear Palsy: As Severe as Progressive Non-Fluent Aphasia. *Journal of Alzheimer's Disease : JAD*, *61*(2), 705–715. https://doi.org/10.3233/JAD-170743

Caso, F., Agosta, F., Volonté, M. A., Ferraro, P. M., Tiraboschi, P., Copetti, M., Valsasina, P., Falautano, M., Comi, G., Falini, A., & Filippi, M. (2016). Cognitive impairment in progressive supranuclear palsy-Richardson's syndrome is related to white matter damage. *Parkinsonism & Related Disorders*, *31*, 65–71. https://doi.org/10.1016/j.parkreldis.2016.07.007

Chen, A. L., Riley, D. E., King, S. A., Joshi, A. C., Serra, A., Liao, K., Cohen, M. L., Otero-Millan, J., Martinez-Conde, S., Strupp, M., & Leigh, R. J. (2010). The disturbance of gaze in progressive supranuclear palsy: Implications for pathogenesis. *Frontiers in Neurology*, *1*, 147. https://doi.org/10.3389/fneur.2010.00147

Christopher, L., Koshimori, Y., Lang, A. E., Criaud, M., & Strafella, A. P. (2014). Uncovering the role of the insula in non-motor symptoms of Parkinson's disease. *Brain*, *137*(Pt 8), 2143–2154. https://doi.org/10.1093/brain/awu084

Chunowski, P., Madetko-Alster, N., & Alster, P. (2024). Asymmetry in Atypical Parkinsonian Syndromes-A Review. *Journal of Clinical Medicine*, *13*(19). https://doi.org/10.3390/jcm13195798

Clark, H. M., Stierwalt, J. A. G., Tosakulwong, N., Botha, H., Ali, F., Whitwell, J. L., & Josephs, K. A. (2020). Dysphagia in Progressive Supranuclear Palsy. *Dysphagia*, *35*(4), 667–676. https://doi.org/10.1007/s00455-019-10073-2

Cordato, N. J., Duggins, A. J., Halliday, G. M., Morris, J. G. L., & Pantelis, C. (2005). Clinical deficits correlate with regional cerebral atrophy in progressive supranuclear palsy. *Brain*, *128*(Pt 6), 1259–1266. https://doi.org/10.1093/brain/awh508

Cordato, N. J., Pantelis, C., Halliday, G. M., Velakoulis, D., Wood, S. J., Stuart, G. W., Currie, J., Soo, M., Olivieri, G., Broe, G. A., & Morris, J. G. L. (2002). Frontal atrophy correlates with behavioural changes in progressive supranuclear palsy. *Brain*, *125*(Pt 4), 789–800. https://doi.org/10.1093/brain/awf082

Costa, F., Gatto, R. G., Pham, N. T. T., Ali, F., Clark, H. M., Stierwalt, J., Machulda, M. M., Agosta, F., Filippi, M., Josephs, K. A., & Whitwell, J. L. (2025). Longitudinal assessment of white matter alterations in progressive supranuclear palsy variants using diffusion tractography. *Parkinsonism & Related Disorders*, *132*, 107272. https://doi.org/10.1016/j.parkreldis.2025.107272

Cotelli, M., Borroni, B., Manenti, R., Alberici, A., Calabria, M., Agosti, C., Arévalo, A., Ginex, V., Ortelli, P., Binetti, G., Zanetti, O., Padovani, A., & Cappa, S. F. (2006). Action and object naming in frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration. *Neuropsychology*, *20*(5), 558–565. https://doi.org/10.1037/0894-4105.20.5.558

Coughlin, D. G., Hiniker, A., Peterson, C., Kim, Y., Arezoumandan, S., Giannini, L., Pizzo, D., Weintraub, D., Siderowf, A., Litvan, I., Rissman, R. A., Galasko, D., Hansen, L., Trojanowski, J. Q., Lee, E., Grossman, M., & Irwin, D. (2022). Digital Histological Study of Neocortical Grey and White Matter Tau Burden Across Tauopathies. *Journal of Neuropathology and Experimental Neurology*, *81*(12), 953–964. https://doi.org/10.1093/jnen/nlac094

Coyle-Gilchrist, I. T. S., Dick, K. M., Patterson, K., Vázquez Rodríquez, P., Wehmann, E., Wilcox, A., Lansdall, C. J., Dawson, K. E., Wiggins, J., Mead, S., Brayne, C., & Rowe, J. B. (2016). Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. *Neurology*, *86*(18), 1736–1743. https://doi.org/10.1212/WNL.0000000000002638

Cui, S.-S., Ling, H.-W., Du, J.-J., Lin, Y.-Q., Pan, J., Zhou, H.-Y., Wang, G., Wang, Y., Xiao, Q., Liu, J., Tan, Y.-Y., & Chen, S.-D. (2020). Midbrain/pons area ratio and clinical features predict the prognosis of progressive Supranuclear palsy. *BMC Neurology*, *20*(1), 114. https://doi.org/10.1186/s12883-020-01692-6

D'Angelo, E., & Casali, S. (2012). Seeking a unified framework for cerebellar function and dysfunction: From circuit operations to cognition. *Frontiers in Neural Circuits*, *6*, 116. https://doi.org/10.3389/fncir.2012.00116

Das, M. K. (2022). Multicenter Studies: Relevance, Design and Implementation. *Indian Pediatrics*, *59*(7), 571–579. https://doi.org/10.1007/s13312-022-2561-y

DeTure, M. A., & Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. *Molecular Neurodegeneration*, *14*(1), 32. https://doi.org/10.1186/s13024-019-0333-5

Dickson, D. W. (2008). Neuropathology of Progressive Supranuclear Palsy. In *Dementias* (Vol. 89, pp. 487–491). Elsevier. https://doi.org/10.1016/S0072-9752(07)01245-6

Dickson, D. W., Rademakers, R., & Hutton, M. L. (2007). Progressive supranuclear palsy: Pathology and genetics. *Brain Pathology (Zurich, Switzerland)*, *17*(1), 74–82. https://doi.org/10.1111/j.1750-3639.2007.00054.x

Donker Kaat, L., Boon, A. J. W., Kamphorst, W., Ravid, R., Duivenvoorden, H. J., & van Swieten, J. C. (2007). Frontal presentation in progressive supranuclear palsy. *Neurology*, *69*(8), 723–729. https://doi.org/10.1212/01.wnl.0000267643.24870.26

Dukart, J., Jech, R., Ruziska, F., Vyzamal, J., Rullmann, M., Hesse, S., Barthel, H., Sabri, O., & Eickhoff, S.B. (2020). Juspace: A Tool for Spatial Correlation Analyses of Functional and Structural Magnetic Resonance Imaging Data With Positron Emission Tomography Derived Receptor Maps. *Biological Psychiatry*, *87*(9), S190. https://doi.org/10.1016/j.biopsych.2020.02.497

Dutt, S., Binney, R. J., Heuer, H. W., Luong, P., Attygalle, S., Bhatt, P., Marx, G. A., Elofson, J., Tartaglia, M. C., Litvan, I [Irene], McGinnis, S. M., Dickerson, B. C., Kornak, J., Waltzman, D., Voltarelli, L., Schuff, N., Rabinovici, G. D., Kramer, J. H., Jack, C. R [Clifford R.], . . . Boxer, A. L. (2016). Progression of brain atrophy in PSP and CBS over 6 months and 1 year. *Neurology*, *87*(19), 2016–2025. https://doi.org/10.1212/WNL.0000000000003305

Eickhoff, S. B., Bzdok, D., Laird, A. R., Kurth, F., & Fox, P. T. (2012). Activation likelihood estimation meta-analysis revisited. *NeuroImage*, *59*(3), 2349–2361. https://doi.org/10.1016/j.neuroimage.2011.09.017

Eickhoff, S. B., Laird, A. R., Grefkes, C., Wang, L. E., Zilles, K., & Fox, P. T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping*, *30*(9), 2907–2926. https://doi.org/10.1002/hbm.20718

Eickhoff, S. B., Nichols, T. E., Laird, A. R., Hoffstaedter, F., Amunts, K., Fox, P. T., Bzdok, D., & Eickhoff, C. R. (2016). Behavior, sensitivity, and power of activation likelihood estimation characterized by massive empirical simulation. *NeuroImage*, *137*, 70–85. https://doi.org/10.1016/j.neuroimage.2016.04.072

Erlinger, M., Molina-Ruiz, R., Brumby, A., Cordas, D., Hunter, M., Ferreiro Arguelles, C., Yus, M., Owens-Walton, C., Jakabek, D., Shaw, M., Lopez Valdes, E., & Looi, J. C. L. (2023). Striatal and thalamic automatic segmentation, morphology, and clinical correlates in Parkinsonism: Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. *Psychiatry Research. Neuroimaging*, *335*, 111719. https://doi.org/10.1016/j.pscychresns.2023.111719

Fathy, Y. Y., Hoogers, S. E., Berendse, H. W., van der Werf, Y. D., Visser, P. J., Jong, F. J. de, & van de Berg, W. D. (2020). Differential insular cortex sub-regional atrophy in neurodegenerative diseases: A systematic review and meta-analysis. *Brain Imaging and Behavior*, *14*(6), 2799–2816. https://doi.org/10.1007/s11682-019-00099-3

Flynn, É., Regan, J., Glinzer, J., O'Dowd, S., & Walshe, M. (2024). Dysphagia in progressive supranuclear palsy: A scoping review. *Clinical Parkinsonism & Related Disorders*, *11*, 100283. https://doi.org/10.1016/j.prdoa.2024.100283

Focke, N. K., Helms, G., Scheewe, S., Pantel, P. M., Bachmann, C. G., Dechent, P., Ebentheuer, J., Mohr, A., Paulus, W., & Trenkwalder, C. (2011). Individual voxel-based subtype prediction can differentiate progressive supranuclear palsy from idiopathic Parkinson syndrome and healthy controls. *Human Brain Mapping*, *32*(11), 1905–1915. https://doi.org/10.1002/hbm.21161

Friedman, N. P., & Robbins, T. W. (2022). The role of prefrontal cortex in cognitive control and executive function. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *47*(1), 72–89. https://doi.org/10.1038/s41386-021-01132-0

Fujioka, S., van Gerpen, J. A., Uitti, R. J., Dickson, D. W., & Wszolek, Z. K. (2014). Familial progressive supranuclear palsy: A literature review. *Neurodegenerative Diseases*, *13*(2-3), 180–182. https://doi.org/10.1159/000354975

Gardner, R. C., Boxer, A. L., Trujillo, A., Mirsky, J. B., Guo, C. C., Gennatas, E. D., Heuer, H. W., Fine, E., Zhou, J., Kramer, J. H., Miller, B. L., & Seeley, W. W. (2013). Intrinsic connectivity network disruption in progressive supranuclear palsy. *Annals of Neurology*, *73*(5), 603–616. https://doi.org/10.1002/ana.23844

Gasquoine, P. G. (2014). Contributions of the insula to cognition and emotion. *Neuropsychology Review*, *24*(2), 77–87. https://doi.org/10.1007/s11065-014-9246-9

Gatto, R. G., Martin, P. R., Ali, F., Clark, H. M., Duffy, J. R., Utianski, R. L., Botha, H., Machulda, M. M., Dickson, D. W., Josephs, K. A., & Whitwell, J. L. (2022). Diffusion tractography of superior cerebellar peduncle and dentatorubrothalamic tracts in two autopsy confirmed progressive supranuclear palsy variants: Richardson syndrome and the speech-language variant. *NeuroImage: Clinical*, *35*, 103030. https://doi.org/10.1016/j.nicl.2022.103030

Gellersen, H. M., Guo, C. C., O'Callaghan, C., Tan, R. H., Sami, S., & Hornberger, M. (2017). Cerebellar atrophy in neurodegeneration-a meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *88*(9), 780–788. https://doi.org/10.1136/jnnp-2017-315607

Genon, S., Reid, A., Li, H., Fan, L., Müller, V. I., Cieslik, E. C., Hoffstaedter, F., Langner, R., Grefkes, C., Laird, A. R., Fox, P. T., Jiang, T., Amunts, K., & Eickhoff, S. B. (2018). The heterogeneity of the left dorsal premotor cortex evidenced by multimodal connectivity-based parcellation and functional characterization. *NeuroImage*, *170*, 400–411. https://doi.org/10.1016/j.neuroimage.2017.02.034

Gerstenecker, A., Duff, K., Mast, B., & Litvan, I. (2013). Behavioral abnormalities in progressive supranuclear palsy. *Psychiatry Research*, *210*(3), 1205–1210. https://doi.org/10.1016/j.psychres.2013.08.045

Giordano, A., Tessitore, A., Corbo, D., Cirillo, G., Micco, R. de, Russo, A., Liguori, S., Cirillo, M., Esposito, F., & Tedeschi, G. (2013). Clinical and cognitive correlations of regional gray matter atrophy in progressive supranuclear palsy. *Parkinsonism & Related Disorders*, *19*(6), 590–594. https://doi.org/10.1016/j.parkreldis.2013.02.005

Godeiro-Junior, C., Felício, A. C., Barsottini, O. G. P., Aguiar, Patricia M. de Carvalho, Silva, S. M. A., Borges, V., & Ferraz, H. B. (2008). Clinical features of dystonia in atypical parkinsonism. *Arquivos De Neuro-Psiquiatria*, *66*(4), 800–804. https://doi.org/10.1590/S0004-282X2008000600004

Golbe, L. I. (2008). The Epidemiology of Progressive Supranuclear Palsy. In *Dementias* (pp. 457–459). Elsevier. https://doi.org/10.1016/s0072-9752(07)01242-0

Golbe, L. I. (2014). Progressive supranuclear palsy. *Seminars in Neurology*, *34*(2), 151–159. https://doi.org/10.1055/s-0034-1381736

Graber, J. J., & Staudinger, R. (2009). Teaching NeuroImages: "Penguin" or "hummingbird" sign and midbrain atrophy in progressive supranuclear palsy. *Neurology*, *72*(17), e81. https://doi.org/10.1212/WNL.0b013e3181a2e815

Gröschel, K., Kastrup, A., Litvan, I., & Schulz, J. B. (2006). Penguins and hummingbirds: Midbrain atrophy in progressive supranuclear palsy. *Neurology*, *66*(6), 949–950. https://doi.org/10.1212/01.wnl.0000203342.77115.bf

Haber, S. N., & Calzavara, R. (2009). The cortico-basal ganglia integrative network: The role of the thalamus. *Brain Research Bulletin*, *78*(2-3), 69–74. https://doi.org/10.1016/j.brainresbull.2008.09.013

Han, H. J., Kim, H., Park, J.-H., Shin, H.-W., Kim, G. U., Kim, D. S., Lee, E. J., Oh, H. E., Park, S.-H., & Kim, Y. J. (2010). Behavioral changes as the earliest clinical manifestation of progressive supranuclear palsy. *Journal of Clinical Neurology (Seoul, Korea)*, *6*(3), 148–151. https://doi.org/10.3988/jcn.2010.6.3.148

Heide, R. J. von der, Skipper, L. M., Klobusicky, E., & Olson, I. R. (2013). Dissecting the uncinate fasciculus: Disorders, controversies and a hypothesis. *Brain*, *136*(Pt 6), 1692–1707. https://doi.org/10.1093/brain/awt094

Heim, B., Krismer, F., & Seppi, K. (2021). Differentiating PSP from MSA using MR planimetric measurements: A systematic review and meta-analysis. *Journal of Neural Transmission*, *128*(10), 1497–1505. https://doi.org/10.1007/s00702-021-02362-8

Hertrich, I., Dietrich, S., Blum, C., & Ackermann, H. (2021). The Role of the Dorsolateral Prefrontal Cortex for Speech and Language Processing. *Frontiers in Human Neuroscience*, *15*, 645209. https://doi.org/10.3389/fnhum.2021.645209

Höglinger, G. U., Respondek, G., Stamelou, M., Kurz, C., Josephs, K. A., Lang, A. E., Mollenhauer, B., Müller, U., Nilsson, C., Whitwell, J. L., Arzberger, T., Englund, E., Gelpi, E., Giese, A., Irwin, D. J., Meissner, W. G., Pantelyat, A., Rajput, A., van Swieten, J. C., . . . Litvan, I. (2017). Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Movement Disorders*, *32*(6), 853–864. https://doi.org/10.1002/mds.26987

Hong, J., Lu, J., Liu, F., Wang, M., Li, X., Clement, C., Lopes, L., Brendel, M., Rominger, A [Axel], Yen, T.-C., Guan, Y., Tian, M., Wang, J., Zuo, C., & Shi, K. (2023). Uncovering distinct progression patterns of tau deposition in progressive supranuclear palsy using 18FFlorzolotau PET imaging and subtype/stage inference algorithm. *EBioMedicine*, *97*, 104835. https://doi.org/10.1016/j.ebiom.2023.104835

Hori, Y., Endo, H., Tagai, K., Kataoka, Y., Goto, R., Kurose, S., Momota, Y., Kokubo, N., Seki, C., Moriguchi, S., Shimada, H., Shinotoh, H., Tokuda, T., Takahata, K., Minamimoto, T., Higuchi, M., & Hirabayashi, T. (2025). Remote Cortical Network for Frontal Cognitive Symptoms derived from Tau Accumulation in Progressive Supranuclear Palsy. *BioRxiv*, 2025.02.05.636578. https://doi.org/10.1101/2025.02.05.636578

Horta-Barba, A., Pagonabarraga, J., Martínez-Horta, S., Busteed, L., Pascual-Sedano, B., Illán-Gala, I., Marin-Lahoz, J., Aracil-Bolaños, I., Pérez-Pérez, J., Sampedro, F., Bejr-Kasem, H., & Kulisevsky, J. (2021). Cognitive and behavioral profile of progressive supranuclear palsy and its phenotypes. *Journal of Neurology*, *268*(9), 3400–3408. https://doi.org/10.1007/s00415-021-10511-y

Hosp, J. A., Coenen, V. A., Rijntjes, M., Egger, K., Urbach, H., Weiller, C., & Reisert, M. (2019). Ventral tegmental area connections to motor and sensory cortical fields in humans. *Brain Structure and Function*, *224*(8), 2839–2855. https://doi.org/10.1007/s00429-019-01939-0

Hughes, A. J., Daniel, S. E., Ben-Shlomo, Y., & Lees, A. J. (2002). The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain*, *125*(Pt 4), 861–870. https://doi.org/10.1093/brain/awf080

Ichikawa-Escamilla, E., Velasco-Martínez, R. A., & Adalid-Peralta, L. (2024). Progressive Supranuclear Palsy Syndrome: An Overview. *IBRO Neuroscience Reports*, *16*, 598–608. https://doi.org/10.1016/j.ibneur.2024.04.008

Jackson, J. A., Jankovic, J., & Ford, J. (1983). Progressive supranuclear palsy: Clinical features and response to treatment in 16 patients. *Annals of Neurology*, *13*(3), 273–278. https://doi.org/10.1002/ana.410130308

Jalal, M. J., & Menon, M. (2017). 'Humming bird sign', 'Mickey Mouse sign', and 'morning glory sign' in progressive supranuclear palsy. *Menoufia Medical Journal*, *30*(1), 325. https://doi.org/10.4103/mmj.mmj_204_16

Janelle, F., Iorio-Morin, C., D'amour, S., & Fortin, D. (2022). Superior Longitudinal Fasciculus: A Review of the Anatomical Descriptions With Functional Correlates. *Frontiers in Neurology*, *13*, 794618. https://doi.org/10.3389/fneur.2022.794618

Jellinger, K. A. (2023). Pathomechanisms of cognitive impairment in progressive supranuclear palsy. *Journal of Neural Transmission (Vienna, Austria : 1996)*, *130*(4), 481–493. https://doi.org/10.1007/s00702-023-02613-w

Ji, G.-J., Hu, P., Liu, T.-T., Li, Y., Chen, X., Zhu, C., Tian, Y., Chen, X., & Wang, K. (2018). Functional Connectivity of the Corticobasal Ganglia-Thalamocortical Network in Parkinson Disease: A Systematic Review and Meta-Analysis with Cross-Validation. *Radiology*, *287*(3), 973–982. https://doi.org/10.1148/radiol.2018172183

Kaasinen, V., Kangassalo, N., Gardberg, M., Isotalo, J., Karhu, J., Parkkola, R., & Sonninen, P. (2015). Midbrain-to-pons ratio in autopsy-confirmed progressive supranuclear palsy: Replication in an independent cohort. *Neurological Sciences*, *36*(7), 1251–1253. https://doi.org/10.1007/s10072-015-2184-3

Kannenberg, S., Caspers, J., Dinkelbach, L., Moldovan, A.S., Ferrea, S., Butz, M., Schnitzler, A., & Hartmann, C.J. (2021). Investigating the 1-year Decline in Midbrain-to-Pons Ratio in the Differential Diagnosis of PSP and IPD. Journal of Neurology, 268, 1526–1532. https://doi.org/10.1007/s00415-020-10327-2.

Kawabata, K., Banno, F., Mizutani, Y., Maeda, T., Nagao, R., Shima, S., Murayama, K., Ohno, Y., Maeda, T., Sasaki, M., Ueda, A., Ito, M., & Watanabe, H. (2025). Flattened red nucleus in progressive supranuclear palsy detected by quantitative susceptibility mapping. *Parkinsonism & Related Disorders*, *131*, 107251. https://doi.org/10.1016/j.parkreldis.2024.107251

Kim, J.-H., & McCann, C. M. (2015). Communication impairments in people with progressive supranuclear palsy: A tutorial. *Journal of Communication Disorders*, *56*, 76–87. https://doi.org/10.1016/j.jcomdis.2015.06.002

Knake, S., Belke, M., Menzler, K., Pilatus, U., Eggert, K. M., Oertel, W. H., Stamelou, M., & Höglinger, G. U. (2010). In vivo demonstration of microstructural brain pathology in progressive supranuclear palsy: A DTI study using TBSS. *Movement Disorders*, *25*(9), 1232–1238. https://doi.org/10.1002/mds.23054

Koizumi, R., Akagi, A., Riku, Y., Sone, J., Miyahara, H., Tanaka, F., Yoshida, M., & Iwasaki, Y. (2023). Clinicopathological features of progressive supranuclear palsy with asymmetrical atrophy of the superior cerebellar peduncle. *Neuropathology : Official Journal of the Japanese Society of Neuropathology*, *43*(3), 233–243. https://doi.org/10.1111/neup.12868

Kovacs, G. G., Lukic, M. J., Irwin, D. J., Arzberger, T., Respondek, G., Lee, E. B., Coughlin, D., Giese, A., Grossman, M., Kurz, C., McMillan, C. T., Gelpi, E., Compta, Y., van Swieten, J. C., Laat, L. D., Troakes, C., Al-Sarraj, S., Robinson, J. L., Roeber, S., . . . Höglinger, G. U. (2020). Distribution patterns of tau pathology in progressive supranuclear palsy. *Acta Neuropathologica*, *140*(2), 99–119. https://doi.org/10.1007/s00401-020-02158-2

Kurth, F., Zilles, K., Fox, P. T., Laird, A. R., & Eickhoff, S. B. (2010). A link between the systems: Functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Structure and Function*, *214*(5), 519–534. https://doi.org/10.1007/s00429-010-0255-z

Lambert, C., Chowdhury, R., Fitzgerald, T. H. B., Fleming, S. M., Lutti, A., Hutton, C., Draganski, B., Frackowiak, R., & Ashburner, J. (2013). Characterizing aging in the human brainstem using quantitative multimodal MRI analysis. *Frontiers in Human Neuroscience*, *7*, 462. https://doi.org/10.3389/fnhum.2013.00462

Levin, J., Kurz, A., Arzberger, T., Giese, A., & Höglinger, G. U. (2016). The Differential Diagnosis and Treatment of Atypical Parkinsonism. *Deutsches Ärzteblatt International*, *113*(5), 61–69. https://doi.org/10.3238/arztebl.2016.0061

Liang, D., & Labrakakis, C. (2024). Multiple Posterior Insula Projections to the Brainstem Descending Pain Modulatory System. *International Journal of Molecular Sciences*, *25*(17), 9185. https://doi.org/10.3390/ijms25179185

Litvan, I., Agid, Y., Calne, D., Campbell, G., Dubois, B., Duvoisin, R. C., Goetz, C. G., Golbe, L. I., Grafman, J., Growdon, J. H., Hallett, M., Jankovic, J., Quinn, N. P., Tolosa, E., & Zee, D. S. (1996). Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): Report of the NINDS-SPSP international workshop. *Neurology*, *47*(1), 1–9. https://doi.org/10.1212/WNL.47.1.1

Litvan, I. (2003). Update on epidemiological aspects of progressive supranuclear palsy. *Movement Disorders: Official Journal of the Movement Disorder Society*, *18 Suppl 6*(S6), S43-50. https://doi.org/10.1002/mds.10562

Litvan, I., & Kong, M. (2014). Rate of decline in progressive supranuclear palsy. *Movement Disorders*, *29*(4), 463–468. https://doi.org/10.1002/mds.25843

Lopez, G., Bayulkem, K., & Hallett, M. (2016). Progressive supranuclear palsy (PSP): Richardson syndrome and other PSP variants. *Acta Neurologica Scandinavica*, *134*(4), 242–249. https://doi.org/10.1111/ane.12546

Lupascu, N., Lupescu, I. C., Caloianu, I., Naftanaila, F., Glogojeanu, R. R., Sirbu, C. A., & Mitrica, M. (2023). Imaging Criteria for the Diagnosis of Progressive Supranuclear Palsy: Supportive or Mandatory? *Diagnostics*, *13*(11). https://doi.org/10.3390/diagnostics13111967

Lyons, S., Trépel, D., Lynch, T., Walsh, R., & O'Dowd, S. (2023). The prevalence and incidence of progressive supranuclear palsy and corticobasal syndrome: A systematic review and meta-analysis. *Journal of Neurology*, 1–15. https://doi.org/10.1007/s00415-023-11791-2

Macedo, A. C., Mariano, L. I., Martins, M. I., Friedlaender, C. V., Ventura, J. M., Faria Rocha, J. V. de, Camargos, S. T., Cardoso, F. E. C., Caramelli, P., & Souza, L. C. de (2022). Do Patients with Progressive Supranuclear Palsy Have Episodic Memory Impairment? A Systematic Review. *Movement Disorders Clinical Practice*, *9*(4), 436–445. https://doi.org/10.1002/mdc3.13435

Madden, D. J., Bennett, I. J., Burzynska, A., Potter, G. G., Chen, N., & Song, A. W. (2012). Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochimica Et Biophysica Acta*, *1822*(3), 386–400. https://doi.org/10.1016/j.bbadis.2011.08.003

Mahale, R. R., Krishnan, S., Divya, K. P., Jisha, V. T., & Kishore, A. (2022). Gender differences in progressive supranuclear palsy. *Acta Neurologica Belgica*, *122*(2), 357–362. https://doi.org/10.1007/s13760-021-01599-0

Massey, L. A., Jäger, H. R., Paviour, D. C., O'Sullivan, S. S., Ling, H., Williams, D. R., Kallis, C., Holton, J., Revesz, T., Burn, D. J., Yousry, T., Lees, A. J., Fox, N. C., & Micallef, C. (2013). The midbrain to pons ratio: A simple and specific MRI sign of progressive supranuclear palsy. *Neurology*, *80*(20), 1856–1861. https://doi.org/10.1212/WNL.0b013e318292a2d2

Mazzola, L., Mauguière, F., & Isnard, J. (2019). Functional mapping of the human insula: Data from electrical stimulations. *Revue Neurologique*, *175*(3), 150–156. https://doi.org/10.1016/j.neurol.2018.12.003

McFarland, N. R. (2016). Diagnostic Approach to Atypical Parkinsonian Syndromes. *Continuum (Minneapolis, Minn.)*, *22*(4 Movement Disorders), 1117–1142. https://doi.org/10.1212/CON.0000000000000348

Millar, D., Griffiths, P., Zermansky, A. J., & Burn, D. J. (2006). Characterizing behavioral and cognitive dysexecutive changes in progressive supranuclear palsy. *Movement Disorders : Official Journal of the Movement Disorder Society*, *21*(2), 199–207. https://doi.org/10.1002/mds.20707

Molnar-Szakacs, I., & Uddin, L. Q. (2022). Anterior insula as a gatekeeper of executive control. *Neuroscience and Biobehavioral Reviews*, *139*, 104736. https://doi.org/10.1016/j.neubiorev.2022.104736

Mueller, C., Hussl, A., Krismer, F., Heim, B., Mahlknecht, P., Nocker, M., Scherfler, C., Mair, K., Esterhammer, R., Schocke, M., Wenning, G. K., Poewe, W., & Seppi, K. (2018). The diagnostic accuracy of the hummingbird and morning glory sign in patients with neurodegenerative parkinsonism. *Parkinsonism & Related Disorders*, *54*, 90–94. https://doi.org/10.1016/j.parkreldis.2018.04.005

Mueller, K., Jech, R., Bonnet, C., Tintěra, J., Hanuška, J., Möller, H. E., Fassbender, K., Ludolph, A., Kassubek, J., Otto, M., Růžička, E., & Schroeter, M. L. (2017). Disease-Specific Regions Outperform Whole-Brain Approaches in Identifying Progressive Supranuclear Palsy: A Multicentric MRI Study. *Frontiers in Neuroscience*, *11*, 100. https://doi.org/10.3389/fnins.2017.00100

Namkung, H., Kim, S.-H., & Sawa, A. (2017). The Insula: An Underestimated Brain Area in Clinical Neuroscience, Psychiatry, and Neurology. *Trends in Neurosciences*, *40*(4), 200–207. https://doi.org/10.1016/j.tins.2017.02.002

Nguyen, T.-T., Cheng, J.-S., Chen, Y.-L., Lin, Y.-C., Tsai, C.-C., Lu, C.-S., Weng, Y.-H., Wu, Y.-M., Hoang, N.-T., & Wang, J.-J. (2021). Fixel-Based Analysis of White Matter Degeneration in Patients With Progressive Supranuclear Palsy or Multiple System Atrophy, as Compared to Parkinson's Disease. *Frontiers in Aging Neuroscience*, *13*, 625874. https://doi.org/10.3389/fnagi.2021.625874

Oba, H., Yagishita, A., Terada, H., Barkovich, A. J., Kutomi, K., Yamauchi, T., Furui, S., Shimizu, T., Uchigata, M., Matsumura, K., Sonoo, M., Sakai, M., Takada, K., Harasawa, A., Takeshita, K., Kohtake, H., Tanaka, H., & Suzuki, S. (2005). New and reliable MRI diagnosis for progressive supranuclear palsy. *Neurology*, *64*(12), 2050–2055. https://doi.org/10.1212/01.WNL.0000165960.04422.D0

Osaki, Y., Morita, Y., Miyamoto, Y., Furuta, K., & Furuya, H. (2017). Freezing of gait is an early clinical feature of progressive supranuclear palsy. *Neurology and Clinical Neuroscience*, *5*(3), 86–90. https://doi.org/10.1111/ncn3.12122

Ossenkoppele, R., Cohn-Sheehy, B. I., La Joie, R., Vogel, J. W., Möller, C., Lehmann, M., van Berckel, B. N. M., Seeley, W. W., Pijnenburg, Y. A., Gorno-Tempini, M. L., Kramer, J. H., Barkhof, F., Rosen, H. J., van der Flier, W. M., Jagust, W. J., Miller, B. L., Scheltens, P., & Rabinovici, G. D. (2015). Atrophy patterns in early clinical stages across distinct phenotypes of Alzheimer's disease. *Human Brain Mapping*, *36*(11), 4421–4437. https://doi.org/10.1002/hbm.22927

Padovani, A., Borroni, B., Brambati, S. M., Agosti, C., Broli, M., Alonso, R., Scifo, P., Bellelli, G., Alberici, A., Gasparotti, R., & Perani, D. (2006). Diffusion tensor imaging and voxel based morphometry study in early progressive supranuclear palsy. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(4), 457–463. https://doi.org/10.1136/jnnp.2005.075713

Palesi, F., Tournier, J.-D., Calamante, F., Muhlert, N., Castellazzi, G., Chard, D., D'Angelo, E., & Wheeler-Kingshott, C. A. M. (2015).Contralateral cerebello-thalamo-cortical pathways with prominent involvement of associative areas in humans in vivo. *Brain Structure and Function*, *220*(6), 3369–3384. https://doi.org/10.1007/s00429-014-0861-2

Palmisano, S., Fasotti, L., & Bertens, D. (2020). Neurobehavioral Initiation and Motivation Problems After Acquired Brain Injury. *Frontiers in Neurology*, *11*, 484687. https://doi.org/10.3389/fneur.2020.00023

Palop, J. J., & Mucke, L. (2016). Network abnormalities and interneuron dysfunction in Alzheimer disease. *Nature Reviews Neuroscience*, *17*(12), 777–792. https://doi.org/10.1038/nrn.2016.141

Pan, P. L., Shi, H. C., Zhong, J. G., Xiao, P. R., Shen, Y., Wu, L. J., Song, Y. Y., He, G. X., & Li, H. L. (2013). Gray matter atrophy in Parkinson's disease with dementia: Evidence from meta-analysis of voxel-based morphometry studies. *Neurological Sciences*, *34*(5), 613–619. https://doi.org/10.1007/s10072-012-1250-3

Pan, P., Liu, Y., Zhang, Y., Zhao, H., Ye, X., & Xu, Y. (2017). Brain gray matter abnormalities in progressive supranuclear palsy revisited. *Oncotarget*, *8*(46), 80941–80955. https://doi.org/10.18632/oncotarget.20895

Pandya, S., Mezias, C., & Raj, A. (2017). Predictive Model of Spread of Progressive Supranuclear Palsy Using Directional Network Diffusion. *Frontiers in Neurology*, *8*, 692. https://doi.org/10.3389/fneur.2017.00692

Pansuwan, T., Quaegebeur, A., Kaalund, S. S., Hidari, E., Briggs, M., Rowe, J. B., & Rittman, T. (2023). Accurate digital quantification of tau pathology in progressive supranuclear palsy. *Acta Neuropathologica Communications*, *11*(1), 178. https://doi.org/10.1186/s40478-023-01674-y

Pantelyat, A. (2022). Progressive Supranuclear Palsy and Corticobasal Syndrome. *Continuum (Minneapolis, Minn.)*, *28*(5), 1364–1378. https://doi.org/10.1212/CON.0000000000001158

Paulus, J. K., Dahabreh, I. J., Balk, E. M., Avendano, E. E., Lau, J., & Ip, S. (2014). Opportunities and challenges in using studies without a control group in comparative effectiveness reviews. *Research Synthesis Methods*, *5*(2), 152–161. https://doi.org/10.1002/jrsm.1101

Paviour, D. C., Price, S. L., Jahanshahi, M., Lees, A. J., & Fox, N. C. (2006). Regional brain volumes distinguish PSP, MSA-P, and PD: Mri-based clinico-radiological correlations. *Movement Disorders: Official Journal of the Movement Disorder Society*, *21*(7), 989–996. https://doi.org/10.1002/mds.20877

Peralta, C., Strafella, A. P., van Eimeren, T., Ceravolo, R., Seppi, K., Kaasinen, V., Arena, J. E., & Lehericy, S. (2022). Pragmatic Approach on Neuroimaging Techniques for the Differential Diagnosis of Parkinsonisms. *Movement Disorders Clinical Practice*, *9*(1), 6–19. https://doi.org/10.1002/mdc3.13354

Piattella, M. C., Tona, F., Bologna, M., Sbardella, E., Formica, A., Petsas, N., Filippini, N., Berardelli, A., & Pantano, P. (2015b). Disrupted resting-state functional connectivity in progressive supranuclear palsy. *American Journal of Neuroradiology*, *36*(5), 915–921. https://doi.org/10.3174/ajnr.A4229

Piattella, M. C., Upadhyay, N., Bologna, M., Sbardella, E., Tona, F., Formica, A., Petsas, N., Berardelli, A., & Pantano, P. (2015a). Neuroimaging evidence of gray and white matter damage and clinical correlates in progressive supranuclear palsy. *Journal of Neurology*, *262*(8), 1850–1858. https://doi.org/10.1007/s00415-015-7779-3

Polo, T. C. F., & Miot, H. A. (2020). Use of ROC curves in clinical and experimental studies. *Jornal Vascular Brasileiro*, *19*, e20200186. https://doi.org/10.1590/1677-5449.200186

Price, S., Paviour, D., Scahill, R., Stevens, J., Rossor, M., Lees, A., & Fox, N. (2004). Voxel-based morphometry detects patterns of atrophy that help differentiate progressive supranuclear palsy and Parkinson's disease. *NeuroImage*, *23*(2), 663–669. https://doi.org/10.1016/j.neuroimage.2004.06.013

Prodoehl, J., Li, H., Planetta, P. J., Goetz, C. G., Shannon, K. M., Tangonan, R., Comella, C. L., Simuni, T., Zhou, X. J., Leurgans, S., Corcos, D. M., & Vaillancourt, D. E. (2013). Diffusion tensor imaging of Parkinson's disease, atypical parkinsonism, and essential tremor. *Movement Disorders*, *28*(13), 1816–1822. https://doi.org/10.1002/mds.25491

Qu, J., Zhu, R., Wu, Y., Xu, G., & Wang, D. (2024). Abnormal structural–functional coupling patterning in progressive supranuclear palsy is associated with diverse gradients and histological features. *Communications Biology*, *7*(1), 1195. https://doi.org/10.1038/s42003-024-06877-0

Qu, J., Zhu, R., Wu, Y., Xu, G., & Wang, D. (2025). Abnormal Structural-Functional Coupling and MRI Alterations of Brain Network Topology in Progressive Supranuclear Palsy. *Journal of Magnetic Resonance Imaging*, *61*(4), 1770–1781. https://doi.org/10.1002/jmri.29620

Quattrone, A., Morelli, M., Nigro, S., Quattrone, A., Vescio, B., Arabia, G., Nicoletti, G., Nisticò, R., Salsone, M., Novellino, F., Barbagallo, G., Le Piane, E., Pugliese, P., Bosco, D., Vaccaro, M. G., Chiriaco, C., Sabatini, U., Vescio, V., Stanà, C., . . . Caracciolo, M. (2018). A new MR imaging index for differentiation of progressive supranuclear palsy-parkinsonism from Parkinson's disease. *Parkinsonism & Related Disorders*, *54*, 3–8. https://doi.org/10.1016/j.parkreldis.2018.07.016

Quattrone, A., Morelli, M., Williams, D. R., Vescio, B., Arabia, G., Nigro, S., Nicoletti, G., Salsone, M., Novellino, F., Nisticò, R., Pucci, F., Chiriaco, C., Pugliese, P., Bosco, D., & Caracciolo, M. (2016). Mr parkinsonism index predicts vertical supranuclear gaze palsy in patients with PSP-parkinsonism. *Neurology*, *87*(12), 1266–1273. https://doi.org/10.1212/WNL.0000000000003125

Quattrone, A., Franzmeier, N., Huppertz, H.-J., Klietz, M., Roemer, S. N., Boxer, A. L., Levin, J., & Höglinger, G. U. (2024). Magnetic Resonance Imaging Measures to Track Atrophy Progression in Progressive Supranuclear Palsy in Clinical Trials. *Movement Disorders*, *39*(8), 1329–1342. https://doi.org/10.1002/mds.29866

Quattrone, A., Zappia, M., & Quattrone, A. (2024). Simple biomarkers to distinguish Parkinson's disease from its mimics in clinical practice: A comprehensive review and future directions. *Frontiers in Neurology*, *15*, 1460576. https://doi.org/10.3389/fneur.2024.1460576

Quattrone A, Nicoletti G, Messina D, Fera F, Condino F, Pugliese P, Lanza P, Barone P, Morgante L, Zappia M, Aguglia U, Gallo O. (2008). MR imaging index for differentiation of progressive supranuclear palsy from Parkinson disease and the Parkinson variant of multiple system atrophy. *Radiology*. 2008 Jan;246(1):214-21. doi: 10.1148/radiol.2453061703

Querbach, S. K., Eickhoff, S. B., Hausmann, A.C., Schnitzler, A., Caspers, J., & Eickhoff, C.R. (2025). Consistent PSP Atrophy involves Regions connecting the Salience Network to Subcortical Circuits [Manuscript submitted for publication].

Querbach, S.K., Hausmann, A.C., Schnitzler, A., Hartmann, C. J., Rubbert, C. & Caspers, Julian (2025). Tract-specific DTI Scalars and Clinical Correlates in Progressive Supranuclear Palsy [Manuscript submitted for publication].

Rajput, A., & Rajput, A. H. (2001). Progressive supranuclear palsy: Clinical features, pathophysiology and management. *Drugs & Aging*, *18*(12), 913–925. https://doi.org/10.2165/00002512-200118120-00003

Rajput, A. H., Rozdilsky, B., Rajput, A., & Ang, L. (1990). Levodopa Efficacy and Pathological Basis of Parkinson Syndrome. *Clinical Neuropharmacology*, *13*(6), 553. https://doi.org/10.1097/00002826-199012000-00007

Rampello, L., Buttà, V., Raffaele, R., Vecchio, I., Battaglia, G., Cormaci, G., & Alvano, A. (2005). Progressive supranuclear palsy: A systematic review. *Neurobiology of Disease*, *20*(2), 179–186. https://doi.org/10.1016/j.nbd.2005.03.013

Reid, A. T., Hoffstaedter, F., Gong, G., Laird, A. R., Fox, P., Evans, A. C., Amunts, K., & Eickhoff, S. B. (2017). A seed-based cross-modal comparison of brain connectivity measures. *Brain Structure and Function*, *222*(3), 1131–1151. https://doi.org/10.1007/s00429-016-1264-3

Rektor, I., Svátková, A., Vojtíšek, L., Zikmundová, I., Vaníček, J., Király, A., & Szabó, N. (2018). White matter alterations in Parkinson's disease with normal cognition precede grey matter atrophy. *PLOS ONE*, *13*(1), e0187939. https://doi.org/10.1371/journal.pone.0187939

Respondek, G., Breslow, D., Amirghiasvand, C., Ghosh, B., Bergmans, B., van Wyk, L., Irfan, T., Dossin, R., & Vanderavero, C. (2023). The Lived Experiences of People with Progressive Supranuclear Palsy and Their Caregivers. *Neurology and Therapy*, *12*(1), 229–247. https://doi.org/10.1007/s40120-022-00420-1

Respondek, G., Stamelou, M., Kurz, C., Ferguson, L. W., Rajput, A., Chiu, W. Z., van Swieten, J. C., Troakes, C., Al Sarraj, S., Gelpi, E., Gaig, C., Tolosa, E., Oertel, W. H., Giese, A., Roeber, S., Arzberger, T., Wagenpfeil, S., & Höglinger, G. U. (2014). The phenotypic spectrum of progressive supranuclear palsy: A retrospective multicenter study of 100 definite cases. *Movement Disorders*, *29*(14), 1758–1766. https://doi.org/10.1002/mds.26054

Rittman, T., Coyle-Gilchrist, I. T., & Rowe, J. B. (2016). Managing cognition in progressive supranuclear palsy. *Neurodegenerative Disease Management*, *6*(6), 499–508. https://doi.org/10.2217/nmt-2016-0027

Robinson, J. L., Yan, N., Caswell, C., Xie, S. X., Suh, E., van Deerlin, V. M., Gibbons, G., Irwin, D. J., Grossman, M., Lee, E. B., Lee, V. M.-Y., Miller, B., & Trojanowski, J. Q. (2020). Primary Tau Pathology, Not Copathology, Correlates With Clinical Symptoms in PSP and CBD. *Journal of Neuropathology and Experimental Neurology*, *79*(3), 296–304. https://doi.org/10.1093/jnen/nlz141

Romano, S., & Colosimo, C. (2001). Procerus sign in progressive supranuclear palsy. *Neurology*, *57*(10), 1928. https://doi.org/10.1212/wnl.57.10.1928

Rosenberg-Katz, K., Herman, T., Jacob, Y., Giladi, N., Hendler, T., & Hausdorff, J. M. (2013). Gray matter atrophy distinguishes between Parkinson disease motor subtypes. *Neurology*, *80*(16), 1476–1484. https://doi.org/10.1212/WNL.0b013e31828cfaa4

Rottschy, C., Caspers, S., Roski, C., Reetz, K., Dogan, I., Schulz, J. B., Zilles, K., Laird, A. R., Fox, P. T., & Eickhoff, S. B. (2013). Differentiated parietal connectivity of frontal regions for "what" and "where" memory. *Brain Structure and Function*, *218*(6), 1551–1567. https://doi.org/10.1007/s00429-012-0476-4

Rowe, J. B., Holland, N., & Rittman, T. (2021). Progressive supranuclear palsy: Diagnosis and management. *Practical Neurology*, *21*(5), 376–383. https://doi.org/10.1136/practneurol-2020-002794

Ruberg, M., Javoy-Agid, F., Hirsch, E., Scatton, B., LHeureux, R., Hauw, J. J., Duyckaerts, C., Gray, F., Morel-Maroger, A., & Rascol, A. (1985). Dopaminergic and cholinergic lesions in progressive supranuclear palsy. *Annals of Neurology*, *18*(5), 523–529. https://doi.org/10.1002/ana.410180503

Ruchalski, K., & Hathout, G. M. (2012). A medley of midbrain maladies: A brief review of midbrain anatomy and syndromology for radiologists. *Radiology Research and Practice*, *2012*, 258524. https://doi.org/10.1155/2012/258524

Saini, J., Bagepally, B. S., Sandhya, M., Pasha, S. A., Yadav, R., & Pal, P. K. (2012). In vivo evaluation of white matter pathology in patients of progressive supranuclear palsy using TBSS. *Neuroradiology*, *54*(7), 771–780. https://doi.org/10.1007/s00234-011-0983-7

Saito, Y., Kamagata, K., Wijeratne, P. A., Andica, C., Uchida, W., Takabayashi, K., Fujita, S., Akashi, T., Wada, A., Shimoji, K., Hori, M., Masutani, Y., Alexander, D. C., & Aoki, S. (2022). Temporal Progression Patterns of Brain Atrophy in Corticobasal Syndrome and Progressive Supranuclear Palsy Revealed by Subtype and Stage Inference (SuStaIn). *Frontiers in Neurology*, *13*, 814768. https://doi.org/10.3389/fneur.2022.814768

Sakai, K., Yokota, H., Akazawa, K., & Yamada, K. (2014). Brainstem white matter tracts and the control of eye movements. *Seminars in Ultrasound, CT, and MR*, *35*(5), 517–526. https://doi.org/10.1053/j.sult.2014.06.009

Sánchez-Ruiz de Gordoa, J., Zelaya, V., Tellechea-Aramburo, P., Acha, B., Roldán, M., López-Molina, C., Coca, V., Galbete, A., Mendioroz, M., & Erro, M. E. (2022). Is the Phenotype Designation by PSP-MDS Criteria Stable Throughout the Disease Course and Consistent With Tau Distribution? *Frontiers in Neurology*, *13*, 827338. https://doi.org/10.3389/fneur.2022.827338

Sarasso, E., Agosta, F., Piramide, N., & Filippi, M. (2021). Progression of grey and white matter brain damage in Parkinson's disease: A critical review of structural MRI literature. *Journal of Neurology*, *268*(9), 3144–3179. https://doi.org/10.1007/s00415-020-09863-8

Scotton, W. J., Shand, C., Todd, E., Bocchetta, M., Cash, D. M., VandeVrede, L., Heuer, H., Young, A. L., Oxtoby, N., Alexander, D. C., Rowe, J. B., Morris, H. R., Boxer, A. L., Rohrer, J. D., & Wijeratne, P. A. (2023). Uncovering spatiotemporal patterns of atrophy in progressive supranuclear palsy using unsupervised machine learning. *Brain Communications*, *5*(2), fcad048. https://doi.org/10.1093/braincomms/fcad048

Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative diseases target large-scale human brain networks. *Neuron*, *62*(1), 42–52. https://doi.org/10.1016/j.neuron.2009.03.024

Sintini, I., Ali, F., Stephens, Y., Clark, H. M., Stierwalt, J. A., Machulda, M. M., Satoh, R., Josephs, K. A., & Whitwell, J. L. (2025). Functional connectivity abnormalities in clinical variants of progressive supranuclear palsy. *NeuroImage: Clinical*, *45*, 103727. https://doi.org/10.1016/j.nicl.2024.103727

Spinelli, E. G., Ghirelli, A., Bottale, I., Basaia, S., Canu, E., Castelnovo, V., Volontè, M. A., Galantucci, S., Magnani, G., Caso, F., Cecchetti, G., Caroppo, P., Prioni, S., Villa, C., Josephs, K. A [Keith A.], Whitwell, J. L., Filippi, M., & Agosta, F. (2024). Stepwise Functional Brain Architecture Correlates with Atrophy in Progressive Supranuclear Palsy. *Movement Disorders*, *39*(9), 1493–1503. https://doi.org/10.1002/mds.29887

Stamelou, M., Knake, S., Oertel, W. H., & Höglinger, G. U [G. U.] (2011). Magnetic resonance imaging in progressive supranuclear palsy. *Journal of Neurology*, *258*(4), 549–558. https://doi.org/10.1007/s00415-010-5865-0

Stamelou, M., & Hoeglinger, G. U. (2013). Atypical parkinsonism: An update. *Current Opinion in Neurology*, *26*(4), 401–405. https://doi.org/10.1097/WCO.0b013e3283632da6

Stamelou, M., & Höglinger, G. (2016). A Review of Treatment Options for Progressive Supranuclear Palsy. *CNS Drugs*, *30*(7), 629–636. https://doi.org/10.1007/s40263-016-0347-2

Stamelou, M., Respondek, G., Giagkou, N., Whitwell, J. L., Kovacs, G. G., & Höglinger, G. U. (2021). Evolving concepts in progressive supranuclear palsy and other 4-repeat tauopathies. *Nature Reviews Neurology*, *17*(10), 601–620. https://doi.org/10.1038/s41582-021-00541-5

Steele, J. C., Richardson, J. C., & Olszewski, J. (1964). Progressive Supranuclear Palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. *Archives of Neurology*, *10*(4), 333–359. https://doi.org/10.1001/archneur.1964.00460160003001

Stezin, A., Lenka, A., Jhunjhunwala, K., Saini, J., & Pal, P. K. (2017). Advanced structural neuroimaging in progressive supranuclear palsy: Where do we stand? *Parkinsonism & Related Disorders*, *36*, 19–32. https://doi.org/10.1016/j.parkreldis.2016.12.023

Surova, Y., Nilsson, M., Lätt, J., Lampinen, B., Lindberg, O., Hall, S., Widner, H., Nilsson, C., van Westen, D., & Hansson, O. (2015). Disease-specific structural changes in thalamus and dentatorubrothalamic tract in progressive supranuclear palsy. *Neuroradiology*, *57*(11), 1079–1091. https://doi.org/10.1007/s00234-015-1563-z

Swallow, D. M. A., Zheng, C. S., & Counsell, C. E. (2022). Systematic Review of Prevalence Studies of Progressive Supranuclear Palsy and Corticobasal Syndrome. *Movement Disorders Clinical Practice*, *9*(5), 604–613. https://doi.org/10.1002/mdc3.13489

Tessitore, A., Giordano, A., Caiazzo, G., Corbo, D., Micco, R. de, Russo, A., Liguori, S., Cirillo, M., Esposito, F., & Tedeschi, G. (2014). Clinical correlations of microstructural changes in progressive supranuclear palsy. *Neurobiology of Aging*, *35*(10), 2404–2410. https://doi.org/10.1016/j.neurobiolaging.2014.03.028

Tolosa, E., Duvoisin, R., & Cruz-Sanchez, F. F. (Eds.). (1994). *Journal of Neural Transmission. Supplementa: Vol. 42*. *Progressive Supranuclear Palsy: Diagnosis, Pathology, and Therapy*. Springer. https://doi.org/10.1007/978-3-7091-6641-3

Tolosa, E., Garrido, A., Scholz, S. W., & Poewe, W. (2021). Challenges in the diagnosis of Parkinson's disease. *The Lancet Neurology*, *20*(5), 385–397. https://doi.org/10.1016/S1474-4422(21)00030-2

Tse, N. Y., Chen, Y., Irish, M., Cordato, N. J., Landin-Romero, R., Hodges, J. R., Piguet, O., & Ahmed, R. M. (2020). Cerebellar contributions to cognition in corticobasal syndrome and progressive supranuclear palsy. *Brain Communications*, *2*(2), fcaa194. https://doi.org/10.1093/braincomms/fcaa194

Turkeltaub, P. E., Eden, G. F., Jones, K. M., & Zeffiro, T. A. (2002). Meta-analysis of the functional neuroanatomy of single-word reading: Method and validation. *NeuroImage*, *16*(3 Pt 1), 765–780. https://doi.org/10.1006/nimg.2002.1131

Turkeltaub, P. E., Eickhoff, S. B., Laird, A. R., Fox, M., Wiener, M., & Fox, P. (2012). Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. *Human Brain Mapping*, *33*(1), 1–13. https://doi.org/10.1002/hbm.21186

Uddin, L. Q., Nomi, J. S., Hebert-Seropian, B., Ghaziri, J., & Boucher, O. (2017). Structure and function of the human insula. *Journal of Clinical Neurophysiology : Official Publication of the American Electroencephalographic Society*, *34*(4), 300–306. https://doi.org/10.1097/WNP.0000000000000377

van der Knaap, L. J., & van der Ham, I. J. M. (2011). How does the corpus callosum mediate interhemispheric transfer? A review. *Behavioural Brain Research*, *223*(1), 211–221. https://doi.org/10.1016/j.bbr.2011.04.018

Virhammar, J., Blohmé, H., Nyholm, D., Georgiopoulos, C., & Fällmar, D. (2022). Midbrain area and the hummingbird sign from brain MRI in progressive supranuclear palsy and idiopathic normal pressure hydrocephalus. *Journal of Neuroimaging : Official Journal of the American Society of Neuroimaging*, *32*(1), 90–96. https://doi.org/10.1111/jon.12932

Wen, Y., Yang, Q., Jiao, B., Zhang, W., Lin, J., Zhu, Y., Xu, Q., Zhou, H., Weng, L., Liao, X., Zhou, Y., Wang, J [Junling], Guo, J., Yan, X., Jiang, H., Tang, B., & Shen, L. (2023). Clinical features of progressive supranuclear palsy. *Frontiers in Aging Neuroscience*, *15*, 1229491. https://doi.org/10.3389/fnagi.2023.1229491

Whiteside, D. J., Jones, P. S., Ghosh, B. C. P., Coyle-Gilchrist, I., Gerhard, A., Hu, M. T., Klein, J. C., Leigh, P. N., Church, A., Burn, D. J., Morris, H. R., Rowe, J. B., & Rittman, T. (2021). Altered network stability in progressive supranuclear palsy. *Neurobiology of Aging*, *107*, 109–117. https://doi.org/10.1016/j.neurobiolaging.2021.07.007

Whiteside, D. J., Street, D., Murley, A. G., Jones, P. S., Malpetti, M., Ghosh, B. C. P., Coyle-Gilchrist, I., Gerhard, A., Hu, M. T., Klein, J. C., Leigh, P. N., Church, A., Burn, D. J., Morris, H. R., Rowe, J. B., & Rittman, T. (2023). Network connectivity and structural correlates of survival in progressive supranuclear palsy and corticobasal syndrome. *Human Brain Mapping*, *44*(11), 4239–4255. https://doi.org/10.1002/hbm.26342

Whiting, P. F., Weswood, M. E., Rutjes, A. W. S., Reitsma, J. B., Bossuyt, P. N. M., & Kleijnen, J. (2006). Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. *BMC Medical Research Methodology*, *6*, 9. https://doi.org/10.1186/1471-2288-6-9

Whitwell, J. L., Duffy, J. R., Strand, E. A., Machulda, M. M., Senjem, M. L., Gunter, J. L., Kantarci, K., Eggers, S. D., Jack, C. R., & Josephs, K. A. (2013a). Neuroimaging comparison of primary progressive apraxia of speech and progressive supranuclear palsy. *European Journal of Neurology*, *20*(4), 629–637. https://doi.org/10.1111/ene.12004

Whitwell, J. L., Jack, C. R., Parisi, J. E., Gunter, J. L., Weigand, S. D., Boeve, B. F., Ahlskog, J. E., Petersen, R. C., Dickson, D. W., & Josephs, K. A. (2013b). Midbrain atrophy is not a biomarker of progressive supranuclear palsy pathology. *European Journal of Neurology*, *20*(10), 1417–1422. https://doi.org/10.1111/ene.12212

Whitwell, J. L., Avula, R., Master, A., Vemuri, P., Senjem, M. L., Jones, D. T., Jack, C. R., & Josephs, K. A. (2011). Disrupted thalamocortical connectivity in PSP: A resting-state fMRI, DTI, and VBM study. *Parkinsonism & Related Disorders*, *17*(8), 599–605. https://doi.org/10.1016/j.parkreldis.2011.05.013

Whitwell, J. L., Höglinger, G. U., Antonini, A., Bordelon, Y., Boxer, A. L., Colosimo, C., van Eimeren, T., Golbe, L. I., Kassubek, J., Kurz, C., Litvan, I., Pantelyat, A., Rabinovici, G., Respondek, G., Rominger, A., Rowe, J. B., Stamelou, M., & Josephs, K. A. (2017). Radiological biomarkers for diagnosis in PSP: Where are we and where do we need to be? *Movement Disorders*, *32*(7), 955–971. https://doi.org/10.1002/mds.27038

Whitwell, J. L., Schwarz, C. G., Reid, R. I., Kantarci, K., Jack, C. R., & Josephs, K. A. (2014). Diffusion tensor imaging comparison of progressive supranuclear palsy and corticobasal syndromes. *Parkinsonism & Related Disorders*, *20*(5), 493–498. https://doi.org/10.1016/j.parkreldis.2014.01.023

Whitwell, J. L., Tosakulwong, N., Clark, H. M., Ali, F., Botha, H., Weigand, S. D., Sintini, I., Machulda, M. M., Schwarz, C. G., Reid, R. I., Jack, C. R., Ahlskog, J. E., & Josephs, K. A. (2021). Diffusion tensor imaging analysis in three progressive supranuclear palsy variants. *Journal of Neurology*, *268*(9), 3409–3420. https://doi.org/10.1007/s00415-020-10360-1

Whitwell, J. L., Xu, J., Mandrekar, J., Gunter, J. L., Jack, C. R., & Josephs, K. A. (2012a). Imaging measures predict progression in progressive supranuclear palsy. *Movement Disorders*, *27*(14), 1801–1804. https://doi.org/10.1002/mds.24970

Whitwell, J. L., Xu, J., Mandrekar, J. N., Gunter, J. L., Jack, C. R., & Josephs, K. A. (2012b). Rates of brain atrophy and clinical decline over 6 and 12-month intervals in PSP: Determining sample size for treatment trials. *Parkinsonism & Related Disorders*, *18*(3), 252–256. https://doi.org/10.1016/j.parkreldis.2011.10.013

Williams, D. R., Holton, J. L., Strand, C., Pittman, A., Silva, R. de, Lees, A. J., & Revesz, T. (2007). Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome. *Brain*, *130*(Pt 6), 1566–1576. https://doi.org/10.1093/brain/awm104

Williams, D. R., & Lees, A. J. (2009). Progressive supranuclear palsy: Clinicopathological concepts and diagnostic challenges. *The Lancet. Neurology*, *8*(3), 270–279. https://doi.org/10.1016/S1474-4422(09)70042-0

Williams, D. R., & Lees, A. J. (2010). What features improve the accuracy of the clinical diagnosis of progressive supranuclear palsy-parkinsonism (PSP-P)? *Movement Disorders*, *25*(3), 357–362. https://doi.org/10.1002/mds.22977

Williams, D. R., & Litvan, I [Irene] (2013). Parkinsonian syndromes. *Continuum (Minneapolis, Minn.)*, *19*(5 Movement Disorders), 1189–1212. https://doi.org/10.1212/01.CON.0000436152.24038.e0

Willis, B. H., & Quigley, M. (2011). The assessment of the quality of reporting of meta-analyses in diagnostic research: A systematic review. *BMC Medical Research Methodology*, *11*(1), 163. https://doi.org/10.1186/1471-2288-11-163

Worker, A., Blain, C., Jarosz, J., Chaudhuri, K. R., Barker, G. J., Williams, S. C. R., Brown, R. G., Leigh, P. N., Dell'Acqua, F., & Simmons, A. (2014). Diffusion tensor imaging of Parkinson's disease, multiple system atrophy and progressive supranuclear palsy: A tract-based spatial statistics study. *PLOS ONE*, *9*(11), e112638. https://doi.org/10.1371/journal.pone.0112638

Wycoco, V., Shroff, M., Sudhakar, S., & Lee, W. (2013). White matter anatomy: What the radiologist needs to know. *Neuroimaging Clinics*, *23*(2), 197–216. https://doi.org/10.1016/j.nic.2012.12.002

Yu, F., Barron, D. S., Tantiwongkosi, B., & Fox, P. (2015). Patterns of gray matter atrophy in atypical parkinsonism syndromes: A VBM meta-analysis. *Brain and Behavior*, *5*(6), e00329. https://doi.org/10.1002/brb3.329

Zhang, J., Zhu, X., Wang, X., Gao, J., Shi, H., Huang, B., Situ, W., Yi, J., Zhu, X., & Yao, S. (2014). Increased structural connectivity in corpus callosum in adolescent males with conduct disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(4), 466-75.e1. https://doi.org/10.1016/j.jaac.2013.12.015

Zhang, X., Wang, J., Zhang, Z., & Ye, K. (2024). Tau in neurodegenerative diseases: Molecular mechanisms, biomarkers, and therapeutic strategies. *Translational Neurodegeneration*, *13*(1), 40. https://doi.org/10.1186/s40035-024-00429-6

Zhang, Y., & Burock, M. A. (2020). Diffusion Tensor Imaging in Parkinson's Disease and Parkinsonian Syndrome: A Systematic Review. *Frontiers in Neurology*, *11*, 531993. https://doi.org/10.3389/fneur.2020.531993

Ziegler, J., & Fiedler, K. (2024). Small Sample Size and Group Homogeneity: A Crucial Ingredient to Inter-Group Bias. *Personality and Social Psychology Bulletin*, Article 01461672231223335, 1461672231223335. https://doi.org/10.1177/01461672231223335

Zuo, X.-N., Ehmke, R., Mennes, M., Imperati, D., Castellanos, F. X., Sporns, O., & Milham, M. P. (2012). Network centrality in the human functional connectome. *Cerebral Cortex (New York, N.Y.: 1991)*, *22*(8), 1862–1875. https://doi.org/10.1093/cercor/bhr269

Zwergal, A., La Fougère, C., Lorenzl, S., Rominger, A., Xiong, G., Deutschenbaur, L., Linn, J., Krafczyk, S., Dieterich, M., Brandt, T., Strupp, M., Bartenstein, P., & Jahn, K. (2011). Postural imbalance and falls in PSP correlate with functional pathology of the thalamus. *Neurology*, *77*(2), 101–109. https://doi.org/10.1212/WNL.0b013e318223c79d

Appendix 1: STUDY 1

Consistent PSP atrophy involves Regions Connecting the Salience Network to Subcortical Circuits

Querbach, S., Eickhoff, S. B., Hausmann, A. C., Schnitzler, A., Caspers, J. & Eickhoff, C.R. (2025). Consistent PSP atrophy affects regions connecting the salience network to subcortical circuits [Manuscript submitted for publication].

Conceptualization & methodology: I developed the research question and analysis plan in consultation with C.R. Eickhoff and J. Caspers, drawing on the experimental algorithm designed by S.B. Eickhoff.

Investigation & project administration: I conducted the search for relevant research articles, independently reviewing them for suitability in the data collection process. C. Hausmann performed a secondary check of suitable articles. I was responsible for curating the data. Project administration was jointly managed by C.R. Eickhoff and me, with a second data verification conducted by me, including preparing the data for analysis.

Formal analysis: I conducted the statistical analyses in collaboration with C.R. Eickhoff, and data interpretation was done in consultation with both C.R. Eickhoff and S.B. Eickhoff.

Resources: S.B. Eickhoff provided the ALE algorithm used in this study. Additional resources were contributed by A. Schnitzler.

Manuscript: I wrote the initial manuscript, which encompassed all stages from comprehensive literature review to the final formulation. I created the figures and tables in consultation with C.R. Eickhoff. I also coordinated the scientific review process with the journals, making revisions with the assistance of C.R. Eickhoff. All authors critically reviewed the manuscript.

Meta-Analysis Movement Disorders

Consistent PSP-atrophy involves Regions connecting the Salience Network to Subcortical Circuits

Silja K. Querbach[1,]; Simon B. Eickhoff[2,3]; Ann Carolin Hausmann[1]; Alfons Schnitzler[1,4]; Julian Caspers[5]; Claudia R. Eickhoff[1,6]*

[1] Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany
[2] Institute of Systems Neuroscience, Medical Psychology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany
[3] Institute of Neuroscience and Medicine (INM-7), Research Centre Jülich, Germany
[4] Department of Neurology, Medical Psychology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany
[5] Department of Diagnostic and Interventional Radiology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany
[6] Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Germany

*Corresponding author: M.Sc. Silja Querbach Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Moorenstraße 5, 40225 Düsseldorf (Germany); silja.querbach@med.uni-duesseldorf.de

Running title: ***PSP atrophy: delineation & characterization***

Keywords: Progressive supranuclear palsy, VBM, meta-analysis, atrophy, gray matter

Conflict of Interest: The authors declare that they have no conflict of interest.
Funding sources for study: none

Abstract

Progressive supranuclear palsy (PSP) is a movement disorder characterized by a still poorly understood pattern of neurodegeneration, largely due to prior studies relying on small and heterogeneous cohorts. In this study, we aimed to consolidate existing evidence of brain atrophy in PSP through a coordinate-based meta-analysis. Regions showing robust atrophy were subsequently examined in terms of their functional roles, connectivity profiles, and associations with neurotransmitter distribution patterns, in order to infer disease-specific pathological mechanisms.

We conducted an Anatomical Likelihood Estimation (ALE) meta-analysis of whole-brain morphometry studies investigating atrophy in PSP, followed by functional decoding to evaluate the functions recruiting the atrophied regions and meta-analytic connectivity modelling to evaluate their connectivity patterns. Finally, we explored potential neurochemical underpinnings by correlating the atrophy map with multiple neurotransmitter density distributions.

ALE meta-analysis identified clusters of robust gray matter (GM) atrophy in PSP in the bilateral thalamus & midbrain, left anterior-dorsal insula as well as bilateral caudate nucleus. These regions were shown to be functionally associated with language, body perception, somatosensation and emotion processing and are closely coupled with the salience network as well as subcortical regions. Moreover, the regions of consistent atrophy are marked by high density of dopaminergic, serotonergic and cholinergic neurotransmitter receptors.

We showed consistent GM loss in widespread, interconnected brain regions. The functions associated with the atrophied regions resonate well with PSP-specific symptom manifestations. The robust connectivity between the identified regions may implicate a broader network-disturbance contributing to individual PSP symptom-complexes beyond local atrophy.

Introduction

Progressive supranuclear palsy (PSP), also known as Steele-Richardson-Olszewski syndrome, is a rapidly progressing atypical parkinsonian disorder (APD) characterized clinically by parkinsonism, supranuclear gaze palsy, and cognitive impairment (Steele et al., 1964; Williams et al., 2005; Litvan, 1996, 2003; Stamelou et al., 2013). Neuropathologically, PSP is classified as a tauopathy, marked by the accumulation of neurofibrillary tangles in both cortical and subcortical structures (Steele et al., 1964). While midbrain atrophy is a prominent MRI indicator of PSP (Oba et al., 2005; Massey et al., 2013), the involvement of the forebrain remains poorly understood, despite the likelihood that cortical network disruptions contribute to both motor and non-motor impairments (Horwitz and Rowe, 2011; Koros et al., 2016; Stamelou & Höglinger, 2016).

Investigating gray matter (GM) atrophy through structural magnetic resonance imaging (MRI) offers a crucial method for characterizing patterns of degeneration without the need for pre-defined regions of interest or manual measurements (e.g., Whitwell et al., 2011; Lagarde et al., 2013; Shi et al., 2013; Agosta et al., 2010; Focke et al., 2011). Structural MRI studies have linked various subcortical regions to core symptoms of PSP, such as vertical gaze palsy (Kato et al., 2003; Buch et al., 2022) and postural instability (Zwergal et al., 2011). Additionally, there is evidence of significant forebrain atrophy, particularly in fronto-temporal, prefrontal regions, and the basal ganglia (Cordato et al., 2002; Caso et al., 2016; Scotton et al., 2023; Padovani et al., 2005).

Despite numerous studies, findings on forebrain atrophy in PSP remain highly heterogeneous, and a coherent pattern has yet to be established. This variability reflects broader concerns within neuroimaging, often discussed under the umbrella of the "replication crisis". While voxel-based morphometry (VBM) is generally less affected by analytical flexibility—owing to the limited number of standardized processing pipelines (cf. Antonopolous et al., 2023)—small sample sizes and cohort heterogeneity are likely the primary sources of inconsistency (Keller & Roberts, 2008; Focke et al., 2011). Although individual small-N studies offer limited insights, combining their results through meta-analysis provides a robust strategy for identifying brain regions that consistently show atrophy across different samples, settings, and analytic approaches. The most established tool for neuroimaging meta-analysis is Anatomical Likelihood Estimation (ALE), a well-validated method for statistically integrating reported results from the neuroimaging literature (Eickhoff et al., 2009; Eickhoff et al., 2012;

Turkeltaub et al., 2002). ALE thus enables the assessment of spatial convergence among diverse findings, helping to identify regions with consistent evidence of GM loss.

In this work, ALE is employed to identify convergence across the literature on PSP-related atrophy. The regions identified are then characterized in terms of their functional roles, connectivity, and neurotransmitter receptor profiles to provide a comprehensive assessment of potential network-level disruptions. Functional characterization is achieved by identifying experimental tasks and paradigms that are more likely than chance to activate these regions, while functional connectivity is mapped using statistically significant co-activation patterns. Finally, spatial correlation analyses with multiple in-vivo neurotransmitter receptor maps allow for linking the pattern of PSP-related atrophy to specific molecular characteristics.

Methods

We followed an adapted protocol based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P, Moher et al., 2015) and established best-practice guidelines for neuroimaging meta-analyses (Müller et al., 2017; Tahmasian et al., 2019). Systematic searches were conducted on PubMed and Google Scholar for morphometric analyses of PSP from January 2000 to June 2022 using the following key words: ("voxel", "voxel-based", "voxel-wise", "morphometry", "VBM"), ("gray matter atrophy", "atrophy") and ("PSP", "Progressive Supranuclear Palsy", "Steele–Richardson–Olszewski Syndrome"). The reference lists of identified papers as well as pertinent review articles were searched for additional studies. All identified papers were initially screened, and potentially eligible studies were evaluated against the inclusion and exclusion criteria detailed below. Screening was conducted by one author (SKQ) and independently verified by another (ACH); any disagreements were resolved through discussion with the senior author.

Peer-reviewed English-language studies were included if they met the following criteria:
(1) voxel-based morphometry of GM differences between PSP with control subjects. The control cohort could either represent healthy age-matched subjects (CON) or patients with other movement disorders, e.g., IPD. The number of primary studies comparing PSP with healthy controls, IPD and APD individually, was too low for an approach using separate meta-analyses. Consequently, we performed two analyses, the main meta-analysis pooling across all studies testing PSP-related atrophy, irrespective of the control group, and a supplementary analysis

only testing for convergence in the smaller set of studies comparing PSP to CON (for results see supplementary material).

(2) used established diagnostic criteria (e.g. NINDS, MDS) with PSP-specific symptoms such as oculomotor dysfunction, postural instability, akinesia, and/or cognitive dysfunction. As definite PSP can only be diagnosed upon autopsy, possible and probable PSP were considered sufficient.

(3) results were obtained from a whole-brain analysis without additional asking or focus on a region-of-interest and were reported as stereotaxic coordinates in a standard reference space, i.e., either Talairach or Montreal Neurological Institute (MNI) spatial.

(4) Studies were **excluded** if data on coordinates or reference space could not be obtained (even after contacting authors), if they reported on the same sample as other articles (in order to prevent undue influence of a single cohort) or if they represented clinical case-reports.

ALE Meta-analysis

For the ALE analysis, established in-house scripts were used. First, MNI coordinates of regions with significantly different GM measures were extracted from each study meeting the selection criteria. When coordinates were given in Talairach space they were transformed into MNI space (Lancaster et al., 2007). Then, all coordinates were modeled using a 3D Gaussian probability distribution to reflect the associated spatial uncertainty (Eickhoff et al., 2009, 2012). The ALE map, representing the per-voxel likelihood of finding significant GM-atrophy in the PSP literature, was then constructed by first pooling probabilities within each experiment using a max-operator (non-additivity within sample, cf. Turkeltaub et al., 2012) and then computing the union across the different experiments. Significance was assessed against a null-hypothesis of spatial independence (Eickhoff et al., 2012, 2016), corrected for multiple comparisons at the cluster level using threshold-free cluster enhancement (TFCE) for a family-wise error (FWE) rate of $p \leq 0.05$ (Frahm et al., 2022).

Functional Decoding and Connectivity Modeling

Functional decoding of the resulting clusters (Rottschy et al., 2013; Genon et al., 2018) was carried out to infer the mental processes typically associated with each region. This was achieved by identifying the types of task-based fMRI studies that are more likely than chance to activate the respective areas. For this purpose, we used the BrainMap database, which includes a structured ontology detailing behavioral domains and paradigm classes linked to

each experiment (Fox et al., 2014; Laird et al., 2009; http://www.brainmap.org/scribe). First, all experiments in BrainMap that featured at least one focus of activation within the respective region were identified. Subsequently, for each behavioral domain and paradigm class category, we tested, whether the respective taxonomic labels were significantly over-represented in the retrieved set relative to the database given the density of foci within the region of interest (cf. Cortese et al., 2016, Muller et al., 2013).

To assess which brain regions are functionally connected with the identified clusters, we used the same experiments from BrainMap retrieved for functional decoding, i.e., those that feature at least one activation within the respective cluster. Rather than performing inference on their taxonomic labels, Meta-Analytic Connectivity Modelling (MACM) was performed to investigate for significant convergence of co-activations. For MACM, convergence of activation foci reported by the respective experiments is established with an ALE approach as described above. Evidently, the highest convergence will be found in the region of interest used to filter BrainMap. Any significant convergence outside the seed, however, indicates a significant co-activation pattern, i.e., areas that become activated whenever the seed region is activated and therefore functional connectivity (cf. Reid et al., 2017).

Relationship between Receptor Density and Atrophy

To relate GM alterations to molecular information on neurotransmitter systems, we performed spatial correlation analyses with positron emission tomography (PET)–derived estimates of several receptor/transporter systems such as using the JuSpace toolbox (https://github.com/juryxy/JuSpace). The main idea of this approach is to overcome the limitation of reporting mere differences in structure and test whether MRI-derived information is spatially structured in a way that reflects the distribution of specific receptor types. Hence we assessed to what degree PSP-related atrophy patterns match dopaminergic (dopamine D2; dopamine transporter: DAT, dopamine synthesis capacity: FDOPA), serotonergic (serotonin 5-hydroxytryptamine receptor subtypes 1a, 1b, 2a and 4: 5-HT1a, 5-HT1b, 5-HT2a, 5-HT4; serotonin transporter: SERT), cannabinoid (cannabinoid receptor type 1: CB1), noradrenergic (noradrenaline transporter: NAT), cholinergic (vesicular acetylcholine transporter: VAChT), μ-opioid, gamma-aminobutric acid (GABAergic: GABAa) and glutamate (metabotropic glutamate receptor 5: mGluR5) neurotransmission. This was evaluated conducting a cross-modal correlation of MRI-based measures with PET derived receptor estimates using spin-test derived null-distributions to account for spatial autocorrelation (Dukart et al. 2020).

Results

Systematic Literature Searches

We identified 1.225 potentially eligible articles in the database searches (Suppl. Fig. 1, Suppl. Table 1). Following the removal of 493 duplicate articles, 732 articles were screened at title/abstract level and 42 at full text. 20 papers met the inclusion criteria, without any overlap in the assessed cohorts. 333 PSP patients were included in the studies investigated in this work.

ALE Meta-Analysis

The ALE analysis (20 papers, 27 experiments, including 333 PSP patients) identified several clusters, showing significant GM atrophy in PSP compared to all control studies ($p \leq 0.05$, TFCE-corrected, Fig. 1; Table 1). Clusters were centered upon the following areas: (1) bilateral thalamus & midbrain, (2) left insula extending onto the frontal operculum, (3) left caudate nucleus, (4) right caudate nucleus.

[Insert Figure 1 about here]

[Insert Table 1 about here]

A supplementary ALE analysis (19 papers, 19 experiments, including 323 PSP patients) identified one additional cluster, showing significant GM atrophy in PSP compared to studies including only CON ($p \leq 0.05$, TFCE-corrected, Suppl. Fig. 2). In addition to the clusters already mentioned, another cluster was found, centered upon the right precentral gyrus (x=46, y=16, z=4; Suppl. Table 2).

Functional Decoding and Connectivity Modeling

Functional decoding using the BrainMap database revealed that regions showing robust evidence for PSP-related atrophy were mainly associated with domains related to language, body perception/interoception, somatosensation, cognitive processes and emotion (Suppl. Fig. 4 A-D): In detail, the thalamic regions were associated to cognitive aspects of emotions (negative emotions/punishment, positive emotions/reward) as well as interoception, especially pain monitoring. The region of atrophy in the left insular cortex was related to cognitive aspects

of language semantics/speech, word generation and perception of taste, as well as pain monitoring. The PSP-related atrophy in left and right caudate was mapped to domains related to emotions (positive emotions/gain/reward) and cognitive aspects of reasoning.

MACM analysis of significant co-activation patterns indicated functional connectivity of the atrophied regions with frontal regions, the bilateral insula, bilateral caudate nuclei, thalamus and midbrain, putamen and globus pallidus and claustral parts (Conjunction analysis, Fig. 2).

[Insert Figure 2 about here]

In particular, the bilateral thalamus and midbrain (Cluster 1; **Fig. 3 A)** were shown to be functionally connected with the superior frontal gyrus and paracingulate gyrus. The connectivity pattern for the left insula (Cluster 2, **Fig. 3 B)** entailed large bilateral clusters in caudate nucleus (bridges/medial), globus pallidus and putamen. Connectivity of the left caudate nucleus (Cluster 3, **Fig. 3 C)** was found mainly with the putamen, while the right caudate (Cluster 4, **Fig. 3 D)** was co-activated with the globus pallidus and the putamen.

[Insert Figure 3 about here]

In order to infer networks of functionally coupled regions across the identified atrophied regions, we used the Yeo atlas of cortical parcellations (Figure 4; Yeo et al., 2011). This additional investigation revealed widespread connections of all clusters found with the salience network in particular (Fig. 5); besides connections of the insula to temporal parietal circuitries (N17), as well as networks involved in control (N12; N13), sensorimotor activity (N3; N4), default mode (N14), and attention (N6) the strongest connections of the insula (Fig 5A) were confined to the salience network (N7; N8). Also, for the MACM results of thalamus & midbrain Yeo maps revealed connections to regions associated to the salience network (N7; N8; Fig. 5B), as well as the limbic (N9) and default network (N14). For bilateral caudate nuclei (Fig. 5C), connections were also mostly concentrated on the salience network (N7; N8; Yeo et al., 2011) as well as the limbic system (N10).

[Insert Figure 4 about here]

Relationship to Receptor Density Patterns

GM alterations in PSP were significantly associated with spatial distribution of dopaminergic neurotransmitter systems in healthy cohorts (Suppl. Fig. 3, D2: rs=0.33, $p<.001$; DAT: rs=0.49, $p<.001$). That is, the higher the availability of mentioned receptor/transporter in healthy subjects, the more likely differences between PSP and control groups were found. Further, GM alterations were significantly correlated with serotonergic, cholinergic, opioid and GABAergic neurotransmitter systems: SERT: rs=0.49, $p<.001$; VAChT: rs=0.46, $p<.001$; 5-HT2a: rs=-0.21, $p=.023$; μ-opioid: rs=0.54, $p<.001$, GABAa: rs=-0.40, $p<.001$). For GABAa and 5-HT2a, correlations were negatively directed, meaning the lower the availability of GABAa and 5-HT2a receptors in healthy, the less likely differences between PSP and control groups were found in the original studies.

Discussion

The current study provides a comprehensive investigation of consistent atrophy patterns in PSP, their functional involvement, functional connectivity as well as their neurotransmitter profiles. Consistent GM atrophy in PSP in the bilateral thalamus and midbrain, left insular cortex extending onto the frontal operculum, bilateral caudate nucleus was revealed by whole brain ALE meta-analysis on VBM studies. These regions were shown to be involved in tasks tapping into language, body perception, somatosensation and emotion processing and strongly interconnected with subcortical regions and the salience network. Finally, regions showing consistent atrophy are associated with high receptor density of dopaminergic and cholinergic receptors. Overall, our results provide a robust delineation and detailed characterization of PSP related atrophy, which resonates well with the clinical image of this disorder as well as providing new insights into a potentially key pathophysiological role for a broader network centered on the anterior insula.

Given that the current meta-analysis can only summarize the existent literature, we obviously had to rely on the diagnostic criteria employed in the primary investigations. Considering the challenge to differentiate PSP from other atypical parkinson syndromes, misdiagnosed cases may thus not be ruled out. In order to increase the power of our analysis, the pool of control studies consists of groups of various diseases as well as healthy controls. While the supplementary analysis corroborated our primary findings, we would be careful to not suggest specificity or (differential) diagnostic value. Finally, it may be assumed that analytic flexibility, i.e., different VBM methodologies, may influence the results obtained in the primary studies, though we would argue that pooling across these is actually one of the core strengths

of neuroimaging meta-analyses and the obtained results indicate findings that are robust to methodological variations.

Cortical Atrophy, the Insula and the Salience Network

PSP has been repeatedly studied using voxel-based morphometry, albeit with ambiguous results (Brenneis et al., 2004; Quattrone et al., 2018). In addition, we note a pattern in the respective discussions to focus on a few key findings, trying to explain characteristic symptoms, such as vertical gaze palsy or the backwards falls. Focusing on salient regions in the presentation of individual studies, however, may lead to a self-reinforcing bias. As an example, our quantitative synthesis of the available literature did not reveal any robust evidence for GM loss in the cerebellum, even though this has previously been discussed in the context of saccade abnormalities (Lehericy et al., 2010; Boxer et al., 2006). Conversely, we did observe consistent atrophy in several forebrain regions that were not only connected to each other but also to a key circuit for higher-order control, i.e. the salience network. A key finding in this context is the consistent atrophy of the anterior insular, a region that has yet received little attention in the context of PSP, even though it has commonly been implicated in other neurodegenerative disorders (Fathy et al., 2020; Bennaroch, 2019) and insula dysfunction has been related to non-motor clinical symptoms in PSP (Pan et al., 2012; Colosimo et al., 2010). The insula is a heterogeneous structure harboring not only sensorimotor, visceral / autonomic and nocioceptive processes but also affective and cognitive functions. These are supported by a highly differentiated functional topography (Glasser et al., 2016). Interestingly, though, it is the anterior dorsal insula, i.e., the atrophied region that is also strongly connected to the other clusters emerging from our meta-analysis, which represents the conflux of these different functional domains (Kurth et al., 2010). Consequently, it seems that the "hub-zone" of the insula (Mazzola et al., 2018) that as a part of the saline network controls widespread connections with cortical and subcortical structures (Uddin et al., 2017; Namkung et al., 2017) may be particularly disrupted in PSP. This perspective is corroborated by the strong co-activation patterns of the anterior insular cluster with all of the other regions showing convergent atrophy in PSP placing it in a strategic position in the ensuing network. As local degeneration through PSP pathology will inevitably lead to disruption of the interconnected networks, we would suggest that the salience network and in particular the insula may play a critical role in the development of the PSP symptom complex. This view is not only supported by previous work (e.g. Illán-Gala et al., 2022; Whitwell et al., 2021; Boxer et al., 2006) but also

relates well to the functions associated with the atrophied regions and the psychopathology of PSP. We would support the view of human neural networks being selectively vulnerable to certain neurodegenerative diseases (Seeley et al., 2009). Thus, we propose that disturbed large-scale circuitry centered on the anterior-dorsal insula may play a bigger role in the development of PSP related symptoms than previously thought.

The Caudate Nucleus

We observed significant convergence of atrophy in the bilateral caudate nucleus, a structure involved in planning the execution of movement, learning, memory, reward, motivation and emotion (Driscoll et al., 2022). Various studies implied an important role of this structure in the development of motor deficits (Cordato et al., 2005), like impairment in the programming of postural adjustments (Palmisano et al., 2020) and maintenance of balance (Zwergal et al., 2011). The caudate has also been postulated as the central driver of postural instability and backward falls as a key symptom in PSP (Jacobs et al., 2009, MacKinnon et al., 2007; Rosenberg-Katz et al., 2013). As part of the basal ganglia there is a strong connection with the cortex, thalamus, and brainstem, which further underlines a relevant role in movement initiation and motor control (Arnulfo et al., 2018, Palmisano et al., 2020, Pozzi et al., 2019, Takakusaki, 2017). Specifically in PSP, there is evidence for reduced functional connectivity between the caudate and thalamus, the anterior cingulate, and pre-supplementary motor area (Piatella et al., 2014). Yet, like for the insula, the functional heterogeneity of the human caudate nucleus needs to be considered. While the ventral striatum and hence caudate is mainly involved in affective processing, the anterior dorsal aspects are strongly involved in cognitive tasks and the more posterior aspects in motor functions (Liu et al., 2021). Here, it needs to be noted that compared to the maps found by Liu et al., 2021, the clusters we found for the caudate nuclei were mostly located in dorsal parts, hinting towards impairment in higher cognitive modalities, such as goal-directed behavior (Mucci et al., 2015). Obviously, the presence of (only) a relatively small cluster of significant convergence in a topographically structured, heterogeneous structure poses an interesting question that would need to be addressed by a larger cohort of neuropsychologically well characterized PSP patients: Is caudate atrophy spatially focused and hence only related to a subset of the psychopathological presentation? Or does the convergence represent just the tip of the iceberg with more diffuse affection of the caudate contributing to several aspects of PSP pathology?

Bilateral Thalamus and Midbrain

The thalamus and midbrain are functionally connected to motor and cognitive circuitries. Impairment in these regions have been associated with various PSP-related symptoms (i.e. postural instability, supranuclear gaze palsy as well as cognitive impairments; Zwergal et al., 2011; Brown et al., 2010; Warren et al., 2005; Kato et al, 2003; Messina et al., 2010). Especially imbalance and falls (Zwergal et al., 2011) as well as cognitive symptoms and behavioral changes (Cordato et al., 2005; Gerstenecker et al., 2013). Based on these studies and our functional decoding analysis, these structures may thus mediate the so-called subcortical dementia in PSP (Millar et al., 2006; Whitwell et al., 2011; Piatella et al., 2015). With respect to the molecular pathophysiology, it should be noted that the thalamus and midbrain belong to the core structures of tau deposition (Steele, et al, 1964; Teune et al., 2010). Taken together, thalamic and midbrain atrophy, likely related to the strong and early tau-deposition may combine with the affection of the caudate nucleus to form the basis of the cognitive and behavioral pathologies in PSP patients.

Linking Systemic and Molecular Aspects

Complementing these system-level observations, we found a positive relationship between the likelihood of GM loss and the dopaminergic (D2 and DAT), serotonergic (SERT), and cholinergic (VAChT) system. Of note, Parkinsonian symptoms are linked to and treated by effects on dopamine receptors (Hisahara & Shimohama, 2011; Constantinescu et al., 2007). But while decreased DAT receptors have been shown in PSP and related to nigrostriatal degeneration (Plotkin et al., 2005; Im et al., 2006), PSP is actually known for its poor response to dopaminergic medication (Murphy et al., 2008). There is thus a discrepancy between degeneration patterns and clinical effects, suggesting additional mechanisms compared to IPD. This would fit with the larger variability of PSP symptoms, which we would propose to emerge via atrophy of regions with strong serotoninergic and cholinergic innervation. Disturbances in the serotonin system have long been linked to mood disorders (Moncrieff, 2022) and atrophy of regions high in serotonin transporter density may thus contribute to affective symptoms as well as disruptions of sleep-wake-cycle (Kim et al., 2013; Roselli et al., 2010). In turn, acetylcholine is involved in a wide range of functions but we would highlight its critical role in (the modulation of) attention via the nicotinic acetylcholine receptor, which aligns well with the potential disruption of the saliency network as a mechanism for cognitive dysfunction. In this context, it is also noteworthy that striatal VAChT reduction was suggested as a specific neurochemical imaging marker for PSP (Suzuki et al., 2002). Taken together, it stands to reason

that the heterogeneous range of symptoms in PSP may be attributable to disruption of not only dopaminergic but also serotoninergic and cholinergic circuits.

Conclusion

Overall, the present work provides robust evidence for PSP-related atrophy in the bilateral thalamus, midbrain and caudate as well as the left insular cortex. Activation and connectivity patterns of these regions, including their connection to the salience network, provides a plausible basis for the heterogeneous motor and in particular non-motor symptoms in PSP, including disruptions of higher-order control functions, affective and cognitive processing. This picture is corroborated by multi-scale integration showing that in addition to the dopaminergic system, also serotonergic and cholinergic networks may be affected by the pattern of PSP-related atrophy. In summary, our work corroborates the view of wider brain network disruption in PSP and points to a particularly critical role of insular (dys-) function.

Declarations

Funding
None.

Conflicts of interest/Competing interests
The authors declare that they have no conflict of interest.

Ethics approval
Ethics approval Ethical approval will not be required because this study will retrieve and synthesise data from already published studies.

Author's contributions

SKQ was involved in organization and execution of the research project, execution of statistical analysis and writing of the first draft.

SBE was involved in design and execution of statistical analysis and review and critique on the manuscript.

ACH was involved in execution of the research project and review and critique on the manuscript.

AS was involved in review and critique on statistical analysis and review and critique on the manuscript.

JC was involved in execution of the research project, review and critique on statistical analysis and review and critique on the manuscript.

CRE was involved in conception, organization and execution of the research project, design and execution of statistical analysis and writing of the first draft.

Acknowledgements
None.

References

[1] Steele, J. C., Richardson, J. C., & Olszewski, J. (1964). Progressive supranuclear palsy: a heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. Archives of neurology, 10(4), 333-359.

[2] Williams DR, de Silva R, Paviour DC, et al (2005) Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain 128(6): 1247–1258.

[3] Litvan, I., Agid, Y., Calne, D., Campbell, G., Dubois, B., Duvoisin, R. C., ... & Zee, D. S. (1996). Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology, 47(1), 1-9.

[4] Litvan, I. (2003) Update on epidemiological aspects of progressive supranuclear palsy. Movement Disorders 18(Suppl. 6): 43–50.

[5] Stamelou, M., & Hoeglinger, G. U. (2013). Atypical parkinsonism: an update. Current Opinion in Neurology, 26(4), 401-405.

[6] Morris, H. R., Gibb, G., Katzenschlager, R., Wood, N. W., Hanger, D. P., Strand, C., ... & Revesz, T. (2002). Pathological, clinical and genetic heterogeneity in progressive supranuclear palsy. Brain, 125(5), 969-975.

[7] McFarland NR (2016) Diagnostic approach to atypical parkinsonian syndromes. CONTINUUM: Lifelong Learning in Neurology 22(4 Movement Disorders): 1117.

[8] Horwitz, B., & Rowe, J. B. (2011). Functional biomarkers for neurodegenerative disorders based on the network paradigm. Progress in neurobiology, 95(4), 505-509.

[9] Koros, C., & Stamelou, M. (2016). Interventions in progressive supranuclear palsy. Parkinsonism & Related Disorders, 22, S93-S95.

[10] Stamelou, M., & Höglinger, G. (2016). A review of treatment options for progressive supranuclear palsy. CNS drugs, 30, 629-636.

[11] Whitwell, J. L., Avula, R., Master, A., Vemuri, P., Senjem, M. L., Jones, D. T., ... & Josephs, K. A. (2011). Disrupted thalamocortical connectivity in PSP: a resting-state fMRI, DTI, and VBM study. Parkinsonism & related disorders, 17(8), 599-605.

[12] Lagarde, J., Valabrègue, R., Corvol, J. C., Pineau, F., Le Ber, I., Vidailhet, M., ... & Levy, R. (2013). Are frontal cognitive and atrophy patterns different in PSP and bvFTD? A comparative neuropsychological and VBM study. PloS one, 8(11), e80353.

[13] Shi, H. C., Zhong, J. G., Pan, P. L., Xiao, P. R., Shen, Y., Wu, L. J., ... & Li, H. Y. (2013). Gray matter atrophy in progressive supranuclear palsy: meta-analysis of voxel-based morphometry studies. Neurological Sciences, 34, 1049-1055.

[14] Padovani, A., Borroni, B., Brambati, S. M., Agosti, C., Broli, M., Alonso, R., ... & Perani, D. (2006). Diffusion tensor imaging and voxel based morphometry study in early progressive supranuclear palsy. Journal of Neurology, Neurosurgery & Psychiatry, 77(4), 457-463.

[15] Antonopoulos, G., More, S., Raimondo, F., Eickhoff, S. B., Hoffstaedter, F., & Patil, K. R. (2023). A systematic comparison of VBM pipelines and their application to age prediction. BioRxiv, 2023-01.

[16] Brenneis, C., Seppi, K., Schocke, M., Benke, T., Wenning, G. K., & Poewe, W. (2004). Voxel based morphometry reveals a distinct pattern of frontal atrophy in progressive supranuclear palsy. Journal of Neurology, Neurosurgery & Psychiatry, 75(2), 246-249.

[17] Price, S., Paviour, D., Scahill, R., Stevens, J., Rossor, M., Lees, A., & Fox, N. (2004). Voxel-based morphometry detects patterns of atrophy that help differentiate progressive supranuclear palsy and Parkinson's disease. Neuroimage, 23(2), 663-669.

[18] Agosta, F., Kostić, V. S., Galantucci, S., Mesaroš, Š., Svetel, M., Pagani, E., ... & Filippi, M. (2010). The in vivo distribution of brain tissue loss in Richardson's syndrome and PSP-parkinsonism: A VBM-DARTEL study. European Journal of Neuroscience, 32(4), 640-647.

[19] Focke NK, Helms G, Pantel PM, et al (2011) Differentiation of typical and atypical Parkinson syndromes by quantitative MR imaging. American journal of neuroradiology 32(11): 2087–2092.

[20] Oba H, Yagishita A, Terada H et al (2005) New and reliable MRI diagnosis for progressive supranuclear palsy. Neurology 64: 2050–5.

[21] Massey LA, Micallef C, Paviour DC, et al (2012) Conventional magnetic resonance imaging in confirmed progressive supranuclear palsy and multiple system atrophy. Movement Disorders 27(14): 1754–1762.

[22] Kato, N., Arai, K., & Hattori, T. (2003). Study of the rostral midbrain atrophy in progressive supranuclear palsy. Journal of the neurological sciences, 210(1-2), 57-60.

[23] Buch, K. A., Bouffard, M. A., Kardon, R. H., Wills, A. M. A., Privitera, C. M., Sharma, M., ... & Mollan, S. (2022). Clinical Correlation Between Vertical Gaze Palsy and Midbrain Volume in Progressive Supranuclear Palsy. Journal of Neuro-Ophthalmology, 42(2), 246-250.

[24] Zwergal, A., La Fougère, C., Lorenzl, S., Rominger, A., Xiong, G., Deutschenbaur, L., ... & Jahn, K. (2011). Postural imbalance and falls in PSP correlate with functional pathology of the thalamus. Neurology, 77(2), 101-109.

[25] Cordato, N. J., Pantelis, C., Halliday, G. M., Velakoulis, D., Wood, S. J., Stuart, G. W., ... & Morris, J. G. L. (2002). Frontal atrophy correlates with behavioural changes in progressive supranuclear palsy. Brain, 125(4), 789-800.

[26] Caso, F., Agosta, F., Volonté, M. A., Ferraro, P. M., Tiraboschi, P., Copetti, M., ... & Filippi, M. (2016). Cognitive impairment in progressive supranuclear palsy-Richardson's syndrome is related to white matter damage. Parkinsonism & Related Disorders, 31, 65-71.

[27] Scotton, W. J., Shand, C., Todd, E., Bocchetta, M., Cash, D. M., VandeVrede, L., ... & Wijeratne, P. A. (2023). Uncovering spatiotemporal patterns of atrophy in progressive supranuclear palsy using unsupervised machine learning. Brain Communications, 5(2), fcad048.

[28] Whitwell, J. L., Jack Jr, C. R., Parisi, J. E., Gunter, J. L., Weigand, S. D., Boeve, B. F., ... & Josephs, K. A. (2013). Midbrain atrophy is not a biomarker of progressive supranuclear palsy pathology. European journal of neurology, 20(10), 1417-1422.

[29] Albrecht, F., Bisenius, S., Neumann, J., Whitwell, J., & Schroeter, M. L. (2019). Atrophy in midbrain & cerebral/cerebellar pedunculi is characteristic for progressive supranuclear palsy–A double-validation whole-brain meta-analysis. NeuroImage: Clinical, 22, 101722.

[30] Boxer, A. L., Geschwind, M. D., Belfor, N., Gorno-Tempini, M. L., Schauer, G. F., Miller, B. L., ... & Rosen, H. J. (2006). Patterns of brain atrophy that differentiate corticobasal degeneration syndrome from progressive supranuclear palsy. Archives of neurology, 63(1), 81-86.

[31] Lehéricy, S., Hartmann, A., Lannuzel, A., Galanaud, D., Delmaire, C., Bienaimée, M. J., ... & Vidailhet, M. (2010). Magnetic resonance imaging lesion pattern in Guadeloupean parkinsonism is distinct from progressive supranuclear palsy. Brain, 133(8), 2410-2425.

[32] Whitwell, J. L., Höglinger, G. U., Antonini, A., Bordelon, Y., Boxer, A. L., Colosimo, C., ... & Movement Disorder Society-endorsed PSP Study Group. (2017). Radiological biomarkers for diagnosis in PSP: where are we and where do we need to be?. Movement Disorders, 32(7), 955-971.

[33] Sako, W., Murakami, N., Izumi, Y., & Kaji, R. (2017). Usefulness of the superior cerebellar peduncle for differential diagnosis of progressive supranuclear palsy: a meta-analysis. Journal of the Neurological Sciences, 378, 153-157.

[34] Alster, P., Madetko, N., Koziorowski, D., & Friedman, A. (2020). Progressive supranuclear palsy—parkinsonism predominant (PSP-P)—a clinical challenge at the boundaries of psp and Parkinson's disease (PD). Frontiers in Neurology, 11, 180.

[35] Debnath, M., Dey, S., Sreenivas, N., Pal, P. K., & Yadav, R. (2022). Genetic and Epigenetic Constructs of Progressive Supranuclear Palsy. Annals of Neurosciences, 29(2-3), 177-188.

[36] Bakar, Z. H. A., Kato, T., Yanagisawa, D., Bellier, J. P., Mukaisho, K. I., & Tooyama, I. (2021). Immunohistochemical study of mitochondrial ferritin in the midbrain of patients with progressive supranuclear palsy. Acta Histochemica et Cytochemica, 54(3), 97-104.

[37] Whiteside, D. J., Jones, P. S., Ghosh, B. C., Coyle-Gilchrist, I., Gerhard, A., Hu, M. T., ... & Rittman, T. (2021). Altered network stability in progressive supranuclear palsy. Neurobiology of Aging, 107, 109-117.

[38] Ota, M., Sato, N., Takahashi, Y., Shigemoto, Y., Kimura, Y., Nakaya, M., ... & Matsuda, H. (2023). Correlation between the regional brain volume and glymphatic system activity in progressive supranuclear palsy. Dementia and Geriatric Cognitive Disorders, 1-1.

[39] Pyatigorskaya, N., Sanz-Morère, C. B., Gaurav, R., Biondetti, E., Valabregue, R., Santin, M., ... & Lehéricy, S. (2020). Iron imaging as a diagnostic tool for Parkinson's disease: a systematic review and meta-analysis. Frontiers in Neurology, 11, 366.

[40] Eickhoff, S. B., Laird, A. R., Grefkes, C., Wang, L. E., Zilles, K., & Fox, P. T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. Human brain mapping, 30(9), 2907-2926.

[41] Eickhoff, S. B., Bzdok, D., Laird, A. R., Kurth, F., & Fox, P. T. (2012). Activation likelihood estimation meta-analysis revisited. Neuroimage, 59(3), 2349-2361.

[42] Turkeltaub, P. E., Eden, G. F., Jones, K. M., & Zeffiro, T. A. (2002). Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage, 16(3), 765-780.

[43] Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., ... & Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews, 4(1), 1-9.

[44] Müller, V. I., Cieslik, E. C., Serbanescu, I., Laird, A. R., Fox, P. T., & Eickhoff, S. B. (2017). Altered brain activity in unipolar depression revisited: meta-analyses of neuroimaging studies. JAMA psychiatry, 74(1), 47-55.

[45] Tahmasian, M., Sepehry, A. A., Samea, F., Khodadadifar, T., Soltaninejad, Z., Javaheripour, N., ... & Eickhoff, C. R. (2019). Practical recommendations to conduct a neuroimaging meta-analysis for neuropsychiatric disorders. Human brain mapping, 40(17), 5142-5154.

[46] Lancaster, J. L., Tordesillas-Gutiérrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., ... & Fox, P. T. (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. Human brain mapping, 28(11), 1194-1205.

[47] Frahm, L., Cieslik, E. C., Hoffstaedter, F., Satterthwaite, T. D., Fox, P. T., Langner, R., & Eickhoff, S. B. (2022). Evaluation of thresholding methods for activation likelihood estimation meta-analysis via large-scale simulations. Human brain mapping, 43(13), 3987-3997.

[48] Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage, 25(4), 1325-1335.

[49] Rottschy, C., Caspers, S., Roski, C., Reetz, K., Dogan, I., Schulz, J. B., ... & Eickhoff, S. B. (2013). Differentiated parietal connectivity of frontal regions for “what” and “where” memory. Brain Structure and function, 218, 1551-1567.

[50] Genon, S., Reid, A., Li, H., Fan, L., Müller, V. I., Cieslik, E. C., ... & Eickhoff, S. B. (2018). The heterogeneity of the left dorsal premotor cortex evidenced by multimodal connectivity-based parcellation and functional characterization. Neuroimage, 170, 400-411.

[51] Turner, J. A., & Laird, A. R. (2012). The cognitive paradigm ontology: design and application. Neuroinformatics, 10, 57-66.

[52] Laird, A. R., Eickhoff, S. B., Kurth, F., Fox, P. M., Uecker, A. M., Turner, J. A., ... & Fox, P. T. (2009). ALE meta-analysis workflows via the brainmap database: progress towards a probabilistic functional brain atlas. Frontiers in neuroinformatics, 23.

[53] Fox, P. T., Laird, A. R., Fox, S. P., Fox, P. M., Uecker, A. M., Crank, M., ... & Lancaster, J. L. (2005). BrainMap taxonomy of experimental design: description and evaluation. Human brain mapping, 25(1), 185-198.

[54] Caspers, J., Zilles, K., Amunts, K., Laird, A. R., Fox, P. T., & Eickhoff, S. B. (2014). Functional characterization and differential coactivation patterns of two cytoarchitectonic visual areas on the human posterior fusiform gyrus. Human brain mapping, 35(6), 2754-2767.

[55] Müller, V. I., Cieslik, E. C., Laird, A. R., Fox, P. T., & Eickhoff, S. B. (2013). Dysregulated left inferior parietal activity in schizophrenia and depression: functional connectivity and characterization. Frontiers in human neuroscience, 7, 268.

[56] Cortese, S., Castellanos, F. X., Eickhoff, C. R., D'Acunto, G., Masi, G., Fox, P. T., ... & Eickhoff, S. B. (2016). Functional decoding and meta-analytic connectivity modeling in adult attention-deficit/hyperactivity disorder. Biological psychiatry, 80(12), 896-904.

[57] Kotkowski, E., Price, L. R., Fox, P. M., Vanasse, T. J., & Fox, P. T. (2018). The hippocampal network model: A transdiagnostic metaconnectomic approach. NeuroImage: Clinical, 18, 115-129.

[58] Eickhoff, S. B., Bzdok, D., Laird, A. R., Roski, C., Caspers, S., Zilles, K., & Fox, P. T. (2011). Co-activation patterns distinguish cortical modules, their connectivity and functional differentiation. Neuroimage, 57(3), 938-949.

[59] Robinson, J. L., Laird, A. R., Sanghera, M. K., Glahn, D. C., Bohannon, B., & Fox, P. T. (2010, January). META-ANALYTIC CONNECTIVITY MODELING (MACM) OF THE HUMAN CAUDATE: EVIDENCE FOR BEHAVIORAL SPECIFICITY. In PSYCHOPHYSIOLOGY (Vol. 47, pp. S91-S91). COMMERCE PLACE, 350 MAIN ST, MALDEN 02148, MA USA: WILEY-BLACKWELL PUBLISHING, INC.

[60] Eickhoff, S. B., Jbabdi, S., Caspers, S., Laird, A. R., Fox, P. T., Zilles, K., & Behrens, T. E. (2010). Anatomical and functional connectivity of cytoarchitectonic areas within the human parietal operculum. Journal of Neuroscience, 30(18), 6409-6421.

[61] Laird, A. R., Eickhoff, S. B., Rottschy, C., Bzdok, D., Ray, K. L., & Fox, P. T. (2013). Networks of task co-activations. Neuroimage, 80, 505-514.

[62] Dukart, J., Jech, R., Ruziska, F., Vyzamal, J., Rullmann, M., Hesse, S., ... & Eickhoff, S. (2020). JuSpace: A Tool for Spatial Correlation Analyses of Functional and Structural Magnetic Resonance Imaging Data With Positron Emission Tomography Derived Receptor Maps. Biological Psychiatry, 87(9), S190.

[63] Thomas Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., ... & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. Journal of neurophysiology, 106(3), 1125-1165.

[64] Quattrone, A., Morelli, M., Nigro, S., Quattrone, A., Vescio, B., Arabia, G., ... & Caracciolo, M. (2018). A new MR imaging index for differentiation of progressive supranuclear palsy-parkinsonism from Parkinson's disease. Parkinsonism & related disorders, 54, 3-8.

[65] Alster, P., Madetko-Alster, N., Migda, B., Nieciecki, M., Koziorowski, D., & Królicki, L. (2022). The Assessment of Subregions in the Frontal Lobe May Be Feasible in the Differential Diagnosis of Progressive Supranuclear Palsy—Parkinsonism Predominant (PSP-P) and Multiple System Atrophy (MSA). Diagnostics, 12(10), 2421.

[66] Quattrone, A., Morelli, M., Williams, D. R., Vescio, B., Arabia, G., Nigro, S., ... & Caracciolo, M. (2016). MR parkinsonism index predicts vertical supranuclear gaze palsy in patients with PSP–parkinsonism. Neurology, 87(12), 1266-1273.

[67] Liakakis, G., Nickel, J., & Seitz, R. (2011). Diversity of the inferior frontal gyrus—a meta-analysis of neuroimaging studies. Behavioural brain research, 225(1), 341-347.

[68] Gogolla, N. (2017). The insular cortex. Current Biology, 27(12), R580-R586.

[69] Illán-Gala, I., Nigro, S., VandeVrede, L., Falgàs, N., Heuer, H. W., Painous, C., ... & Boxer, A. L. (2022). Diagnostic accuracy of magnetic resonance imaging measures of brain atrophy across the spectrum of progressive supranuclear palsy and corticobasal degeneration. JAMA network open, 5(4), e229588-e229588.

[70] Whitwell, J. L., Tosakulwong, N., Clark, H. M., Ali, F., Botha, H., Weigand, S. D., ... & Josephs, K. A. (2021). Diffusion tensor imaging analysis in three progressive supranuclear palsy variants. Journal of Neurology, 268, 3409-3420.

[71] Driscoll, M. E., Bollu, P. C., & Tadi, P. (2022). Neuroanatomy, Nucleus Caudate. StatPearls [Internet].

[72] Cordato, N. J., Duggins, A. J., Halliday, G. M., Morris, J. G., & Pantelis, C. (2005). Clinical deficits correlate with regional cerebral atrophy in progressive supranuclear palsy. Brain, 128(6), 1259-1266.

[73] Palmisano, C., Todisco, M., Marotta, G., Volkmann, J., Pacchetti, C., Frigo, C. A., ... & Isaias, I. U. (2020). Gait initiation in progressive supranuclear palsy: brain metabolic correlates. NeuroImage: Clinical, 28, 102408.

[74] Driscoll, M. E., Bollu, P. C., & Tadi, P. (2021). Neuroanatomy, nucleus caudate. In StatPearls [Internet]. StatPearls Publishing.

[75] Jacobs, J. V., Lou, J. S., Kraakevik, J. A., & Horak, F. B. (2009). The supplementary motor area contributes to the timing of the anticipatory postural adjustment during step initiation in participants with and without Parkinson's disease. Neuroscience, 164(2), 877-885.

[76] MacKinnon, C. D., Bissig, D., Chiusano, J., Miller, E., Rudnick, L., Jager, C., ... & Rogers, M. W. (2007). Preparation of anticipatory postural adjustments prior to stepping. Journal of neurophysiology, 97(6), 4368-4379.

[77] Rosenberg-Katz, K., Herman, T., Jacob, Y., Giladi, N., Hendler, T., & Hausdorff, J. M. (2013). Gray matter atrophy distinguishes between Parkinson disease motor subtypes. Neurology, 80(16), 1476-1484.

[78] Arnulfo, G., Pozzi, N. G., Palmisano, C., Leporini, A., Canessa, A., Brumberg, J., ... & Isaias, I. U. (2018). Phase matters: a role for the subthalamic network during gait. PloS one, 13(6), e0198691.

[79] Pozzi, N. G., Canessa, A., Palmisano, C., Brumberg, J., Steigerwald, F., Reich, M. M., ... & Isaias, I. U. (2019). Freezing of gait in Parkinson's disease reflects a sudden derangement of locomotor network dynamics. Brain, 142(7), 2037-2050.

[80] Takakusaki, K., Takahashi, M., Obara, K., & Chiba, R. (2017). Neural substrates involved in the control of posture. Advanced Robotics, 31(1-2), 2-23.

[81] Piattella, M. C., Tona, F., Bologna, M., Sbardella, E., Formica, A., Petsas, N., ... & Pantano, P. (2015). Disrupted resting-state functional connectivity in progressive supranuclear palsy. American Journal of Neuroradiology, 36(5), 915-921.

[82] Buklina, S. B. (1997). The functional heterogeneity of the human caudate nucleus. Zhurnal Nevrologii i Psikhiatrii Imeni SS Korsakova, 97(3), 7-11.

[83] Monchi, O., Hanganu, A., & Bellec, P. (2016). Markers of cognitive decline in PD: the case for heterogeneity. Parkinsonism & related disorders, 24, 8-14.

[84] Fathy, Y. Y., Hoogers, S. E., Berendse, H. W., van der Werf, Y. D., Visser, P. J., de Jong, F. J., & van de Berg, W. D. (2020). Differential insular cortex sub-regional atrophy in neurodegenerative diseases: a systematic review and meta-analysis. Brain Imaging and Behavior, 14, 2799-2816.

[85] Delgado, M. R., Miller, M. M., Inati, S., & Phelps, E. A. (2005). An fMRI study of reward-related probability learning. Neuroimage, 24(3), 862-873.

[86] Schultz, W. (2017). Reward prediction error. Current Biology, 27(10), R369-R371.

[87] Postle, B. R., & D'Esposito, M. (2003). Spatial working memory activity of the caudate nucleus is sensitive to frame of reference. Cognitive, Affective, & Behavioral Neuroscience, 3(2), 133-144.

[88] Brown, R. G., Lacomblez, L., Landwehrmeyer, B. G., Bak, T., Uttner, I., Dubois, B., ... & NNIPPS Study Group. (2010). Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy. Brain, 133(8), 2382-2393.

[89] Warren, N. M., Piggott, M. A., Perry, E. K., & Burn, D. J. (2005). Cholinergic systems in progressive supranuclear palsy. Brain, 128(2), 239-249.

[90] Kato, N., Arai, K., & Hattori, T. (2003). Study of the rostral midbrain atrophy in progressive supranuclear palsy. Journal of the neurological sciences, 210(1-2), 57-60.

[91] Messina, D., Cerasa, A., Condino, F., Arabia, G., Novellino, F., Nicoletti, G., ... & Quattrone, A. (2011). Patterns of brain atrophy in Parkinson's disease, progressive supranuclear palsy and multiple system atrophy. Parkinsonism & related disorders, 17(3), 172-176.

[92] O'Callaghan, C., Bertoux, M., & Hornberger, M. (2014). Beyond and below the cortex: the contribution of striatal dysfunction to cognition and behaviour in neurodegeneration. Journal of Neurology, Neurosurgery & Psychiatry, 85(4), 371-378.

[93] Gerstenecker, A., Duff, K., Mast, B., Litvan, I., & ENGENE-Psp Study Group. (2013). Behavioral abnormalities in progressive supranuclear palsy. Psychiatry research, 210(3), 1205-1210.

[94] Teune, L. K., Bartels, A. L., de Jong, B. M., Willemsen, A. T., Eshuis, S. A., de Vries, J. J., ... & Leenders, K. L. (2010). Typical cerebral metabolic patterns in neurodegenerative brain diseases. Movement Disorders, 25(14), 2395-2404.

[95] Millar, D., Griffiths, P., Zermansky, A. J., & Burn, D. J. (2006). Characterizing behavioral and cognitive dysexecutive changes in progressive supranuclear palsy. Movement disorders, 21(2), 199-207.

[96] Uddin, L. Q., Nomi, J. S., Hébert-Seropian, B., Ghaziri, J., & Boucher, O. (2017). Structure and function of the human insula. Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society, 34(4), 300.

[97] Nieuwenhuys, R. (2012). Chemoarchitecture of the Brain. Springer Science & Business Media.

[98] Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., ... & Van Essen, D. C. (2016). A multi-modal parcellation of human cerebral cortex. Nature, 536(7615), 171-178.

[99] Benarroch, E. E. (2019). Insular cortex: functional complexity and clinical correlations. Neurology, 93(21), 932-938.

[100] Reid, A. T., Hoffstaedter, F., Gong, G., Laird, A. R., Fox, P., Evans, A. C., ... & Eickhoff, S. B. (2017). A seed-based cross-modal comparison of brain connectivity measures. Brain Structure and Function, 222(3), 1131-1151.

[101] Mazzola, L., Mauguière, F., & Isnard, J. (2019). Functional mapping of the human insula: data from electrical stimulations. Revue neurologique, 175(3), 150-156.

[102] Droutman, V., Read, S. J., & Bechara, A. (2015). Revisiting the role of the insula in addiction. Trends in cognitive sciences, 19(7), 414-420.

[103] Augustine, J. R. (1996). Circuitry and functional aspects of the insular lobe in primates including humans. Brain research reviews, 22(3), 229-244.

[104] Pan, P. L., Song, W., & Shang, H. F. (2012). Voxel-wise meta-analysis of gray matter abnormalities in idiopathic Parkinson's disease. European journal of neurology, 19(2), 199-206.

[105] Colosimo, C., Morgante, L., Antonini, A., Barone, P., Avarello, T. P., Bottacchi, E., ... & Priamo Study Group. (2010). Non-motor symptoms in atypical and secondary parkinsonism: the PRIAMO study. Journal of neurology, 257, 5-14.

[106] Ibanez, A., Gleichgerrcht, E., & Manes, F. (2010). Clinical effects of insular damage in humans. Brain Structure and Function, 214, 397-410.

[107] Shu, L., & Wang, Y. (2014). Highlights in basic autonomic neuroscience: insular cortex injury leads to cardiovascular dysfunction. Autonomic Neuroscience, 185, 1-4.

[108] Kurth, F., Zilles, K., Fox, P. T., Laird, A. R., & Eickhoff, S. B. (2010). A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Structure and Function, 214, 519-534.

[109] Shura, R. D., Hurley, R. A., & Taber, K. H. (2014). Insular cortex: structural and functional neuroanatomy. The Journal of neuropsychiatry and clinical neurosciences, 26(4), iv-282.

[110] Higo, T., Mars, R. B., Boorman, E. D., Buch, E. R., & Rushworth, M. F. (2011). Distributed and causal influence of frontal operculum in task control. Proceedings of the National Academy of Sciences, 108(10), 4230-4235.

[111] Jabbi, M., & Keysers, C. (2008). Inferior frontal gyrus activity triggers anterior insula response to emotional facial expressions. Emotion, 8(6), 775.Poewe W, Wenning G (2002) The differential diagnosis of Parkinson's disease. European journal of neurology 9: 23–30.

[112] Pritchard, T. C., Macaluso, D. A., & Eslinger, P. J. (1999). Taste perception in patients with insular cortex lesions. Behavioral neuroscience, 113(4), 663.

[113] Boisgueheneuc, F. D., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., ... & Dubois, B. (2006). Functions of the left superior frontal gyrus in humans: a lesion study. Brain, 129(12), 3315-3328.

[114] Goldberg, T. E., Straub, R. E., Callicott, J. H., Hariri, A., Mattay, V. S., Bigelow, L., ... & Weinberger, D. R. (2006). The G72/G30 gene complex and cognitive abnormalities in schizophrenia. Neuropsychopharmacology, 31(9), 2022-2032.

[115] Wei, X., Yin, Y., Rong, M., Zhang, J., Wang, L., Wu, Y., ... & Jiang, T. (2017). Paracingulate sulcus asymmetry in the human brain: effects of sex, handedness, and race. Scientific Reports, 7(1), 42033.

[116] Hisahara, S., & Shimohama, S. (2011). Dopamine receptors and Parkinson's disease. International journal of medicinal chemistry, 2011.

[117] Constantinescu, D., Weingärtner, H., & Herrmann, C. (2007). Protein denaturation by ionic liquids and the Hofmeister series: a case study of aqueous solutions of ribonuclease A. Angewandte Chemie International Edition, 46(46), 8887-8889.

[118] Plotkin, M., Amthauer, H., Quill, S., Marzinzik, F., Klostermann, F., Klaffke, S., ... & Kupsch, A. (2005). Imaging of dopamine transporters and D2 receptors in vascular parkinsonism: a report of four cases. Journal of neural transmission, 112, 1355-1361.

[119] Im, J. H., Chung, S. J., Kim, J. S., & Lee, M. C. (2006). Differential patterns of dopamine transporter loss in the basal ganglia of progressive supranuclear palsy and Parkinson's disease: Analysis with [123I] IPT single photon emission computed tomography. Journal of the neurological sciences, 244(1-2), 103-109.

[120] Ruberg, M., Javoy-Agid, F., Hirsch, E., Scatton, B., Lheureux, R., Hauw, J. J., ... & Agid, Y. (1985). Dopaminergic and cholinergic lesions in progressive supranuclear palsy. Annals of neurology, 18(5), 523-529.

[121] Pierot, L., Desnos, C., Blin, J., Raisman, R., Scherman, D., Javoy-Agid, F., ... & Agid, Y. (1988). D1 and D2-type dopamine receptors in patients with Parkinson's disease and progressive supranuclear palsy. Journal of the neurological sciences, 86(2-3), 291-306.

[122] Murphy, K. E., Karaconji, T., Hardman, C. D., & Halliday, G. M. (2008). Excessive dopamine neuron loss in progressive supranuclear palsy. Movement disorders: official journal of the Movement Disorder Society, 23(4), 607-610.

[123] Moncrieff, J., Cooper, R. E., Stockmann, T., Amendola, S., Hengartner, M. P., & Horowitz, M. A. (2022). The serotonin theory of depression: a systematic umbrella review of the evidence. Molecular psychiatry, 1-14.

[124] Lanciego, J. L., Luquin, N., & Obeso, J. A. (2012). Functional neuroanatomy of the basal ganglia. Cold Spring Harbor perspectives in medicine, 2(12), a009621.

[125] Kim, J. J., Bridle, B. W., Ghia, J. E., Wang, H., Syed, S. N., Manocha, M. M., ... & Khan, W. I. (2013). Targeted inhibition of serotonin type 7 (5-HT7) receptor function modulates immune responses and reduces the severity of intestinal inflammation. The Journal of Immunology, 190(9), 4795-4804.

[126] Roselli, F., Pisciotta, N. M., Pennelli, M., Aniello, M. S., Gigante, A., De Caro, M. F., ... & Rubini, G. (2010). Midbrain SERT in degenerative parkinsonisms: a 123I-FP-CIT SPECT study. Movement Disorders, 25(12), 1853-1859.

[127] Bohnen, N. I., Kanel, P., Zhou, Z., Koeppe, R. A., Frey, K. A., Dauer, W. T., ... & Müller, M. L. (2019). Cholinergic system changes of falls and freezing of gait in Parkinson's disease. Annals of neurology, 85(4), 538-549.

[128] Suzuki, M., Desmond, T. J., Albin, R. L., & Frey, K. A. (2002). Cholinergic vesicular transporters in progressive supranuclear palsy. Neurology, 58(7), 1013-1018.

[129] Kalivas, P. W., & Volkow, N. D. (2005). The neural basis of addiction: a pathology of motivation and choice. American Journal of Psychiatry, 162(8), 1403-1413.

[130] Gaspar, P., Berger, B., Febvret, A., Vigny, A., & Henry, J. P. (1989). Catecholamine innervation of the human cerebral cortex as revealed by comparative immunohistochemistry of tyrosine hydroxylase and dopamine-beta-hydroxylase. Journal of Comparative Neurology, 279(2), 249-271.

[131] Margeta-Mitrovic, M., Mitrovic, I., Riley, R. C., Jan, L. Y., & Basbaum, A. I. (1999). Immunohistochemical localization of GABAB receptors in the rat central nervous system. Journal of Comparative Neurology, 405(3), 299-321.

[132] Baumgärtner, U., Buchholz, H. G., Bellosevich, A., Magerl, W., Siessmeier, T., Rolke, R., ... & Schreckenberger, M. (2006). High opiate receptor binding potential in the human lateral pain system. Neuroimage, 30(3), 692-699.

[133] Wiebking, C., Duncan, N. W., Tiret, B., Hayes, D. J., Marjańska, M., Doyon, J., ... & Northoff, G. (2014). GABA in the insula—a predictor of the neural response to interoceptive awareness. Neuroimage, 86, 10-18.

[134] Dickson, D. W., Bergeron, C., Chin, S. S., Duyckaerts, C., Horoupian, D., Ikeda, K., ... & Litvan, I. (2002). Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. Journal of Neuropathology & Experimental Neurology, 61(11), 935-946.

[135] Seppi, K., Scherfler, C., Donnemiller, E., Virgolini, I., Schocke, M. F., Goebel, G., ... & Poewe, W. (2006). Topography of dopamine transporter availability in progressive supranuclear palsy: a voxelwise [123I] β-CIT SPECT analysis. Archives of neurology, 63(8), 1154-1160.

[136] Warren, N. M., Piggott, M. A., Lees, A. J., Perry, E. K., & Burn, D. J. (2008). Intact coupling of M1 receptors and preserved M2 and M4 receptors in the cortex in progressive supranuclear palsy: contrast with other dementias. Journal of chemical neuroanatomy, 35(3), 268-274.

[137] Jellinger, K. A. (2023). Pathomechanisms of cognitive impairment in progressive supranuclear palsy. Journal of Neural Transmission, 130(4), 481-493.

[138] Boxer, A. L., Geschwind, M. D., Belfor, N., Gorno-Tempini, M. L., Schauer, G. F., Miller, B. L., ... & Rosen, H. J. (2006). Patterns of brain atrophy that differentiate corticobasal degeneration syndrome from progressive supranuclear palsy. Archives of neurology, 63(1), 81-86.

[139] Brenneis, C., Seppi, K., Schocke, M., Benke, T., Wenning, G. K., & Poewe, W. (2004). Voxel based morphometry reveals a distinct pattern of frontal atrophy in progressive supranuclear palsy. Journal of Neurology, Neurosurgery & Psychiatry, 75(2), 246-249.

[140] Cordato, N. J., Duggins, A. J., Halliday, G. M., Morris, J. G., & Pantelis, C. (2005). Clinical deficits correlate with regional cerebral atrophy in progressive supranuclear palsy. Brain, 128(6), 1259-1266.

[141] Focke, N. K., Helms, G., Scheewe, S., Pantel, P. M., Bachmann, C. G., Dechent, P., ... & Trenkwalder, C. (2011). Individual voxel-based subtype prediction can differentiate progressive supranuclear palsy from idiopathic Parkinson syndrome and healthy controls. Human brain mapping, 32(11), 1905-1915.

[142] Ghosh, B. C., Calder, A. J., Peers, P. V., Lawrence, A. D., Acosta-Cabronero, J., Pereira, J. M., ... & Rowe, J. B. (2012). Social cognitive deficits and their neural correlates in progressive supranuclear palsy. Brain, 135(7), 2089-2102.

[143] Giordano, A., Tessitore, A., Corbo, D., Cirillo, G., de Micco, R., Russo, A., ... & Tedeschi, G. (2013). Clinical and cognitive correlations of regional gray matter atrophy in progressive supranuclear palsy. Parkinsonism & Related Disorders, 19(6), 590-594.

[144] Kamiya, K., Sato, N., Ota, M., Nakata, Y., Ito, K., Kimura, Y., ... & Ohtomo, K. (2013). Diffusion tensor tract-specific analysis of the uncinate fasciculus in patients with progressive supranuclear palsy. Journal of Neuroradiology, 40(2), 121-129.

[145] Mueller, K., Jech, R., Bonnet, C., Tintěra, J., Hanuška, J., Möller, H. E., ... & FTLDc Study Group. (2017). Disease-specific regions outperform whole-brain approaches in

identifying progressive supranuclear palsy: a Multicentric MRI Study. Frontiers in neuroscience, 11, 100.

[146] Piattella, M. C., Upadhyay, N., Bologna, M., Sbardella, E., Tona, F., Formica, A., ... & Pantano, P. (2015). Neuroimaging evidence of gray and white matter damage and clinical correlates in progressive supranuclear palsy. Journal of neurology, 262, 1850-1858.

[147] Takahashi, R., Ishii, K., Kakigi, T., Yokoyama, K., Mori, E., & Murakami, T. (2011). Brain alterations and mini-mental state examination in patients with progressive supranuclear palsy: voxel-based investigations using 18F-fluorodeoxyglucose positron emission tomography and magnetic resonance imaging. Dementia and Geriatric Cognitive Disorders Extra, 1(1), 381-392.

[148] Wang, Guihong, et al. "Quantitative assessment of cerebral gray matter density change in progressive supranuclear palsy using voxel based morphometry analysis and cerebral MR T1-weighted FLAIR imaging." Journal of the Neurological Sciences 359.1-2 (2015): 367-372.

[149] Whitwell, J. L., Duffy, J. R., Strand, E. A., Machulda, M. M., Senjem, M. L., Gunter, J. L., ... & Josephs, K. A. (2013). Neuroimaging comparison of primary progressive apraxia of speech and progressive supranuclear palsy. European Journal of Neurology, 20(4), 629-637.

[150] Worker, A., Blain, C., Jarosz, J., Chaudhuri, K. R., Barker, G. J., Williams, S. C., ... & Simmons, A. (2014). Cortical thickness, surface area and volume measures in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. PloS one, 9(12), e114167.

[151] Sandhya, M., Saini, J., Pasha, S. A., Yadav, R., & Pal, P. K. (2014). A voxel based comparative analysis using magnetization transfer imaging and T1-weighted magnetic resonance imaging in progressive supranuclear palsy. Annals of Indian Academy of Neurology, 17(2), 193.

[152] Lagarde, J., Valabrègue, R., Corvol, J. C., Pineau, F., Le Ber, I., Vidailhet, M., ... & Levy, R. (2013). Are frontal cognitive and atrophy patterns different in PSP and bvFTD? A comparative neuropsychological and VBM study. PloS one, 8(11), e80353.

[153] Lagarde, J., Valabregue, R., Corvol, J. C., Garcin, B., Volle, E., Le Ber, I., ... & Levy, R. (2015). Why do patients with neurodegenerative frontal syndrome fail to answer:'In what way are an orange and a banana alike?'. Brain, 138(2), 456-471.

[154] Santos-Santos, M. A., Mandelli, M. L., Binney, R. J., Ogar, J., Wilson, S. M., Henry, M. L., ... & Gorno-Tempini, M. L. (2016). Cross-sectional and longitudinal features of non-fluent/agrammatic primary progressive aphasia with underlying corticobasal degeneration or progressive supranuclear palsy pathology. JAMA neurology, 73(6), 733.

[155] Seppi K, Poewe W (2010) Brain magnetic resonance imaging techniques in the diagnosis of parkinsonian syndromes. Neuroimaging Clinics 20(1): 29–55.

[156] Quattrone A, Nicoletti G, Messina D et al (2008) MR imaging index for differentiation of progressive supranuclear palsy from Parkinson disease and the Parkinson variant of multiple system atrophy. Radiology 246: 214–21.

[157] Mahlknecht P, Hotter A, Hussl A, Esterhammer R, Schocke M, Seppi K (2010) Significance of MRI in diagnosis and differential diagnosis of Parkinson's disease. Neurodegener. Dis. 7(5): 300–318.

[158] Stamelou M, Knake S, Oertel WH, et al (2011) Magnetic resonance imaging in progressive supranuclear palsy. J. Neurol. 258 (4): 549–558.

[159] Schrag A, Good CD, Miszkiel K, et al (2000) Differentiation of atypical parkinsonian syndromes with routine MRI. Neurology 54: 697–702.

[160] Kato N, Arai K, Hattori T (2003) Study of the rostral midbrain atrophy in progressive supranuclear palsy. Journal of the neurological sciences 210(1-2): 57–60.

[161] Mueller C, Hussl A, Krismer F, et al (2018) The diagnostic accuracy of the hummingbird and morning glory sign in patients with neurodegenerative parkinsonism. Parkinsonism & related disorders 54; 90–94.

[162] Kaasinen V, Kangassalo N, Gardberg M, et al (2015) Midbrain-to-pons ratio in autopsy-confirmed progressive supranuclear palsy: replication in an independent cohort. Neurological Sciences 36(7): 1251–1253.

[163] Josephs KA, Whitwell JL, Boeve BF, et al (2006) Rates of cerebral atrophy in autopsy-confirmed progressive supranuclear palsy. Annals of neurology 59(1): 200–203.

[164] Hwang M, Yang H, Kim Y, et al (2013) Differential progression of midbrain atrophy in parkinsonism: longitudinal MRI study. Neurodegenerative Diseases 2017; 17(1): 31–37. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310:2191–4.

[165] Paviour DC, Price SL, Jahanshahi M, Lees AJ, Fox NC (2006) Regional brain volumes distinguish PSP, MSA-P, and PD: MRI-based clinico-radiological correlations. Movement disorders: official journal of the Movement Disorder Society 21(7): 989–996.

[166] Warmuth-Metz M, Naumann M, Csoti I, Solymosi L (2001) Measurement of the midbrain diameter on routine magnetic resonance imaging: a simple and accurate method of differentiating between Parkinson disease and progressive supranuclear palsy. Arch Neurol 58: 1076–1079.

[167] Dutt S, Binney RJ, Heuer HW, et al (2016) Progression of brain atrophy in PSP and CBS over 6 months and 1 year. Neurology 87(19).

[168] van Eimeren T, Antonini A, Berg D, et al (2019) Neuroimaging biomarkers for clinical trials in atypical parkinsonian disorders: Proposal for a Neuroimaging Biomarker Utility System. Alzheimers Dement (Amst) 11:301–309.

[169] Ahn JH, Kim M, Kim JS, et al (2019) Midbrain atrophy in patients with presymptomatic progressive supranuclear palsy-Richardson's syndrome. Parkinsonism & related disorders 66: 80–86.

[170] Owens E, Krecke K, Ahlskog JE, et al (2016) Highly specific radiographic marker predates clinical diagnosis in progressive supranuclear palsy. Parkinsonism & related disorders 28: 107–111.

[171] Lambert C, Chowdhury R, Fitzgerald Tet al (2013) Characterizing aging in the human brainstem using quantitative multimodal MRI analysis. Frontiers in human neuroscience 7, 462.

[172] Liu, X., Eickhoff, S. B., Caspers, S., Wu, J., Genon, S., Hoffstaedter, F., ... & Patil, K. R. (2021). Functional parcellation of human and macaque striatum reveals human-specific connectivity in the dorsal caudate. Neuroimage, 235, 118006.

[173] Mucci, A., Dima, D., Soricelli, A., Volpe, U., Bucci, P., Frangou, S., ... & Maj, M. (2015). Is avolition in schizophrenia associated with a deficit of dorsal caudate activity? A functional magnetic resonance imaging study during reward anticipation and feedback. Psychological medicine, 45(8), 1765-1778.

[174] Luft AR, Skalej, M, Schulz JB, et al (1999) Patterns of age-related shrinkage in cerebellum and brainstem observed in vivo using three-dimensional MRI volumetry. Cerebral Cortex 9(7), 712–721.

Figure Legend

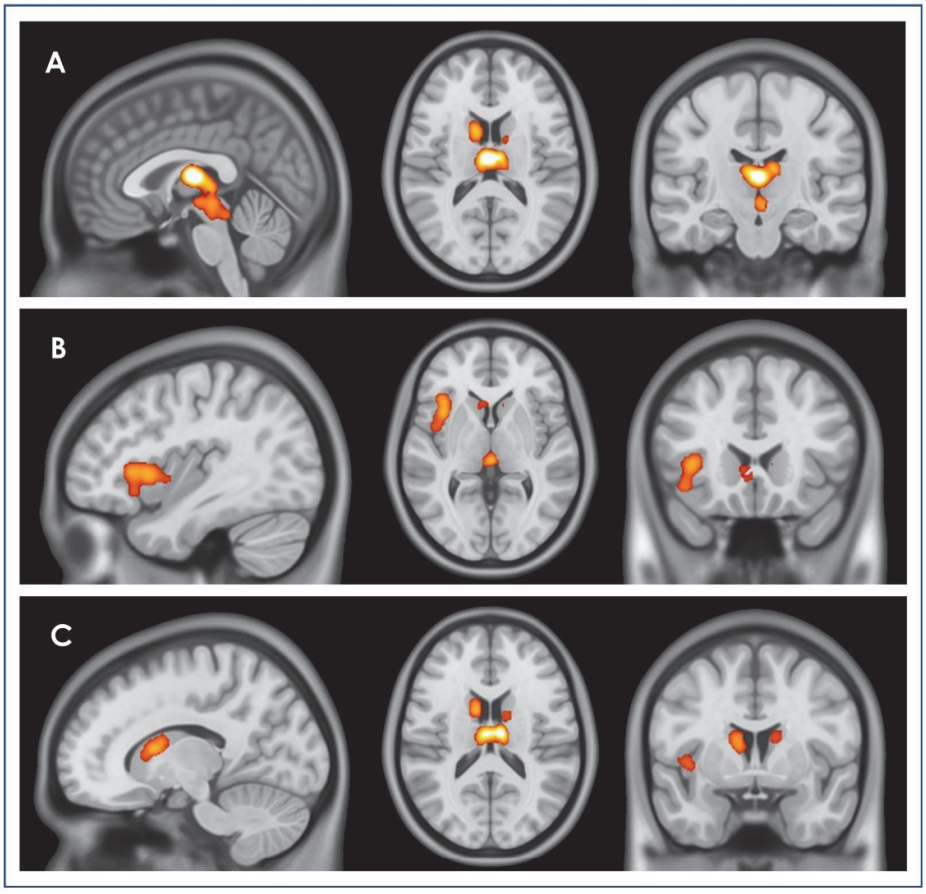


Fig. 1. ALE main results: Clusters of PSP-related significant GM reduction (red-yellow) in the Bilateral (A) Thalamus & Midbrain, (B) Left Insula and Frontal Operculum and (C) Bilateral Caudate Nucleus at $p \leq 0.05$ (FWE corrected for multiple comparisons).

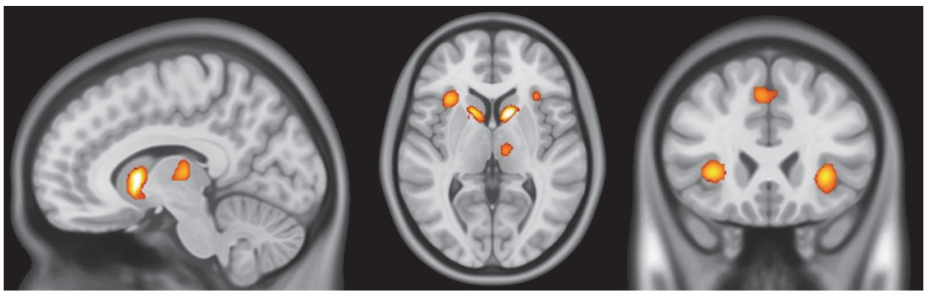


Fig. 2. Results MACM analysis. Significant co-activation patterns (red-yellow) for the conjunction analysis of the coactivation maps of all areas at $p \leq 0.05$ (FWE corrected for multiple comparisons).

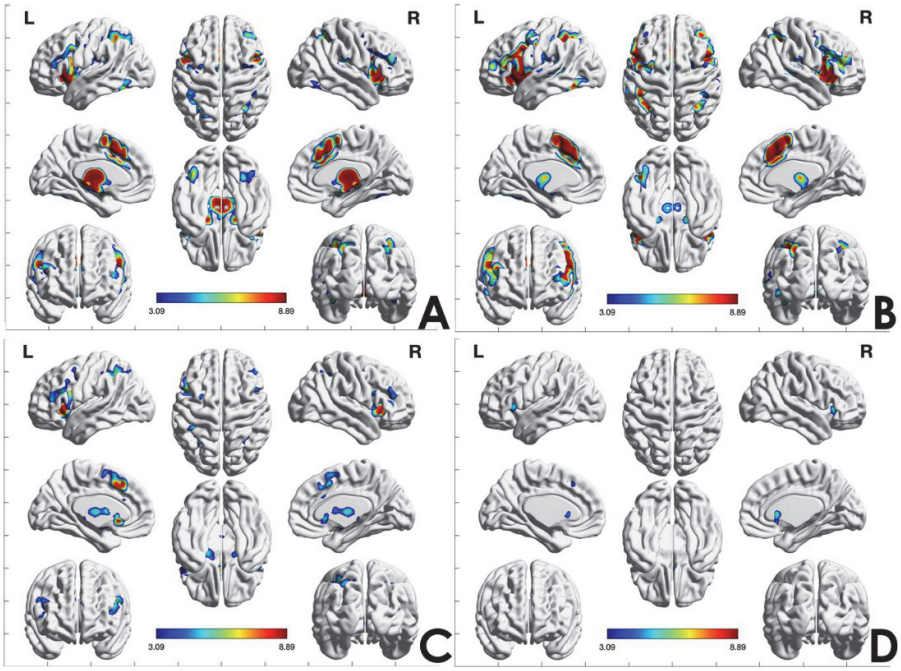


Fig. 3. MACM results for (A) Thalamus and Midbrain, (B) Left Insula, (C) Left Caudate Nucleus, (D) Right Caudate Nucleus. Results showing coactivated regions (blue to red, with red strongest activation) for the four regions (FEW-corrected $p \leq 0.05$ at cluster level) L: left hemisphere, R: right hemisphere.

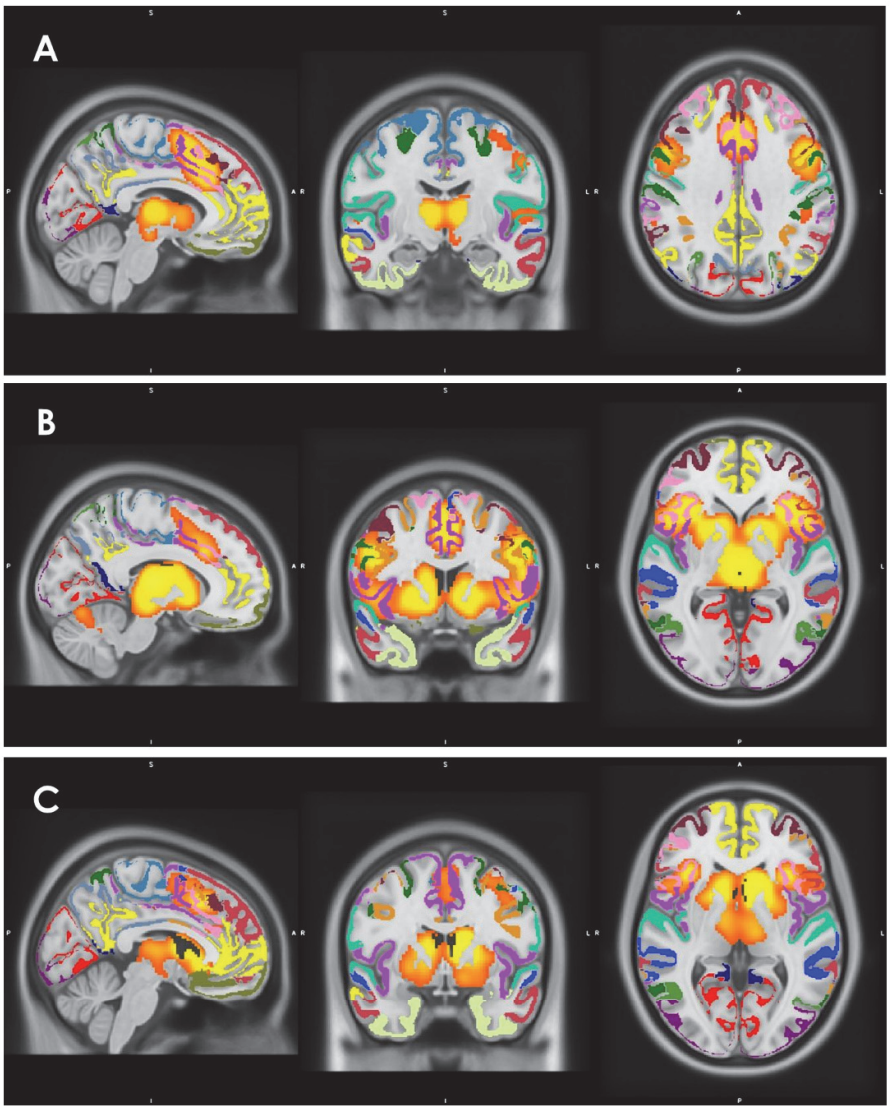


Fig. 4. Functionally coupled regions revealed by Yeo cortical maps. Yeo maps were overlayed onto (A) MACM results Insula, (B) MACM results Thalamus, (C) MACM results Bilateral Caudate Nuclei (Yeo et al., 2011).

Table Legend

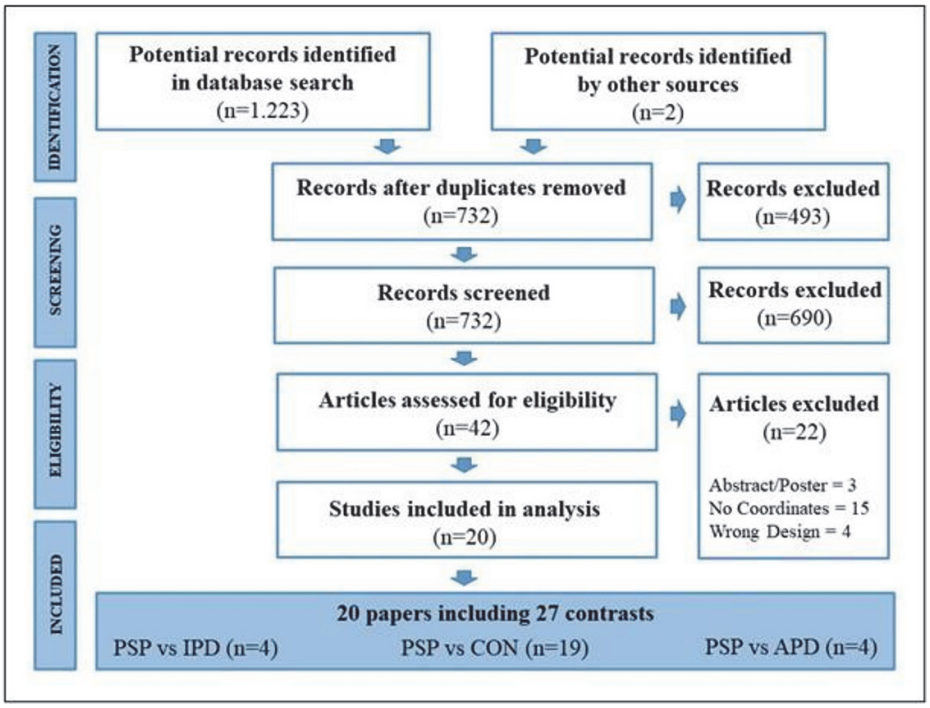
Table 1. Localization of significant clusters of convergence for the ALE analysis.

Cluster #	Weighted center [a]			Anatomical Label
	x	y	z	
1 (v=1394)	0	-20	8	Bilateral Thalamus & Midbrain
2 (v=548)	−40	18	2	Left Insula & Frontal Operculum
3 (v=348)	−10	10	12	Left Caudate Nucleus
4 (v=17)	10	18	4	Right Caudate Nucleus

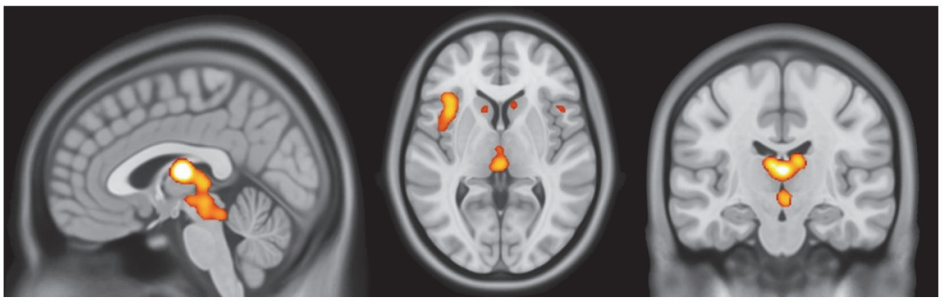
Note. [a] Montreal Neurological Institute (MNI) coordinates; x,y,z = peak coordinates of GM atrophy; v=number of voxels of each cluster.

Supplementary material Querbach et al., 2025

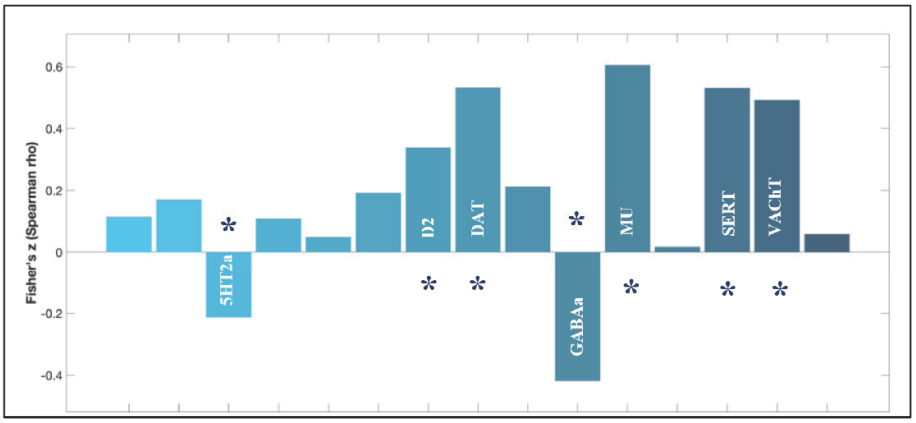
Consistent PSP-atrophy



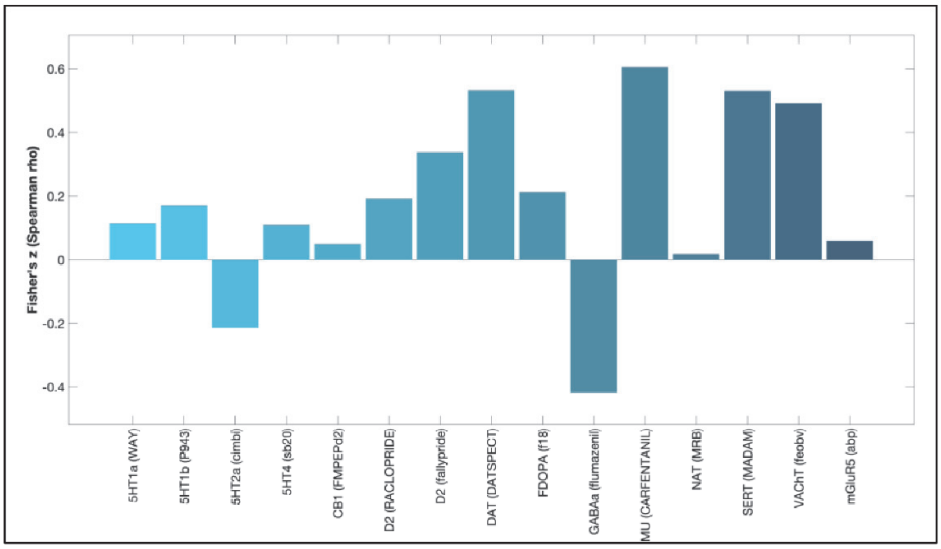
Supplementary Fig. 1. Flowchart of study selection adapted from PRISMA-P scheme. PSP=progressive supranuclear palsy, CON=healthy controls, APD=atypical parkinsonian diseases (including coticobasal degeneration, frontotemporal dementia, guadeloupean parkinson's disease).



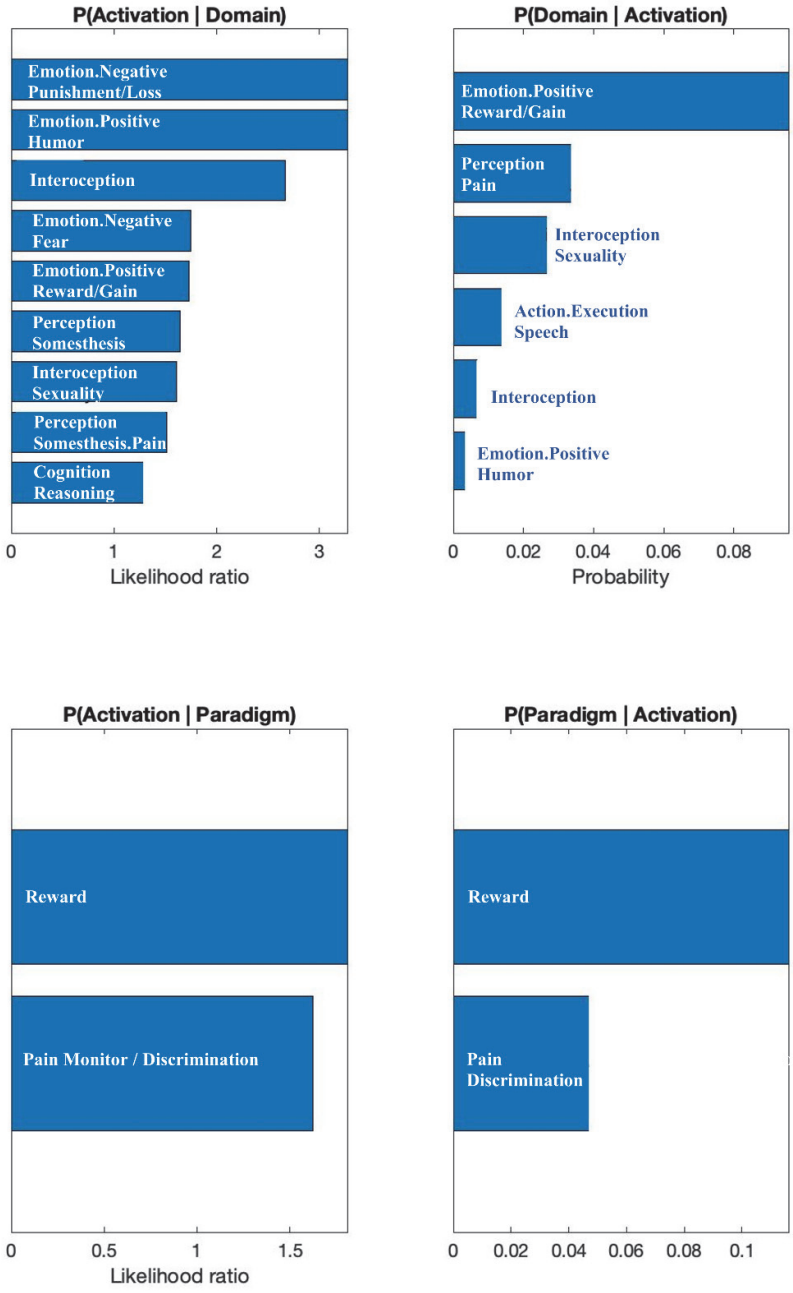
Supplementary Fig. 2 ALE supplementary results: Clusters of PSP-related GM reduction in the bilateral thalamus and midbrain, left insula and frontal operculum and bilateral caudate nucleus and right precentral gyrus.



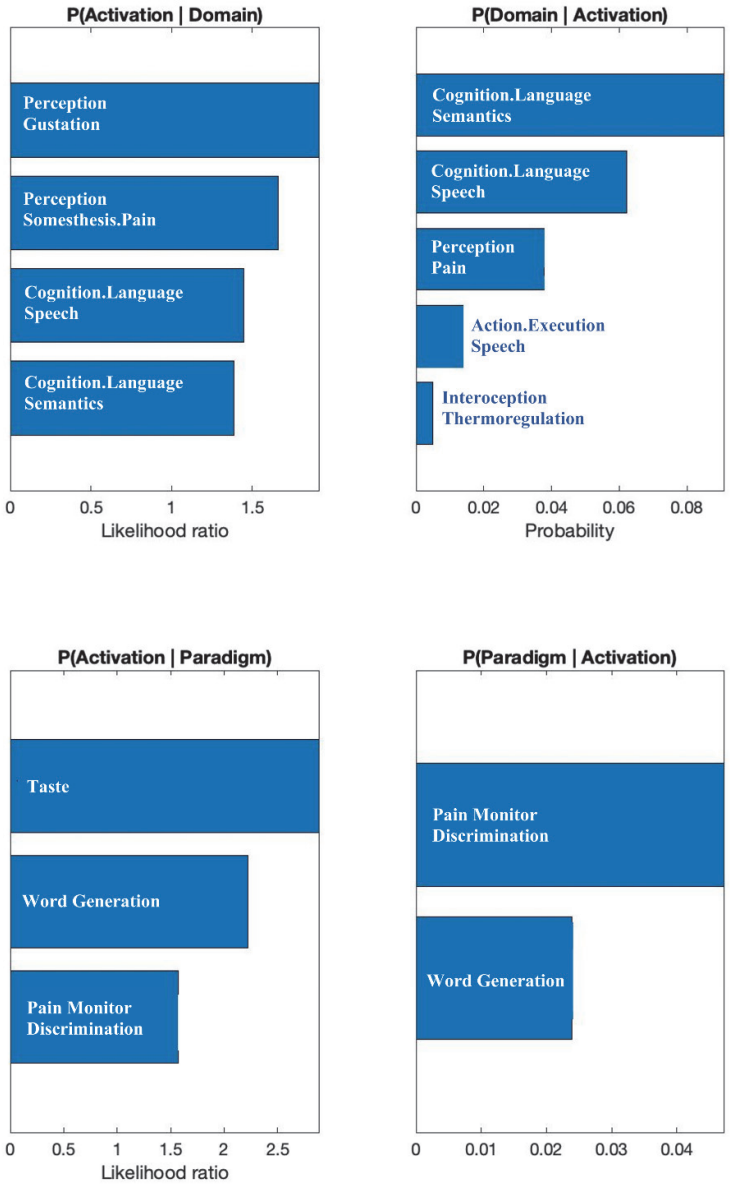
Supplementary Fig. 3 A Spatial correlation analyses. Significant correlations of regions of GM alterations with density maps of tested neurotransmitter systems. * significant correlation at p<.001.



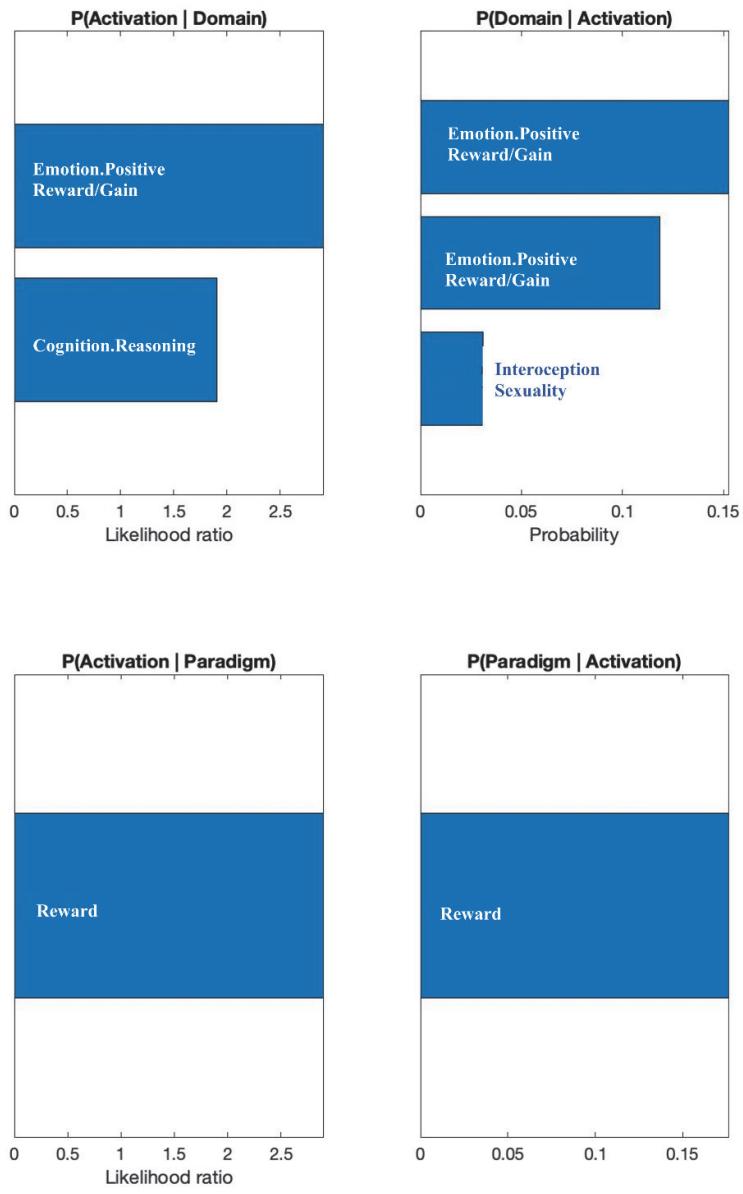
Supplementary Fig. 3 B Spatial correlation analyses: regions of GM alterations correlated with density maps of tested neurotransmitter systems.



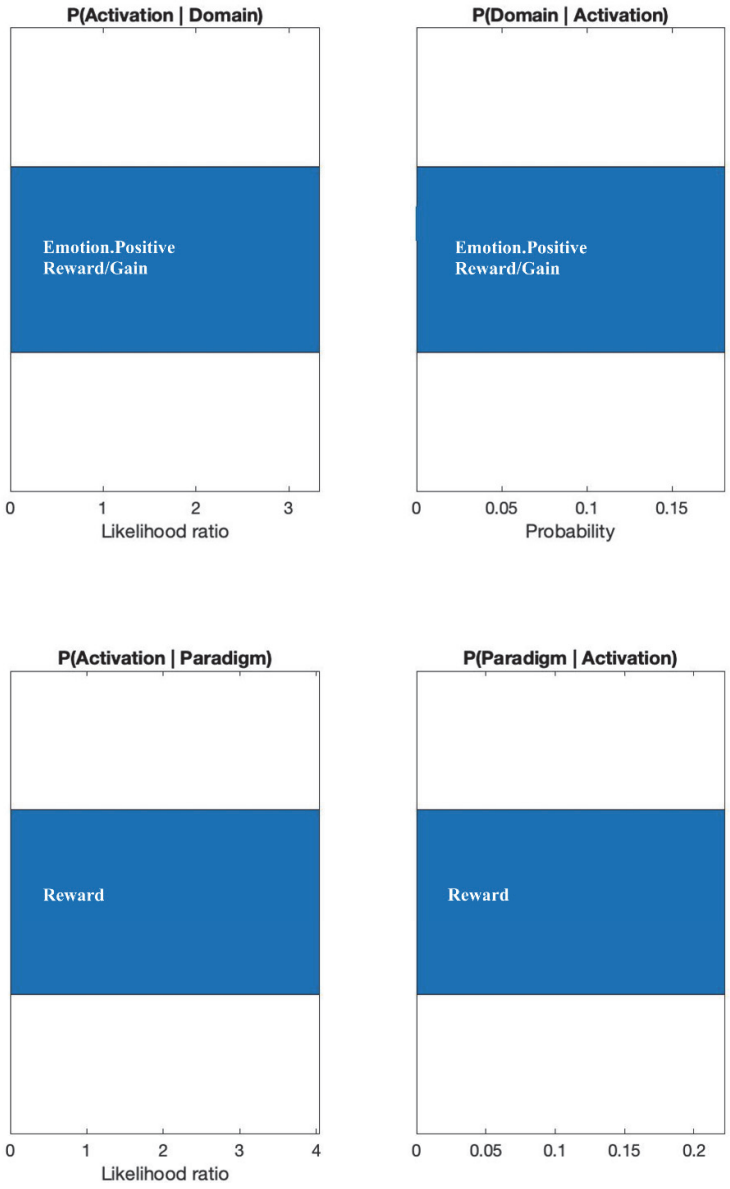
Supplementary Fig. 4 A Results Functional decoding: Functional Domains mainly associated with PSP-related GM alterations in Midbrain and Thalamus.



Supplementary Fig. 4 B Results Functional decoding: Functional Domains mainly associated with PSP-related GM alterations in the Insula.



Supplementary Fig. 4 C Results Functional decoding: Functional Domains mainly associated with PSP-related GM alterations in Left Caudate Nucleus.



Supplementary Fig. 4 D Results Functional decoding: Functional Domains mainly associated with PSP-related GM alterations in Right Caudate Nucleus.

Supplementary Table 1. Overview on the papers included in the meta-analysis.

Paper Authors	Year	PSP Subjects	Space	Contrasts	Diagnostic Criteria
Boxer et al.	2006	15	MNI	PSP<CON; PSP<CBD	n.a.
Brenneis et al.,	2004	12	TAL	PSP<CON	n.a.
Cordato et al.	2005	21	MNI	PSP<CON	NINDS
Focke et al.	2011	10	MNI	PSP<IPD; PSP>IPD	NINDS
Ghosh et al.	2012	23	MNI	PSP<CON	MDS
Giordano et al.	2013	15	TAL	PSP<CON; PSP<IPD	NINDS
Kamiya et al.	2013	16	MNI	PSP<CON	NINDS
Mueller et al.	2017	20	MNI	PSP<CON	n.a.
Padovani et al.	2006	14	MNI	PSP<CON	NINDS
Piatella et al.	2015	16	MNI	PSP<CON	NINDS
Takahashi et al.	2011	32	TAL	PSP<CON	NINDS
Wang et al.,	2014	24	MNI	PSP<CON	NINDS
Whitwell et al.	2013	16	MNI	PSP<CON	NINDS
Worker et al.	2014	14	TAL	PSP<CON; PSP<IPD	n.a.
Sandhya et al.	2014	10	TAL	PSP<CON	NINDS
Lagarde et al.	2013	19	MNI	PSP<CON; PSP>FTD	NINDS
Lagarde et al.	2015	21	MNI	PSP<CON	NINDS
Lehericy et al.	2010	10	MNI	PSP<CON; PSP>GPD	NINDS
Agosta et al.	2010	20	MNI	PSP<CON	NINDS
Santos-Santos et al.	2016	5	MNI	PSP<CON; PSP<CBD	NINDS

Notes. PSP=progressive supranuclear palsy; CON=healthy controls; FTD=frontotemporal dementia; IPD=idiopathic Parkinson's disease; CBD=Corticobasal Degeneration.

Supplementary Table 2. Localization of significant clusters of convergence for the secondary ALE analysis.

Cluster #	Weighted center [a]			Anatomical Label
	x	y	z	
1 (v=1351)	0	-20	8	Bilateral Thalamus & Midbrain
2 (v=514)	−40	18	2	Left Insula & Frontal Operculum
5 (v=285)	-12	8	12	Left Caudate Nucleus
4 (v=22)	10	19	4	Right Caudate Nucleus
5 (v=20)	46	16	4	Right Precentral Gyrus

[a] Montreal Neurological Institute (MNI) coordinates; x,y,z=peak coordinates of GM atrophy; v=number of voxels of each cluster.

Appendix 2: STUDY 2

Investigating the 1-year decline in midbrain-to-pons ratio in the differential diagnosis of PSP and IPD.

Kannenberg, S., Caspers, J., Dinkelbach, L., Moldovan, A.S., Ferrea, S., Butz, M., Schnitzler, A. & Hartmann, C.J. (2021). Investigating the 1-year decline in midbrain-to-pons ratio in the differential diagnosis of PSP and IPD. *Journal of Neurology, 268*, 1526–1532. https://doi.org/10.1007/s00415-020-10327-2.

Conceptualization & methodology: I developed the research question and analysis plan in consultation with C.J. Hartmann.

Investigation & project administration: I supervised the search for retrospective imaging data, independently reviewing them for suitability in the data collection process. Project administration was performed by me. Imaging measurements were performed by me and J. Caspers. I was responsible for curating the data. Project administration was jointly managed by C.J. Hartmann and me, with data verification and preparing the data for analysis by me.

Formal analysis: I conducted the statistical analyses independently and reviewed them for correctness.

Resources: Resources were contributed by A. Schnitzler.

Manuscript: I wrote the initial manuscript, which encompassed all stages from comprehensive literature review to the final formulation. I created the figures and tables independently, reviewed for comprehensiveness by M. Butz. I coordinated the scientific review process with the journals, making revisions with the assistance of M. Butz. I prepared the final version of the manuscript. All authors critically reviewed the manuscript.

Journal of Neurology (2021) 268:1526–1532
https://doi.org/10.1007/s00415-020-10327-2

ORIGINAL COMMUNICATION

Investigating the 1-year decline in midbrain-to-pons ratio in the differential diagnosis of PSP and IPD

Silja Kannenberg[1] · Julian Caspers[2] · Lars Dinkelbach[1] · Alexia-S. Moldovan[1,3] · Stefano Ferrea[1] · Martin Südmeyer[1,4] · Markus Butz[1] · Alfons Schnitzler[1] · Christian J. Hartmann[1,3]

Received: 18 June 2020 / Revised: 10 November 2020 / Accepted: 19 November 2020 / Published online: 4 December 2020
© The Author(s) 2020

Abstract

Background A reliable measure of PSP-specific midbrain atrophy, the midbrain-to-pons ratio (MTPR) has been reported to support the differential diagnosis of progressive supranuclear palsy (PSP) from idiopathic Parkinson's disease (IPD). Since longitudinal analyses are lacking so far, the present study aimed to evaluate the diagnostic value of the relative change of MTPR (relΔt_MTPR) over a 1-year period in patients with PSP, IPD, and healthy controls (HC).

Methods Midsagittal individual MRIs of patients with PSP ($n = 15$), IPD ($n = 15$), and healthy controls (HC; $n = 15$) were assessed and the MTPR at baseline and after 1 year were defined. The diagnostic accuracy of the MTPR and its relative change were evaluated using ROC curve analyses.

Results PSP-patients had a significantly lower MTPR at baseline ($M = 0.45 \pm 0.06$), compared to both non-PSP groups ($F(2, 41) = 62.82$, $p < 0.001$), with an overall predictive accuracy of 95.6% for an MTPR ≤ 0.54. PSP-patients also presented a significantly stronger 1-year decline in MTPR compared to IPD ($p < 0.001$). Though predictive accuracy of $rel\Delta_t$_MTPR for PSP ($M = -4.74\% \pm 4.48$) from IPD ($M = +1.29 \pm 3.77$) was good (76.6%), ROC analysis did not reveal a significant improvement of diagnostic accuracy by combining the MTPR and $rel\Delta_t$_MTPR ($p = 0.670$). Still, specificity for PSP increased, though not significantly ($p = 0.500$).

Conclusion The present results indicate that the $rel\Delta_t$_MTPR is a potentially useful tool to support the differential diagnosis of PSP from IPD. For its relative 1-year change, still, more evaluation is needed.

Keywords Progressive supranuclear palsy · Idiopathic Parkinson's disease · Midbrain-to-pons ratio · Atypical parkinsonism · MRI

Introduction

The differential diagnosis of progressive supranuclear palsy (PSP) from Parkinson's disease (IPD) is not trivial [1, 2]. At present, the clinical diagnosis of PSP is primarily based on identifying disease-specific symptoms, which may not have fully developed in early stages of the disease [3, 4]. Accordingly, misdiagnoses occur frequently due to a substantial overlap of symptoms [5]. Still, a more rapid progression and an overall poor prognosis in PSP underline the clinical need for objective biomarkers to facilitate early and precise diagnosis [6, 7].

As specific brain structures are known to be atrophic to different extents in different Parkinsonian diseases, disease-specific alterations detectable by structural magnetic resonance imaging (MRI) were suggested to support the diagnosis of PSP [8–13].

✉ Julian Caspers
julian.caspers@med.uni-duesseldorf.de

[1] Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich Heine University Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany

[2] Department of Diagnostic and Interventional Radiology, Medical Faculty, University Hospital Düsseldorf, Moorenstraße 5, 40225 Düsseldorf, Germany

[3] Department of Neurology, Medical Faculty, University Hospital Düsseldorf, Moorenstraße 5, 40225 Düsseldorf, Germany

[4] Department of Neurology, Ernst Von Bergmann Hospital, Charlottenstraße 72, 14467 Potsdam, Germany

A hallmark, known to be highly specific of PSP, is midbrain atrophy [14, 15]. Hence, the so-called midbrain-to-pons ratio (MTPR) was introduced as a potential biomarker to distinguish between PSP and IPD and constitutes a reliable method to quantify PSP-specific midbrain atrophy [16–18]. Since PSP progresses considerably faster than IPD, PSP-specific rates of atrophy can potentially serve as biomarkers of the disease and support differential diagnosis [19, 20].

To substantiate this notion, we aimed to evaluate the diagnostic value of the MTPR and its relative change (relΔ_{t}_MTPR) over time. We analyzed structural MRI scans at a 1-year interval and defined the MTPR in patients with PSP and IPD as well as healthy controls (HC).

Methods

Participants

The study included 15 patients with probable or possible PSP, 15 patients with IPD as well as 15 HC. Trained movement disorders specialists (CJH; MS) confirmed clinical diagnoses of PSP and IPD, based on the NINDS diagnostic criteria [21]. Additionally, the MDS diagnostic criteria were applied, retrospectively to every patient [22]. Clinical records were reviewed, and groups were matched for age and disease duration (DD) at baseline (BL). The study was approved by the local ethics committee (study no. 2849). All participants gave prior written informed consent and all conducted study investigations were performed in accordance with the declaration of Helsinki [23].

Magnetic resonance imaging and analysis

All participants underwent two MRI scans (BL and after 1 year ± 3 months) on a 3-T Siemens Tim Trio scanner (Siemens Healthcare GmbH, Erlangen, Germany). 3D T1-weighted images with 1.0 mm isotropic resolution were collected (MP RAGE, echo time = 2,98 ms, repetition time = 2300 ms, flip angle = 9°, acquisition matrix = 256 × 256, number of excitations = 1, field of view = 256 mm). MRI sequences were visually examined (JC; SK) to exclude relevant confounders such as movement artefacts or additional/differential diagnoses such as vascular lesions.

Morphometric measurements

Morphometric measurements were manually assessed using 3D Slicer Version 4.10.2 (slicer.org). Midsagittal T1-weighted individual MRIs were used for the midbrain and pons measurements, using a simplified version of the methodology described by Massey et al. (2013) [17]. Two independent investigators (JC; SK) blinded to the diagnoses performed the analyses. Each investigator drew line measurements over pons and midbrain (maximal widths perpendicular to the visually estimated oblique superior–inferior axes) in a midsagittal slice to assess the respective area widths. In line with previous research, pons measurements did not include the pontine tegmentum and midbrain measurements did not include the collicular plate [17, 18]. The MTPR was calculated from the determined values dividing the width of the midbrain by the width of the pons for every individual. The relΔ_{t}_MTPR was defined as $\text{rel}\Delta_t\_MTPR = \frac{(MTPR_{1Y} - MTPR_{BL})}{MTPR_{BL}}$ with $MTPR_{BL}$ as baseline MTPR and $MTPR_{1Y}$ as MTPR after 1 year.

Statistical analyses

All data were analyzed using IBM SPSS version 25.0 (IBM SPSS Statistics, Armonk, NY: IBM Corp.) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Data were evaluated for normality using the Shapiro Wilk test. Parametric, non-parametric or Chi-squared tests were used for group comparisons, depending on the distribution of variables.

To assess inter-rater reliability (IRR) the measurements for midbrain and pons were analyzed using intraclass correlation coefficients (ICCs; single measures, consistency).

Between-group comparisons were performed with an unpaired t-test for DD at BL, Kruskal–Wallis analysis of variance (ANOVA) for age at BL and a Chi-squared test for gender distribution. A multivariate analysis of variance (MANOVA) was performed to investigate differences in midbrain, pons, and MTPR between groups and MRI time points. We calculated a combined parameter of MTPR_{BL} and relΔ_{t}_MTPR ($\text{MTPR}_{\text{BL\&}\Delta t}$) using predicted probability values from a binary logistic regression model. This new parameter was used as test variable in ROC analyses. Thus, it could be estimated whether the diagnostic accuracy of MTPR_{BL} can be significantly enhanced by adding relΔ_{t}_MTPR. Receiver operating characteristic curve (ROC) analyses were then performed to evaluate the predictive value of the MTPR, relΔ_{t}_MTPR, and $\text{MTPR}_{\text{BL\&}\Delta t}$ by computing the area under the curve (AUC; 95% CI). Diagnostic accuracy was determined in differentiating PSP *vs.* IPD *vs.* HC using the optimal cutoff value determined by ROC analysis with 95% confidence intervals. The cutoff was defined as the value resulting in the highest Youden Index. ROC curves were analyzed for significant differences using the roc.test command of the pROC package [24] in R (method = bootstrap, paired). We also performed a McNemar's test, to evaluate statistical differences in specificity values. A p value < 0.05 was considered significant for all tests. For all

statistical comparisons, post-hoc Bonferroni analyses were performed, to correct for multiple comparisons.

Results

Group characteristics and main findings for PSP, IPD, and HC are summarized in Table 1 and Figs. 1 and 2. The observed groups did not significantly differ in gender distribution, age, and DD at BL.

Inter-rater reliability

ICCs revealed good IRR for pons measurements at BL (ICC = 0.87, $p < 0.001$), as well as after 1 year (ICC = 0.89, $p < 0.001$). Moreover, there was an excellent IRR for midbrain measurements at BL (ICC = 0.97, $p < 0.001$) and after 1 year (ICC = 0.98, $p < 0.001$). Given this high degree of consistency, averaged values from both raters for midbrain and pons were used to calculate $MTPR_{BL}$ and $MTPR_{1Y}$.

Morphometric analyses

Most collected midbrain MRI measures revealed significant differences between PSP and non-PSP groups: PSP-patients had a smaller $MTPR_{BL}$ ($M = 0.45 \pm 0.06$) as well as $MTPR_{1Y}$ ($M = 0.43 \pm 0.06$) compared to both non-PSP groups (F (2, 42) = 66.87, $p < 0.001$; Fig. 1a). This difference was particularly driven by a smaller midbrain width (MW) at both time points in PSP-patients (F (2, 42) = 60.08, $p < 0.001$), whereas the MTPR and MW did not differ between IPD and HC. Furthermore, there was a significant decline in MTPR (t (14) = . 4.06, $p = 0.001$) over the 1-year period for the PSP group. The $rel\Delta_t$_MTPR was stronger in PSP compared to IPD ($p < 0.001$; Fig. 1b) with a mean decline of 4.7% in MTPR for PSP-patients. Conversely, the $rel\Delta_t$_MTPR did not differ between PSP ($M = -4.74 \pm 4.48$) and HC ($M = -1.58 \pm 2.18$). Here, the $MTPR_{1Y}$ in HC was significantly smaller compared to the corresponding $MTPR_{BL}$ (t (29) = 2.92, $p = 0.011$), which was not the case for patients with IPD. Pontine values did not differ between groups and time points (see Table 1 for statistical details).

ROC analyses

ROC analyses confirmed excellent diagnostic accuracy for the $MTPR_{BL}$ (AUC = 0.98, 95% CI 0.94–1.00, sensitivity = 93.33%, specificity = 93.33%, accuracy = 93.33%) when comparing PSP and IPD-patients (Fig. 2a), as well as PSP and both non-PSP groups (AUC = 0.98, 95% CI 0.94–1.00, cutoff ≤ 0.540, sensitivity = 93.33%, specificity = 96.67%, accuracy = 95.56%; Fig. 2b). Regarding $rel\Delta_t$_MTPR accuracy for distinguishing PSP from IPD was good (AUC = 0.85, 95% CI 0.72–0.98, cutoff ≥ 0.015, sensitivity = 73.33%, specificity = 80.00%, accuracy = 76.67%; Fig. 2c); Moderate diagnostic accuracy could be demonstrated for distinguishing PSP from non-PSP participants (AUC = 0.78, 95% CI 0.63–0.93, sensitivity = 73.33%, specificity = 56.67%, accuracy = 62.22%; Fig. 2d). There was also excellent diagnostic accuracy for $MTPR_{BL\&\Delta t}$ (AUC = 0.97, 95% CI 0.93–1.00, sensitivity = 93.33%, specificity = 100.00%, accuracy = 96.67%; Fig. 2e) when comparing PSP and IPD as well as for comparing PSP and non-PSP subjects (AUC = 0.98, 95% CI 0.92–1.00, OC ≥ 0.520, sensitivity = 93.33%, specificity = 100.00%, accuracy = 97.77%; Fig. 2f). There was no significant difference for the diagnostic accuracy of $MTPR_{BL\&\Delta t}$ and $MTPR_{BL}$ ($D = -0.43$, $p = 0.67$). Additionally, the specificity values did not differ significantly ($p = 0.500$; see Table 1 for all detailed values).

Discussion

This is the first study to investigate the MTPR in a longitudinal setting to the best of our knowledge. Our cross-sectional results confirmed a lower $MTPR_{BL}$ in PSP, when compared both to IPD and to HC; an $MTPR_{BL} \leq 0.54$ was indicative of PSP. Longitudinal evidence revealed a distinct 1-year decline of MTPR in PSP-patients, representing a more pronounced midbrain atrophy rate compared to IPD. The combined $MTPR_{BL\&\Delta t}$ slighty improved the already high diagnostic accuracy of $MTPR_{BL}$ and likewise improved the specificity to 100%; however, these improvements were not statistically significant.

Overall, MTPR values confirm previous findings suggesting an MTPR ≤ 0.52 as highly specific for PSP [17, 18]. Longitudinal results also tally with former research, as differentiation of PSP from IPD is based on studies demonstrating that PSP presents stronger and faster midbrain atrophy [25–27]. However, we were not able to discriminate between PSP and non-PSP groups solely by means of $rel\Delta_t$_MTPR as with the $MTPR_{BL}$. Still, there was good predictive accuracy for distinguishing PSP and IPD only.

Most importantly, we found increased specificity values for the combined parameter $MTPR_{BL\&\Delta t}$. This is of particular clinical relevance considering that a high degree of specificity is very important for distinguishing between various forms of diseases [7]. However, a statistical comparison of specificity values did not reach significance. As the $MTPR_{BL}$ provided already excellent specificity with 96.67%, when comparing PSP and non-PSP groups, it is hard to improve specificity further in fact. However, with $MTPR_{BL\&\Delta t}$ specificity reached 100%.

With a mean DD of 63.1 months we investigated patients in rather progressed disease stages. This is particularly important considering that midbrain atrophy could also

Table 1 Demographic and morphometric data of patients with PSP and IPD as well as HC

	IPD	BL vs. 1Y[c]	PSP	BL vs. 1Y[c]	HC	BL vs. 1Y[c]	PSP vs. non-PSP[c]	PSP vs. IPD*	PSP vs. HC*	HC vs. IPD*
N	15		15		15					
GD (m/f)[a]	9/6		10/5		8/7		n.s	n.s	n.s	n.s
Age_{BL} (years)[b,d]	64.00 ± 7.50		69.60 ± 3.91		64.47 ± 8.39		n.s	n.s	n.s	n.s
DD_{BL} (months)[b,c]	50.20 ± 31.34		63.13 ± 30.69		n.a		n.s	n.s	n.a	n.a
MW_{BL} [b,c]	11.14 ± 0.79	n.s	8.17 ± 0.89	***p = 0.001***	10.99 ± 1.07	***p = 0.047***	***p < 0.001***	***p < 0.001***	***p < 0.001***	n.s
MW_{1Y} [b,c]	11.09 ± 0.73		7.80 ± 1.08		10.84 ± 1.03		***p < 0.001***	***p < 0.001***	***p < 0.001***	n.s
PW_{BL} [b,c]	18.23 ± 1.32	n.s	18.23 ± 1.42	n.s	17.77 ± 1.27	n.s	n.s	n.s	n.s	n.s
PW_{1Y} [b,c]	17.92 ± 1.28		18.24 ± 1.47		17.82 ± 1.15		n.s	n.s	n.s	n.s
$MTPR_{BL}$ [b,c]	0.61 ± 0.05	n.s	0.45 ± 0.06	***p = 0.001***	0.62 ± 0.05	***p = 0.011***	***p < 0.001***	***p < 0.001***	***p < 0.001***	n.s
$MTPR_{1Y}$ [b,c]	0.62 ± 0.04		0.43 ± 0.06		0.61 ± 0.04		***p < 0.001***	***p < 0.001***	***p < 0.001***	n.s
relΔt_MTPR (%) [b,c]	+ 1.29 ± 3.77		− 4.74 ± 4.48		− 1.58 ± 2.18		***p < 0.001***	***p < 0.001***	n.s	n.s
Cutoff MTPR (≤ 0.54)[a]	1 (6.67%)		14 (93.33%)		0 (0.00%)		***p < 0.001***	***p < 0.001***	***p < 0.001***	n.s
Sensitivity							93.33%	93.33%	93.33%	n.a
Specificity							96.67%	93.33%	100.00%	n.a
Predictive Accuracy							95.56%	93.33%	96.67%	n.a
Cutoff Dec. (≥ 1.45%)[a]	3 (20.00%)		11 (73.33%)		10 (66.67%)		n.s	***p = 0.009***	n.s	***p = 0.025***
Sensitivity							73.33%	73.33%	73.33%	n.a
Specificity							56.67%	80.00%	33.33%	n.a
Predictive Accuracy							62.22%	76.67%	53.33%	n.a
Cutoff $MTTPR_{BL\&\Delta t}$ (≥ 0.52)[a]	0 (0.00%)		14 (93.33%)		0 (0.00%)		***p < 0.001***	***p < 0.001***	***p < 0.001***	n.s
Sensitivity							93.33%	93.33%	93.33%	n.a
Specificity							100.00%	100.00%	100.00%	n.a
Predictive Accuracy							97.77%	96.67%	96.67%	n.a

IPD idiopathic Parkinson's disease, *PSP* progressive supranuclear palsy, *HC* healthy controls, *GD* gender distribution, *BL* baseline, *DD* disease duration, *MW* midbrain width, *1Y* 1 year after baseline, *PW* pons width, *MTPR* midbrain-to-pons ratio, *Dec* relative decline, $MTPR_{BL\&\Delta t}$ combined parameter of MTPR and relative change, *n.s.* not significant, *n.a.* not applicable, + increase; − decrease

*Post-hoc, Bonferroni corrected. Significant *p* values are marked in bold

[a]Chi-squared test confirmed by Fisher's exact test

[b]Values are given as mean ± standard deviation

[c]Parametric tests (One-way ANOVA; unpaired t-test; paired t-test; Repeated measures analysis of variance)

[d]Non-parametric tests (Kruskal–Wallis analysis of variance)

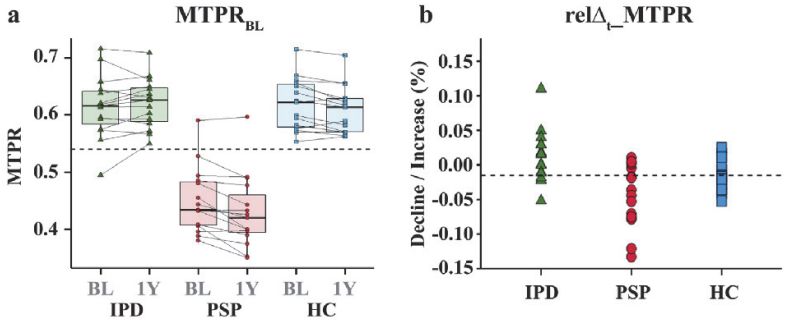


Fig. 1 Main results for the observed groups. **a** MTPR for all groups at both time points; **b** relΔ_t_MTPR (decline/increase; %) for all groups. *MTPR* midbrain-to-pons ratio, *IPD* idiopathic Parkinson's disease, *PSP* progressive supranuclear palsy, *HC* healthy controls, *BL* Baseline, *1Y* 1 year after baseline, *relΔt_MTPR* relative change, *MTPR$_{BL\&\Delta t}$* combined parameter of MTPR$_{BL}$ and relΔ_t_MTPR, + increase; – decrease

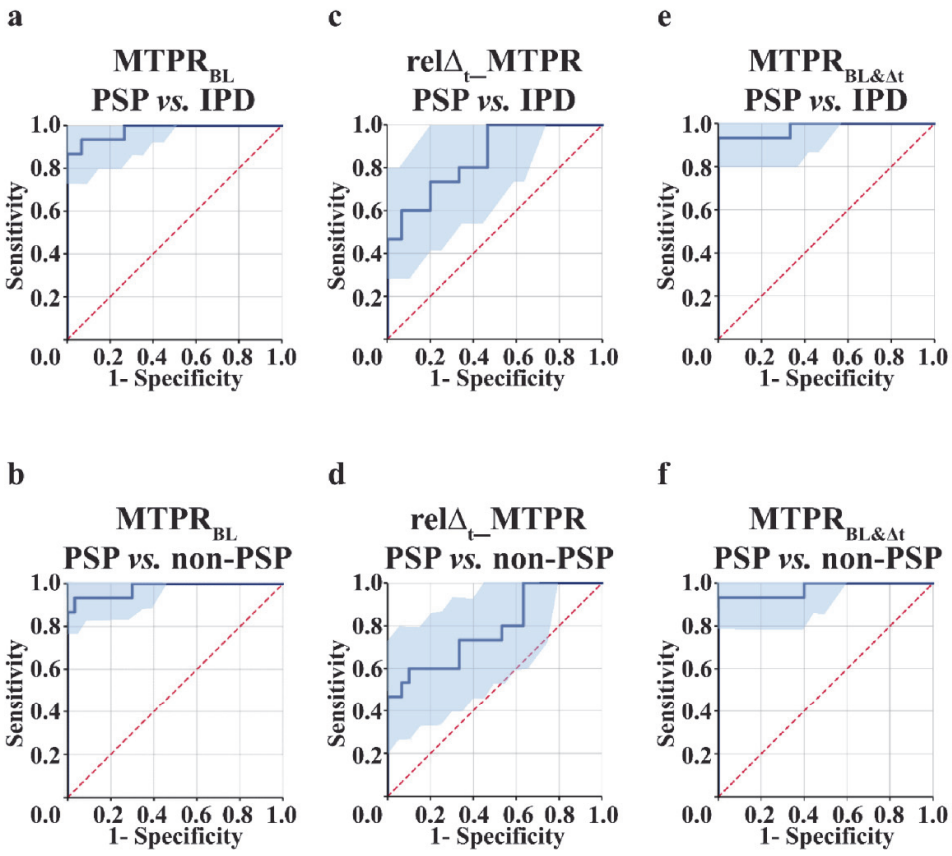


Fig. 2 Main results of ROC analyses. ROC curve for MTPR$_{BL}$ comparing **a** PSP vs. IPD and **b** PSP vs. non-PSP; **c** ROC curve for relΔ_t_MTPR comparing PSP vs. IPD and **d** PSP vs. non-PSP; **e** ROC curve for MTPR$_{BL\&\Delta t}$ comparing PSP vs. IPD and **f** PSP vs. non-PSP. *MTPR* midbrain-to-pons ratio, *IPD* idiopathic Parkinson's disease *PSP* progressive supranuclear palsy, *HC* healthy controls, *BL* Baseline, *1Y* 1 year after baseline, *relΔt_MTPR* relative change, *MTPR$_{BL\&\Delta t}$* combined parameter of MTPR$_{BL}$ and relΔ_t_MTPR

serve as PSP-specific preclinical marker in very early disease stages [28, 29]. Thus, it remains to be studied, whether the relΔ_t_MTPR—as indicator of midbrain atrophy rate—contributes better to diagnostic accuracy, earlier in the disease, i.e., when the overall MTPR has not yet reached PSP-specific values. Again, a larger patient cohort, e.g., from a future multi-centric study, would allow a more detailed analysis of effects of DD, age, and gender. While relΔ_t_MTPR was of limited diagnostic value in our patient cohort with advanced stages of the diseases, it might have a more valuable impact in early stages of PSP, where higher MTPR ratios can be expected.

Moreover, it has to be considered that atrophy rates might differ between different disease stages in PSP, as it was already reported for other neurodegenerative diseases [30]. Additionally, we did not include a quantitative measure of disease severity such as the Progressive Supranuclear Palsy Rating Scale or MDS-Unified Parkinson's Disease Rating Scale. This would have been helpful in estimating disease progression independently from DD.

Patients in this study were diagnosed clinically by expert evaluation; however, misdiagnoses cannot be excluded in the absence of post mortem verification. However, all diagnoses were based on valid diagnostic criteria [21] enhancing the reliability of the clinical diagnosis. Additionally, we have also attempted to retrospectively apply the MDS diagnostic criteria for PSP [22] to allow a more precise description of diagnosis. Four patients, were confirmed to be correctly classified as PSP, by post mortem diagnosis.

In our study, we also did not distinguish between PSP-subtypes, as reported patients were mostly diagnosed with PSP-Richardson`s syndrome. However, it cannot be excluded that distinct subtypes could also differ in atrophy rates, which again points out the importance of further analyses in larger samples.

Moreover, HC presented a decline in MTPR, too. Midbrain shrinkage has been found in healthy ageing previously and, therefore, may have contributed to MTPR reduction, as a significant decline of MW could also be observed [31, 32]. Still, midbrain atrophy is assumed to be more pronounced in PSP. Hence, it should be considered, if intersubject variability in PSP could also account for the results at hand.

The important new finding from the present work apart from the confirmation and replication of previous studies on this topic is that specificity values increase by adding the relΔ_t_MTPR to $MTPR_{BL}$. This is of high clinical relevance in disease differentiation. Statistical comparison of specificity values did not reach significance, as the $MTPR_{BL}$ already had very good values, which were difficult to improve. Still, we believe that the $MTPR_{BL\&\Delta t}$ can further substantiate diagnosis of PSP in follow-up examinations and serve as an additional biomarker of PSP-specific disease progression, which may of particular importance to reveal the efficacy of potential disease-modifying treatments. Finally, the current findings motivate larger patient studies including PSP subtypes and other forms of atypical Parkinsonian diseases to explore the full potential of MTPR and its change as diagnostic tool.

Author contributions SK was involved in execution of the research project, design and execution of statistical analysis and writing of the first draft. JC was involved in execution of the research project, review and critique on statistical analysis and review and critique on the manuscript. LD was involved in execution of the research project, review and critique on statistical analysis and review and critique on the manuscript. ASM was involved involved in execution of the research project, review and critique on statistical analysis and review and critique on the manuscript. SF was involved in execution of the research project, review and critique on statistical analysis and review and critique on the manuscript. MS was involved in conception, organization and execution of the research project. MB was involved in review and critique on statistical analysis and review and critique on the manuscript. AS was involved in conception and organization of the research project, review and critique on statistical analysis and review and critique on the manuscript. CJH was involved in conception, organization and execution of the research project, review and critique on statistical analysis and review and critique on the manuscript.

Funding Open Access funding enabled and organized by Projekt DEAL. The project underlying this report "Helmholtz Alliance for Mental Health in an Ageing Society" (HelMA, HA-215) was supported within the framework of the "Helmholtz Impuls- und Vernetzungsfonds" funded by the German "Bundesministerium für Bildung und Forschung" (BMBF). Furthermore, this work was supported by the "Stiftung für Altersforschung" and the "Forschungskommission", Heinrich-Heine-University, Düsseldorf (Germany).

Data availability The participants of this study did not agree for their data to be shared publicly. Hence, we are not able to offer them for further usage.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the local ethics committee (study no. 2849).

Consent to participate All participants provided written informed consent prior to enrolment in the study.

Consent for publication All participants provided written informed consent for publication of the study results.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will

need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Williams DR, de Silva R, Paviour DC et al (2005) Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain 128(6):1247–1258
2. Litvan I (2003) Update on epidemiological aspects of progressive supranuclear palsy. Mov Disord 18(Suppl. 6):43–50
3. McFarland NR (2016) Diagnostic approach to atypical parkinsonian syndromes. CONTINUUM Lifelong Learn Neurol 22(4 Movement disorders):1117
4. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55:181–184
5. Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 79(4):368–376
6. Poewe W, Wenning G (2002) The differential diagnosis of Parkinson's disease. Eur J Neurol 9:23–30
7. van Eimeren T, Antonini A, Berg D et al (2019a) Neuroimaging biomarkers for clinical trials in atypical parkinsonian disorders: proposal for a neuroimaging biomarker utility system. Alzheimer's Dement Diagn Assess Dis Monit 11:301–309
8. Seppi K, Poewe W (2010) Brain magnetic resonance imaging techniques in the diagnosis of parkinsonian syndromes. Neuroimaging Clin 20(1):29–55
9. Quattrone A, Nicoletti G, Messina D et al (2008) MR imaging index for differentiation of progressive supranuclear palsy from Parkinson disease and the Parkinson variant of multiple system atrophy. Radiology 246:214–221
10. Mahlknecht P, Hotter A, Hussl A, Esterhammer R, Schocke M, Seppi K (2010) Significance of MRI in diagnosis and differential diagnosis of Parkinson's disease. Neurodegener Dis 7(5):300–318
11. Stamelou M, Knake S, Oertel WH et al (2011) Magnetic resonance imaging in progressive supranuclear palsy. J Neurol 258(4):549–558
12. Schrag A, Good CD, Miszkiel K et al (2000) Differentiation of atypical parkinsonian syndromes with routine MRI. Neurology 54:697–702
13. Focke NK, Helms G, Pantel PM et al (2011) Differentiation of typical and atypical Parkinson syndromes by quantitative MR imaging. Am J Neuroradiol 32(11):2087–2092
14. Kato N, Arai K, Hattori T (2003) Study of the rostral midbrain atrophy in progressive supranuclear palsy. J Neurol Sci 210(1–2):57–60
15. Mueller C, Hussl A, Krismer F et al (2018) The diagnostic accuracy of the hummingbird and morning glory sign in patients with neurodegenerative parkinsonism. Parkinsonism Relat Disord 54:90–94
16. Oba H, Yagishita A, Terada H et al (2005) New and reliable MRI diagnosis for progressive supranuclear palsy. Neurology 64:2050–2055
17. Massey LA, Micallef C, Paviour DC et al (2012) Conventional magnetic resonance imaging in confirmed progressive supranuclear palsy and multiple system atrophy. Mov Disord 27(14):1754–1762
18. Kaasinen V, Kangassalo N, Gardberg M et al (2015) Midbrain-to-pons ratio in autopsy-confirmed progressive supranuclear palsy: replication in an independent cohort. Neurol Sci 36(7):1251–1253
19. Josephs KA, Whitwell JL, Boeve BF et al (2006) Rates of cerebral atrophy in autopsy-confirmed progressive supranuclear palsy. Ann Neurol 59(1):200–203
20. Hwang M, Yang H, Kim Y et al (2017) (2013) Differential progression of midbrain atrophy in parkinsonism: longitudinal MRI study. Neurodegener Dis 17(1):31–37
21. Litvan I, Agid Y, Calne D et al (1996) Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 47:1–9
22. Höglinger GU, Respondek G, Stamelou M et al (2017) Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Mov Disord 32:853–864
23. World Medical Association (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310:2191–2194
24. Robin X, Turck N, Hainard A et al (2011) pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinform 12:77
25. Paviour DC, Price SL, Jahanshahi M, Lees AJ, Fox NC (2006) Regional brain volumes distinguish PSP, MSA-P, and PD: MRI-based clinico-radiological correlations. Mov Disord Off J Mov Disord Soc 21(7):989–996
26. Warmuth-Metz M, Naumann M, Csoti I, Solymosi L (2001) Measurement of the midbrain diameter on routine magnetic resonance imaging: a simple and accurate method of differentiating between Parkinson disease and progressive supranuclear palsy. Arch Neurol 58:1076–1079
27. Dutt S, Binney RJ, Heuer HW et al (2016) Progression of brain atrophy in PSP and CBS over 6 months and 1 year. Neurology 87(19):2016
28. Ahn JH, Kim M, Kim JS et al (2019) Midbrain atrophy in patients with presymptomatic progressive supranuclear palsy-Richardson's syndrome. Parkinsonism Relat Disord 66:80–86
29. Owens E, Krecke K, Ahlskog JE et al (2016) Highly specific radiographic marker predates clinical diagnosis in progressive supranuclear palsy. Parkinsonism Relat Disord 28:107–111
30. Fiford CM, Ridgway GR, Cash DM et al (2018) Patterns of progressive atrophy vary with age in Alzheimer's disease patients. Neurobiol Aging 63:22–32. https://doi.org/10.1016/j.neurobiolaging.2017.11.002
31. Lambert C, Chowdhury R, Fitzgerald T et al (2013) Characterizing aging in the human brainstem using quantitative multimodal MRI analysis. Front Hum Neurosci 7:462
32. Luft AR, Skalej M, Schulz JB et al (1999) Patterns of age-related shrinkage in cerebellum and brainstem observed in vivo using three-dimensional MRI volumetry. Cereb Cortex 9(7):712–721

Appendix 3: STUDY 3

Tract-specific DTI Scalars and Clinical Correlates in Progressive Supranuclear Palsy

Querbach, S., Hausmann, A.C., Schnitzler, A., Hartmann, C. J., Rubbert, C. & Caspers, Julian (2025). Tract-specific DTI Scalars and Clinical Correlates in Progressive Supranuclear Palsy [Manuscript submitted for publication].

Conceptualization & methodology: I developed the research question and analysis plan in consultation with J. Caspers.

Investigation & project administration: I supervised recruitment of participants and data collection. I recruited participants and independently performed neuropsychological tests. Me and A. C. Hausmann performed MRI together. I was responsible for data curation. Project administration was performed by me, J. Caspers and C. Rubbert. Review of MRI data was performed by me, A. C. Hausmann, J. Caspers and C. Rubbert C. J. Hartmann contributed to the recruitment of participants.

Formal analysis: I conducted the statistical analyses with contributions by J. Caspers and reviewed them for correctness.

Resources: Resources were contributed by J. Caspers and A. Schnitzler.

Manuscript: I wrote the initial manuscript, which encompassed all stages from comprehensive literature review to the final formulation. I created the figures and tables independently. I also coordinated the scientific review process with the journals, making revisions with the assistance of J. Caspers. All authors critically reviewed the manuscript.

Original Article: NeuroImage:Clinical

Tract-specific DTI Scalars and Clinical Correlates in Progressive Supranuclear Palsy

Silja K. Querbach[1]; Ann Carolin Hausmann[1]; Alfons Schnitzler[1,2]; Christian J. Hartmann[1, 2]; Christian Rubbert[3]; Julian Caspers[3]

Author affiliations:

[1] Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany

[2] Department of Neurology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany

[3] Department of Diagnostic and Interventional Radiology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany

Correspondence to:

Silja Querbach
Institute of Clinical Neurosciences and Medical Psychology,
Medical Faculty and University Hospital Düsseldorf,
Moorenstraße 5, 40225 Düsseldorf (Germany); silja.querbach@med.uni-duesseldorf.de

Running title: DTI scalars in PSP

Keywords: Atypical Parkinsonism, DTI, White Matter Tracts, PSP

Abstract

Progressive Supranuclear Palsy (PSP) is an atypical parkinsonian syndrome, presenting with specific constellations of neurological symptoms. Its exact pattern of neurodegeneration remains ill understood—particularly the role of white matter (WM) degeneration in driving hallmark clinical features and underlying pathology.

This study aimed to investigate WM scalars in PSP, focusing on how alterations, as revealed through various diffusion tensor imaging (DTI) metrics, relate to the disease's typical symptomatology. We used DTI analysis and tract based spatial statistics (TBSS) to investigate WM changes related to disease-specific clinical scores in order to unravel potential structure-function relationships for the atrophied tracts. Additionally, we investigated the relation of structural biomarkers, such as the Midbrain-to-Pons-Ratio (MTPR), to WM scalars in the disease.

We identified various WM tracts in PSP related to markers of cognitive dysfunction and disease severity in PSP, including (but not limited to) corticospinal tract; posterior thalamic radiation; internal and external capsule; body, genu, and splenium of the corpus callosum; superior longitudinal fasciculus; and the inferior and superior fronto-occipital fasciculus. Increased MTPR was significantly correlated with DTI metrics in motor-related fibers around the brain stem.

Our findings of WM tracts can be well linked to PSP-related symptomatology such as disease-specific motor impairment, disease severity, and cognitive decline in certain areas. The results are overall consistent with former findings. As PSP is suggested to be a network-based disorder, the present work confirms that considering disease-specific WM atrophy patterns might provide a better understanding of the complex symptom-characteristics of PSP-related pathologies.

Introduction

Progressive Supranuclear Palsy (PSP) is a rare neurodegenerative disorder marked by progressive motor, cognitive, and behavioral impairments[1–4]. PSP often presents with individual constellations of clinical symptoms, which makes accurate diagnosis a considerable challenge[5–7]. Usually, PSP diagnosis is supported by structural magnetic resonance imaging (MRI) findings: the classical hallmarks of PSP (e.g. supranuclear gaze palsy; backward falls) primarily involve dysfunction caused by grey matter (GM) atrophy within the basal ganglia and midbrain[8,9]. However, conventional MRI may only detect these changes at later disease stages, while earlier microstructural white matter (WM) alterations may precede GM atrophy and clinical symptoms[10–12]. Thus, a sensitive identification of an early neurodegenerative process with routinely available techniques, such as MRI, could be valuable for a rapid monitoring of the disease. Diffusion tensor imaging (DTI) provides quantitative metrics of tissue integrity and connectivity, offering sensitive markers for microstructural degeneration and brain functionality[13].

GM atrophy in PSP predominantly affects the midbrain, often accompanied by third ventricle enlargement, as well as frontal and parietal lobes. Radiological indices such as the Midbrain-to-Pons-Ratio (MTPR) have been proposed as reliable biomarkers[14,15]. Given PSP's potential network-based nature[16], WM alterations—reflected in fractional anisotropy (FA), and mean, axial, and radial diffusivity (MD; AD; RD)—have also gained attention as potential biomarkers in movement disorders[17]. Regarding PSP specifically, emerging evidence highlights the significance of WM alterations contributing to its overall pathology[18–21].

Considering cognitive and motor impairments to be major defining features of the disease, associations between DTI scalars and certain clinical scales may clarify the structural basis of impairment characteristics of PSP. In this regard, former investigations already established a link between WM integrity and the cognitive decline as well as motor dysfunction observed in PSP patients[22–24] and understanding the relationship between microstructural alterations and clinical manifestations is crucial.

This study aims to assess whether PSP is characterized by specific DTI scalar patterns in functionally relevant brain regions and how these patterns relate to disease severity and cognitive changes. By integrating DTI metrics with clinical scales, we aim to advance the understanding of PSP pathology and its structural-clinical relationships.

Materials and methods

Participants

15 patients with PSP Richardson syndrome were included in the study (see Table 1). All patients were diagnosed according to standardized clinical criteria for probable or possible PSP. Subjects were excluded if they did not consent to participate, if MRI was contraindicated or if MRI revealed a lesion that would affect final analyses. Patients were instructed to withhold regular antiparkinsonian medication for at least 8 hours before assessments. Clinical examination of all patients was performed by an experienced physician (CJH) and included standardized neurological testing and medical history. Clinical scores were assessed, including the PSP-Rating Scale (PSPRS) as measure of disease severity, the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) for evaluating severity of motor symptoms, as well as the the Montreal Cognitive Assessment (MoCA) and the Mattis Dementia Rating Scale (MDRS) were assessed to evaluate global cognitive status. The study protocol complied with the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board. The trial is registered with the German Clinical Trials Register (DRKS-ID: DRKS00034050).

Table 1
Demographic Data of All Patients

	n	Sex (m/f)	Age at MRI	Disease Duration	YOE	Levodopa Responsive
Mean±SD	15	5/10	70.07±7.03	14.07±14.24	13.13±2.70	n/a

Note. SD=standard deviation, YOE=years of education, Disease Duration is given in months.

MRI Acquisition

All patients underwent T1-weighted and multi-shell diffusion MRI (dMRI) on a 3T Siemens Prisma (Siemens Healthcare GmbH, Erlangen, Germany). The MRI protocol incorporated sequences adapted from the Lifespan Human Connectome Project in Aging (HCP-A) including dMRI (msDWI: 64 channel head coil, voxel-size 1.5mm³, 92 slices, FOV 210x210mm, TR=3230ms, TE=89,2ms, flip angle=90°, 98 gradient directions, b-values 0, 1500, 3000 s/mm², multiband-factor 3) and high-resolution structural MRI (T1w: 3D MPRAGE, voxel size 0.8mm³, FOV 240x256mm, TR=2500ms, TE=2,22ms, TI=1000ms, flip angle = 8°). To minimize motion-artifacts, the head of every subject was firmly positioned in the head coil with cushions. MRI sequences were visually examined (JC; CR; SK) to exclude relevant confounders such as strong movement artefacts or incidental findings.

Morphometric Measurements

Morphometric measurements were manually assessed using 3D Slicer Version 4.11. (slicer.org). Midsagittal T1-weighted individual MRIs were used for the midbrain and pons measurements, using the methodology described by Massey et al. (2013). Line measurements were drawn over pons and midbrain (maximal widths perpendicular to the visually estimated oblique superior–inferior axes). Pons measurements did not include the pontine tegmentum and midbrain measurements did not include the collicular plate[14,25]. The MTPR was calculated by dividing the midbrain width by the pons width for each patient. Additionally, we measured the maximum width of the superior cerebellar peduncles (SCP) in the coronal plane and the middle cerebellar peduncles (MCP) in the sagittal plane.

Preprocessing & Analysis

Further analyses were run using FSL toolbox v. 6.0 (FMRIB Software Library). dMRI data were pre-processed according to the HCP minimal preprocessing pipeline for diffusion data[26]:

1. **Structural Pipelines**

   Utilizing *PreFreeSurfer*, a native structural volume space for each subject was produced and the acquired T1w and T2w images were registered to this space. The images were distortion corrected for gradient and b0 distortions and rigidly aligned to the MNI space. Following a B_1 correction, in *FreeSurfer,* volumes were segmented into predefined structures and white and pial surfaces were reconstructed. This was followed by a standard folding-based surface registration to the surface atlas (fsaverage). During *PostFreeSurfer*, a surface registration to the Conte69 surface template was performed[27]. Registered surfaces were downsampled, creating the final brain mask.

2. **Diffusion Pipeline**

   The mean b_0 image across six diffusion series was intensity normalized and used to estimate the Echo Planar Imaging (EPI) distortion[28]. A Gaussian Process predictor modeled eddy-current-induced field inhomogeneities and head motion for each image volume. All identified distortions were corrected in one resampling step using the "eddy" tool. The diffusion data output from the eddy tool was resampled into a 1.25 mm native structural space and masked to exclude non-brain tissue from further analyses.

DTI scalar images were then computed from pre-processed diffusion data using dtifit in FSL v. 6.0 and further processed with tract-based spatial statistics (TBSS). Diffusion tensors were estimated at each voxel providing information about the magnitude and direction of water diffusion. From the diffusion tensor, scalar measures were computed as follows:

The FA map was derived from the eigenvalues of the diffusion tensor to characterize voxel-wise anisotropy, reflecting WM structural integrity. MD, calculated as the average of the three eigenvalues, indicates the overall magnitude of diffusion and is sensitive to tissue density and cellular structure. AD, corresponding to the principal eigenvalue ($\lambda 1$), reflects diffusion along the main axis of WM tracts, while RD, the average of the two smaller eigenvalues ($\lambda 2$ and $\lambda 3$), captures diffusion perpendicular to this axis and is sensitive to myelin and axonal changes. Scalar maps for each subject were nonlinearly registered to a target image in MNI space. A WM skeleton, representing the core of major tracts (Smith et al., 2006), was generated from the center of the group FA distribution, excluding peripheral voxels with high inter-subject variability. Each subject's FA, MD, RD, and AD data were projected onto the mean FA skeleton. Regions with mean FA values below 0.2 were masked to exclude cerebrospinal fluid and GM.

Statistical Analyses

Statistical analyses were applied on the skeletonized DTI scalar maps to identify regions of significant correlations with MoCA, MDRS, UPDRS-III, PSPRS sum score, as well as its gait and oculomotor sub scores, and the MTPR, using general linear models and permutation testing (5000 permutations) in TBSS controlling for multiple comparisons and applying Threshold-Free Cluster Enhancement (TFCE; $p \leq .05$, family-wise error-corrected). All significant results were visualized on the WM skeleton, providing insights into the specific WM tracts that exhibit significant relations to the assessed clinical measures. Significant clusters were located and labelled anatomically according to the Johns Hopkins University WM tractography atlas. To assess the relationship between the clinical scores and manual measures among each other, we additionally performed spearman correlations. Results were corrected for multiple comparisons using the family-wise error correction at $p \leq .05$.

Results

Clinical Assessments and Morphological Measurements

Clinical data of the included patients is given in Table 2. Most PSPRS sum scores were above a value of 30/100 impairment and show a progressed disease severity for most patients. The mean MoCA score was below the clinical cutoff (<26), which indicates that the group tended to be cognitively impaired[29].

[Insert Table 2 about here]

Table 2
Clinical Scores of all patients

	PSPRS	PSPRS_O	PSPRS_G	UPDRS-III	MDRS	MoCA
Mean±SD [Range]	36.07±9.07 [18–51]	7.33±3.22 [3–12]	8.93±3.79 [2–15]	37.16±10.11 [14–57]	127.20±8.99 [109–140]	19.62±4.50 [10–27]
Max Score	100	16	20	108	144	30

Note. SD=standard deviation, PSPRS=PSP rating scale, PSPRS_O=PSP rating scale oculomotor subscore, PSPRS_G=PSP rating scale gait subscore.

Table 3 indicates the morphological measurements of the observed patients. The mean for the midbrain width as well as the MTPR were mostly below the proposed cutoff of 9.35mm / 0.52[14] indicating PSP. Values for the SCP did not show a PSP-related decrease (0.18±0.07; [30]).

[Insert Table 3 about here]

Table 3
Manual Brain Measurements

	MB width [a]	SCP width [a]	MCP width [a]	Pons Width [a]	MTPR	MCP/SCP
Mean±SD [Range]	8.79±1.24 [6.6–10.6]	5.34±0.89 [3.7–6.8]	10.96±0.98 [9.4–12.6]	17.09±1.24 [13.9–18.5]	0.51±0.06 [0.38–0.6]	2.12±0.48 [1.5–3.2]

Note. MB = Midbrain, SCP = superior cerebellar peduncle, MCP = middle cerebellar peduncle, MTPR = midbrain to pons ratio, SD = standard deviation.

[a] Values given in mm.

Table 4 visualizes the correlations between morphological measures and clinical scores. Significant correlations were found for the cognitive scores amongst each other. Motor scores also correlated significantly with each other, and the structural measures correlated with the parameters of which they are composed. MDRS specifically correlated with DD.

[Insert Table 4 about here]

Table xx
Clinical Scores

Variable	Mean±SD	Age	DD	YOE	MW	PW	MTPR	SCP	MCP	MCP_SCP	PSPRS	PSP_O	PSP_G	UPDRS-III	MDRS	MoCA
Age	70.07±7.03															
DD	5.33±6.12	.10 [-.44-.58]														
YOE	13.13±2.70	**-.54*** **[-.82-.-02]**	**.52*** **[-.81-.01]**													
MW [a]	8.79±1.24	.23 [-.33-.66]	.04 [-.48-.54]	.23 [-.33-.66]												
PW [a]	17.09±1.24	.24 [-.32-.67]	.13 [-.42-.45]	**.20** [-.35-.64]	.45 [-.10-.78]											
MTPR	0.51±0.06	.11 [-.43-.59]	-.05 [-.55-.48]	.13 [-.41-.60]	**.84**** **[.54-.94]**	-.11 [-.59-.43]										
SCP [a]	5.34±0.89	.05 [-.48-.55]	-.07 [-.56-.46]	.27 [-.29-.68]	.04 [-.49-.54]	.21 [-.35-.65]	-.08 [-.57-.45]									
MCP [a]	10.96±0.98	.04 [-.48-.54]	-.08 [-.57-.45]	.22 [-.33-.66]	**.61*** **[.12-.85]**	**.55*** **[-.03-.82]**	.35 [-.21-.73]	-.26 [-.68-.30]								
MCP_SCP	2.12±0.48	-.01 [-.52-.50]	.12 [-.43-.59]	.18 [-.63-.37]	.21 [-.34-.65]	-.01 [-.51-.51]	.24 [-.32-.66]	**-.93**** **[-.97-.-.77]**	**.57*** **[.06-.83]**							
PSPRS	36.07±9.07	.34 [-.23-.72]	.10 [-.44-.58]	**-.60*** **[-.84-.66]**	-.28 [-.69-.28]	-.26 [-.66-.33]	-.17 [-.62-.38]	-.47 [-.78-.08]	.11 [-.43-.59]	.44 [-.11-.77]						
PSP_O	7.33±3.22	.07 [-.46-.56]	.20 [-.36-.64]	-.50 [-.80-.04]	-.50 [-.80-.04]	-.28 [-.69-.28]	-.37 [-.74-.19]	**-.51*** **[-.81-.02]**	-.01 [-.52-.40]	.44 [-.11-.77]	**.89**** **[.67-.96]**					
PSP_G	8.93±3.79	.44 [-.12-.77]	.12 [-.43-.58]	**-.63**** **[-.86-.-.15]**	.04 [-.49-.54]	-.01 [-.52-.51]	.06 [-.47-.55]	-.37 [-.73-.19]	.47 [-.07-.79]	.50 [-.03-.80]	**.70**** **[.27-.89]**	**.52*** **[-.01-.81]**				
UPDRS-III	37.16±10.11	.31 [-.25-.70]	.36 [-.20-.73]	**-.78**** **[-.86-.-.15]**	-.07 [-.56-.46]	-.04 [-.54-.49]	-.06 [-.55-.47]	-.47 [-.78-.08]	.17 [-.38-.62]	.50 [-.03-.80]	**.63**** **[.15-.86]**	**.53*** **[.01-.82]**	**.79**** **[.45-.92]**			
MDRS	127.20±8.99	-.22 [-.66-.35]	**.53*** **[-.01-.81]**	-.05 [-.55-.47]	-.28 [-.69-.28]	.18 [-.37-.63]	-.42 [-.76-.13]	.44 [-.12-.77]	-.23 [-.66-.33]	-.40 [-.75-.15]	-.26 [-.68-.30]	-.15 [-.61-.39]	-.25 [-.68-.31]	-.17 [-.62-.38]		
MoCA	19.62±4.50	-.50 [-.79-.04]	.446 [-.09-.78]	.08 [-.45-.57]	-.09 [-.58-.45]	.01 [-.41-.52]	-.11 [-.59-.43]	.27 [-.29-.68]	-.10 [-.58-.44]	-.22 [-.65-.33]	-.39 [-.74-.17]	-.33 [-.71-.23]	-.27 [-.68-.29]	-.18 [-.63-.37]	**.85**** **[.58-.95]**	

Note. Vaues in square brackets indicate the 95% confidence interval for each correlation. * indicates p≤.05. **indicates p≤.01. SD = standard deviation, PSPRS=PSP rating scale, PSPRS_O=PSP rating scale oculomotor subscore, PSPRS_G=PSP rating scale gait subscore. [a] Values given in mm.

DTI Scalars

Correlations with Motor Scores

Regions of significant correlations with PSPRS and UPDRS with DTI metrics are visualized in Figure 1 and 2.

We found small clusters of FA values negatively correlated with PSPRS sum score (*M*=36.07±9.07) in the following WM tracts: bilateral anterior thalamic radiation; bilateral corticospinal tract; bilateral superior and inferior cerebellar peduncle; bilateral superior longitudinal fasciculus; corpus callosum (body, genu); bilateral medial lemniscus; cingulum (cingulate gyrus).

The further analysis of FA values revealed significantly negative correlations with UPDRS motor score (*M*=37.16±10.11) in these WM tracts: bilateral superior longitudinal fasciculus; bilateral corticospinal tract; corpus callosum (genu, body); right anterior thalamic radiation; right inferior fronto-occipital fasciculus; left inferior cerebellar peduncle; left superior corona radiata.

We also found positively correlated MD values with the PSPRS sum score in the WM tracts: bilateral anterior and posterior thalamic radiation; bilateral corticospinal tract; bilateral superior longitudinal fasciculus; bilateral retrolenticular part of the internal capsule; bilateral superior and posterior corona radiata; corpus callosum (splenium).

The more specific analysis of PSPRS sub scores revealed that MD values correlated positively with PSPRS gait sub score (*M*=8.93±3.79) in the following WM tracts: bilateral corticospinal tract; bilateral superior longitudinal fasciculus; corpus callosum (splenium); right anterior limb of internal capsule.

Significantly positive correlations between RD and PSPRS sum score were found in: bilateral anterior thalamic radiation; bilateral corticospinal tract; cingulum (cingulate gyrus); corpus callosum (genu; body); bilateral inferior and superior cerebellar peduncle; middle cerebellar peduncle; bilateral superior longitudinal fasciculus; right external capsule.

[Insert Figure 1 about here]

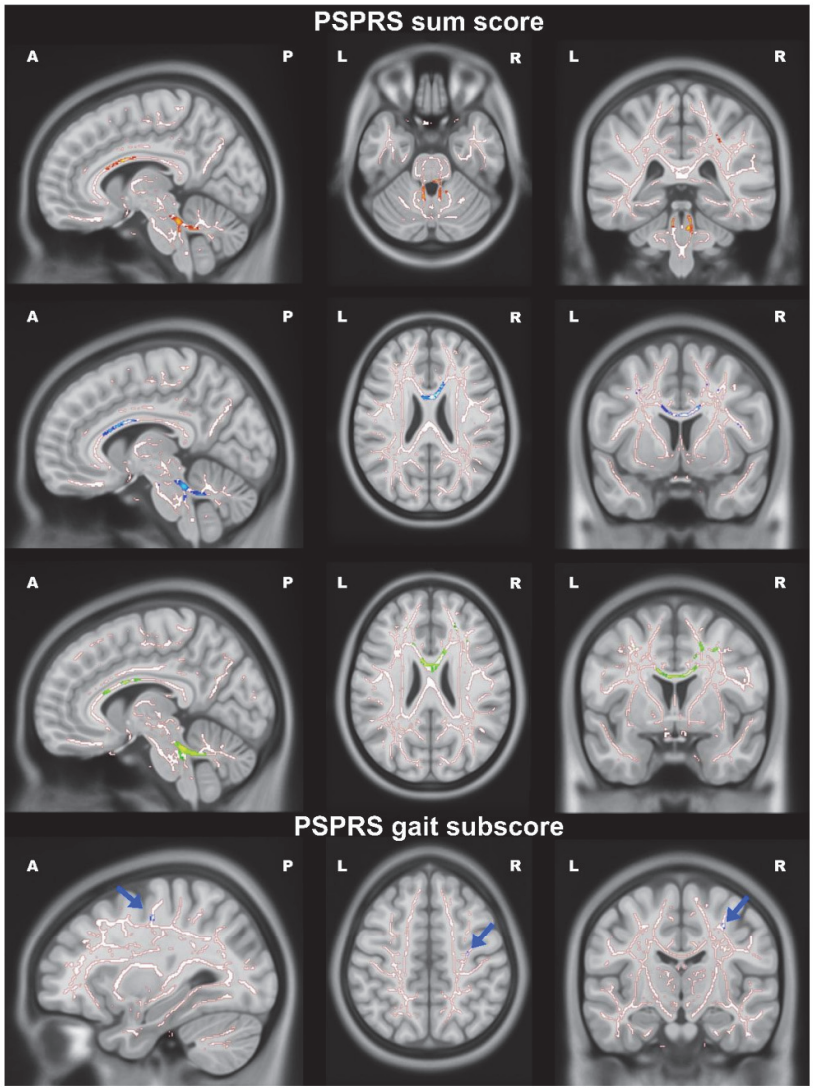


Fig. 1 TBSS results showing voxels where an increase in PSPRS scores were significantly correlated with FA decrease (red-yellow), MD increase (blue-lightblue), RD increase (green-lightgreen), at $p<0.05$ (FWE corrected for multiple comparisons). White represents the mean FA skeleton of all participants.

[Insert Figure 2 about here]

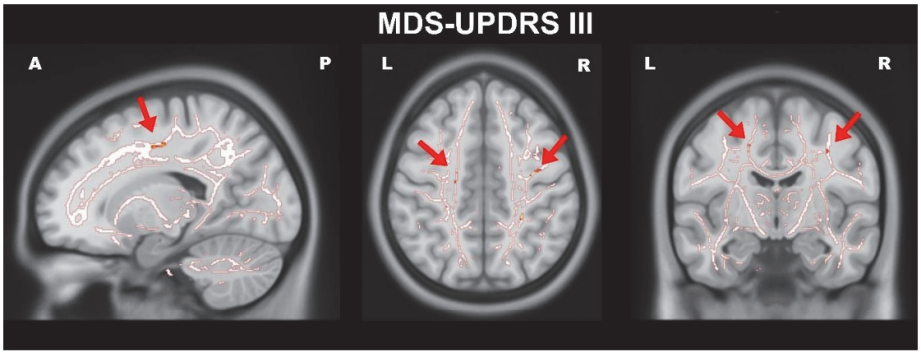


Fig. 2 TBSS results showing voxels where an increase in UPDRS score was significantly correlated with FA decrease (red-yellow), at $p<0.05$ (FWE corrected for multiple comparisons). White represents the mean FA skeleton of all participants.

Correlations with Cognitive Scores

Significant correlations of MoCA and MDRS with all DTI metrics are visualized in Figure 3 and 4.

Across the observed patients we found clusters of FA values positively correlated with MoCA score (M=19.62±4.50) in the following WM tracts: bilateral anterior and posterior thalamic radiation; bilateral corticospinal tract; bilateral inferior fronto-occipital fasciculus; bilateral superior longitudinal fasciculus; corpus callosum (body); bilateral anterior, superior, and posterior corona radiata; cingulum (cingulate gyrus); forceps major; forceps minor.

For RD, we found negative correlations with MoCA score in: bilateral anterior and posterior thalamic radiation; bilateral corticospinal tract; cingulum (cingulate gyrus); corpus callosum (genu; body; splenium); middle cerebellar peduncle; bilateral inferior fronto-occipital fasciculus; bilateral inferior and superior longitudinal fasciculus.

Additionally negative correlations for RD were found with MDRS sum score in: bilateral anterior and posterior thalamic radiation; bilateral inferior fronto-occipital fasciculus; bilateral longitudinal fasciculus; bilateral anterior, superior and posterior corona radiata; corpus callosum (genu, body, splenium); forceps minor and major.

For AD, we found negative correlations with MoCA score in: bilateral anterior and posterior thalamic radiation; bilateral corticospinal tract; cingulum (cingulate gyrus); bilateral anterior, superior and posterior corona radiata; corpus callosum (genu; body; splenium); middle cerebellar peduncle; bilateral inferior fronto-occipital fasciculus; bilateral inferior and superior longitudinal fasciculus; forceps minor and major.

Additionally negative correlations for AD were found with MDRS sum score in: bilateral anterior and posterior thalamic radiation; bilateral inferior fronto-occipital fasciculus; bilateral longitudinal fasciculus; bilateral anterior, superior and posterior corona radiata; corpus callosum (genu, body, splenium); forceps minor and major.

[Insert Figure 3 about here]

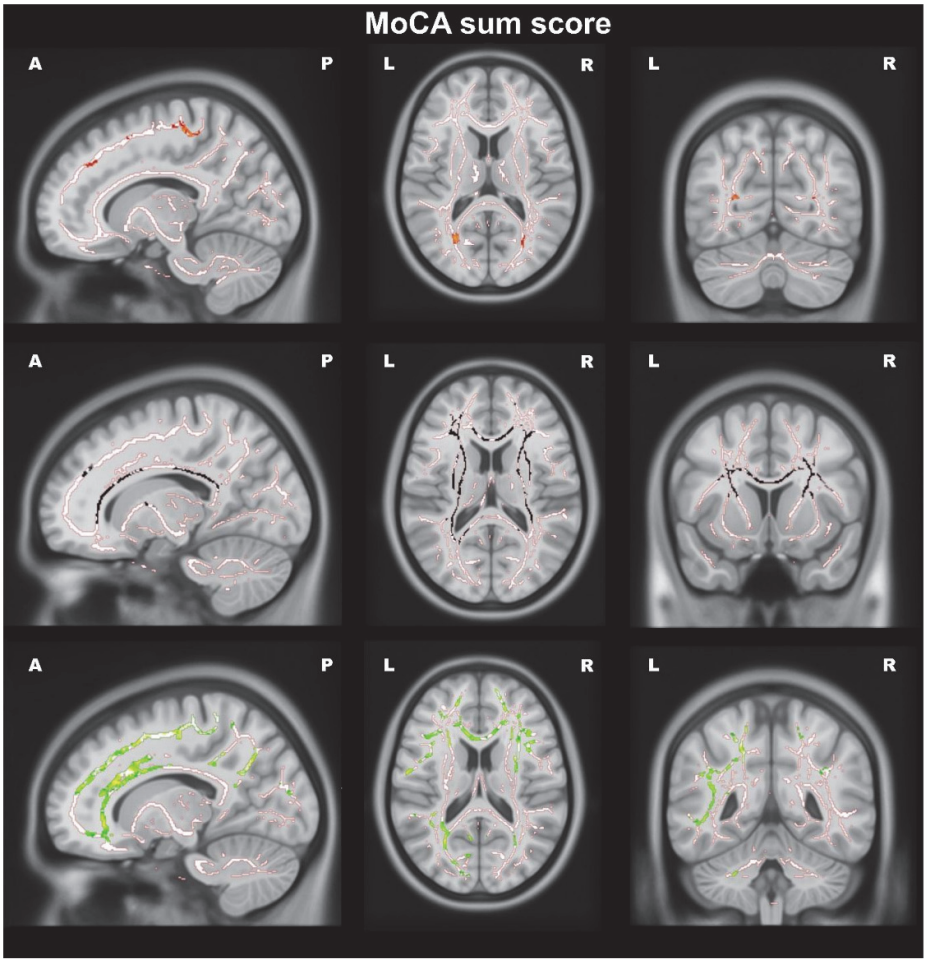


Fig. 3 TBSS results showing voxels where an increase in MoCA score was significantly correlated with FA increase (red-yellow), AD decrease (black-grey), and RD decrease (green-lightgreen), at $p<0.05$ (FWE corrected for multiple comparisons). White represents the mean FA skeleton of all participants.

[Insert Figure 4 about here]

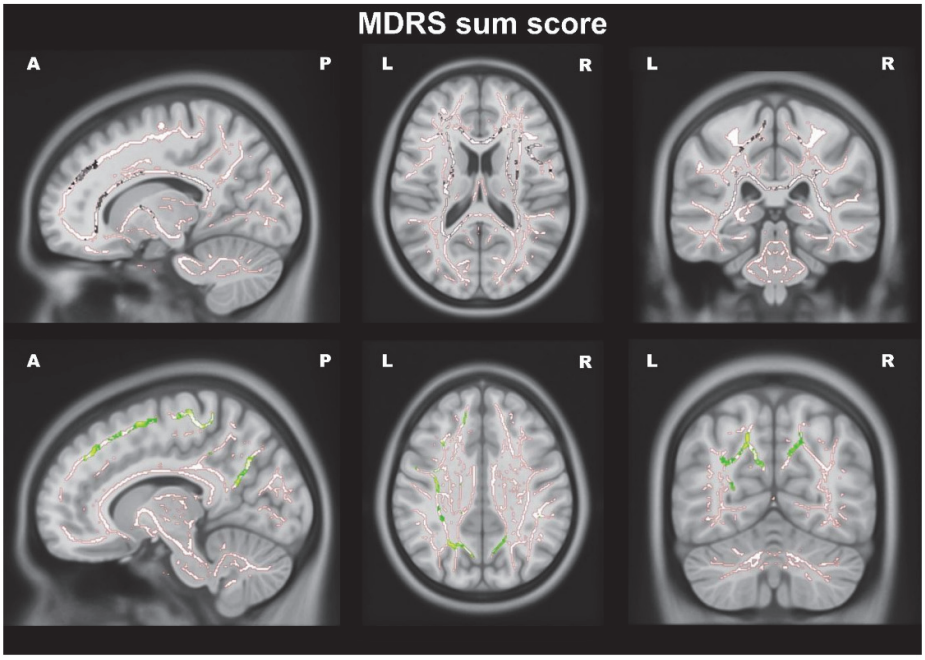


Fig. 4 TBSS results showing voxels where an increase in MDRS score was significantly correlated with AD decrease (black-grey) and RD decrease (green-lightgreen), at $p<0.05$ (FWE corrected for multiple comparisons). White represents the mean FA skeleton of all participants.

Correlation with Morphological Measures

Regions of significant correlations of MTPR with DTI metrics are visualized in Figure 5.

For the manual midbrain measurements, we revealed significant positive correlations between FA and MTPR in the following tracts: right corticospinal tract; right cingulum; bilateral forceps minor; bilateral inferior fronto-occipital fasciculus; bilateral inferior and superior longitudinal fasciculus; middle cerebellar peduncle; corpus callosum (genu; body; splenium); bilateral internal capsule; bilateral anterior, superior and posterior corona radiata; bilateral posterior thalamic radiation (includes optic radiation).

In the manual measurements, MD showed significantly negative correlations with the MTPR in the following tracts: bilateral anterior thalamic radiation; bilateral corticospinal tract; bilateral inferior fronto-occipital fasciculus; bilateral inferior and superior longitudinal fasciculus; corpus callosum (body; splenium); right internal capsule; bilateral superior and posterior corona radiata; bilateral posterior thalamic radiation.

Significantly negative correlations of RD with MTPR were found in: bilateral anterior thalamic radiation; bilateral corticospinal tract; right cingulum; right inferior fronto-occipital fasciculus; right inferior and bilateral longitudinal fasciculus; corpus callosum (body; splenium); right internal capsule; bilateral superior and posterior corona radiata; bilateral posterior thalamic radiation (includes optic radiation).

[Insert Figure 5 about here]

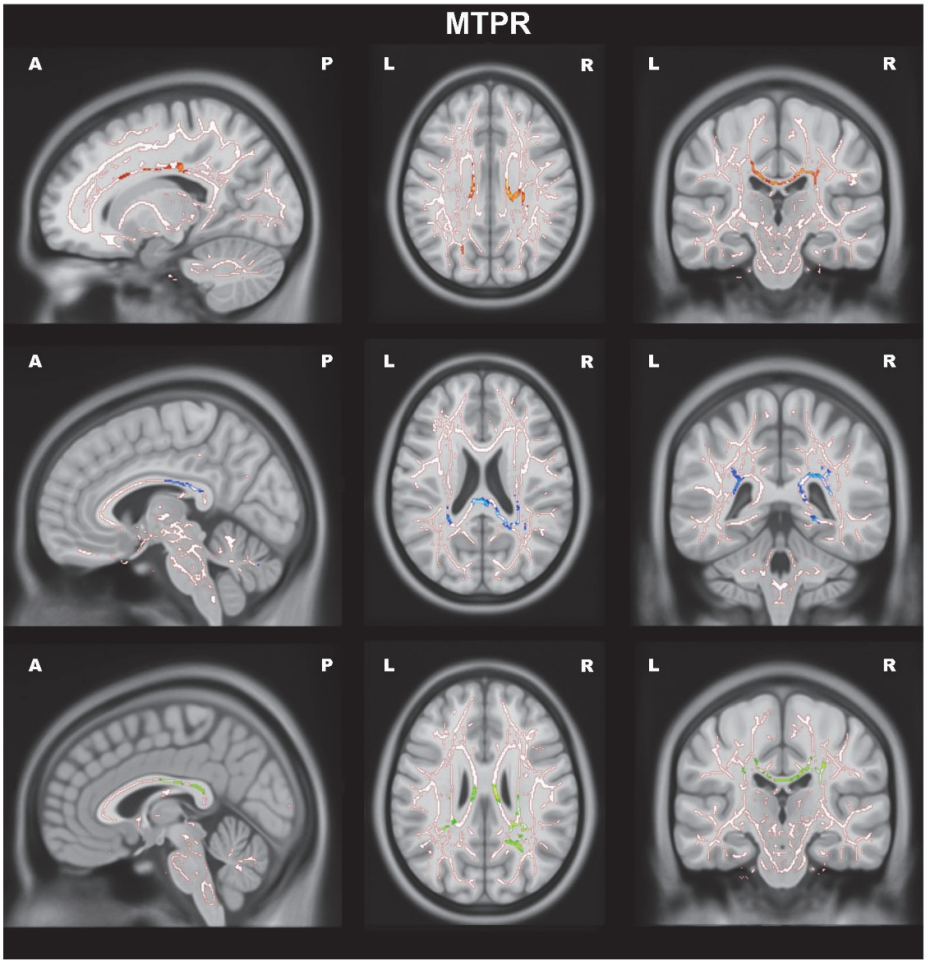


Fig. 5 TBSS results showing voxels where an increase in MTPR was significantly correlated with FA increase (red-yellow), MD decrease (blue-lightblue), RD decrease (green-lightgreen), at $p<0.05$ (FWE corrected for multiple comparisons). White represents the mean FA skeleton of all participants.

Discussion

In the present work, we employed DTI to analyze the relationship between microstructural changes and clinical manifestations in PSP patients. Our results demonstrate widespread correlations between WM integrity and clinical scores, particularly in regions involved in cognitive functions (e.g., executive control, memory, language), emotion regulation, motor control, visual processing, and interhemispheric communication. WM scalars in these key regions were strongly associated with cognitive and motor impairment. These findings highlight the role of broad WM networks in the PSP symptom complex and offer valuable insights into the disease's underlying mechanisms, with important diagnostic and prognostic implications.

We observed consistent alterations across multiple DTI scalars in overlapping pathways. The affected tracts align with major large-scale brain networks, including the limbic system, sensorimotor, default mode, frontoparietal, executive control, and salience networks—all essential for motor and cognitive functions such as executive processing and memory[31]. This aligns with the understanding that disruptions in WM microstructure contribute to both, motor and cognitive dysfunction in several neurodegenerative disorders[32] and reinforces the presence of this structure-function relationship in PSP.

Correlation with Motor Scores

In terms of motor performance and disease severity we found significant relationships with the PSPRS as well as UPDRS-III; FA exhibited negative correlations with both motor scores. MD and RD showed positive correlations with PSPRS only. This is consistent with the assumption that higher FA values typically correspond to regions with well-oriented fiber bundles, thus, indicating sustained WM integrity resulting in conductive functioning. In contrast, high MD is suggested to reflect tissue damage. Since higher RD may indicate axonal degeneration and demyelination, motor impairment and reduced performance could result from several pathological processes[33,34]. The observed correlations support the idea that reduced WM integrity leads to more severe motor symptoms of varying intensity and modality. Also, different WM degeneration processes appear to contribute to specific motor symptoms, as shown here by varying combinations of DTI metrics correlated with PSPRS and UPDRS scores.

The key regions identified, including (but not limited to) the corticospinal tract, superior longitudinal fasciculus, and corpus callosum are integral to motor control and coordination,

implicating their involvement in movement disorders. The corpus callosum, as the brain's largest commissural fiber bundle, plays a vital role in interhemispheric communication[35]. Past research has already highlighted its significance in motor control, confirming microstructural alterations in this area to be related to motor impairment caused by diseases such as idiopathic Parkinson's disease (IPD) or stroke[36–38]. As the corpus callosum corresponds to premotor and supplementary motor areas, the question could be raised whether PSP-related motor-symptoms might also originate from there[39,40].

The medial lemniscus conveys proprioceptive, tactile, and sensory information from the body to the thalamus and somatosensory cortex. Changes, indicated by reduced FA, might not be direct contributors to motor performance. However, they could lead to a loss of proprioception. This loss disrupts the feedback loop necessary for coordinated movement[41]. Thus, the observed correlations here, might hint towards functional loss in network communication causing disrupted proprioception in PSP[42].

The thalamus, known for its PSP-related pathology, is closely linked to disease stage and motor dysfunction[18]. The anterior thalamic radiation connects thalamic nuclei with the prefrontal cortex and influences motor function through higher-order cognitive processes, thus, damage to these fibers leads to impairment in executive functions like motor planning[43,44]. Additionally, microstructural damage in the fronto-occipital fasciculus might lead to difficulties integrating visual information, further complicating motor planning. This can be complemented by assumably impaired transmission of motor commands in the superior corona radiata and left inferior cerebellar peduncle, important for limb movement coordination[45]. The correlations found, hint towards FA reduction and MD increase in the above-mentioned fibers to be related to coordinative impairment in PSP.

Functions of the identified tracts correspond well to PSP-related symptoms: It is well-known for its ocular motor abnormalities, which can be linked to changes in superior longitudinal fasciculus[20]. Higher MD values are generally connected to disease severity in neurological disorders, which is supported by our positive correlations of PSPRS and MD[46,47]. Overall, the observed correlations of the gait subscore in PSPRS with DTI scalars suggest that damage of specific WM tracts might account for individual gait disturbances, a common symptom in neurodegenerative diseases[48]; Here, the gait subscore of PSPRS showed less widespread but more specific correlations in: bilateral corticospinal tract, bilateral superior longitudinal fasciculus, and right anterior limb of internal capsule. These findings are

consistent with WM correlates of gait abnormalities found in PSP in a previous study investigating structural changes in PSP in relation to disease-specific motion[49].

In this context, it's important to note that PSP initially exhibits overlapping symptoms with IPD. This suggests that the underlying mechanisms producing these symptoms are likely similar. Thus, we have indirect support from IPD evidence; Overall, our findings align with evidence indicating a significant role of WM lesions in IPD-related motor impairment[50]. Our results strongly support the complexity of various combinations of WM changes contributing to individual motor dysfunction, impacting the sensorimotor network. The widespread pattern of tracts included in MD changes related to the motor scores hints towards a potential supporting role of myelin disruption in motor impairment, consistent with previous findings[23,51,52].

Correlation with Cognitive Scores

Even though PSP is primarily recognised as a movement disorder, cognitive impairment is a common symptom. Cognitive symptoms in PSP encompass executive dysfunction, attention deficits, and memory impairment[2,53,54]. Here, we found widespread correlations of cognitive scores with DTI scalars in a number of WM tracts attributable to several large-scale networks[55]; Generally, FA was positively correlated with MoCA score, and RD as well as AD showed negative correlations with MoCA and MDRS score, indicating that loss of WM integrity of the respective tracts is associated with worse cognitive performance.

These findings support the general notion that higher FA accompanies better cognitive performance[33] and underline the link between WM integrity, particularly in regions involved in cognitive processing, and the severity of cognitive symptoms. Besides its important role in motor function, there has been evidence of callosal involvement in cognitive processes in neurological diseases; WM alterations in the corpus callosum lead to a loss of complexity in connections to other regions. Thus, cognitive impairment could be seen as a result of callosal disconnection[56–58]. This can be supported by our finding of correlations for FA, AD and RD with MoCA score within the corpus callosum as well as the forceps minor, which mainly connects the frontal lobes of both hemispheres. Taking our results into account, changes in WM integrity in those regions might hint towards impaired cognitive functions, attributable to disrupted connectivity affecting attention and working memory[59].

Various correlations in tracts such as the superior longitudinal fasciculus, corona radiata, cingulum bundle, inferior longitudinal fasciculus, and the thalamocortical radiations

support a strong involvement of the attention / salience network in PSP-related cognitive impairment (Bharti et al. 2017). The salience network is responsible for filtering salient stimuli from the environment and select stimuli that need immediate attention. The attention network encompasses several subsystems responsible for different aspects of attention, including sustained attention, selective attention, and executive control of attention. In PSP, apathy, cognitive rigidity, and executive dysfunction are common symptoms, leading to deficits maintaining focus, and shifting attention (Gerstenecker et al., 2013). Patients with PSP often exhibit symptoms such as distractibility, slow processing speeds, and difficulty in handling complex or multitasking situations, which contributes to impaired cognitive scores (Rittman et al., 2016). The present correlations hint towards a crucial role of WM integrity changes in these networks, when it comes to cognitive symptoms.

The mentioned tracts are also part of the frontoparietal network, important for cognitive control, working memory, and decision making, which is also in line with our correlations[16]. Cognitive control and working memory are important to succeed in cognitive screening tests. Additionally, related findings in the inferior longitudinal fasciculus also draw attention to the default mode network. This network is typically active when individuals do not focus on the outside world and are instead engaged in internal mental processes like future planning and preparation for upcoming decisions[20]. The observed correlations could hint towards widespread WM tract networks of internal processes potentially impairing cognitive functioning and decision making when disrupted.

We also found evidence for relationships to the visual network: observed correlations of FA and MD with the optic radiation and superior longitudinal fasciculus might be related to the hallmark of PSP, i.e. supranuclear gaze palsy[60]. Negative AD correlations with MoCA and MDRS score in the fronto-occipital fasciculus might explain axonal impairment in visuospatial processing, a rather common problem in PSP[57,61].

Intriguingly, RD and AD showed negative correlations with MDRS sum score in several regions. The inverse relationship between RD and cognitive performance suggests that alterations in myelin integrity may underlie cognitive decline[62,63]. However, the absence of a correlation between FA and the MDRS score suggests that the relationship between FA and cognitive function may vary depending on the specific cognitive domain being assessed. Notably, MDRS and MoCA are cognitive screening tools that evaluate different domains of cognitive function, including attention, memory, language, and visuospatial skills. Most of all,

MDRS is more sensitive to more pronounced cognitive problems, while the MoCA is more sensitive to mild cognitive impairments. A similar pattern could be seen in former studies[64].

Correlation with Morphological Measures

To investigate a possible relationship between GM and WM changes, we also analysed correlations with the MTPR. For GM, we found widespread DTI scalar relationships with midbrain involvement, seen in the mostly pathological midbrain measures. FA correlated positively, MD and RD correlated negatively with MTPR. The positive correlation between FA and MTPR in various tracts suggests that higher FA values correspond to greater structural organization of fibers passing through the midbrain region, such as the corticospinal tract, which consists mostly of motor fibers[65]. This correlation could indicate decreased motor connectivity, potentially leading to less efficient transmission of neural signals and worse motor outcomes. MTPR is generally considered a valuable biomarker for the diagnosis of PSP and its progression[66,67]. In this context, the observed WM tracts and their association with clinical outcomes fit well with the morphologic GM imaging of the disease found.

Here, we observed widespread correlations with tracts passing through midbrain and frontal regions as part of the central executive (frontoparietal) network, such as the superior longitudinal fasciculus and cingulum bundle. This can be complemented by former research, where alterations in those regions were related to motor symptoms and disease progression[40,68]. Agosta et al. (2012) found that MD changes in specific brain regions, including the midbrain and pons, correlated with various clinical symptoms such as postural instability and cognitive impairment in PSP patients. These findings, once more, underline the involvement of interconnected large-scale networks in reflecting the individual, neuropathological and clinical features of these disorders[23]. Overall, the observed correlations hint towards wide-spread overlapping networks that degenerate on an individual basis and can thus cause very distinct symptom complexes, thus, heterogeneous disease patterns.

Limitations

Our study had some limitations, which need to be considered when interpreting the results. First of all, we chose to utilise a whole-brain TBSS approach, rather than a region-of-interest approach, to best characterise all of the regions that may be related to specific impairments in PSP. This comes with an increased risk of Type I errors (false positives) given the multiple comparisons. Although, we employed family-wise-error correction with TFCE to reduce the Type I error risk, it is still important to consider that some significant voxels might

represent Type I error. Further, our sample size was rather low, as is common in PSP research, which may have also limited the statistical power of our analyses. Nevertheless, also in this limited sample we were able to observe significant and consistent alterations of WM tracts in PSP. When it comes to interpreting some DTI metrics, there have been ambiguous findings in former literature: AD alterations have been related to cognitive impairment with inconsistent directions sometimes with increases[69,70] or decreases[71]. This does not allow for clear interpretation of the connection's nature, so, further research is needed.

The present analyses were based on patients who were diagnosed with the most common variant of PSP (i.e. PSP-Richardson syndrome). This means that we were unable to take the various subtypes into account. PSP is a heterogeneous disorder, and individual cases may vary in terms of clinical presentation and microstructural alterations[72]. Still, our sample was at quite early disease stages in mean. The additional analysis of patients with longer disease duration could show more pronounced results. Ultimately, our analysis shows correlative relationships, which do not directly allow for implications on cause-and-effect relationships. In addition, there is no control group for direct comparison. Nevertheless, the discussed preliminary studies provide support for our conclusions.

Clinical Implications

We found that WM connections widely affected the brainstem, cerebellar, and thalamic projections, as well as associative fibers, which is in keeping with the findings of previous studies[60]. PSP causes progressive, incapacitating cognitive, behavioral, and motor dysfunction to varying extends. As in other neurodegenerative diseases, later-affected regions bear anatomical connections with brain areas which were impaired earlier in the course of the disease[73]. Alzheimer's disease, for example, is characterised by the progressive dysfunction and degeneration of interconnected neural networks rather than isolated brain regions (DeTure & Dickson 2019). Pathology accumulates and dysfunction develops gradually over time. Individual brain regions deteriorate gradually as pathology accumulates over years and remain in a semi-functional state with increasingly impaired function[74]. This still enables interaction between diseased regions and still-intact parts of the whole brain network. It is, therefore, plausible that this diseased region can propagate dysfunction through its interactions with other healthy regions in stages. The present results show support of the idea of a broad functional network in PSP to be interconnected and in charge of individual symptom-complexes. Thus, overall neurodegeneration may relate to neural network dysfunction[75,75,76] Cognitive and motor

impairment in PSP is likely multifactorial, involving many different pathological processes: changes in WM topology and connectivity are driven by patterns of progressive aggregation of tau in PSP, which is in line with the network degeneration hypothesis[77].

Understanding the relationship between pathology spread and symptom manifestation, offers the opportunity to make certain predictions about the possible course of the disease in the future. In order to provide predictive evidence, it could certainly be beneficial to evaluate DTI changes over time to establish more precise relationships between clinical outcomes and WM. In neurological and psychiatric disorders, changes in FA, MD, AD, and RD are often observed[78]. Though AD is reportedly less affected than other DTI parameters[23,79], exact mechanisms underlying those changes need to be clarified.

Conclusion

Interpreting the overall results, microstructural alterations in interconnected brain regions are associated with both cognitive decline and motor impairment in PSP. Our results provide strong evidence that disease-specific WM patterns in large-scale networks account for distinct symptom complexes. Overall, our findings highlight the utility of DTI scalars in characterizing the individual relationship between WM, clinical measures of GM atrophy, and cognitive and motor impairment in PSP. We provide profound evidence that supports the idea of a PSP-related intrinsic connectivity network. This is one more step towards unraveling the nuanced underlying pathology of the disease.

Author Contributions

SKQ was involved in design, organization and execution of the research project, execution of statistical analysis and writing of the first draft.

ACH was involved in execution of the research project and review and critique on the manuscript.

CJH was involved in conception, design, review and critique on the manuscript.

AS was involved in review and critique on the manuscript.

CR was involved in conception, organization and execution of the research project, design and execution of statistical analysis.

JC was involved in conception and execution of the research project, review and critique on statistical analysis and review and critique on the manuscript.

All authors have read and approved the manuscript.

Competing Interests

The authors declare no competing interests.

Acknowledgements

Not applicable.

Ethics Approval

The study was approved by the local ethics committee (study no. 2019-470).

Consent to participate

All participants provided written informed consent prior to enrolment in the study.

Consent for publication

All participants provided written informed consent for publication of the study results.

Availability of data and material

The participants of this study did not agree for their data to be shared publicly. Hence, we are not able to offer them for further usage.

References

1. Höglinger, G. U. *et al.* Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Movement Disorders* **32,** 853–864; 10.1002/mds.26987 (2017).

2. Gerstenecker, A., Duff, K., Mast, B. & Litvan, I. Behavioral abnormalities in progressive supranuclear palsy. *Psychiatry research* **210,** 1205–1210; 10.1016/j.psychres.2013.08.045 (2013).

3. Litvan, I. *et al.* Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology* **47,** 1–9; 10.1212/WNL.47.1.1 (1996).

4. STEELE, J. C., RICHARDSON, J. C. & OLSZEWSKI, J. PROGRESSIVE SUPRANUCLEAR PALSY. A HETEROGENEOUS DEGENERATION INVOLVING THE BRAIN STEM, BASAL GANGLIA AND CEREBELLUM WITH VERTICAL GAZE AND PSEUDOBULBAR PALSY, NUCHAL DYSTONIA AND DEMENTIA. *Arch Neurol* **10,** 333–359; 10.1001/archneur.1964.00460160003001 (1964).

5. Golbe, L. I. Progressive supranuclear palsy. *Semin Neurol* **34,** 151–159; 10.1055/s-0034-1381736 (2014).

6. Williams, D. R. & Lees, A. J. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *The Lancet. Neurology* **8,** 270–279; 10.1016/S1474-4422(09)70042-0 (2009).

7. Dickson, D. W. Neuropathology of Progressive Supranuclear Palsy. In *Dementias* (Elsevier2008), Vol. 89, pp. 487–491.

8. Pan, P. *et al.* Brain gray matter abnormalities in progressive supranuclear palsy revisited. *Oncotarget* **8,** 80941–80955; 10.18632/oncotarget.20895 (2017).

9. Shi, H. C. *et al.* Gray matter atrophy in progressive supranuclear palsy: meta-analysis of voxel-based morphometry studies. *Neurol Sci* **34,** 1049–1055; 10.1007/s10072-013-1406-9 (2013).

10. Rektor, I. *et al.* White matter alterations in Parkinson's disease with normal cognition precede grey matter atrophy. *PLOS ONE* **13,** e0187939; 10.1371/journal.pone.0187939 (2018).

11. Agosta, F. *et al.* White matter damage in Alzheimer disease and its relationship to gray matter atrophy. *Radiology* **258,** 853–863; 10.1148/radiol.10101284 (2011).

12. Varga, A. W. *et al.* White matter hemodynamic abnormalities precede sub-cortical gray matter changes in multiple sclerosis. *Journal of the Neurological Sciences* **282,** 28–33; 10.1016/j.jns.2008.12.036 (2009).

13. Maj, E. *et al.* Role of DTI-MRI parameters in diagnosis of ALS: useful biomarkers for daily practice? Tertiary centre experience and literature review. *Neurologia i Neurochirurgia Polska* **56,** 490–498; 10.5603/PJNNS.a2022.0070 (2022).

14. Massey, L. A. *et al.* The midbrain to pons ratio: a simple and specific MRI sign of progressive supranuclear palsy. *Neurology* **80,** 1856–1861; 10.1212/WNL.0b013e318292a2d2 (2013).

15. Oba, H. *et al.* New and reliable MRI diagnosis for progressive supranuclear palsy. *Neurology* **64,** 2050–2055; 10.1212/01.WNL.0000165960.04422.D0 (2005).

16. Whiteside, D. J. *et al.* Network connectivity and structural correlates of survival in progressive supranuclear palsy and corticobasal syndrome. *Human brain mapping* **44,** 4239–4255; 10.1002/hbm.26342 (2023).

17. Meyyappan, M. *et al.* Role of Diffusion Tensor Imaging in Early Diagnosis and Characterization of Movement Disorders. *Cureus* **16,** e53580; 10.7759/cureus.53580 (2024).

18. Surova, Y. *et al.* Disease-specific structural changes in thalamus and dentatorubrothalamic tract in progressive supranuclear palsy. *Neuroradiology* **57,** 1079–1091; 10.1007/s00234-015-1563-z (2015).

19. Armstrong, R. A. White matter pathology in progressive supranuclear palsy (PSP): a quantitative study of 8 cases. *Clinical neuropathology* **32,** 399–405; 10.5414/NP300608 (2013).

20. Whitwell, J. L. *et al.* Disrupted thalamocortical connectivity in PSP: a resting-state fMRI, DTI, and VBM study. *Parkinsonism & Related Disorders* **17,** 599–605; 10.1016/j.parkreldis.2011.05.013 (2011).

21. Knake, S. *et al.* In vivo demonstration of microstructural brain pathology in progressive supranuclear palsy: a DTI study using TBSS. *Movement Disorders* **25,** 1232–1238; 10.1002/mds.23054 (2010).

22. Caso, F. *et al.* Cognitive impairment in progressive supranuclear palsy-Richardson's syndrome is related to white matter damage. *Parkinsonism & Related Disorders* **31,** 65–71; 10.1016/j.parkreldis.2016.07.007 (2016).

23. Agosta, F. *et al.* Clinical, cognitive, and behavioural correlates of white matter damage in progressive supranuclear palsy. *J Neurol* **261,** 913–924; 10.1007/s00415-014-7301-3 (2014).

24. Whitwell, J. L. *et al.* Clinical correlates of white matter tract degeneration in progressive supranuclear palsy. *Arch Neurol* **68,** 753–760; 10.1001/archneurol.2011.107 (2011).

25. Kaasinen, V. *et al.* Midbrain-to-pons ratio in autopsy-confirmed progressive supranuclear palsy: replication in an independent cohort. *Neurol Sci* **36,** 1251–1253; 10.1007/s10072-015-2184-3 (2015).

26. Glasser, M. F. *et al.* The minimal preprocessing pipelines for the Human Connectome Project. *NeuroImage* **80,** 105–124; 10.1016/j.neuroimage.2013.04.127 (2013).

27. van Essen, D. C. *et al.* The Human Connectome Project: a data acquisition perspective. *NeuroImage* **62,** 2222–2231; 10.1016/j.neuroimage.2012.02.018 (2012).

28. Andersson, J. L. R., Skare, S. & Ashburner, J. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *NeuroImage* **20,** 870–888; 10.1016/S1053-8119(03)00336-7 (2003).

29. *Montreal Cognitive Assessment* (2015).

30. Shetty, N., Koteshwar, P. & Priyanka. Identification of optimal value of magnetic resonance planimetry and the parkinsonism index for the diagnosis of Parkinson's disease and progressive supranuclear palsy. *Journal of Taibah University Medical Sciences* **18,** 1577–1585; 10.1016/j.jtumed.2023.07.004 (2023).

31. Park, H.-J. & Friston, K. Structural and functional brain networks: from connections to cognition. *Science* **342,** 1238411; 10.1126/science.1238411 (2013).

32. Roberts, R. E., Anderson, E. J. & Husain, M. White matter microstructure and cognitive function. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry* **19,** 8–15; 10.1177/1073858411421218 (2013).

33. Bennett, I. J. & Madden, D. J. Disconnected aging: cerebral white matter integrity and age-related differences in cognition. *Neuroscience* **276,** 187–205; 10.1016/j.neuroscience.2013.11.026 (2014).

34. Bosch, B. *et al.* Multiple DTI index analysis in normal aging, amnestic MCI and AD. Relationship with neuropsychological performance. *Neurobiology of aging* **33,** 61–74; 10.1016/j.neurobiolaging.2010.02.004 (2012).

35. van der Knaap, L. J. & van der Ham, I. J. M. How does the corpus callosum mediate interhemispheric transfer? A review. *Behavioural Brain Research* **223,** 211–221; 10.1016/j.bbr.2011.04.018 (2011).

36. Zhang, J. *et al.* Increased structural connectivity in corpus callosum in adolescent males with conduct disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* **53,** 466-75.e1; 10.1016/j.jaac.2013.12.015 (2014).

37. Wiltshire, K., Foster, S., Kaye, J. A., Small, B. J. & Camicioli, R. Corpus callosum in neurodegenerative diseases: findings in Parkinson's disease. *Dement Geriatr Cogn Disord* **20,** 345–351; 10.1159/000088526 (2005).

38. Li, Y., Wu, P., Liang, F. & Huang, W. The microstructural status of the corpus callosum is associated with the degree of motor function and neurological deficit in stroke patients. *PLOS ONE* **10,** e0122615; 10.1371/journal.pone.0122615 (2015).

39. Ito, S., Makino, T., Shirai, W. & Hattori, T. Diffusion tensor analysis of corpus callosum in progressive supranuclear palsy. *Neuroradiology* **50,** 981–985; 10.1007/s00234-008-0447-x (2008).

40. Padovani, A. *et al.* Diffusion tensor imaging and voxel based morphometry study in early progressive supranuclear palsy. *Journal of neurology, neurosurgery, and psychiatry* **77,** 457–463; 10.1136/jnnp.2005.075713 (2006).

41. Nieuwenhuys, R. & Voogd, J. *The Human Central Nervous System. A Synopsis and Atlas* (Springer Berlin Heidelberg, Berlin, Heidelberg, 2008).

42. Dale, M. L. *et al.* Impaired perception of surface tilt in progressive supranuclear palsy. *PLOS ONE* **12,** e0173351; 10.1371/journal.pone.0173351 (2017).

43. George, K. & M Das, J. *StatPearls. Neuroanatomy, Thalamocortical Radiations* (Treasure Island (FL), 2024).

44. Sommer, M. A. The role of the thalamus in motor control. *Current Opinion in Neurobiology* **13,** 663–670; 10.1016/j.conb.2003.10.014 (2003).

45. Nguyen, T.-T. *et al.* Fixel-Based Analysis of White Matter Degeneration in Patients With Progressive Supranuclear Palsy or Multiple System Atrophy, as Compared to Parkinson's Disease. *Front. Aging Neurosci.* **13,** 625874; 10.3389/fnagi.2021.625874 (2021).

46. Vercruysse, S. *et al.* Microstructural changes in white matter associated with freezing of gait in Parkinson's disease. *Movement Disorders* **30,** 567–576; 10.1002/mds.26130 (2015).

47. Senda, J. *et al.* MRI mean diffusivity detects widespread brain degeneration in multiple sclerosis. *Journal of the Neurological Sciences* **319,** 105–110; 10.1016/j.jns.2012.04.019 (2012).

48. Herman, T. *et al.* White matter hyperintensities in Parkinson's disease: do they explain the disparity between the postural instability gait difficulty and tremor dominant subtypes? *PLOS ONE* **8,** e55193; 10.1371/journal.pone.0055193 (2013).

49. Sintini, I. *et al.* Neuroimaging correlates of gait abnormalities in progressive supranuclear palsy. *NeuroImage: Clinical* **32,** 102850; 10.1016/j.nicl.2021.102850 (2021).

50. Veselý, B., Antonini, A. & Rektor, I. The contribution of white matter lesions to Parkinson's disease motor and gait symptoms: a critical review of the literature. *J Neural Transm* **123,** 241–250; 10.1007/s00702-015-1470-9 (2016).

51. Höglinger, G. U. *et al.* Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. *Nature genetics* **43,** 699–705; 10.1038/ng.859 (2011).

52. Piattella, M. C. *et al.* Neuroimaging evidence of gray and white matter damage and clinical correlates in progressive supranuclear palsy. *Journal of neurology* **262,** 1850–1858; 10.1007/s00415-015-7779-3 (2015).

53. Donker Kaat, L. *et al.* Frontal presentation in progressive supranuclear palsy. *Neurology* **69,** 723–729; 10.1212/01.wnl.0000267643.24870.26 (2007).

54. Bak, T. H., Crawford, L. M., Hearn, V. C., Mathuranath, P. S. & Hodges, J. R. Subcortical dementia revisited: similarities and differences in cognitive function between progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA). *Neurocase* **11,** 268–273; 10.1080/13554790590962997 (2005).

55. Ahmed, R. M. *et al.* Neuronal network disintegration: common pathways linking neurodegenerative diseases. *J Neurol Neurosurg Psychiatry* **87,** 1234–1241; 10.1136/jnnp-2014-308350 (2016).

56. Kantarci, K. *et al.* White-matter integrity on DTI and the pathologic staging of Alzheimer's disease. *Neurobiology of aging* **56,** 172–179; 10.1016/j.neurobiolaging.2017.04.024 (2017).

57. Bagga, D. *et al.* Decreased white matter integrity in fronto-occipital fasciculus bundles: relation to visual information processing in alcohol-dependent subjects. *Alcohol* **48,** 43–53; 10.1016/j.alcohol.2013.10.009 (2014).

58. Rimkus, C. d. M. *et al.* Corpus callosum microstructural changes correlate with cognitive dysfunction in early stages of relapsing-remitting multiple sclerosis: axial and radial diffusivities approach. *Multiple Sclerosis International* **2011,** 304875; 10.1155/2011/304875 (2011).

59. Goldman, J. G. *et al.* Corpus callosal atrophy and associations with cognitive impairment in Parkinson disease. *Neurology* **88,** 1265–1272; 10.1212/WNL.0000000000003764 (2017).

60. Tessitore, A. *et al.* Clinical correlations of microstructural changes in progressive supranuclear palsy. *Neurobiology of aging* **35,** 2404–2410; 10.1016/j.neurobiolaging.2014.03.028 (2014).

61. Sala-Llonch, R., Palacios, E. M., Junqué, C., Bargalló, N. & Vendrell, P. Functional networks and structural connectivity of visuospatial and visuoperceptual working memory. *Front. Hum. Neurosci.* **9,** 340; 10.3389/fnhum.2015.00340 (2015).

62. Gong, Z. *et al.* Lower myelin content is associated with more rapid cognitive decline among cognitively unimpaired individuals. *Alzheimer's & Dementia* **19,** 3098–3107; 10.1002/alz.12968 (2023).

63. Madden, D. J. *et al.* Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochimica et biophysica acta* **1822,** 386–400; 10.1016/j.bbadis.2011.08.003 (2012).

64. Zhang, J., Cortese, R., Stefano, N. de & Giorgio, A. Structural and Functional Connectivity Substrates of Cognitive Impairment in Multiple Sclerosis. *Front. Neurol.* **12,** 671894; 10.3389/fneur.2021.671894 (2021).

65. Kamada, K. *et al.* Functional identification of the primary motor area by corticospinal tractography. *Neurosurgery* **61,** 166-76; discussion 176-7; 10.1227/01.neu.0000279213.23010.cb (2007).

66. Cui, S.-S. *et al.* Midbrain/pons area ratio and clinical features predict the prognosis of progressive Supranuclear palsy. *BMC Neurol* **20,** 114; 10.1186/s12883-020-01692-6 (2020).

67. Kannenberg, S. *et al.* Investigating the 1-year decline in midbrain-to-pons ratio in the differential diagnosis of PSP and lPD. *J Neurol* **268,** 1526–1532; 10.1007/s00415-020-10327-2 (2021).

68. Worker, A. *et al.* Diffusion tensor imaging of Parkinson's disease, multiple system atrophy and progressive supranuclear palsy: a tract-based spatial statistics study. *PLOS ONE* **9,** e112638; 10.1371/journal.pone.0112638 (2014).

69. Acosta-Cabronero, J., Williams, G. B., Pengas, G. & Nestor, P. J. Absolute diffusivities define the landscape of white matter degeneration in Alzheimer's disease. *Brain* **133,** 529–539; 10.1093/brain/awp257 (2010).

70. Salat, D. H. *et al.* White matter pathology isolates the hippocampal formation in Alzheimer's disease. *Neurobiology of aging* **31,** 244–256; 10.1016/j.neurobiolaging.2008.03.013 (2010).

71. Huang, J., Friedland, R. P. & Auchus, A. P. Diffusion tensor imaging of normal-appearing white matter in mild cognitive impairment and early Alzheimer disease: preliminary evidence of axonal degeneration in the temporal lobe. *AJNR. American journal of neuroradiology* **28,** 1943–1948; 10.3174/ajnr.A0700 (2007).

72. Whitwell, J. L. *et al.* Radiological biomarkers for diagnosis in PSP: Where are we and where do we need to be? *Movement Disorders* **32,** 955–971; 10.1002/mds.27038 (2017).

73. Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L. & Greicius, M. D. Neurodegenerative diseases target large-scale human brain networks. *Neuron* **62,** 42–52; 10.1016/j.neuron.2009.03.024 (2009).

74. Brier, M. R., Thomas, J. B. & Ances, B. M. Network dysfunction in Alzheimer's disease: refining the disconnection hypothesis. *Brain Connectivity* **4,** 299–311; 10.1089/brain.2014.0236 (2014).

75. Palop, J. J. & Mucke, L. Network abnormalities and interneuron dysfunction in Alzheimer disease. *Nat Rev Neurosci* **17,** 777–792; 10.1038/nrn.2016.141 (2016).

76. Gardner, R. C. *et al.* Intrinsic connectivity network disruption in progressive supranuclear palsy. *Annals of neurology* **73,** 603–616; 10.1002/ana.23844 (2013).

77. Whiteside, D. J. *et al.* Altered network stability in progressive supranuclear palsy. *Neurobiology of aging* **107,** 109–117; 10.1016/j.neurobiolaging.2021.07.007 (2021).

78. Tae, W. S., Ham, B. J., Pyun, S. B., Kang, S. H. & Kim, B. J. Current Clinical Applications of Diffusion-Tensor Imaging in Neurological Disorders. *Journal of clinical neurology (Seoul, Korea)* **14,** 129–140; 10.3988/jcn.2018.14.2.129 (2018).

79. Saini, J. *et al.* In vivo evaluation of white matter pathology in patients of progressive supranuclear palsy using TBSS. *Neuroradiology* **54,** 771–780; 10.1007/s00234-011-0983-7 (2012).

Appendix 4: List of further publications

In addition to the studies included in this thesis, I published the following research articles:

Bahners, B. H., Waterstraat, G., **Kannenberg, S.**, Curio, G., Schnitzler, A., Nikulin, V., & Florin, E. (2022). Electrophysiological characterization of the hyperdirect pathway and its functional relevance for subthalamic deep brain stimulation. Experimental Neurology, 352, 114031.

Krösche, M., **Kannenberg, S.**, Butz, M., Hartmann, C. J., Florin, E., Schnitzler, A., & Hirschmann, J. (2023). Slowing of frontal β oscillations in atypical parkinsonism. Movement Disorders, 38(5), 806-817.

Schoenwald, H., Bahners, B. H., **Kannenberg, S.**, Dembek, T. A., Barbe, M. T., Sylaj, D., ... & Groiss, S. J. (2025). Antero-Lateral Subthalamic Nucleus Theta Stimulation Improves Verbal Fluency in Parkinson's Disease. Movement Disorders.

Appendix 5: Affidavit

Eidesstattliche Erklärung gemäß **§ 5 der Promotionsordnung vom 15.06.2018 der Mathematisch-Naturwissenschaftlichen Fakultät** der Heinrich-Heine-Universität Düsseldorf:

Ich, Silja Querbach, versichere an Eides Statt, dass die Dissertation von mir selbstständig und ohne unzulässige fremde Hilfe unter Beachtung der „**Grundsätze zur Sicherheit guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf**“ erstellt worden ist.

Ich habe die Arbeit weder in der vorliegenden noch in ähnlicher Form oder auszugsweise im Rahmen einer anderen Prüfung vorgelegt. Ich versichere, dass ich bisher keine erfolglosen Promotionsversuche unternommen habe.

Ich versichere hiermit zusätzlich, dass ich generative KI-Technologien ausschließlich zur sprachlichen Überarbeitung und Korrektur von Rechtschreibung, Grammatik und Stil verwendet habe. Inhaltliche Recherchen, Argumentationsaufbau sowie wissenschaftliche Ausarbeitungen wurden eigenständig und ohne inhaltliche Unterstützung durch KI-Systeme durchgeführt.

Düsseldorf, den 04.06.2025

(Silja Querbach)