NeuroImage: Clinical 51 (2026) 104032

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

PSP-specific atrophy targets regions connecting the salience network and subcortical circuits

Silja K. Querbach [a,*], Simon B. Eickhoff [b,c], Ann Carolin Hausmann [a], Alfons Schnitzler [a,d], Julian Caspers [e], Claudia R. Eickhoff [a]

[a] Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany
[b] Institute of Systems Neuroscience, Medical Psychology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany
[c] Institute of Neuroscience and Medicine (INM-7), Research Centre Jülich, Germany
[d] Department of Neurology, Medical Psychology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany
[e] Department of Diagnostic and Interventional Radiology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany

ARTICLE INFO

Keywords:
Progressive supranuclear palsy
VBM
Meta-analysis
Atrophy
Network degeneration

ABSTRACT

Progressive supranuclear palsy (PSP) shows a characteristic but incompletely defined pattern of neurodegeneration, in part because prior imaging studies have been limited by small and heterogeneous cohorts. Here, we consolidated evidence for PSP-related gray matter (GM) loss using a coordinate-based meta-analysis and interpreted the resulting atrophy pattern in a network and molecular framework to infer disease-relevant 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 to delineate co-activation–based connectivity profiles. Finally, we explored potential neurochemical underpinnings by correlating the atrophy map with PET-derived 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. Connectivity analyses indicated coupling with fronto-insular salience-network circuitry and with key subcortical nodes, consistent with a distributed systems-level disturbance. At the molecular level, PSP-related atrophy aligned with higher densities of dopaminergic, serotonergic, and—most prominently—cholinergic markers, suggesting multi–transmitter-system vulnerability with a critical role of the cholinergic architecture.

Together, these findings identify an interconnected set of cortical–subcortical targets in PSP whose functional and molecular profiles map onto core clinical features, supporting a network-based view of PSP neurodegeneration beyond isolated local atrophy with critical roles of the insula and the cholinergic system.

1. Introduction

Progressive supranuclear palsy (PSP) 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 a primary tauopathy, marked by selective neurodegeneration across cortical and subcortical structures (Steele et al., 1964; Hsu et al., 2024). On structural magnetic resonance imaging (MRI), midbrain atrophy is a characteristic structural signature of the disease (Oba et al., 2005; Massey et al., 2013). However, evidence suggests that PSP-related degeneration extends into the forebrain, including frontal cortical regions and their subcortical projections. Still, the involvement of the forebrain remains poorly understood, limiting our understanding of how PSP-related network disruption contributes to motor and non-motor impairment (Horwitz and Rowe, 2011; Koros et al., 2016; Stamelou and Höglinger, 2016).

MRI provides a robust, unbiased approach to quantifying gray matter

* Corresponding author at: Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Moorenstraße 5, 40225 Düsseldorf, Germany.
E-mail address: silja.querbach@med.uni-duesseldorf.de (S.K. Querbach).

https://doi.org/10.1016/j.nicl.2026.104032
Received 3 March 2026; Received in revised form 12 June 2026; Accepted 5 July 2026
Available online 9 July 2026

(GM) atrophy without reliance on predefined regions of interest (e.g., Whitwell et al., 2011; Focke et al., 2011; Lagarde et al., 2013; Shi et al., 2013;). In PSP, MRI studies have linked subcortical atrophy to core clinical features, including vertical gaze palsy (Buch et al., 2022) and postural instability (Zwergal et al., 2011). Beyond brainstem involvement, substantial forebrain atrophy has been reported, particularly affecting frontotemporal and prefrontal cortices as well as the basal ganglia (Cordato et al., 2002; Caso et al., 2016; Scotton et al., 2023; Price et al., 2004).

Despite numerous studies, findings on forebrain atrophy in PSP remain highly heterogeneous, and a coherent pattern has yet to emerge. This variability reflects broader concerns in neuroimaging often framed as the "replication crisis". Although voxel-based morphometry (VBM) is relatively constrained by standardized processing pipelines (cf. Antonopoulos et al., 2023), small sample sizes and cohort heterogeneity likely drive much of the inconsistency (Focke et al., 2011; Button et al., 2013). Meta-analytic approaches offer a strategy to overcome these limitations by identifying regions that show consistent atrophy across independent studies. Anatomical Likelihood Estimation (ALE) is the most established method for coordinate-based neuroimaging meta-analysis, providing a statistically rigorous framework to assess spatial convergence across reported findings (Turkeltaub et al., 2002; Eickhoff et al., 2009; Eickhoff et al., 2012).

Especially if the Network Degeneration Hypothesis (NDH) applies to PSP—i.e., that pathology preferentially propagates within interconnected large-scale networks rather than affecting isolated regions (Seeley et al., 2009)—convergence meta-analysis is essential to identify reproducible, network-level atrophy patterns by quantifying spatial consistency across independent studies.

In this work, ALE was employed to identify convergence across the literature on PSP-related atrophy. To go beyond the structural approach, regions identified were subsequently characterized with respect to their functional profiles, co-activation–based connectivity, and neurotransmitter receptor architecture to delineate potential network-level vulnerabilities. Functional roles were inferred from task-based activation probabilities, connectivity from statistically significant co-activation patterns, and molecular associations from spatial correlations with in vivo neurotransmitter receptor maps.

2. 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 (CRE).

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, APD.

(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 focusing 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.

2.1. 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., 2002) and then computing the union across the different experiments. Significance was assessed against a null-hypothesis of spatial independence (Eickhoff et al., 2012), corrected for multiple comparisons at the cluster level using threshold-free cluster enhancement (TFCE) for a family-wise error (FWE) rate of $p \leq .05$ (Frahm et al., 2022).

2.2. Functional decoding and connectivity modelling

Functional decoding of the resulting clusters (Rottschy et al., 2013; Genon et al., 2018) was performed to infer the mental processes associated with each region. Specifically, we identified the types of task-based fMRI studies that are more likely than chance to activate the a given cluster of brain 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., 2005; 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 functional connectivity, we applied Meta-Analytic Connectivity Modelling (MACM) to the same set of experiments identified for decoding. Rather than examining taxonomic labels, MACM evaluates convergence of co-activation across experiments using the ALE framework described above. While the highest convergence is expected within the seed region, significant convergence outside the seed indicates consistent co-activation patterns, reflecting functional connectivity (Reid et al., 2017).

2.3. Relationship between receptor density and atrophy

To link GM alterations with molecular neurotransmitter architecture, we performed spatial correlation analyses using PET-derived receptor and transporter maps implemented in the JuSpace toolbox (https://github.com/juryxy/JuSpace). This approach tests whether MRI-derived atrophy patterns are spatially aligned with the distribution of specific neurotransmitter systems, thereby moving beyond purely structural differences.

We quantified the spatial correspondence between PSP-related atrophy and maps of dopaminergic (D2 receptors, DAT, FDOPA),

serotonergic (5-HT1a, 5-HT1b, 5-HT2a, 5-HT4, SERT), cannabinoid (CB1), noradrenergic (NAT), cholinergic (VAChT), μ-opioid, GABAergic (GABAa), and glutamatergic (mGluR5) systems. Cross-modal correlations between MRI-based measures and PET receptor density maps were computed and tested against spin-test–derived null distributions to control for spatial autocorrelation (Dukart et al., 2020).

3. Results

3.1. 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.

3.2. 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 ($p \leq .05$, 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.

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.

As the number of primary studies comparing PSP with healthy controls, IPD and APD individually, was too low and we pooled all groups into a big control group, a supplementary analysis only testing for convergence in the smaller set of studies comparing PSP to CON (for results see supplementary material).

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 ($p \leq .05$, 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).

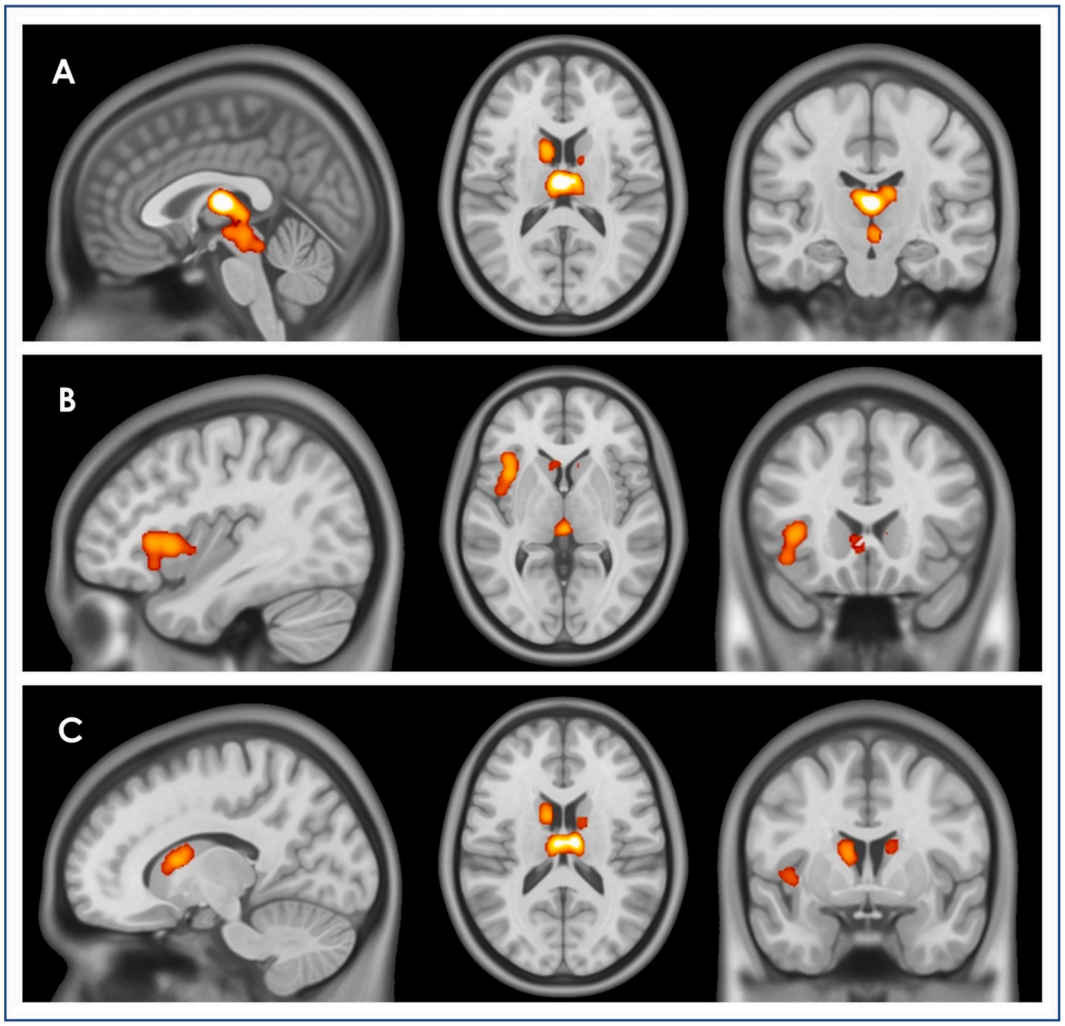

Fig. 1. ALE main results: Clusters of PSP-related significant GM reduction (red-yellow) in the Bilateral (A) Thalamus & Midbrain, (B) Left Insula and Frontal Operculum and (C) Bilateral Caudate Nucleus at $p \leq .05$ (FWE corrected for multiple comparisons).

3.3. Functional decoding and connectivity modelling

Functional decoding using the BrainMap database indicated that regions showing robust PSP-related atrophy were primarily linked to language, interoception/body perception, somatosensation, cognitive processes, and emotion (Suppl. Fig. 4A–D). Thalamic atrophy was most consistently associated with affective–cognitive processes (e.g., reward and punishment) and interoceptive functions, particularly pain monitoring. The left insular cortex was linked to semantic/speech-related language processes (including word generation), as well as gustation and pain monitoring. Atrophy in the left and right caudate nuclei mapped mainly to reward-related emotional processing and higher-order cognition, including reasoning.

MACM revealed convergent co-activation patterns suggesting functional coupling of the atrophied regions with a fronto-–insular–striato–thalamic network encompassing the frontal cortex, bilateral insula, bilateral caudate, thalamus and midbrain, as well as putamen, globus pallidus, and claustral regions (conjunction analysis; Fig. 2).

Examining clusters individually (Fig. 3A–D), the bilateral thalamus/midbrain cluster (Cluster 1) co-activated primarily with the superior frontal gyrus and paracingulate cortex. The left insula cluster (Cluster 2) showed broad co-activation with bilateral striatal and pallidal regions, including the caudate, putamen, and globus pallidus. The left caudate cluster (Cluster 3) co-activated mainly with the putamen, whereas the right caudate cluster (Cluster 4) co-activated with globus pallidus and putamen.

To contextualize these co-activation patterns at the network level, we overlaid MACM-derived maps onto the Yeo cortical parcellation (Yeo et al., 2011; Fig. 4). Across all clusters, overlap was strongest with the salience network (Fig. 4). The insular cluster additionally showed overlap with temporo-parietal (N17), control (N12; N13), sensorimotor (N3; N4), default-mode (N14), and attention networks (N16), although the most prominent involvement remained within salience components (N7; N8; Fig. 4A). Thalamus and midbrain co-activation patterns similarly overlapped with salience, with additional involvement of limbic (N9) and default-mode networks (N14; Fig. 4B), as well as the limbic (N9) and default network (N14). For both caudate clusters (Fig. 4C), overlap was again concentrated in salience (N7; N8) and limbic (N10; Yeo et al., 2011).

3.4. Relationship with 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.

4. Discussion

The present study provides an integrated, multimodal characterization of reproducible atrophy patterns in PSP, and its functional connectivity, and molecular correlates. A whole-brain ALE meta-analysis of VBM studies revealed a convergent pattern of GM loss encompassing the bilateral thalamus and midbrain, the left anterior insula extending into the frontal operculum, and the bilateral caudate nucleus. Functional decoding linked these regions to tasks involving language, body perception, somatosensation, and emotion processing. Connectivity profiling indicated strong coupling with subcortical structures and the salience network. Spatial correlation with PET-derived receptor maps further suggested that the atrophy pattern aligns with regions of high dopaminergic and cholinergic receptor density. Collectively, these findings delineate a robust PSP-related atrophy pattern that accords with key clinical features and highlights a potentially central role of an anterior insula–anchored network in PSP pathophysiology.

The regional pattern identified in this meta-analysis is consistent with the concept that PSP shows prominent subcortical involvement and affects multiple cellular compartments, including neurons, astrocytes, and oligodendroglia (Kovacs et al., 2020). Rather than reflecting a random distribution of tissue loss, neuropathological and imaging studies increasingly suggest that PSP-related degeneration follows vulnerable cortico-subcortical and brainstem networks (Palleis et al., 2025; Spinelli et al., 2024). Consistent with this network-based view, Scotton et al. (2023) identified subcortical and cortical PSP atrophy trajectories, the latter involving early frontal and insular degeneration, while connectome-based evidence suggests that PSP-RS atrophy spreads across interconnected frontal and subcortical regions (Palleis et al., 2025). Within this framework, MRI-detectable atrophy may be viewed as a structural marker of progressive tau-related degeneration affecting brainstem, basal ganglia, cerebellar, and frontal-subcortical circuits (Dickson, 2002; Höglinger et al., 2017). Midbrain and superior cerebellar peduncle involvement likely reflects motor-circuit degeneration, whereas frontal, insular, and subcortical changes may contribute to cognitive, behavioral, and executive dysfunction (Höglinger et al., 2017; Howard et al., 2022). Thus, the present convergence in salience-network nodes and subcortical circuits may address disease progression and phenotype-specific vulnerability in PSP.

4.1. Cortical atrophy, the insula and the salience network

A key finding in this context is the consistent atrophy of the anterior

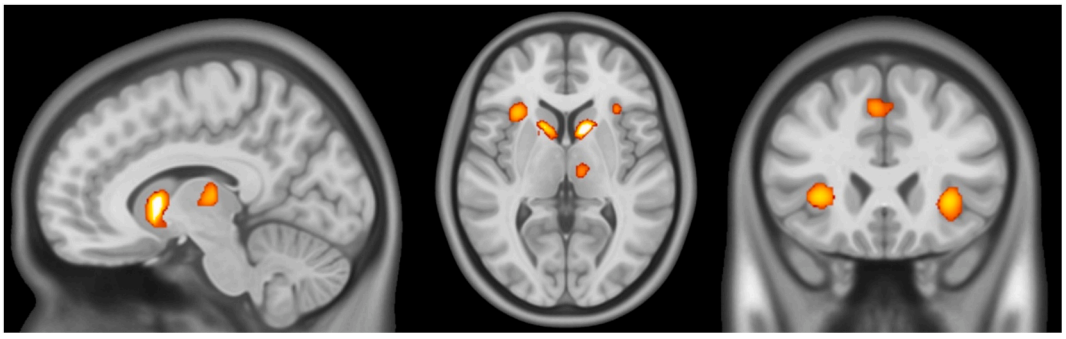

Fig. 2. Results MACM analysis. Significant co-activation patterns (red-yellow) for the conjunction analysis of the coactivation maps of all areas at p ≤ .05 (FWE corrected for multiple comparisons).

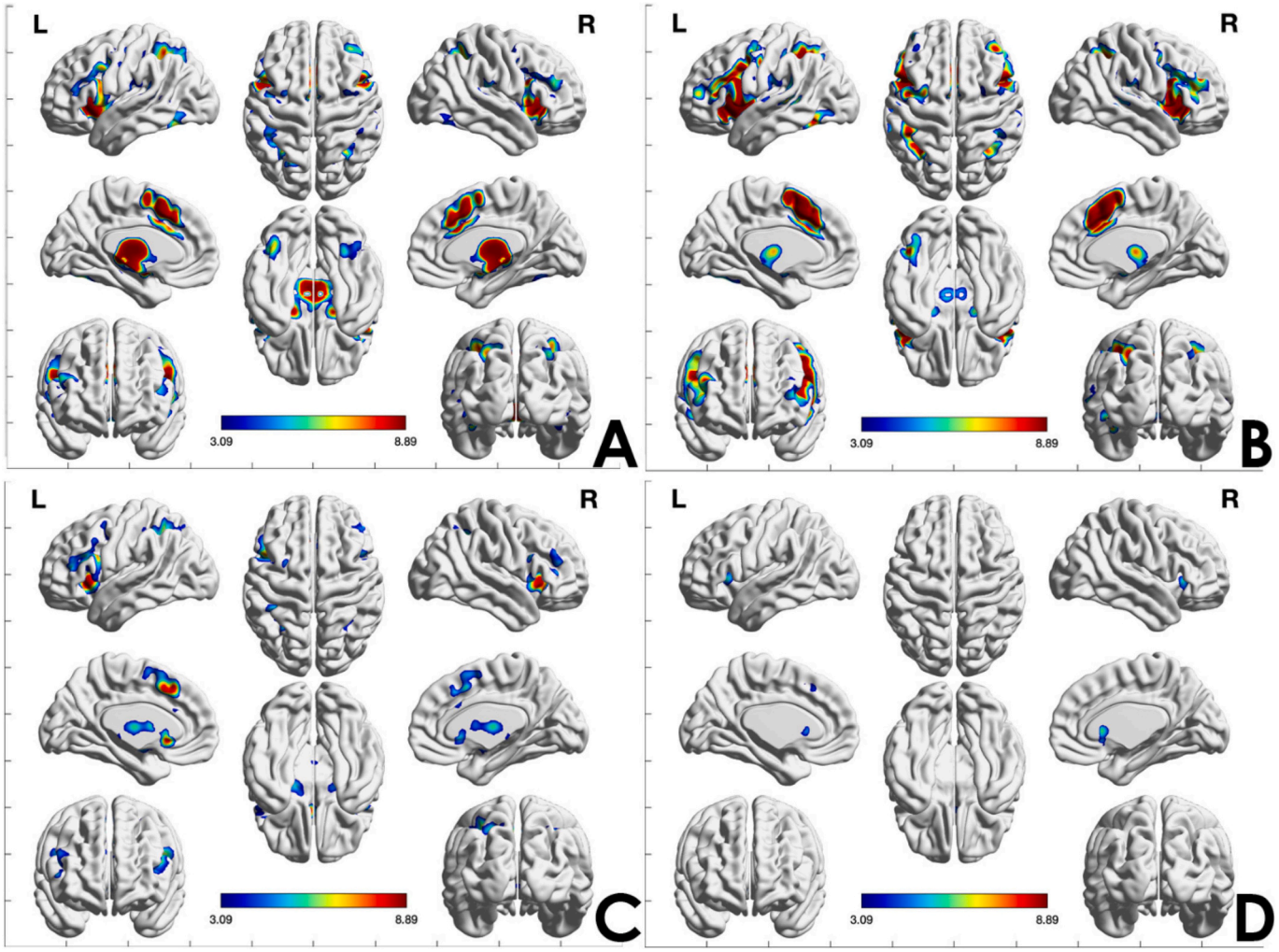

Fig. 3. MACM results for (A) Thalamus and Midbrain, (B) Left Insula, (C) Left Caudate Nucleus, (D) Right Caudate Nucleus. Results showing coactivated regions (blue to red, with red strongest activation) for the four regions (FEW-corrected $p \leq .05$ at cluster level) L: left hemisphere, R: right hemisphere.

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; Benarroch, 2019) and insula dysfunction has been related to non-motor clinical symptoms in PSP (Pan et al., 2012; Colosimo et al., 2010). The insula supports sensorimotor, visceral/autonomic, nociceptive, affective, and cognitive processes within a differentiated functional topography (Glasser et al., 2016). Notably, the anterior dorsal insula—the subregion implicated here—has been described as a convergence zone integrating these domains (Kurth et al., 2010) and as a "hub-zone" (Mazzola et al., 2019) within the salience network, coordinating widespread cortical and subcortical interactions (Uddin et al., 2017; Namkung et al., 2017). This interpretation is reinforced by the strong co-activation of the anterior insula cluster with the other convergently atrophied regions, positioning it as a strategic node within the affected network.

The insula is a heterogeneous structure supporting sensorimotor, visceral/autonomic and nocioceptive, affective and cognitive processes within a highly differentiated functional topography (Glasser et al., 2016). Notably, the anterior dorsal insula—the subregion implicated here—has been described as a convergence zone integrating these domains (Kurth et al., 2010) and as a "hub-zone" (Mazzola et al., 2019) within the salience network, coordinating widespread cortical and subcortical interactions (Uddin et al., 2017; Namkung et al., 2017). This interpretation is reinforced by the strong co-activation of the anterior insula cluster with the other convergently atrophied regions, positioning it as a strategic node within the affected 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 significance of PSP-related atrophy may differ across clinical phenotypes, making interpretation of pooled atrophy patterns challenging. The observed convergence in the four regions should therefore be interpreted cautiously as a trans-phenotypic PSP signature, because subtype composition was inconsistently reported across the included studies. Pooled maps may disproportionately reflect the most frequently represented phenotype, typically PSP-Richardson syndrome, rather than the full PSP spectrum. PSP-RS is commonly associated with prominent midbrain, superior cerebellar peduncle, thalamic/basal ganglia, and medial frontal involvement, whereas cortical variants such as PSP-F, PSP-CBS, and PSP-SL may show stronger frontal, perirolandic, insular, or asymmetric cortical changes (Höglinger et al., 2017). This

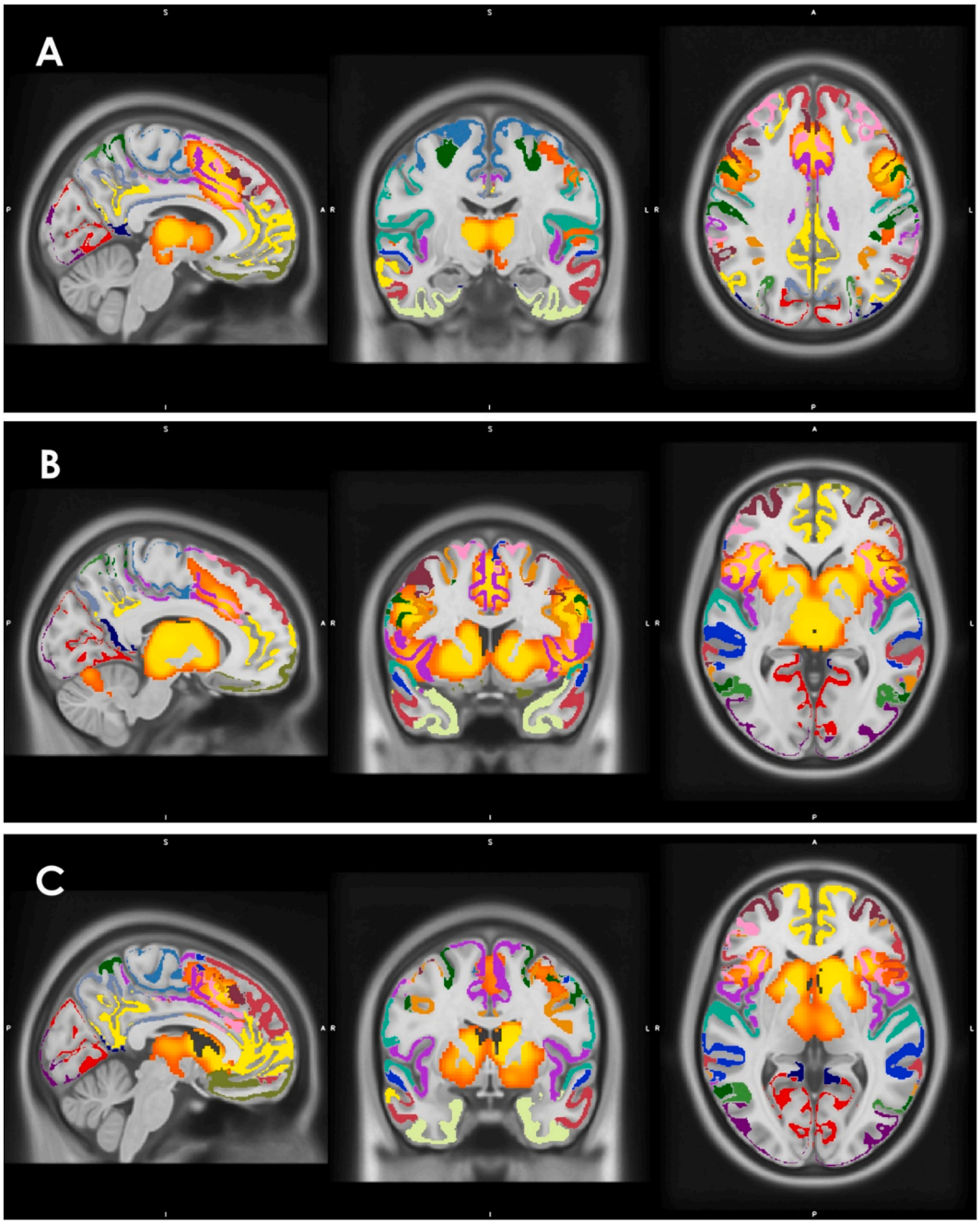

Fig. 4. Functionally coupled regions revealed by Yeo cortical maps. Yeo maps were overlayed onto (A) MACM results Insula, (B) MACM results Thalamus, (C) MACM results Bilateral Caudate Nuclei (Yeo et al., 2011).

heterogeneity may also partly explain why we did not observe convergent cerebellar atrophy, despite previous reports of cerebellar involvement in PSP (Spiegel et al., 2025). Overall, interpretation of MRI markers should consider PSP subtype, disease duration, and clinical severity; however, these factors could not be systematically assessed in the present meta-analysis because the available studies substantially differed in design, imaging methodology, and clinical characterization.

4.2. The caudate nucleus

We observed significant convergence of atrophy in the bilateral caudate nucleus, a structure implicated in movement planning, as well as 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 key contributor of postural instability and backward falls 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 (Piattella et al., 2015).

Importantly, the caudate is functionally heterogeneous: the ventral 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 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: does caudate atrophy show focal, domain-specific vulnerability (and thus relate to only a subset of clinical features), or does our convergence estimate reflect only the most consistent "peak" of a more diffuse caudate involvement contributing more broadly to PSP pathophysiology?

4.3. 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., 2011). 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). 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.

4.4. Linking systemic and molecular aspects

Complementing our system-level findings, the spatial likelihood of GM loss covaried with PET-derived maps of dopaminergic, serotonergic, and—most strongly in relation to higher-order impairment—cholinergic (VAChT) systems. This pattern motivates a cholinergic framing of cognitive decline in PSP: acetylcholine is critical for attention, learning/memory, sleep–wake regulation, and executive control, and reduced cholinergic integrity has recently been linked to poorer cognition in PSP (Nai et al., 2025). Mechanistically, cholinergic projections stabilize large-scale control by increasing signal-to-noise and supporting salience detection and flexible, goal-directed behavior, with nicotinic receptor–mediated modulation of attention being particularly relevant. This aligns with our network interpretation in which disruption of a salience-network–centred architecture yields domain-general cognitive dysfunction. Notably, cholinergic vulnerability is also consistent with a prominent subcortical component: reduced VAChT binding in the striatum has been proposed as a neurochemical imaging marker for PSP (Suzuki et al., 2002), arguing that cholinergic dysfunction is not merely secondary to atrophy but a potentially mechanistically relevant pathway and candidate target for intervention. In addition, the insula—a core salience-network hub—shows strong cholinergic linkage (Chakraborty et al., 2023; Toyoda, 2018), including dense expression of cholinergic receptor systems and robust basal-forebrain cholinergic innervation, providing a plausible molecular bridge between insular involvement and salience-network failure.

By comparison, dopaminergic abnormalities map more directly onto parkinsonian motor features and are central treatment targets (Hisahara and Shimohama, 2011; Constantinescu et al., 2007). Although reduced DAT binding is well documented in PSP and reflects nigrostriatal degeneration (Plotkin et al., 2005; Im et al., 2006), dopaminergic therapy typically yields limited benefit (Murphy et al., 2008), indicating that dopamine loss alone cannot explain the broader phenotype. Serotonergic disruption may contribute to affective and sleep–wake symptoms (Kim et al., 2013; Roselli et al., 2010), but our receptor-mapping results highlight acetylcholine as a particularly plausible driver of higher-order cognitive deterioration, with dopamine and serotonin adding symptom-specific variance.

4.5. Limitations and future research

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 APD, 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 refrain from inferring specificity or differential diagnostic utility. Finally, heterogeneity in VBM preprocessing and statistical pipelines may contribute to between-study variance; however, integrating across methodological choices is a key strength of coordinate-based meta-analysis, and the observed convergence suggests that the identified effects are robust to analytic variation.

Several limitations of the included studies should be considered when interpreting the meta-analytic findings. First, clinical subtype composition was inconsistently reported, and many studies were enriched for PSP-RS, limiting inference across the broader PSP spectrum. Second, included studies differed in MRI acquisition parameters, preprocessing pipelines, statistical thresholds, correction methods, and covariates such as age, disease duration, disease severity, and total intracranial volume. Third, many studies were cross-sectional, preventing strong conclusions about the temporal sequence of atrophy. Fourth, publication bias and coordinate-reporting bias may have favored studies reporting significant regional effects, while null or diffuse findings may be underrepresented. Fifth, the meta-analysis could not incorporate emerging molecular markers such as IL-1, IL-6, peripheral inflammatory ratios, CSF tau, or GDNF because these variables were rarely measured alongside whole-brain structural MRI in the eligible studies.

PSP has been repeatedly studied using VBM, yet findings remain heterogeneous (Brenneis et al., 2004; Quattrone et al., 2018). Interpretations often emphasize a small set of so-called "signature regions" to account for disease-specific hallmark symptoms (e.g. vertical gaze palsy, early backward falls), still, such selective focus can foster self-reinforcing bias. As an example, our quantitative synthesis of the available literature did not reveal any robust evidence for cerebellar GM loss, despite prior discussion of cerebellar involvement in 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.

Beyond neurotransmitter systems, PSP-related atrophy may also be shaped by neuroinflammatory and neurotrophic mechanisms. Recent exploratory studies reported phenotype-dependent alterations in glial cell line-derived neurotrophic factor, including increased CSF GDNF in PSP-RS and increased serum GDNF in PSP-P, as well as associations between MRI-derived measures and inflammatory markers such as IL-6 and IL-1 in PSP-RS (Alster et al., 2024a, 2024b). These findings suggest that MRI-visible atrophy may reflect not only regional vulnerability to 4R-tau pathology, but also subtype-dependent inflammatory and neurotrophic responses. Despite the mentioned limitations, meta-analyses remain a valuable tool for identifying robust and convergent pattern of brain atrophy across studies.

5. 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 coherent basis for the heterogeneous motor and in particular non-motor symptoms in PSP, mainly disruptions of higher-order control functions, affective and cognitive processing. This picture is corroborated by multiscale integration linking the systems-level atrophy pattern to molecular topographies, indicating multi–transmitter-system vulnerability beyond dopamine—especially cholinergic involvement—with acetylcholine emerging as a plausible key driver of cognitive decline.

Taken together, our results support PSP as a disorder of network degeneration, with insula-centered salience-network disruption and cholinergic vulnerability emerging as especially critical components.

CRediT authorship contribution statement

Silja K. Querbach: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Simon B. Eickhoff:** Writing – review & editing, Software, Resources, Methodology, Formal analysis, Conceptualization. **Ann Carolin Hausmann:** Writing – review & editing, Investigation. **Alfons Schnitzler:** Writing – review & editing, Resources. **Julian Caspers:** Writing – review & editing, Conceptualization. **Claudia R. Eickhoff:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Ethics approval

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

Funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2026.104032.

Data availability

The data underlying this meta-analysis are not publicly available. The study was conducted using data extracted from previously published sources, and no new dataset has been made available by the authors.

References

Alster, P., Otto-Ślusarczyk, D., Szlufik, S. Duszyńska-Wąs, K., Drzewińska, A., Wiercińska-Drapało, A., Struga, M., Kutyłowski, M., Friedman, A. & Madetko-Alster, N. (2024a). The significance of glial cell line-derived neurotrophic factor analysis in progressive supranuclear palsy. Sci. Rep. **14**, 2805 (2024a).

Alster P., Otto-Ślusarczyk D., Kutyłowski M., Migda B., Wiercińska-Drapało A., Jabłońska J., Struga M., Madetko-Alster N. (2024b) The associations between common neuroimaging parameters of progressive supranuclear palsy in magnetic resonance imaging and non-specific inflammatory factors - pilot study. *Front Immunol.* Aug 8; 15:1458713.

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.

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.

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

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. Arch. Neurol. 63 (1), 81–86.

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. J. Neurol. Neurosurg. Psychiatry 75 (2), 246–249.

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.

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. J. Neuroophthalmol. 42 (2), 246–250.

Button, K.S., Ioannidis, J.P.A., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S.J., Munafò, M.R., 2013. Power failure: why small sample size undermines the reliability of neuroscience. Nat. Rev. Neurosci. 14 (5), 365–376.

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 Relat. Disord. 31, 65–71.

Chakraborty, S., Lee, S.K., Arnold, S.M., Haast, R.A.M., Khan, A.R., Schmitz, T.W., 2023. Focal acetylcholinergic modulation of the human midcingulo-insular network during attention: meta-analytic neuroimaging and behavioral evidence. J. Neurochem. 168 (4), 397–413.

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. J. Neurol. 257, 5–14.

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. Angew. Chem. Int. Ed. 46 (46), 8887–8889.

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.

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.

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. Biol. Psychiatry 80 (12), 896–904.

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. J. Neuropathol. Exp. Neurol. 61 (11), 935–946.

Driscoll, M.E., Bollu, P.C., Tadi, P., 2022. Neuroanatomy, Nucleus Caudate. In: *StatPearls* [Internet]. StatPearls Publishing.

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. Biol. Psychiatry 87 (9), S190.

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. Hum. Brain Mapp. 30 (9), 2907–2926.

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.

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 Behav. 14, 2799–2816.

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. Hum. Brain Mapp. 32 (11), 1905–1915.

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. Hum. Brain Mapp. 25 (1), 185–198.

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. Hum. Brain Mapp. 43 (13), 3987–3997.

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.

Gerstenecker, A., Duff, K., Mast, B., Litvan, I., ENGENE-Psp Study Group, 2013. Behavioral abnormalities in progressive supranuclear palsy. Psychiatry Res. 210 (3), 1205–1210.
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.
Hisahara, S., & Shimohama, S. (2011). Dopamine receptors and Parkinson's disease. Int. J. Med. Chem., 2011.
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., Troakes, C., Movement Disorder Society-endorsed PSP Study Group, 2017. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Movement disorders : official journal of the Movement Disorder Society 32 (6), 853–864.
Horwitz, B., Rowe, J.B., 2011. Functional biomarkers for neurodegenerative disorders based on the network paradigm. Prog. Neurobiol. 95 (4), 505–509.
Howard, E., Ballinger, S., Kinney, N.G., Balgenorth, Y., Ehrhardt, A., Phillips, J.S., Irwin, D.J., Grossman, M., Cousins, K.A.Q., 2022. Frontal atrophy and executive dysfunction relate to complex numbers impairment in progressive supranuclear palsy. Journal of Alzheimer's disease : JAD 88 (4), 1553–1566.
Hsu, J.L., Wei, Y.C., Hsiao, I.T., Lin, K.J., Yen, T.C., Lu, C.S., Wang, H.C., Leemans, A., Weng, Y.H., Huang, K.L., 2024. Dominance of tau burden in cortical over subcortical regions mediates glymphatic activity and clinical severity in PSP. Clin. Nucl. Med. 49 (5), 387–396.
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 Netw. Open 5 (4), e229588.
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. J. Neurol. Sci. 244 (1–2), 103–109.
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.
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.
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. J. Immunol. 190 (9), 4795–4804.
Koros, C., Stamelou, M., 2016. Interventions in progressive supranuclear palsy. Parkinsonism Relat. Disord. 22, S93–S95.
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., Xie, S.X., Höglinger, G.U., 2020. Distribution patterns of tau pathology in progressive supranuclear palsy. Acta Neuropathol. 140 (2), 99–119.
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 Struct. Funct. 214, 519–534.
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.
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. Front. Neuroinform. 3, 23.
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. Hum. Brain Mapp. 28 (11), 1194–1205.
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.
Litvan, I., 2003. Update on epidemiological aspects of progressive supranuclear palsy. Mov. Disord. 18 (6), 43–50.
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.
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.
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. J. Neurophysiol. 97 (6), 4368–4379.
Massey, L.A., Micallef, C., Paviour, D.C., et al., 2013. Conventional magnetic resonance imaging in confirmed progressive supranuclear palsy and multiple system atrophy. Mov. Disord. 27 (14), 1754–1762.
Mazzola, L., Mauguière, F., Isnard, J., 2019. Functional mapping of the human insula: data from electrical stimulations. Rev. Neurol. 175 (3), 150–156.
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 Relat. Disord. 17 (3), 172–176.
Millar, D., Griffiths, P., Zermansky, A.J., Burn, D.J., 2006. Characterizing behavioral and cognitive dysexecutive changes in progressive supranuclear palsy. Mov. Disord. 21 (2), 199–207.
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. Syst. Rev. 4 (1), 1–9.
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. Psychol. Med. 45 (8), 1765–1778.
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.
Murphy, K.E., Karaconji, T., Hardman, C.D., Halliday, G.M., 2008. Excessive dopamine neuron loss in progressive supranuclear palsy. Mov. Disord. 23 (4), 607–610.
Nai, Y.H., O'Donnell, J.L., Tanenbaum, A., Soda, A.K., Jiang, H., Moerlein, S.M., Norris, S.A., Perlmutter, J.S., Tu, Z., 2025. PET evaluation of cholinergic system differences in progressive supranuclear palsy and age-matched controls using [^{18}F] VAT. Nucl. Med. Biol. 21 (152–153), 109599.
Namkung, H., Kim, S.H., Sawa, A., 2017. The insula: an underestimated brain area in clinical neuroscience, psychiatry, and neurology. Trends Neurosci. 40 (4), 200–207.
Oba, H., Yagishita, A., Terada, H., et al., 2005. New and reliable MRI diagnosis for progressive supranuclear palsy. Neurology 64, 2050–2055.
Palleis, C., Quattrone, A., Dehsarvi, A., Roemer-Cassiano, S.N., Bernhardt, A.M., The AL-108-231 Investigators, the PASSPORT Study Group, Huppertz, H.-J., Malpetti, M., Boxer, A.L., Gnörich, J., Frontzkowski, L., Levin, J., Brendel, M., Höglinger, G.U., Franzmeier, N., 2025. Brain networks route neurodegeneration patterns in patients with progressive supranuclear palsy. Mov. Disord. 40, 2102–2115.
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.
Pan, P.L., Song, W., Shang, H.F., 2012. Voxel-wise meta-analysis of gray matter abnormalities in idiopathic Parkinson's disease. Eur. J. Neurol. 19 (2), 199–206.
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. Am. J. Neuroradiol. 36 (5), 915–921.
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. J. Neural Transm. 112, 1355–1361.
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.
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.
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 Relat. Disord. 54, 3–8.
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.
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. Mov. Disord. 25 (12), 1853–1859.
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.
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 Struct. Funct. 218, 1551–1567.
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 Commun. 5 (2), 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.
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. Neurol. Sci. 34, 1049–1055.
Spiegel, C., Marotta, C., Bertram, K., Vivash, L., Harding, I.H., 2025. Brainstem and cerebellar radiological findings in progressive supranuclear palsy. Brain communications 7 (1), fcaf051.
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., Whitwell, J.L., Filippi, M., Agosta, F., 2024. Stepwise functional brain architecture correlates with atrophy in progressive supranuclear palsy. Mov. Disord. 39 (9), 1493–1503.
Stamelou, M., Hoeglinger, G.U., 2013. Atypical parkinsonism: an update. Curr. Opin. Neurol. 26 (4), 401–405.
Stamelou, M., Höglinger, G., 2016. A review of treatment options for progressive supranuclear palsy. CNS Drugs 30, 629–636.
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. Arch. Neurol. 10 (4), 333–359.
Suzuki, M., Desmond, T.J., Albin, R.L., Frey, K.A., 2002. Cholinergic vesicular transporters in progressive supranuclear palsy. Neurology 58 (7), 1013–1018.
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. Hum. Brain Mapp. 40 (17), 5142–5154.
Takakusaki, K., Takahashi, M., Obara, K., Chiba, R., 2017. Neural substrates involved in the control of posture. Adv. Robot. 31 (1–2), 2–23.
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. Mov. Disord. 25 (14), 2395–2404.
Toyoda, H., 2018. Role of nicotinic acetylcholine receptors for modulation of microcircuits in the agranular insular cortex. J Oral Biosci. 61 (1), 5–11.
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.
Uddin, L.Q., Nomi, J.S., Hébert-Seropian, B., Ghaziri, J., Boucher, O., 2017. Structure and function of the human insula. J. Clin. Neurophysiol. 34 (4), 300.
Warren, N.M., Piggott, M.A., Perry, E.K., Burn, D.J., 2005. Cholinergic systems in progressive supranuclear palsy. Brain 128 (2), 239–249.
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 Relat. Disord. 17 (8), 599–605.
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. J. Neurol. 268, 3409–3420.
Williams, D.R., de Silva, R., Paviour, D.C., 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.
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. J. Neurophysiol. 106 (3), 1125–1165.
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.