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Current Opinion of Neurology – Neuroimaging:

Clinical and neuroimaging features of the PSP-CBD continuum

Jennifer L. Whitwell, PhD

Department of Radiology, Mayo Clinic, Rochester, MN, USA

Abstract

Purpose of review: To discuss how recent work has increased our understanding of progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). The investigation of large and autopsy-confirmed cohorts, imaging modalities to assess different aspects of pathophysiology, clinical phenotypes, and the application of advanced machine learning techniques, have led to recent advances in the field that will be discussed.

Recent findings: Literature over the past 18 months will be discussed under the following themes: 1) studies assessing how different neuroimaging modalities can improve the diagnosis of PSP and CBD from other neurodegenerative and parkinsonian disorders, including the investigation of pathological targets such as tau, iron, neuromelanin and dopamine and cholinergic systems; 2) work improving our understanding of clinical, neuroanatomical and pathological heterogeneity in PSP and CBD; and 3) work using advanced neuroimaging tools to investigate patterns of disease spread, as well as biological mechanisms potentially driving spread through the brain in PSP and CBD.

Summary: The findings help improve the imaging-based diagnosis of PSP and CBD, allow more targeted prognostic estimates for patients accounting for phenotype or pathology, and will aid in the development of appropriate and better-targeted disease biomarkers for clinical treatment trials.

Keywords

corticobasal syndrome; Richardson syndrome; variants; magnetic resonance imaging; positron emission tomography

Introduction

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are neurodegenerative diseases characterized by the presence of 4-repeat tau deposits throughout the brain and are often referred to as 4R tauopathies. While PSP-Richardson's syndrome (PSP-RS) and corticobasal syndrome (CBS) are the clinical presentations most typically associated with PSP and CBD respectively, there is well recognized clinical heterogeneity in both diseases and pathological heterogeneity within these syndromes. Other clinical variants of PSP include those related to subcortical dysfunction, including PSP with predominant

Corresponding author: Jennifer L. Whitwell, PhD, Professor of Radiology, Mayo Clinic, 200 1st St SW, Rochester MN 55905, Tel: 507-284-5576, Whitwell.jennifer@mayo.edu.

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parkinsonism and PSP with gait freezing, and those related to cortical dysfunction, including PSP with corticobasal syndrome, PSP with frontal dysfunction and PSP with predominant speech/language disorder; the diagnosis of which were operationalized in the diagnostic criteria for PSP(1). CBD can also present with frontal dysfunction, speech/language disorders and as PSP-RS (2–4). It is well established that PSP-RS is associated with atrophy of the midbrain and superior cerebellar peduncles, and brainstem measurements including midbrain-to-pons ratio and MRI parkinsonism index (MRPI) have performed well as diagnostic biomarkers(5). In contrast, CBD is associated with asymmetric atrophy of the frontoparietal cortex. However, the field lacks neuroimaging biomarkers of PSP and CBD pathology and biomarkers for the different clinical variants of PSP and CBD (5). Many studies over the past 18 months have investigated ways to improve the **imaging-based diagnosis of PSP and CBD** to differentiate them from other neurodegenerative diseases. These studies have utilized structural MRI, ^{18}F-fluorodeoxyglucose (FDG) PET, tau-PET and modalities to assess other biological processes, such as iron, neuromelanin, and dopamine and cholinergic system dysfunction. The 1st generation tau ligands, such as ^{18}F-flortaucipir, showed well-defined and characteristic patterns in PSP and CBS(6, 7), although significant limitations, including off-target binding in relevant disease regions and poor sensitivity to 4R tau in autoradiographic studies, have led to the assessment of 2nd generation ligands aiming to improve the detection of 4R tau. Many recent studies have also sought to **better understand disease heterogeneity** in PSP and CBD. Studies have characterized the clinical and neuroimaging features of the PSP clinical variants, including assessing midbrain measurements across PSP variants. Previous studies have suggested that neuroimaging outcomes differ according to pathology within 4R tauopathy clinical syndromes and these have recently been expanded and furthered in larger cohorts to identify predictors of pathology. Advanced machine learning techniques have also been utilized to identify data-driven **imaging subtypes and characterize patterns of progression of brain atrophy**, providing insight into the heterogeneity in disease spread across the PSP-CBD continuum and studies have begun to assess mechanisms related to disease spread.

Improving imaging-based differential diagnosis

Studies have assessed the role of neuroimaging in the diagnosis of the 4R tauopathies, including utilizing MRI and FDG-PET to assess atrophy and hypometabolism, 2nd generation tau-PET ligands, and imaging of other biological targets.

Atrophy and hypometabolism

A large autopsy-confirmed study of PSP and CBD assessed the ability of MRI to differentiate these 4R tauopathies from other pathologies (including frontotemporal lobar degeneration with TDP-43 [FTLD-TDP], Pick’s disease, synucleinopathies and Alzheimer’s disease [AD])(8). Abnormal brainstem measures were, as expected, observed in PSP, and the MRPI provided good differentiation of PSP from other pathologies. However, given the greater cortical involvement in the other pathologies, best differentiation was obtained with a combination of brainstem and cortical regions (area under the receiver operator curve [AUROC]=0.98). The CBD cohort showed brainstem atrophy intermediate between PSP and the other non-4R tau pathologies, as others have observed(9), and a

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combination of brainstem and cortical regions again provided optimum differentiation from these other pathologies (AUROC=0.86) and PSP (AUROC=0.93). Another study found that a support vector machine approach using regional brainstem, subcortical and cortical volumes was able to differentiate clinically diagnosed PSP-RS from other neurodegenerative syndromes (Alzheimer's dementia, primary progressive aphasia, frontotemporal dementia and CBS) with good sensitivity and specificity, with brainstem and midbrain regions showing particularly high importance for classification(10). The classification of CBS in that study was, however, poor, due to the lack of a specific atrophic pattern and greater overlap with other neurodegenerative syndromes in that cohort. Patterns of both brainstem and cortical hypometabolism can also aid in the differentiation of PSP-RS from the parkinsonian disorders, multiple system atrophy (MSA) and Parkinson's disease (PD) (11). Visual assessment of patterns of hypometabolism performed well in another study, providing 90% accuracy to differentiate clinically diagnosed PSP from CBS, MSA and PD (12). However, in that study, accuracy to identify CBS was poor at only 50%. Pattern-based approaches, therefore, have potential to aid clinical diagnosis of PSP, particularly to differentiate PSP from other more cortically mediated neurodegenerative diseases and from other parkinsonian disorders. Discrepancy between the good performance of these approaches for autopsy-confirmed CBD yet but poor performance in clinical CBS cohorts could reflect the heterogeneity observed in CBS, as will be discussed below. Performance of pattern-based approaches will also likely be dependent upon the composition of the comparison cohort and performance across PSP clinical variants will need to be assessed.

Measuring tau deposition with PET

Second generation tau-PET ligands that have received attention are ^{18}F-PI-2620 and ^{18}F-PM-PBB3 which have both shown more promising autoradiographic and pathologic findings suggesting some binding to 4R tau(13–15). Both ligands show characteristic patterns of uptake in PSP involving PSP-related regions such as the globus pallidus, subthalamic nucleus, striatum, substantia nigra, and cerebellar dentate(14, 16–18), with PI-2620 uptake in the globus pallidus, subthalamic nucleus and dorsolateral prefrontal cortex in CBS(17, 19) and PM-PBB3 uptake in globus pallidus in CBS-CBD(17). Visual assessment of PI-2620 images in one study provided better differentiation of PSP-RS from healthy controls compared to visual reads of MRI, and an index considering quantitative values from both PI-2620 (globus pallidus uptake) and MRI (Midbrain-to-pons ratio) performed better than the midbrain-to-pons ratio alone in differentiating PSP and controls (AUROC=0.98 versus 0.93), particularly in clinically less affected patients(20). A machine learning approach was also utilized to demonstrate that PM-PBB3 could differentiate PSP-RS from Alzheimer's dementia with high sensitivity (87.6%) and specificity (98.6%), with the globus pallidus and medial temporal lobe the most important regions for differentiation(21). PM-PBB3 can also differentiate PSP-RS from PD and MSA(18). These studies take different methodological approaches, but both demonstrate utility of these tau-PET ligands for diagnosis of PSP. However, these ligands still have limitations, with off-target binding in both(17, 18) and uptake outside the brain with PI-2620(17). Furthermore, PI-2620 and PM-PBB3 in the same patient showed different uptake patterns with a lack of correlation between tracers raising doubts that they are binding the same tau targets(17). More work is, therefore, still needed to develop tau-PET ligands highly sensitivity and specific to 4R tau.

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Investigating subcortical brain systems

Neuroimaging techniques measuring different biological targets in subcortical structures could have diagnostic utility in 4R tauopathies. Quantitative susceptibility mapping (QSM) or R2* imaging to measure **iron deposition** show elevated signal throughout subcortical, brainstem and cerebellar nuclei in PSP-RS(22, 23), with uptake in the red nucleus showing the best differentiation from PD (AUROC=0.83)(22). However, iron measurements do not outperform brainstem MRI measures (24). **Neuromelanin-sensitive MRI** shows reduced volume and signal in the substantia nigra in PSP compared to PD, and reduced volume in CBS(25). FDG-PET metabolism in the substantia nigra is also abnormal in PSP, although metabolism is comparable to PD and MSA(26). Striatal uptake on **dopamine transporter (DAT)** scans is usually abnormal in parkinsonian disorders but does not typically differentiate between parkinsonian disorders. However, machine learning approaches using deep neural networks and regional values have shown that classification of PSP-RS from PD and MSA can be improved (sensitivity=82%, specificity=94%)(27, 28). Imaging also been used to investigate the **cholinergic system in PSP**. Acetylcholine transporter [18F]-fluoroethoxybenzovesamicol (FEOBV) PET shows cholinergic abnormalities in the tectum, striatal cholinergic interneurons, and projections from the pedunculopontine nucleus, medial vestibular nucleus, and the cholinergic forebrain in PSP-RS compared to controls and PD(29). Volume of the nucleus basalis of Meynert is also smaller in PSP-RS compared to controls and MSA, although no different from PD, suggesting reductions in cholinergic innervation of the forebrain(30). These modalities uncover interesting pathophysiological abnormalities in 4R tauopathies and show potential as diagnostic biomarkers, although more work is needed to validate these findings in other cohorts, including in autopsy-confirmed patients.

Understanding clinical and anatomical heterogeneity

Clinical heterogeneity has been assessed across PSP variants, particularly to compare disease severity and rates of progression. It is clear from several recent studies that the subcortical variants of PSP show the slowest progression in overall disease severity and motor disability(31, 32), have the least ocular motor impairments(31), and show longer survival(33), compared to PSP-RS and cortical variants. The cortical variants of PSP show worse motor disability, cognitive impairment, and activities of daily living compared to subcortical variants of PSP(31, 33). Depression is observed across PSP variants, except in PSP-speech/language(34). The absence of ocular motor impairments was a predictor of long (≥10 years) survival, while early frontal lobe dysfunction predicted shorter survival, in PSP in another study, with PSP-parkinsonism particularly frequent in the long survival group(35). These studies help improve prognostic and survival estimates which will differ dependent upon the specific PSP presentation.

Brainstem measurements, including midbrain-to-pons ratio and the MRPI, are abnormal compared to controls across most PSP clinical variants, except for PSP-gait freezing(9, 36) (Figure 1). Brainstem measurements are typically worst affected in PSP-RS, PSP-corticobasal and PSP-frontal variants, with less striking abnormalities in PSP-parkinsonism and PSP-speech/language variants. As might be expected based on these findings, no

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difference in brainstem measurements were observed when variants were grouped into cortical and subcortical variants of PSP(9). Taken together with evidence from an earlier voxel-level MRI study(37) and findings on FDG-PET (38), differences between cortical and subcortical variants of PSP appear to be driven by the relative involvement of the cortex, rather than differences in subcortical structures (Figure 1). Consistent with this hypothesis is the finding that abnormalities on DAT in the striatum(39), and iron deposition in subcortical structures(23), are similar across PSP variants. Diffusion imaging studies have demonstrated that the superior cerebellar peduncles and dentatorubrothalamic tract are abnormal in PSP-RS, PSP-parkinsonism and PSP-speech/language variants, although show greatest abnormalities in PSP-RS, while PSP-speech/language shows greater involvement of supratentorial white matter tracts(40, 41). The more preserved brainstem in the PSP-speech/language variant may be driven in part by a cohort bias, since these patients are often followed in speech-language studies before they developed features of PSP and hence were captured very early after they started to develop clinical features of PSP. Furthermore, patients with the PSP-Speech/language variant more often have underlying CBD pathology(42), and neuroimaging signatures in these patients with speech and language deficits (defined predominantly by progressive apraxia of speech) differ according to whether the pathology is PSP or CBD(4). Those with CBD show faster rates of degeneration in cortical and striatal regions, while those with PSP show faster degeneration of midbrain and cerebellar dentate. Midbrain measurements, particularly the MRPI, can differentiate patients with PSP from non-PSP pathology within patients diagnosed with a PSP clinical variant(9). An important take-home message from this work is that brainstem measurements show utility as useful diagnostic markers across PSP variants and could be used as outcome measures in clinical treatment trials that recruit heterogeneous cohorts.

Clinical and anatomical heterogeneity is also observed in CBS related to underlying pathology(43). 4R tauopathies are observed at autopsy in approximately 60% of patients (35% with CBD), and 20-30% showing underlying AD. The largest CBS autopsy study to date (n=113) found that clinical features at presentation and last visit differ by pathology, with apraxia of speech associated with CBS-CBD, PSP clinical features (ocular motor impairment and postural instability) at the last visit associated with CBS-PSP, and greater myoclonus, episodic memory loss and posterior cortical signs throughout the disease associated with CBS-AD(44). Alien limb phenomenon and asymmetric rigidity was observed and did not differ across pathologies. Dysarthria was also more common in non-AD CBS in another study(45). Anatomically, CBS-CBD showed asymmetric posterior frontal and motor cortex atrophy with different patterns observed in the other pathologies, such as more brainstem involvement in CBS-PSP, widespread posterior cortical involvement in CBS-AD and prefrontal involvement in FTLD-TDP(44). While differences in the hippocampus were not observed, another study found greater hippocampal atrophy in CBS patients with beta-amyloid deposition suggesting AD(46). Tau uptake on PET scans has also been found to be greater in CBS patients with beta-amyloid deposition(19, 47, 48), as may be expected. This work suggests that both clinical and MRI features could help provide clues to the underlying pathology during life in CBS; critically important to help target treatments/interventions and to provide better prognostic estimates for patients.

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Characterizing patterns of disease spread

Interesting recent work has employed a machine learning model, known as Subtype and Stage Inference (SuStaIn), to identify disease subtypes and characterize disease spread based on regional MRI measurements. When applied to a heterogeneous cohort of clinically diagnosed PSP patients, a ‘MRI-subcortical’ and ‘MRI-cortical’ subtype of PSP was identified(49). These subtypes mapped well onto the subcortical and cortical clinical diagnoses. The ‘MRI-subcortical’ subtype showed early atrophy in the midbrain, followed by involvement of pons, superior cerebellar peduncle, and ventral diencephalon, and then the cerebellar dentate, thalamus, lentiform nucleus before spreading to cortex (Figure 2). This pattern of spread was concordant to that identified in PSP-RS using similar methodology(50, 51). The ‘cortical’ subtype also showed early midbrain and insula atrophy, with spread to involve posterior frontal lobes, thalamus, ventral diencephalon, and basal ganglia at a similar time, and then spread into other cortical regions (Figure 2). The end-stage atrophy pattern was very similar in the two subtypes. These patterns of spread may argue for a common brainstem epicenter of disease for both cortical and subcortical variants of PSP, rather than cortical epicenters in the cortical variants. While this may be the case in some instances, we must be careful not to draw strong longitudinal conclusions from cross-sectional data analysis. It has been shown that PSP-speech/language patients have atrophy restricted to the frontal lobes before the development of PSP features and midbrain atrophy (52) with disease epicenters in cortical regions(53). Findings may, therefore, be influenced by the specific disease stage being captured and the mix of clinical variants in the groups. Nevertheless, this study provides insight into patterns of disease spread in PSP that can help inform the development of appropriate MRI biomarkers. The SuStaIn model has also been used to demonstrate that patterns of disease spread differ between PSP-RS and CBS(51). In contrast to the patterns of spread in PSP-RS which start in midbrain and superior cerebellar peduncle, earliest atrophy in CBS was identified in the frontoparietal lobe, followed by temporo-occipital lobe and basal ganglia, and later reached the cingulate and brainstem. Interestingly, the end-stage atrophy pattern was very similar in the two groups, which taken together with the findings from the PSP subtype study, suggest that atrophy in 4R tauopathies spreads through a 4R-tau network of regions, involving these regions in a different order but ultimately converging to involve the entire network. These patterns conform well with patterns of tau deposition observed at autopsy, and with proposed spread of tau pathology(54) in PSP, and there is evidence that atrophy and white matter tract degeneration in the 4R tauopathies are associated with tau burden (55). In fact, there is growing evidence that the spread of atrophy and tau deposition in the 4R tauopathies is related to the brains functional connectivity, with studies identifying relationships between disruptions in functional connectivity measured using resting state fMRI and both regional tau burden, measured at autopsy or on PET(56, 57), and rates of brain atrophy(53). The disease may, therefore, spread through a network of functionally connected regions supporting the trans-neuronal tau spreading hypothesis, although we should be cautious in our interpretation given that associations do not prove causality or directionality in these biological mechanisms. Future longitudinal studies will be needed to specifically link the differential patterns of spread observed across PSP variants and CBS to

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syndrome specific disruptions in connectivity, to support the hypothesis that spread may be related to syndrome-specific disruptions in connectivity.

Conclusion

Neuroimaging studies have increased understanding of the pathophysiology of the PSP/CBD continuum and made progress in improving disease biomarkers that can help support the clinical diagnosis and predict pathology. More work is needed to assess performance of these biomarkers across the clinical and pathological spectrum of 4R tauopathies and the field still needs tau PET ligands to allow definitive diagnosis of a 4R tauopathy during life.

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Key points

- Biomarkers that consider patterns of brainstem, subcortical and cortical degeneration may improve the imaging-based diagnosis of PSP and CBD.
- Measurement of iron, neuromelanin and neuromodulatory systems could prove useful but require further work.
- 2nd generation tau PET ligands show uptake in disease characteristic regions with utility to aid diagnosis, although ligands that show less off target uptake and greater sensitivity and specificity for 4R tau are still needed.
- Brainstem measurements have utility as biomarkers to predict PSP pathology and as disease biomarkers across most of the PSP variants, except for PSP-gait freezing.
- Patterns of disease spread differ across clinical variants of PSP and CBD and there is evidence that the disease may spread through functionally connected regions.

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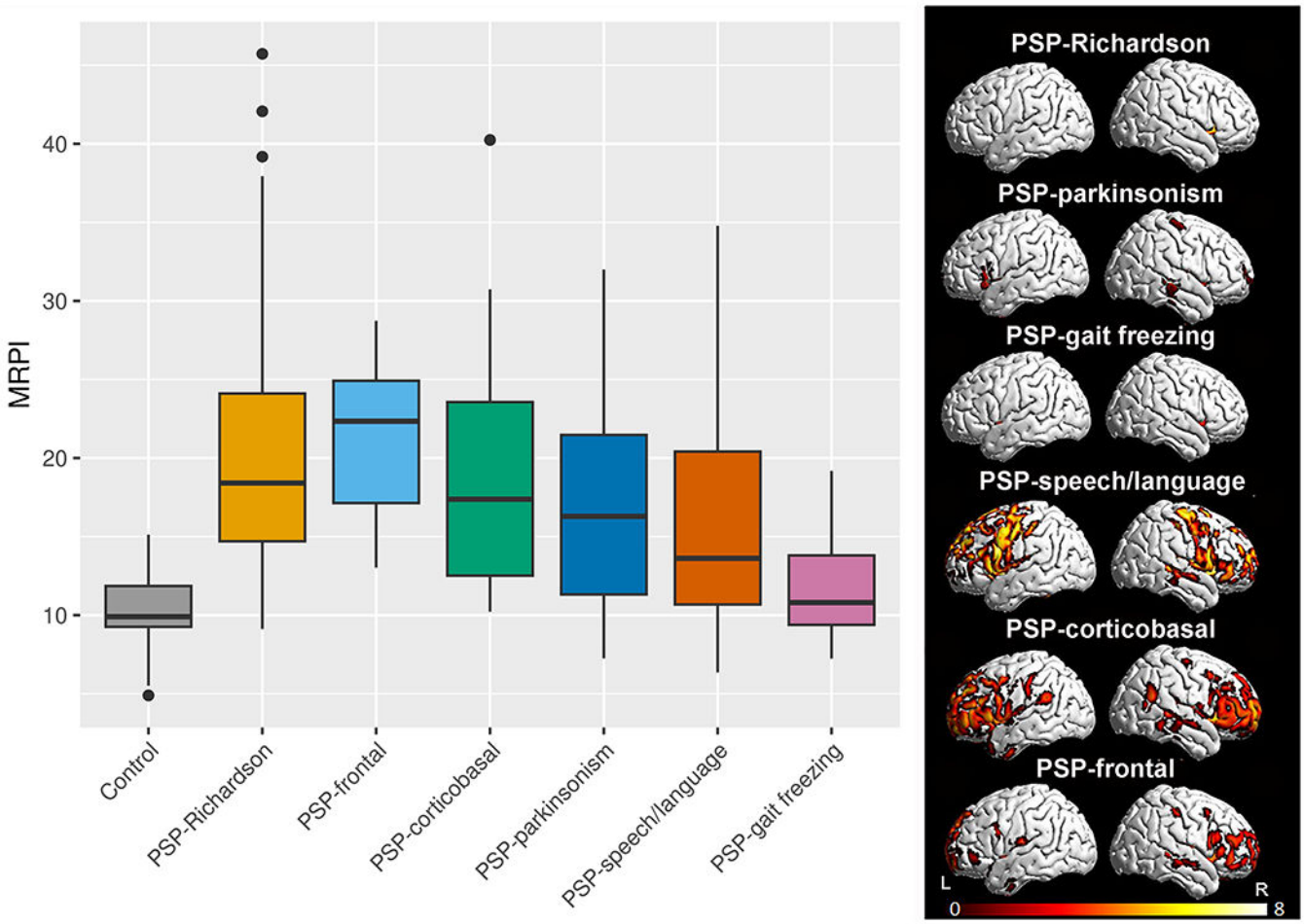

Figure 1: Brainstem and cortical findings across PSP clinical variants

Left panel shows boxplots of MRI parkinsonism index (MRPI) values across PSP variants, highlighting abnormal MRPI values in all PSP variants, except for PSP-gait freezing which did not differ from controls. Right panel shows group-level SPM maps of cortical grey matter loss, highlighting relative absence of cortical volume loss in PSP-Richardson, PSP-parkinsonism and PSP-gait freezing compared to PSP-speech/language, PSP-corticobasal and PSP-frontal.

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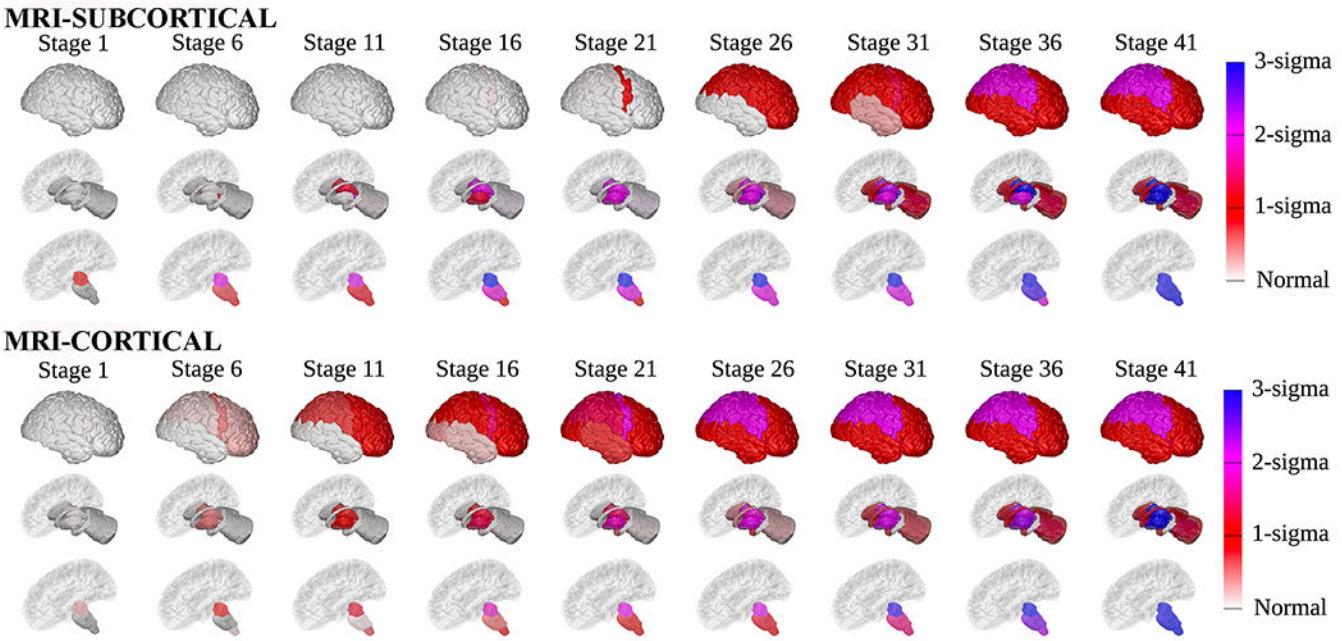

Figure 2: Patterns of anatomical spread in machine learning identified MRI-subcortical and MRI-cortical variants of PSP.

The spatial distribution and severity of atrophy are shown for each subtype at each SuStaIn stage at which brain volumes in PSP cases reach different z-scores relative to controls (49). The The earliest SuStaIn stages in the 'MRI-subcortical' subtype (75% of cases) involved the midbrain followed by other brainstem structures (medulla, pons, and superior cerebellar peduncle) and ventral diencephalon. Atrophy then progressed to the dentate nucleus of the cerebellum, thalamus, globus pallidus and putamen before spreading to cortex after stage 13. Cortical atrophy progressed from the insula and posterior frontal lobe to the temporal, parietal, and occipital lobe. The earliest SuStaIn stages in the 'cortical' subtype involved the midbrain and insula, followed by the frontal lobes (posterior > anterior), thalamus, ventral diencephalon, and the basal ganglia which were all affected at a similar time (before stage 13). Only 5% of cases were not able to be subtyped.