RESEARCH ARTICLE

Brainstem Biomarkers of Clinical Variant and Pathology in Progressive Supranuclear Palsy

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ABSTRACT: **Background:** Magnetic resonance brainstem measurements are useful structural biomarkers in the Richardson's syndrome variant of progressive supranuclear palsy (PSP). However, it is unclear how these biomarkers differ across the phenotypic spectrum of PSP and how they relate to underlying pathology.
Objective: The aim of this study was to compare brainstem imaging measures across clinical variants of PSP and determine sensitivity and specificity based on pathologically diagnosed cases.
Methods: A total of 153 patients with PSP who represented eight clinical variants were recruited at Mayo Clinic (Rochester, MN, USA) and underwent structural magnetic resonance imaging (MRI). Midbrain and pons area and superior and middle cerebellar peduncle width measurements were performed, and midbrain/pons ratio and Magnetic Resonance Parkinsonism Index (MRPI) were calculated. Among the 43 patients who later died, PSP pathology was confirmed in 29, whereas 14 had other pathology.
Results: Brainstem measurements varied across PSP clinical variants and were most abnormal in PSP-Richardson's syndrome and frontal variants, followed by PSP-corticobasal, PSP-speech/language, and PSP-parkinsonism variants. All these variants showed abnormalities compared with controls. The PSP-gait freezing variant and patients with prominent corticospinal tract signs showed normal brainstem measures. Among cases with confirmed PSP pathology, the midbrain area, midbrain/pons ratio, and MRPI were all more abnormal compared to those with other pathologies, with best differentiation obtained with the MRPI (sensitivity = 83%; specificity = 85%).
Conclusions: MRI brainstem measures show utility as diagnostic biomarkers across PSP clinical variants and have the potential to be useful in predicting underlying pathology.

Key Words: PSP-RS; PSP-P; MRPI; MRI; autopsy

Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized by abnormal tau aggregations in the brain.[1-3] The prototypical clinical presentation includes prominent and early imbalance with falls, and parkinsonism and axial rigidity; supranuclear gaze palsy is often the confirmatory feature but may occur later, as may cognitive dysfunction. This classic PSP presentation, as originally described,[3] has now been designated Richardson's syndrome (PSP-Richardson's) to distinguish this condition from variant PSP phenotypes that have subsequently been reported. Many PSP variants have been described, including PSP with predominant parkinsonism (PSP-parkinsonism),[4] PSP with progressive gait freezing (PSP-gait freezing),[5,6] PSP with predominant corticobasal syndrome (PSP-corticospinal),[7,8] PSP with predominant speech/language disorder (PSP-speech/language),[9]

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Received: 30 September 2021; **Revised:** 6 December 2021; **Accepted:** 13 December 2021

Published online 31 December 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28901

PSP with predominant frontal presentation (PSP-frontal),[10] PSP with predominant ocular motor dysfunction (PSP-ocular motor), PSP with predominant postural instability (PSP-postural instability),[11] and PSP with prominent corticospinal signs (PSP-corticospinal).[12] Most of these clinical variants can be classified into those that predominantly involve the brainstem/subcortical structures versus cortex. Brainstem/subcortical PSP variants include PSP-Richardson's, PSP-parkinsonism, PSP-gait freezing, and PSP-ocular motor,[2,12,13] while PSP-speech/language, PSP-corticobasal, and PSP-frontal predominantly involve the cortex. Two variants cannot be classified as cortical versus subcortical with certainty: PSP-postural instability and PSP-corticospinal.

A structural biomarker leading to an objective, specific, and higher certainty diagnosis of PSP pathology across clinical variants remains an important goal. Magnetic resonance (MR) imaging (MRI) studies have focused mainly on PSP-Richardson's[14] and identified severe atrophy in both the midbrain[15-19] and superior cerebellar peduncle (SCP) as indicative of classic PSP.[20-23] The structural brainstem biomarkers of midbrain area, midbrain/pons ratio, and the Magnetic Resonance Parkinsonism Index (MRPI) have proven to be specific measures for PSP-Richardson's.[21,24-31] However, less is known about the utility of these brainstem measures across the variants of PSP. The MRPI and midbrain/pons ratio have shown utility in differentiating PSP-parkinsonism from controls and patients with Parkinson's disease (PD), although these measures are typically less affected in PSP-parkinsonism compared with PSP-Richardson's.[32-34] Studies show that the midbrain and SCP are more degenerated in PSP-Richardson's compared with PSP-parkinsonism and PSP-speech/language,[13,34,35] and midbrain volume varies across PSP-speech/language, PSP-corticobasal, and PSP-frontal.[13] In fact, midbrain area relates to the presence of typical PSP clinical features rather than to underlying PSP pathology.[36]

Our primary aim was to assess MR brainstem measures for their potential to distinguish PSP variants from controls. Second, we were interested in determining whether brainstem biomarkers were predominantly useful for subcortical/brainstem predominant PSP cases versus cortical. Finally, among the PSP cases who had undergone postmortem brain analysis, we analyzed the brainstem biomarkers to determine how well they could distinguish PSP from other pathologies.

Patients and Methods

Patient Recruitment

One hundred fifty-three patients with possible or probable PSP[11] were recruited by the Neurodegenerative Research Group from the Department of Neurology, Mayo Clinic, between September 2009 and June 2021. For study inclusion, all patients must have been older than 40 years, have presented with gradual progression of PSP-related symptoms, and have an informant to provide independent evaluation of functioning. Patients were excluded if they met only criteria suggestive of PSP.[11] They were also excluded if they met criteria for another neurodegenerative disease (eg, corticobasal syndrome,[37] frontotemporal dementia,[38] primary progressive aphasia,[39] primary progressive apraxia of speech,[40] Alzheimer's disease,[41] multiple system atrophy,[42] or PD[43]) and did not fulfill inclusion criteria for possible/probable PSP, or if they had concurrent conditions that could account for the symptoms. All patients underwent a detailed neurological evaluation by a movement disorders specialist, and patients seen from 2012 onward were evaluated by a speech-language pathologist. All patients underwent a 3-T volumetric head MRI. All patients were given a PSP syndromic diagnosis according to the Movement Disorder Society (MDS)-PSP criteria.[11,44] The criteria were applied based on clinical judgment and using operational definitions based on scores from neurological tests that we have previously published.[45] The criteria were retrospectively applied to cases evaluated before 2017 using these same operational definitions. The Multiple Allocations eXtinction (MAX) criteria were used in situations when patients met criteria for more than one diagnostic label.[44] A diagnosis of PSP-corticospinal was rendered if a patient had clinical features of PSP (early unexplained falls, bradykinesia, rigidity, vertical supranuclear slowing or palsy, and poor levodopa responsiveness) plus prominent upper motor neuron signs, such as spasticity, hyperreflexia, clonus, and Babinski sign.[12] Of the 153 patients, 70 met criteria for PSP-Richardson's, 26 for PSP-speech/language, 21 for PSP-parkinsonism, 12 for PSP-corticobasal, 10 for PSP-gait freezing, 6 for PSP-frontal, 5 for PSP-corticospinal, 2 for PSP-postural instability, and 1 for PSP-ocular motor. The two PSP-postural instability patients and one PSP-ocular motor patient were excluded because of small sample size.

Twenty-eight cognitively normal individuals were consecutively recruited by the Neurodegenerative Research Group between April 2017 and June 2021. All controls underwent identical 3-T MRI; none had any complaints of cognitive, motor, or behavioral abnormalities, and all performed normally on the Montreal Cognitive Assessment (MoCA)[46] (≥26) and were documented to be Hoehn and Yahr stage 0.[47]

The study was approved by the Mayo Clinic Institutional Review Board, and all individuals consented for participation in the study.

Clinical Evaluations

The neurological evaluations of patients with PSP included testing on the PSP Rating Scale[48] to assess disease severity, MDS-sponsored revision of the Unified

Parkinson's Disease Rating Scale[49] to assess nonmotor and motor aspects of experiences of daily living and motor parkinsonism, PSP Oculomotor Impairment Scale (PSIS)[50] to assess eye movement abnormalities, Frontal Assessment Battery (FAB)[51] to assess executive dysfunction, and MoCA[46] to assess general cognitive impairment. Severity of apraxia of speech was rated using the Apraxia of Speech Rating Scale (ASRS).[52]

Imaging Measurements

All patients and healthy controls underwent a standardized MRI protocol at 3 T that included a magnetization-prepared rapid gradient echo sequence (repetition time/echo time/inversion time, 2300/3/900 ms; flip angle, 8 degrees; 26-cm field of view; 256 × 256 in-plane matrix with a phase field of view = 0.94; slice thickness = 1.2 mm).[53] MRPI measurements were completed according to published criteria[26] by one trained and blinded rater (R.M.G.) using ITK-SNAP software (Supporting Information Fig. S1). One MRI scan was excluded from the study because of unmeasurable SCP width (PSP-parkinsonism). Midbrain and pons areas were measured on the first midsagittal slice from the left, where the superior colliculi completely separated from the midbrain. The middle cerebellar peduncle (MCP) width was measured on the parasagittal slice while the pons was intact, and the cerebellar tonsil was connected. Left and right MCPs were measured and averaged. SCP width was measured on coronal images on the first slice where the inferior colliculi separated from the SCP tracts moving posteriorly from the midbrain. This width measurement was made on three consecutive slices in both hemispheres. The six SCP measurements were averaged, and the ratio of MCP to SCP was multiplied by the pons/midbrain ratio to derive the MRPI. The midbrain/pons ratio was also calculated as midbrain area divided by pons area.[17]

After all measurements were completed, the primary rater remeasured 20 scans to assess intrarater reproducibility. The same 20 scans were also measured by a second blinded rater (N.T.T.P.) to assess interrater reproducibility.

Statistical Analysis

Sex was compared across groups with a Fisher's exact test. Continuous variables were assessed with either a Kruskal–Wallis or Mann–Whitney *U* test. The primary analysis compared brainstem metrics across all PSP variants and controls with post hoc testing using a Wilcoxon rank-sum test. Given the large number of post hoc tests, *P* values were considered at $P < 0.01$ and $P < 0.001$. For the smaller variant groups, PSP-frontal and PSP-corticospinal were excluded from statistical analysis because of small sample size (n < 6) and a lack of power. To adjust for the effect of normal aging, we fit linear regressions in each imaging measure predicting the measurement value by an intercept and age at scan in the healthy controls. We then used these model fits to predict expected measures in cases, calculated the difference between the observed and expected values, and divided this value by the standard deviation of the residuals from the original model. The resulting quantity can be interpreted as standard deviations from the mean measurement in controls, adjusted for age. An analysis was also performed to compare brainstem/subcortical PSP variants (combining PSP-Richardson's, PSP-parkinsonism, and PSP-gait freezing) and cortical PSP variants (combining PSP-speech/language, PSP-corticobasal, and PSP-frontal). Lastly, comparisons were performed between those who have died with PSP pathology versus other pathology, with a subanalysis to specifically look at the patient with PSP who died with corticobasal syndrome.

Group differentiation was assessed using the area under the receiver operator curve (AUROC), and sensitivity and specificity values were calculated using Youden's index to find the optimum cutpoint. Interclass correlation coefficients were used to assess agreement for both interrater and intrarater measurements.

Data Sharing

The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

Demographics and Clinical Findings

Demographic and clinical findings are shown in Table 1. No group differences were observed in sex or education. Differences were observed in age at scan, with PSP-Richardson's younger than PSP-speech/language and PSP-gait freezing, and PSP-gait freezing older than PSP-parkinsonism ($P < 0.01$ for all). PSP-gait freezing was also older at onset than PSP-parkinsonism ($P = 0.005$). PSP-speech/language showed longer disease duration than PSP-Richardson's ($P < 0.001$), PSP-corticobasal ($P < 0.001$), and PSP-gait freezing ($P = 0.005$), and PSP-parkinsonism showed longer disease duration than PSP-Richardson's ($P = 0.003$). Several clinical assessments, including the MoCA, FAB, ASRS, and PSIS, showed a significant difference among clinical variants. PSP-speech/language performed worse on the FAB compared with PSP-Richardson's ($P = 0.008$); PSP-Richardson's performed worse on the PSIS compared with PSP-speech/language ($P = 0.005$) and PSP-gait freezing ($P < 0.001$); and PSP-speech/language performed worse on the ASRS compared with all other PSP variants ($P < 0.01$ for all).

Measurement Reproducibility

The intrarater and interrater reliability scores (interclass correlation coefficients) were 0.97/0.94 for the MRPI, 0.97/0.97 for midbrain area, 0.99/0.98 for pons

TABLE 1 *Demographic and clinical scores across PSP clinical variants*

	PSP-Richardson's (n = 70)	PSP-speech/language (n = 26)	PSP-parkinsonism (n = 21)	PSP-corticobasal (n = 12)	PSP-gait freezing (n = 10)	PSP-frontal (n = 6)	PSP-corticospinal (n = 5)	Control (n = 28)	*P* value
Female sex, n (%)	30 (43%)	15 (58%)	7 (33%)	7 (58%)	8 (80%)	4 (67%)	2 (40%)	18 (64%)	**0.054**
Education, y	14 (12, 16)	15 (12, 16)	16 (14, 16)	16 (12, 16)	16 (14, 18)	14 (12, 14)	14 (12, 17)	16 (14, 16)	**0.800**
Age at scan, y	70 (65, 74)[a]	74 (70, 79)[b]	70 (63, 72)	71 (67, 76)	76 (72, 79)[b,c]	71 (60, 76)	66 (64, 70)	61 (60, 67)	**<0.001**
Age at onset, y	65 (61, 69)	69 (64, 72)	64 (57, 67)	68 (63, 72)	72 (66, 77)[c]	68 (56, 71)	64 (60, 67)		0.012
Disease duration, y	3 (2, 4)[a]	6 (4, 8)[b]	5 (3, 10)[b]	3 (2, 3)[a]	3 (2, 3)[a]	4 (3, 5)	4 (2, 4)		<0.001
MoCA (/30)	24 (20, 27)	19 (16, 25)	26 (22, 27)	21 (17, 24)	26 (24, 27)	5 (5, 5)	25 (24, 26)	28 (26, 29)	**<0.001**
FAB (/18)	14 (12, 15)	12 (6, 14)	14 (13, 16)[a]	14 (9, 14)	15 (13, 16)	14 (11, 16)	17 (17, 17)		0.018
MDS-UPDRS Part I	11 (7, 17)	11 (8, 15)	12 (9, 17)	12 (8, 16)	12 (10, 14)	17 (15, 19)	5 (2, 8)		0.961
MDS-UPDRS Part II	21 (12, 27)	20 (17, 35)	24 (17, 31)	22 (14, 31)	22 (20, 24)	24 (15, 36)	18 (16, 20)		0.630
MDS-UPDRS Part III (/132)	40 (32, 53)	52 (40, 67)	42 (36, 56)	44 (29, 50)	40 (29, 53)	40 (25, 62)	25 (23, 51)		0.099
PSP Rating Scale (/100)	37 (29, 47)	41 (37, 58)	38 (33, 42)	40 (28, 50)	32 (28, 37)[a]	43 (29, 64)	29 (18, 30)		0.099
PSP Rating Scale gait-midline (/20)	11 (6, 15)	11 (7, 14)	13 (10, 15)	12 (6, 16)	12 (12, 14)	11 (6, 16)	5 (4, 14)		0.872
PSIS (/5)	3 (2, 4)[a]	2 (2, 3)[b]	2 (2, 3)[b]	3 (3, 3)	1 (1, 2)[b]	3 (2, 3)	1 (1, 2)		<0.001
ASRS (/64)	4 (2, 6)[a]	21 (16, 32)[b]	4 (2, 5)[a]	3 (2, 5)[a]	3 (2, 3)[a]	2 (2, 3)	15 (15, 15)		<0.001

Data are shown as n (%) or median (interquartile range). *P* values were calculated using Fisher's exact test or Kruskal–Wallis test. *P* values are for the PSP-Richardson's, PSP-speech/language, PSP-parkinsonism, PSP-corticobasal, and PSP-gait freezing groups. The PSP-frontal and PSP-corticospinal groups were not compared with other groups statistically. Bolded *P* values also include the control group.

[a]PSP variant differs from PSP-speech/language, $P < 0.01$.

[b]PSP variant differs from PSP-Richardson's, $P < 0.01$.

[c]PSP-parkinsonism differs from PSP-gait freezing, $P < 0.01$.

PSP, progressive supranuclear palsy; MoCA, Montreal Cognitive Assessment Battery; FAB, Frontal Assessment Battery; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PSIS, PSP Saccadic Impairment Scale; ASRS, Apraxia of Speech Rating Scale.

area, 0.91/0.96 for SCP width, and 0.94/0.90 for MCP width.

Brainstem Measures Across PSP Variants

PSP-Richardson's showed abnormal midbrain area, midbrain/pons ratio, MRPI, and SCP width compared to healthy controls ($P < 0.001$ for all) (Table 2 and Fig. 1). Midbrain/pons ratio provided the highest AUROC estimate for differentiating PSP-Richardson's from controls (Table 3).

Of the PSP variants, PSP-parkinsonism, PSP-speech/language, and PSP-corticobasal showed abnormal midbrain area, midbrain/pons ratio, and MRPI compared with healthy controls ($P < 0.01$ for all) (Table 2 and Fig. 1). Midbrain/pons ratio provided the highest AUROC estimates for PSP-speech/language and PSP-parkinsonism versus controls, and midbrain area for PSP-corticobasal versus controls (Table 3). The PSP-gait freezing group did not show abnormal brainstem metrics compared with controls. When comparing across the five largest PSP groups, we found differences in midbrain area, midbrain/pons ratio, and MRPI (Table 2). These differences across groups remained significant when accounting for age ($P < 0.001$ for all three measures). Post hoc testing showed that midbrain area was smaller in PSP-Richardson's compared to PSP-speech/language ($P = 0.001$) and PSP-gait freezing ($P = 0.003$), and smaller in PSP-corticobasal compared to PSP-gait freezing ($P = 0.007$). Midbrain/pons ratio was larger in PSP-Richardson's compared to PSP-speech/language ($P = 0.003$) and PSP-gait freezing ($P = 0.003$). The MRPI was larger in PSP-Richardson's and PSP-corticobasal compared to PSP-gait freezing ($P = 0.006$).

The PSP-corticospinal and PSP-frontal variants were not statistically compared because of small sample size (Table 2 and Fig. 1). However, PSP-corticospinal showed relatively preserved brainstem metrics, with only moderate differentiation versus controls (Table 3). Conversely, PSP-frontal showed brainstem abnormalities like PSP-Richardson's, with small midbrain area and high midbrain/pons ratio and MRPI; MRPI provided excellent discrimination of PSP-frontal from healthy controls (Table 3).

Cortical Versus Brainstem/Subcortical Variants

All brainstem measures were abnormal in both the cortical and brainstem/subcortical PSP groups compared with healthy controls (Fig. 1), with no significant differences observed between cortical and brainstem/subcortical groups.

Brainstem Measures by Pathology

A total of 43 patients subsequently died and underwent brain autopsy: 29 had a pathological diagnosis

TABLE 2 . *Brainstem measurements across PSP clinical variants*

Midbrain area, mm^2	PSP-Richardson's (n = 70) 82 (67, 98)[a]	PSP-speech/language (n = 26) 106 (87, 131)[a]	PSP-parkinsonism (n = 21) 87 (67, 104)[a]	PSP-corticobasal (n = 12) 82 (73, 90)[a]	PSP-gait freezing (n = 10) 104 (97, 130)	PSP-frontal (n = 6) 76 (64, 85)	PSP-corticospinal (n = 5) 139 (124, 142)	Control (n = 28) 126 (113, 142)	*P* value★ <0.001	0.001[b,c,d]
Pons area, mm^2	606 (447, 670)	642 (607, 682)	464 (448, 628)	512 (454, 585)	547 (490, 681)	540 (463, 633)	643 (454, 665)	500 (468, 585)	0.093	0.114
MCP width, mm	9.5 (8.9, 9.9)[a]	9.3 (9.0, 9.8)[a]	9.5 (9.3, 10.0)	9.0 (8.7, 9.9)	9.4 (8.7, 10.3)	8.7 (8.2, 9.0)	9.7 (9.6, 10.2)	10.1 (9.8, 10.4)	0.009	0.797
SCP width, mm	3.4 (2.7, 4.4)[a]	3.8 (2.9, 4.4)	3.6 (2.9, 4.3)	3.3 (2.5, 3.9)[a]	4.5 (3.8, 4.8)	3.0 (2.7, 4.0)	3.6 (3.6, 4.2)	4.1 (3.6, 4.6)	0.006	0.073[d]
Midbrain/pons ratio	0.14 (0.13, 0.17)[a]	0.17 (0.15, 0.20)[a]	0.16 (0.12, 0.21)[a]	0.17 (0.13, 0.19)[a]	0.21 (0.15, 0.25)	0.13 (0.13, 0.14)	0.22 (0.21, 0.23)	0.24 (0.23, 0.26)	<0.001	0.004[b,c]
MRPI	18 (15, 24)[a]	14 (11, 20)[a]	16 (11, 21)[a]	17 (13, 24)[a]	11 (9, 14)	22 (17, 25)	12 (11, 12)	10 (9, 12)	<0.001	0.002[c,d]

Data are shown as median (interquartile range).
★*P* values were calculated using the Kruskal–Wallis test and include the PSP-Richardson's, PSP-speech/language, PSP-parkinsonism, PSP-corticobasal, PSP-gait freezing, and control groups in the first column and the same PSP variants without the control group in the second *P* value column. The PSP-frontal and PSP-corticospinal were not compared with other groups statistically. Post hoc Wilcoxon rank-sum tests were performed.
[a]PSP variant differs from controls, $P < 0.01$.
[b]PSP-Richardson's differs from PSP-speech/language, $P < 0.01$.
[c]PSP-Richardson's differs from PSP-gait freezing, $P < 0.01$.
[d]PSP-corticobasal differs from PSP-gait freezing, $P < 0.01$.
PSP, progressive supranuclear palsy; MCP, middle cerebellar peduncle; SCP, superior cerebellar peduncle; MRPI, Magnetic Resonance Parkinsonism Index.

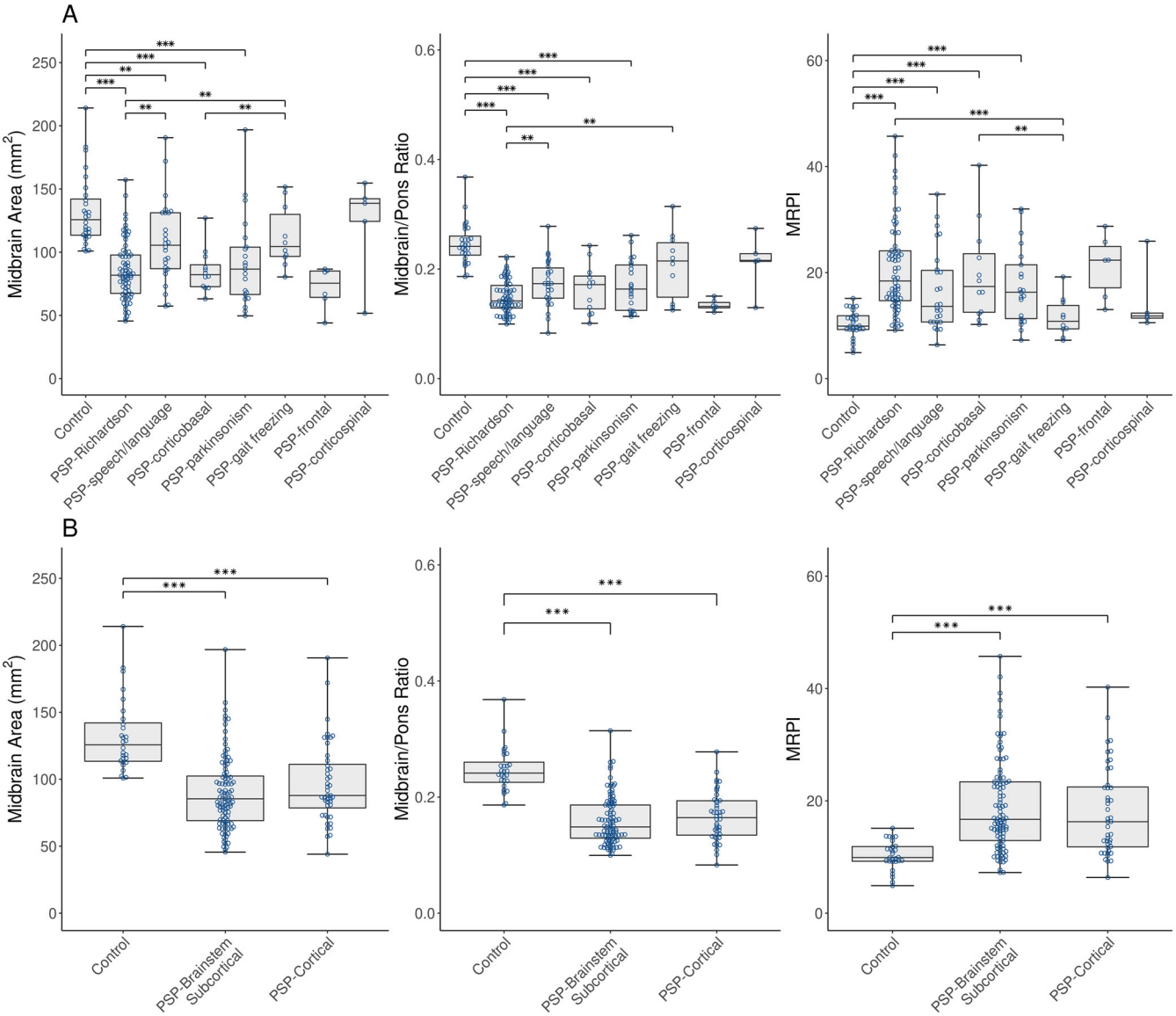

FIG. 1. Midbrain and Magnetic Resonance Parkinsonism Index (MRPI) measures differ across clinical variants of progressive supranuclear palsy (PSP) and healthy control subjects. (**A**) The measurements for each PSP variant and controls. (**B**) The measurements for the same patients but lumped as either cortical (PSP-frontal, PSP-corticobasal, PSP-speech/language) or brainstem/subcortical (PSP-Richardson's, PSP-parkinsonism, PSP-gait freezing). Blue dots represent each individual participant. Boxes represent 25th, 50th, and 75th percentile, with whiskers representing the minimum and maximum values. $^{**}P < 0.01$, $^{***}P < 0.001$.

of PSP and 14 had a non-PSP pathological diagnosis (9 corticobasal degeneration, 2 multiple system atrophy, 1 multisystem tauopathy with globular glial inclusions, 1 diffuse Lewy body disease, and 1 mitochondrial encephalopathy with lactic acidosis and stroke-like episodes).

There were no differences between the PSP and non-PSP autopsy groups in age or time from onset to death (Supporting Information Table S1). The distribution of clinical variants differed between groups; most notably there were more PSP-Richardson's cases in the PSP-autopsy group compared to the non-PSP group (Supporting Information Table S1). The PSP-autopsy group had smaller midbrain area ($P = 0.037$), greater midbrain/pons ratio ($P = 0.004$), greater MRPI ($P < 0.001$), and smaller SCP width ($P = 0.003$) compared to the non-PSP group (Fig. 2 and Supporting Information Table S1). MRPI showed the highest AUROC estimate of 0.83 between non-PSP and PSP-autopsy groups with sensitivity of 83% and specificity of 86% (Table 3). The patients with corticobasal degeneration pathology showed abnormal brainstem measures compared to healthy controls, but more preserved MRPI ($P = 0.022$) and SCP width ($P = 0.019$) compared to the PSP-autopsy group (Supporting Information Table S2).

TABLE 3 *Sensitivity and specificity data to differentiate PSP clinical variants from controls and to differentiate PSP from non-PSP pathology*

Group 1	Group 2	Midbrain	Midbrain/Pons	SCP width	MCP width	MRPI
Differentiating PSP clinical variant from controls						
PSP-Richardson's	Control	0.92 (1.00, 0.79)	0.98 (0.93, 0.97)	0.69 (0.96, 0.43)	0.73 (0.75, 0.70)	0.92 (0.79, 0.96)
PSP-speech/language	Control	0.73 (0.86, 0.62)	0.91 (0.93, 0.77)	0.61 (1.00, 0.31)	0.74 (0.86, 0.73)	0.77 (0.50, 0.96)
PSP-parkinsonism	Control	0.84 (1.00, 0.67)	0.89 (0.79, 0.81)	0.69 (0.86, 0.48)	0.70 (0.86, 0.57)	0.83 (0.67, 0.96)
PSP-corticobasal	Control	0.96 (1.00, 0.92)	0.93 (0.93, 0.83)	0.79 (1.00, 0.50)	0.75 (0.86, 0.67)	0.89 (0.67, 1.00)
PSP-gait freezing	Control	0.73 (0.86, 0.60)	0.69 (0.96, 0.40)	0.60 (0.60, 0.71)	0.65 (0.93, 0.50)	0.60 (0.30, 0.96)
PSP-frontal	Control	0.77 (1.00, 0.67)	0.89 (0.93, 0.83)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.97 (0.83, 1.00)
PSP-corticospinal	Control	0.72 (0.46, 1.00)	0.63 (0.86, 0.60)	0.56 (0.60, 0.71)	0.69 (0.68, 0.80)	0.74 (1.00, 0.54)
Differentiating autopsy-confirmed diagnoses						
PSP	Non-PSP	0.70 (0.57, 0.79)	0.77 (0.79, 0.83)	0.79 (1.00, 0.66)	0.56 (0.43, 0.79)	0.83 (0.83, 0.86)

Data are shown as area under the receiver operator curve (sensitivity, specificity).
PSP, progressive supranuclear palsy; SCP, superior cerebellar peduncle; MCP, middle cerebellar peduncle; MRPI, Magnetic Resonance Parkinsonism Index.

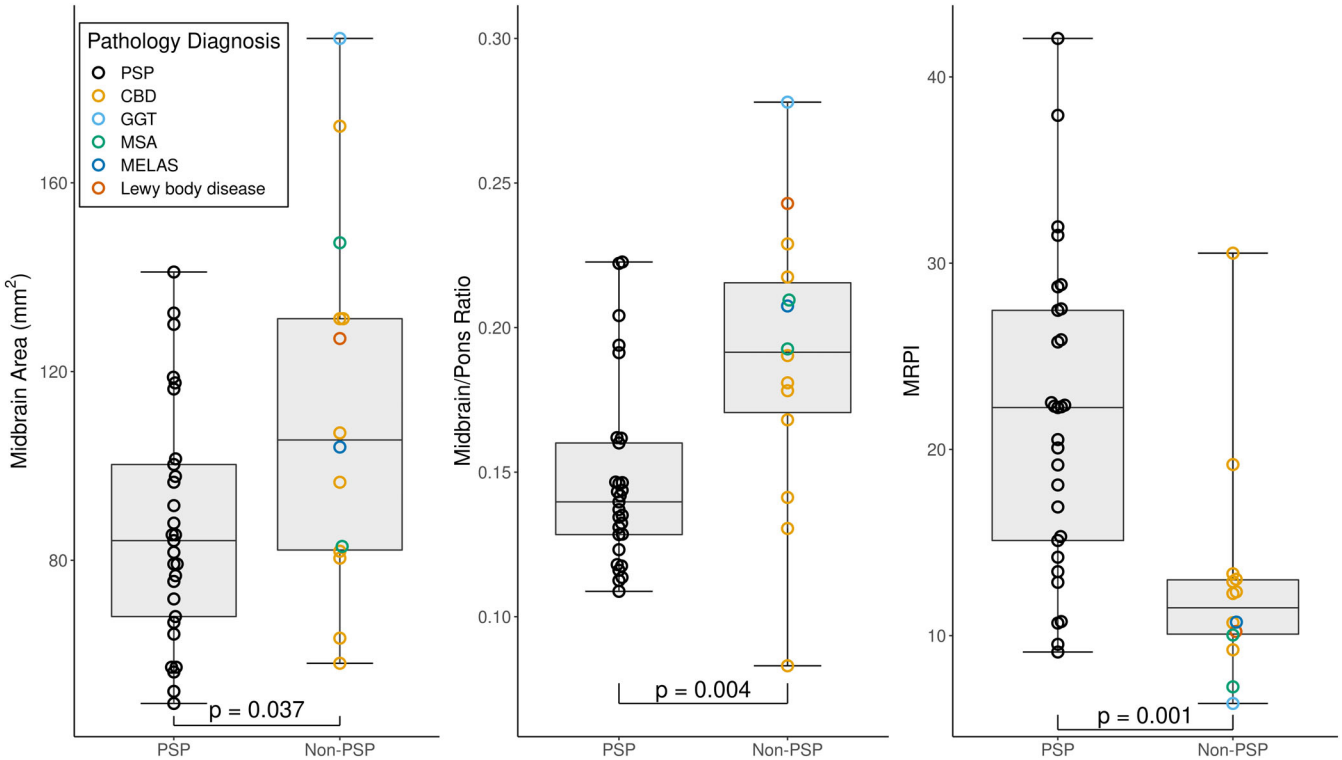

FIG. 2. Midbrain and Magnetic Resonance Parkinsonism Index (MRPI) measures between patients with PSP and non-PSP pathologies. Individual points are shown and the points for the non-PSP group are color coded according to pathology. CBD, corticobasal syndrome; GGT, globular glial tauopathy; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

Discussion

Our findings show that brainstem biomarkers, including MRPI, midbrain area, and midbrain/pons ratio, are abnormal across many of the clinical variants of PSP, suggesting diagnostic utility across the PSP phenotypic spectrum. However, the degree of abnormality in these measures varies across variants. The PSP-Richardson's, PSP-corticobasal, PSP-parkinsonism, and PSP-frontal groups showed the most severe abnormalities, followed by PSP-speech/language, with PSP-gait freezing and PSP-corticospinal showing relatively normal brainstem biomarkers. Findings also showed that brainstem biomarkers differed between PSP patients with versus

without PSP pathology, suggesting potential value in predicting underlying pathology in patients diagnosed with PSP.

Brainstem Measures as Diagnostic Biomarkers in PSP Variants

The PSP-Richardson's group showed the expected abnormalities in midbrain area, midbrain/pons ratio, and MRPI. The midbrain/pons ratio performed better than the MRPI and midbrain area in differentiating PSP-Richardson's from healthy controls with a sensitivity of 93% and specificity of 97%, although all three metrics performed well. Previous studies have produced mixed findings, with some finding that the midbrain/pons ratio performed better than MRPI in differentiating PSP-Richardson's from controls,[34,54] and others finding that the MRPI was equivalent or superior to the midbrain/pons ratio in differentiating PSP-Richardson's from healthy controls, multiple system atrophy parkinsonian variant, and PD.[26,27,29,55,56]

Midbrain area, midbrain/pons ratio, and MRPI were also abnormal in PSP-parkinsonism, PSP-speech/language, and PSP-corticobasal compared to controls. The midbrain/pons ratio performed better than the MRPI in all three variants, although specificity to differentiate these variants from controls was lower than achieved for PSP-Richardson's. The sensitivity of the midbrain/pons ratio to differentiate these PSP variants from controls was lowest for PSP-parkinsonism (sensitivity 79%, specificity 81%). Hence although abnormalities in these biomarkers suggest some diagnostic utility in these PSP variants, overlap with controls may limit their sensitivity, particularly in PSP-parkinsonism. Previous studies have similarly identified abnormal brainstem metrics in PSP-parkinsonism.[28,32,34] The diagnostic sensitivity and specificity of differentiating PSP-parkinsonism from healthy controls has, however, varied, with midbrain/pons ratio giving 80% sensitivity and 67% specificity in one study[28] and 81% and 87% in another.[34] Performance of the MRPI has also varied from a sensitivity and specificity of 60% and 100% in one study[28] to 85% and 98% in another.[32] This variability may be because of cohort differences or variability in manual measurements. No previous studies have assessed these brainstem measures in PSP-speech/language or PSP-corticobasal. We have shown in an independent cohort of PSP-corticobasal patients that these patients have the imaging features of both corticobasal syndrome and PSP, including degeneration of the midbrain and SCP.[8] We have also previously observed midbrain atrophy in patients with PSP-speech/language.[45] We also observed abnormal midbrain area, midbrain/pons ratio, and MRPI in PSP-frontal, with excellent sensitivity and specificity to differentiate PSP-frontal from healthy controls. This finding is not particularly surprising given that all these patients also met criteria for probable PSP-Richardson's prior to applying MAX criteria.

The PSP-gait freezing group did not show abnormal brainstem metrics compared with healthy controls, suggesting a lack of clinical diagnostic utility of brainstem measures in this PSP variant. This variant also performed relatively well on the PSP Rating Scale and showed only mild ocular motor dysfunction. However, we had only 10 patients in this group and hence these findings should be confirmed in a larger cohort.

Variability Across PSP Variants

Across brainstem measures, we did not find significant differences between PSP-Richardson's, PSP-parkinsonism, or PSP-corticobasal, and little difference was observed with PSP-frontal. Some previous studies have found more abnormal midbrain/pons ratio and MRPI in PSP-parkinsonism compared to PSP-Richardson's.[28,34] The PSP-parkinsonism group in our study tended to show more preserved brainstem measures compared to PSP-Richardson's, although measures were variable within groups and differences did not reach significance. The PSP-gait freezing group had more preserved midbrain area, midbrain/pons ratio, and MRPI compared to PSP-Richardson's, and more preserved midbrain area and MRPI compared to PSP-corticobasal. A previous study similarly found more abnormal midbrain area and midbrain/pons ratio, but not MRPI, in PSP-Richardson's compared to PSP-gait freezing.[57]

The PSP-speech/language patients showed significantly more preserved midbrain and midbrain/pons ratio compared with PSP-Richardson's. This confirms our previous findings that showed only mild midbrain atrophy in PSP-speech/language[13,45] but extends the findings to also show how the midbrain/pons and MRPI biomarkers perform in this cohort. The findings suggest that these brainstem measures could be useful to help differentiate PSP-Richardson's from PSP-speech/language. Also notable is that all PSP-speech/language patients met at least possible PSP criteria[11]; we did not include patients who only met suggestive of PSP-speech/language because they have a lower probability of having underlying PSP pathology.[58,59] We have previously shown that patients with suggestive of PSP-speech/language do not show midbrain atrophy.[45]

Cortical Versus Brainstem/Subcortical Variants

We did not find any significant differences in midbrain area, midbrain/pons ratio, or MRPI between the brainstem/subcortical variants of PSP compared to the cortical variants, reflecting the fact that the brainstem measures were highly abnormal in both the PSP-corticobasal and PSP-frontal cortical variants. Another study similarly identified midbrain atrophy as a common feature across PSP-Richardson's, cortical (PSP-

corticobasal + PSP-frontal), and subcortical (PSP-parkinsonism, PSP-gait freezing, and PSP-ocular motor) variants.[60] Differences between the cortical and brainstem/subcortical variants therefore appear to be driven by the greater degree of cortical involvement in the cortical variants, rather than by the degree of involvement of the midbrain.[13,60]

Brainstem Measurements in PSP-Corticospinal

Most of the PSP-corticospinal patients had brainstem measures within the normal range. The PSP-corticospinal diagnosis was originally described by our group[12] and is not part of the MDS-PSP diagnostic criteria.[11] These patients show clinical evidence of corticospinal tract degeneration, in addition to PSP features, particularly parkinsonism and postural instability, and do not fit into any of the other PSP clinical diagnostic categories. Apraxia of speech was observed in one PSP-corticospinal patient showing overlap with PSP-speech/language. On clinical testing, these patients showed less parkinsonism and gait abnormalities and less ocular motor dysfunction compared with the other groups; this may explain the lack of brainstem abnormalities because midbrain atrophy has been strongly associated with the presence of PSP-related features.[36] Indeed, ocular motor dysfunction is relatively rare in PSP-corticospinal.[12] Alternatively, different brain networks and regions may be involved in the abnormalities observed in PSP-corticospinal. Further follow-up of this group will be important to determine whether brainstem abnormalities develop with worsening of the disease.

Brainstem Measures for Predicting Pathology in PSP

Our analysis of the subset of patients with brain autopsy demonstrated that those with underlying PSP pathology had greater abnormalities across the brainstem measures compared to those without underlying PSP pathology, including smaller midbrain area and higher midbrain/pons ratio and MRPI, suggesting utility in predicting PSP pathology. The MRPI showed the best prediction of underlying pathology with sensitivity of 83% and specificity of 85%. The PSP pathology group did, however, have a much higher proportion of cases with an antemortem diagnosis of PSP-Richardson's, with the non-PSP group having a higher proportion of cases with PSP-speech/language; hence the findings could reflect these syndromic differences. These syndromic differences likely reflect the reality and confidence in diagnosing varying forms of PSP because PSP-Richardson's patients are more likely to have underlying PSP compared with PSP-speech/language.[58] We have previously found in an independent sample that midbrain area was more strongly related to PSP-Richardson's than to underlying pathology, although that study included a broader range of clinical diagnoses.[36] In contrast, we have found that speech/language patients with underlying PSP pathology have greater midbrain atrophy than those with corticobasal degeneration pathology.[61] In this study, when we specifically assessed the corticobasal degeneration cases, we found that they did show abnormal brainstem measures but showed more preserved MRPI compared to PSP, again supporting the diagnostic utility of the MRPI. Hence there is growing evidence that brainstem biomarkers may help to predict the presence of underlying PSP pathology in patients diagnosed clinically with a PSP clinical variant.[24,31] It will be important for future studies to determine the pathological specificity of these measures in other cohorts with a different breakdown of syndromic diagnoses to determine the generalizability of these results.

Strengths and Limitations

Strengths of our study include the standardized clinical and neuroimaging evaluations across the cohort and the large number of participants, which allowed the assessment of many different PSP clinical variants. Our measurements were all performed manually and followed standardized protocols, and intrarater and interrater reproducibility were excellent. The small number of participants in some of the clinical variants was a limitation and precluded statistical analysis of the PSP-frontal and PSP-corticospinal groups. We were not able to assess the PSP-ocular motor and PSP-postural instability variants in this study because of small sample size. Further analysis should be done with larger numbers of these uncommon variants of PSP to allow more confident conclusions regarding the predictive utility of these brainstem metrics across the whole PSP phenotypic spectrum. Another potential limitation is that we used the original MRPI, and there is now a second version that includes the ratio of the third ventricle width and the frontal horn width, which may show improved sensitivity for distinguishing PSP-parkinsonism patients from healthy controls and PD.[32] However, another study found similar diagnostic ability of the MRPI and MRPI 2.0 in PSP-Richardson's and PSP-parkinsonism.[34] Measurement of midbrain-to-pons midsagittal distance ratio has also shown utility for identifying autopsy-confirmed PSP,[24] but this variation on the midbrain/pons ratio was not assessed in this study.

Conclusions

The results of this study assessed the diagnostic utility of midbrain area, midbrain/pons ratio, and the MRPI across the phenotypic spectrum of PSP. Abnormal brainstem measures were observed in the PSP-Richardson's, PSP-speech/language, PSP-corticobasal,

PSP-frontal, and PSP-parkinsonism variants, suggesting they could be supportive of the clinical diagnosis in these clinical variants of PSP,[14] although variability was observed across variants, which will need to be considered. The results from the autopsy subset also support the value of these structural measures as surrogate biomarkers of PSP pathology. These insights will be particularly important to guide the selection of MRI outcome measures for clinical treatment trials that enroll participants with different clinical variants of PSP.

Acknowledgments: This study was supported by the Neuman Family Foundation, the National Institutes of Health (grants R01-NS89757, R01-DC12519, R01-DC010367, and R01-DC14942), and the Dana Foundation.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

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