Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Longitudinal Videofluorographic Dysphagia Measures in Progressive Supranuclear Palsy

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Abstract: Background: Dysphagia can lead to fatal aspiration pneumonia in progressive supranuclear palsy (PSP). Little is known about the longitudinal progression of dysphagia or whether it differs across PSP clinical variants.

Objectives: To characterize longitudinal changes in dysphagia across PSP variants and determine relationships with disease severity and rate of atrophy in PSP-related regions.

Methods: Sixty-one PSP patients were recruited and underwent at least two serial evaluations, comprising neurological and videofluorographic exams, and MRI. Variables-of-interest were the oral and pharyngeal total sum scores (OTSS/PTSS) from the Modified Barium Swallow Impairment Profile, the Penetration Aspiration Scale (PAS), Functional Oral Intake Scale (FOIS), and lingual pressure assessments. Rates of change were compared across PSP variants and related to baseline scores, PSP Rating Scale and regional brain atrophy rates.

Results: Dysphagia progressed longitudinally, particularly with worsening in OTSS and anterior and posterior lingual pressures. Rate of change in OTSS was fastest in PSP with predominant speech-language disorder. Negative correlations were observed between rates of change and baseline scores for OTSS, PTSS and PAS. Rates of change in lingual pressure measures correlated with rates of change in the PSP Rating Scale. Rate of change in the FOIS correlated with rates of change in OTSS and lingual pressure. Rates of brain atrophy were associated with baseline OTSS, PTSS, and PAS.

Conclusions: Dysphagia and lingual pressure worsen over time in PSP, with variability in rates of change in the OTSS across PSP variants and evidence that dysphagia is related to rates of atrophy.

Progressive Supranuclear Palsy (PSP) is a neurodegenerative disorder characterized by four-repeat tau protein accumulation.[1] The core clinical features, proposed by the Movement Disorder Society, include ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction.[2] The combination of core clinical criteria, supportive clinical cues, and supportive imaging findings allows the diagnosis of clinical variants of the disease, including PSP-Richardson (PSP-RS), PSP with postural instability (PSP-PI), PSP with predominant Parkinsonism (PSP-P), PSP with progressive gait freezing (PSP-PGF), PSP with predominant corticobasal syndrome (PSP-CBS), and PSP with predominant speech-language disorder (PSP-SL). The PSP-SL and PSP-CBS variants have been referred to as cortical variants of PSP, whereas PSP-PGF, PSP-PI, and PSP-P are referred to as subcortical variants of PSP. The most common variant is PSP-RS, which clinically reflects the earliest phenotypic description of the disease, characterized by postural instability and ocular motor impairment.[3]

Early dysphagia is associated with shorter survival[4] as it affects intake of food, liquid, and medication. Dysphagia is a risk factor for aspiration pneumonia, which is a leading cause of death in PSP patients.[5] Oral phase impairments are more prominent than pharyngeal phase impairments[6] and occur more frequently in

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PSP than observed in Parkinson's Disease (PD).[7] Additionally, it has been revealed recently that lingual strength is reduced in PSP, compared to healthy controls and patients with PD.[8] However, little is known about how dysphagia progresses over time in PSP, limiting the ability to provide prognostic estimates to patients and their families. Furthermore, understanding how dysphagia differs across different PSP variants will further inform prognosis. Previous longitudinal studies in PSP have found that the subcortical variants of PSP show slower rate of progression in terms of the PSP Rating Scale,[9] compared to PSP-RS and cortical variants of PSP.[10]

Neuroimaging findings show that PSP is associated with degeneration in a network of brain regions, including striatum, globus pallidum, thalamus, midbrain, frontal lobes and dentatorubrothalamic tract[11,12] However, the relative involvement of different parts of this network differ across the different clinical variants.[11] Patients with PSP-RS show striking degeneration of the dentatorubrothalamic tract, midbrain and subcortical structures, with milder involvement of the frontal lobes.[11,13–15] Patients with the subcortical variants of PSP show degeneration more restricted to subcortical structures, including the basal ganglia, subthalamic nucleus and thalamus, and patients with the cortical variants of PSP show degeneration predominantly in the frontal lobes with milder involvement of other regions in the PSP network.[11,13–15] Additionally, oral phase impairments have been associated with cortical abnormalities, especially in the parietal and sensorimotor cortex, whereas pharyngeal phase impairments were related to disruption of corticospinal tract and cerebral peduncle[16,17] Establishing a connection between PSP-related neuroimaging disruptions and dysphagia measures will lend insight into the pathophysiology of dysphagia in PSP.

The primary aim of our study was to assess whether dysphagia worsens over time in PSP patients and to determine whether the pattern of dysphagia or rate of worsening differs across the PSP clinical variants. In our study, we assessed longitudinal changes in five primary quantitative dysphagia measures: Oral Total Sum Score (OTSS) and Pharyngeal Total Sum Score (PTSS) from the Modified Barium Swallow Impairment Profile (MBSImP),[18] the Penetration Aspiration Scale (PAS),[19] and anterior and posterior lingual strength. The secondary aim was to determine whether the rates of change in the primary dysphagia measures were associated with rates of change in the Functional Oral Intake Scale (FOIS), to determine whether changes in the quantitative measurements were associated with diet restrictions. Lastly, we investigated the relationship between rates of atrophy in PSP-related regions and baseline and rates of change in dysphagia measures to determine whether rate of change in these key PSP regions are associated with dysphagia. Based on dysphagia patterns observed in our previous cross-sectional studies,[6,16] we hypothesized that worsening over time will be predominantly observed in OTSS and will be related to worsening on the FOIS and rates of atrophy in cortical brain regions. We hypothesized that rates of worsening of OTSS will be slowest in the subcortical variants of PSP since these variants show the slowest rate of overall disease worsening.[9,10]

Methods

Study Design and Participants

Patients who met diagnostic criteria for PSP[2,20] were recruited prospectively into a longitudinal cohort design NIH-funded research grant by the Neurodegenerative Research Group from the Department of Neurology, Mayo Clinic, between February 2, 2016 and October 24, 2023. Inclusion criteria included age at onset over 40, a history of gradual progression of PSP-related symptoms and evidence of ocular motor impairment, postural instability or progressive gait freezing at enrollment. Exclusion criteria included diagnosis of another neurodegenerative disorder, concurrent illness or symptoms that could be explained by structural brain abnormalities, such as tumors or infarcts. All patients underwent a detailed neurological and neuropsychological evaluation, 3 T head MRI and a videofluorographic dysphagia examination, and were brought back annually for identical research visits for the grant. For the current study, we retrospectively analyzed data that was collected for the grant. We included all patients who had completed at least two annual research visits with a videofluorographic examination at both visits ($n = 61$). Patients were included regardless of whether they had symptoms of dysphagia or a diagnosis of dysphagia based on the videofluorographic examination. All patients were diagnosed by one of two specialist fellowship-trained neurologists (KAJ and FA) with one of the PSP clinical variants based on the Movement Disorders Society PSP diagnostic criteria.[2] Eleven patients underwent their baseline visit before the diagnostic criteria were published. For these 11 patients, the criteria were retrospectively applied using operationalized definitions previously published to determine whether each patient met the oculomotor, postural instability, and akinesia sections of the criteria.[21] The cohort included 30 patients with PSP-RS, 12 with PSP-P, eight with PSP-PGF, three with PSP-PI, three with PSP-CBS, and five with PSP-SL. At the last follow-up visit, four patients met criteria for PSP-RS (two with a baseline diagnosis of PSP-CBS who developed postural instability and/or falls at a follow-up visit that was within three years from onset and two with baseline PSP-PI who developed ocular motor slowing).

The study was approved by the Mayo Clinic Institutional Review Board and all patients provided written consent.

Neurological and Neuropsychological Assessments

All patients underwent clinical evaluation comprising neurological and neuropsychological protocols. The clinical evaluation for this study included the PSP Rating Scale[22] to assess disease severity, Montreal Cognitive Assessment (MoCA) to quantify cognition, Movement Disorder Society sponsored revision of the Unified Parkinson Disorder Scale (MDS UPDRS III) to assess parkinsonism,[23] PSP Saccadic Impairment Scale (PSIS) to assess saccadic ocular movement, Test for Upper Limb Apraxia (TULIA) to assess ideomotor limb

apraxia, Frontal Assessment Battery (FAB)[24] to assess frontal lobe function, Apraxia of Speech Rating Scale (ASRS) to assess apraxia of speech,[25,26] and Motor Speech Disorder Functional Rating Scale (MSD)[27] to quantify the severity of motor speech impairments. The MSD was initially developed to describe decline in functional motor speech abilities and has been successfully applied in other neurodegenerative conditions, including PSP,[28] progressive apraxia of speech[26] and frontotemporal dementia.[29] Dysarthria severity was assessed on a four-point scale (0–4) by a speech-language pathologist based on spoken language tasks of the Western Aphasia Battery[30] plus additional speech tasks that included vowel prolongation, speech alternating motion rates (eg, rapid repetition of "puhpuhpuh…"), speech sequential motion rates (eg, rapid repetition of "puhtuhkuh") and a conversational speech sample. Non-verbal Oral Apraxia (NVOA) was assessed using an eight-item scale.[31]

Dysphagia Assessment

Data Collection

The videofluorographic swallowing assessment was performed using the Modified Barium Swallow Impairment Profile (MBSImP) protocol.[18] Videofluorographic recordings were performed using Seimens Luminos Agile Max at fluoroscopic rate of 30 and a recording rate of 30 frames per second. Consistencies were Varibar products Thin Liquid (<15cPs), corresponding to International Dysphagia Diet Standardization Initiative (IDDSI)[32] Level 0, nectar (300cPs, IDDSI level 2), pudding (puree consistency, IDDSI level 4), and Lorna Doone shortbread cookie with barium pudding coating (solid consistency, IDDSI level 7). The volume and order of recorded swallows are listed in Table 1.

TABLE 1 *Videofluoroscopic swallowing examination protocol*

Lateral view	Volume	Modality
Thin liquid (not included in OI score)	5 ml	Teaspoon
Thin liquid	5 ml	Teaspoon
Thin liquid	Self-selected	Single cup sip
Thin liquid	Self-selected	Sequential swallow
Nectar liquid	5 ml	Teaspoon
Nectar liquid	Self-selected	Single cup sip
Nectar liquid	Self-selected	Sequential swallow
Pudding	5 ml	Teaspoon
Solid	½ Shortbread cookie coated with 3 ml pudding consistency	
Anterior–posterior view		
Nectar liquid	5 ml	Teaspoon
Pudding	5 ml	Teaspoon

Data Analysis

Videofluorographic images were reviewed using QREADS. The MBSImP[18] yields ratings for 17 individual components of swallowing function as well as the OTSS and PTSS components. The PAS[19] was scored for all consistencies but scores above 1 were rare for nectar, pudding, and solid. Therefore, only PAS scores for thin liquids were included in the analysis. Based on the exam findings, scores on the FOIS[33] were assessed to characterize the extent to which the clinician recommended modifying the oral diet or the degree to which nonoral nutrition was recommended.

Score ranges for OTSS are normal to mild (0–10), moderate (11–18), severe (19–22); for PTSS: normal to mild (0–13), moderate (14–24), severe (25–29).[34] PAS ranges from least impaired (1: "Material does not enter the airway") to most impaired (8: "Material enters the airway, passes below the vocal folds, and no effort is made to eject"). FOIS ranges from least restricted (7: "Total oral intake with no restriction") to most restricted (1: "Nothing by mouth"). Normal ranges for anterior lingual strength for individuals older than 60 years refer to normal (57), mild weakness (37–29), moderate 28–20), severe (<19).[35] Mean posterior lingual strength values are usually 5–10% lower than anterior lingual strength.[8]

Lingual Strength Analysis

Anterior and posterior lingual strength were assessed using the IOPI (formerly known as the Iowa Oral Performance Instrument), which measures pressure exerted by the tongue on an air-filled bulb positioned behind the front teeth (anterior) and at the hard-soft palate junction (posterior).[36] Three motivated trials were obtained from each position with the highest of the three pressures (in kilopascals kpA) recorded as the measure of lingual strength used in statistical analyses.

Neuroimaging Analysis

To be included in the MRI longitudinal analysis, patients must have performed at least two MRI scans on the same MRI scanner manufacturer (either Siemens or GE Medical). All baseline MRI scans were no more than two months apart from the baseline dysphagia assessment. Eight patients were excluded from this analysis: five were excluded due to inconsistency in the scanner manufacturer over time, one for missing baseline scan matching baseline videofluorographic, and two for segmentation issues.

The 53 patients included in the MRI analysis underwent MRI protocol on a 3 T Siemens Prisma or GE Medical scanner. The protocol included a T1-weighted 3D magnetization prepared rapid gradient echo sequence.[37] To minimize the number of comparisons being performed, region-level data were generated for five regions-of-interest that capture different parts of the PSP network.[11] Volumes of the precentral (motor) cortex,

superior frontal lobe and pallidum were generated using the Mayo Clinic Adult Lifespan Template (https://www.nitrc.org/projects/mcalt), and volumes of the midbrain and cerebellar dentate were measured using in-house-developed atlases.[38] Volumes were calculated for all available MRI scans for all patients. Total intracranial volume (TIV) was also measured.

Statistical Analysis

Patient-level annualized rates of change for each dysphagia measure and the PSP Rating Scale were calculated from the slopes obtained from a linear regression model for each test. The cross-variant comparisons were performed using the non-parametric Kruskal-Wallis test, with a post hoc Dunn's test correcting for multiple comparisons. Spearman rank-order partial correlations adjusted for disease duration were used to assess relationships between rates of change in the quantitative dysphagia measures and either baseline scores for the same test or rate of change in other tests. The annual rates of change in cortical volumes were calculated using a linear regression model. In total, 45 patients had two serial visits, 12 patients had three serial visits, two patients had four serial visits, two patients had five serial visits. Lastly, rates of change for anterior lingual pressure and posterior lingual strength were calculated for 46 and 55 patients, respectively. This was due to the unavailability of data for at least two visits.

The relationship between the dysphagia variables and neuroimaging was assessed using a multivariable regression model with a single response variable, adjusted for MRI manufacturer (SIEMENS or GE Medical), TIV, age at baseline and disease duration. The regression lines representing this analysis were performed by setting Siemens as the MRI manufacturer, 70 years as age at baseline, 1500 mL as the total intracranial volume, and a disease duration of 3 years. All analyses were performed using SPSS v.29 and R. The alpha level was set at $P < 0.05$.

Results

Demographic and Clinical Features

Demographic and clinical features are displayed in Table 2. The PSP groups did not differ in sex, education, age at baseline, age at onset, and follow-up time (time between the first visit and the last available visit). The PSP groups differed in duration from onset to baseline, with PSP-SL and PSP-P having the longest disease duration. Regarding the clinical tests, no differences between groups were observed in the MoCA, MDS-UPDRS III, ASRS, and dysarthria severity. However, differences were observed in the PSIS, with greatest impairment in PSP-RS, the TULIA, with greatest impairment in PSP-CBS and PSP-SL, and MSD severity scale, with greatest impairment in PSP-SL. The PSP Rating Scale and FAB differed across groups, although no post hoc pair-wise comparisons reached significance.

Rates of Change in Dysphagia across PSP Variants

The baseline scores and rate of change in the dysphagia measures are shown in Table 2. At baseline (Fig. S1), the PSP groups showed mild impairment in all dysphagia measures, although no differences across groups were observed. Additionally, the median baseline FOIS score across the entire cohort was 7, indicating that examiners advised the patients to proceed with total oral intake with no restrictions. Longitudinally, the cohort progressed slowly over time in all the primary quantitative dysphagia measures and the FOIS. Annual decline was more evident in OTSS and anterior and posterior lingual strength, compared to the PTSS, PAS, and FOIS (Fig. 1). The FOIS score did not change in most patients. Rates of change in OTSS differed across the PSP groups, with PSP-SL showing the fastest rates of annual progression; in particular, the difference between PSP-SL and PSP-PGF was significant. No differences in any other dysphagia rates were demonstrated across groups.

Rates of Change in Dysphagia Versus Other Clinical Features

Less impaired (ie, lower) baseline scores correlated with faster rates of progression for OTSS ($R = -0.42$, $P < 0.001$), PTSS ($R = -0.27$, $P = 0.03$), and PAS scores ($R = -0.40$, $P = 0.002$) (Fig. 2). No significant relationship was identified between baseline score and rate of change in anterior or posterior lingual strength or FOIS. As reported in Figure 3, faster rates of worsening in OTSS ($R = -0.33$, $P = 0.01$) and posterior lingual strength ($R = 0.37$, $P = 0.01$) were associated with faster worsening in the FOIS. Similarly, faster rates of worsening in OTSS ($R = 0.32$, $P = 0.01$) and anterior lingual strength ($R = -0.34$, $P = 0.01$) were associated with faster worsening in the PSP Rating Scale.

Rates of Atrophy Versus Dysphagia

Table S1 and Figure 4 display the results of the multivariable regression analysis between dysphagia measures and the rate of atrophy of the PSP-related regions. Worse baseline OTSS was related to a faster rate of atrophy in the cerebellar dentate, and worse baseline PTSS was associated with a faster rate of atrophy of midbrain and precentral cortex. Conversely, worse baseline PTSS correlated with a slower rate of brain atrophy in the pallidum. Additionally, a slower rate of change in PTSS was associated with faster rate of atrophy of the precentral cortex. In contrast, faster progression in PAS rate was related to a faster rate of atrophy in the cerebellar dentate.

Discussion

In this longitudinal study we demonstrate that dysphagia worsens over time in all PSP variants, with most pronounced changes

TABLE 2 *Demographic and clinical features across PSP groups*

	PSP-RS ($N = 30$)	PSP-PGF ($N = 8$)	PSP-P ($N = 12$)	PSP-PI ($N = 3$)	PSP-CBS ($N = 3$)	PSP-SL ($N = 5$)	*P* value
Demographic and neurological features							
Male	17 (57%)	2 (25%)	5 (42%)	3 (100%)	2 (67%)	2 (40%)	0.30
Education (y)	15 (13, 16)	14 (12, 16)	16 (14, 16)	12 (12, 15)	14 (13, 16)	18 (16, 20)	0.45
Age baseline (y)	70 (65, 76)	73 (72, 78)	70 (61, 72)	68 (64, 73)	67 (65, 68)	75 (72, 76)	0.11
Age onset (y)	67 (61, 71)	70 (66, 75)	62 (56, 67)	62 (58, 69)	63 (62, 66)	68 (67, 69)	0.13
Time from baseline to last visit (y)	1 (1, 1)	1.5 (1, 3)	1.2 (1, 2)	1.0 (1, 2)	2 (2, 3)	1 (1, 1)	0.46
Time from onset to baseline visit (y)	3 (2, 4)	4 (3, 4)	6 (5, 8)	6 (4, 6)	2 (2, 3)	8 (6, 8)	**<0.001**[a,b,e,f]
Number of visits	2 (2, 2)	2 (2, 3)	2 (2, 3)	2 (2, 2)	2 (2, 4)	2 (2, 2)	0.67
PSP Rating Scale	37 (29, 43)	30 (24, 34)	38 (35, 42)	20 (19, 24)	25 (21, 32)	44 (38, 51)	**0.01**
PSP Rating scale rate/yr	10 (5, 13)	4 (2, 7)	5 (4, 8)	1 (−4, 11)	8 (8, 11)	16 (11, 17)	0.07
MoCA	24 (21, 26)	25 (23, 25)	26 (24, 27)	24 (22, 26)	21 (20, 24)	25 (18, 25)	0.63
FAB	14 (13, 16)	16 (14, 18)	15 (13, 17)	13 (11, 15)	9 (9, 13)	13 (11, 15)	0.36
MDS-UPDRS III	36 (30, 46)	35 (30, 40)	42 (36, 52)	35 (24, 38)	26 (26, 34)	45 (40, 52)	0.20
PSIS	3 (2, 4)	1 (0, 2)	2 (2, 4)	0 (0, 0)	3 (2, 3)	2 (2, 3)	**0.003**[c,d]
TULIA	11 (10, 12)	12 (11, 12)	12 (11, 12)	12 (11, 12)	8 (6, 10)	9 (9, 10)	**0.02**[f,g]
ASRS	4 (1, 6)	2 (1, 3)	4 (2, 5)	4 (2, 4)	4 (3, 4)	22 (21, 24)	0.15
MSD	7 (6, 8)	8 (6, 8)	6 (6, 7)	6 (6, 8)	9 (8, 9)	2 (2, 4)	**0.005**[b,e,h]
Dysarthria sev.	1 (1, 2)	1 (1, 2)	2 (1, 3)	2 (2, 3)	2 (2, 2)	3 (2, 3)	0.14
NVOA	32 (30, 32)	32 (30, 32)	32 (31, 32)	32 (30, 32)	32 (32, 32)	12 (5, 20)	0.01
Baseline dysphagia findings							
OTSS (/22)	6 (4, 9)	6 (4, 8)	6 (5, 8)	5 (2, 6)	7 (6, 8)	6 (4, 8)	0.82
PTSS (/29)	2 (2, 5)	2 (1, 2)	2 (1, 2)	2 (1, 4)	5 (4, 6)	5 (4, 5)	0.08
PAS (/8)	1 (1, 4)	2 (1, 2)	2 (2, 2)	1 (1, 2)	2 (2, 2)	2 (2, 2)	0.62
FOIS score (/7)	7 (6, 7)	7 (7, 7)	7 (7, 7)	7 (7, 7)	7 (7, 7)	7 (7, 7)	0.31
PmaxA (kPa)	35 (26, 47)	38 (33, 42)	44 (40, 48)	52 (48, 58)	40 (39, 40)	40 (32, 41)	0.21
PmaxP (kPa)	29 (20, 38)	32 (30, 39)	42 (34, 47)	45 (42, 46)	35 (28, 37)	35 (32, 42)	0.08
Dysphagia annualized rate of change							
OTSS	1 (−0, 2)	0 (−2, 1)	3 (0, 4)	2 (2, 5)	2 (2, 2)	4 (4, 6)	**0.03**[h]
PTSS	0 (−1, 2)	0.4 (0, 1)	1 (0, 2)	0 (−1, 0)	−1 (−1, 0)	0 (−2, 3)	0.61
PAS	0 (0, 1)	0 (−0, 1)	0 (0, 1)	1 (1, 3)	0 (−0, 1)	0 (0, 0)	0.76
FOIS	0 (−1, 0)	0 (−0.4, 0)	0 (−1, 0)	0 (−1, 0)	−1 (−1, −0)	-1 (−2, 0)	0.84
PmaxA	−3 (−7, −1)	−1 (−2, 5)	−4 (−10, −1)	−3 (−9, −2)	−5 (−6, 1)	−7 (−9, −6)	0.33
PmaxP	−2 (−5, 4)	−1 (−2, −0.1)	−3 (−8, −1)	0 (−5, 1)	−3 (−4, −1)	−6 (−6, −6)	0.82

Note: Data are shown as median (25th, 75th quartiles) or *N* (%). *P* values calculated using Kruskal-Wallis rank sum test for continuous variables and Fisher's Exact Test for categorical data. Dunn's test with FDR correction was used for pair-wise comparisons.

[a]Difference between PSP-RS and PSP-P.
[b]Difference between PSP-RS and PSP-SL.
[c]Difference between PSP-RS and PSP-PGF.
[d]Difference between PSP-RS and PSP-PI.
[e]Difference between PSP-CBS and PSP-SL.
[f]Difference between PSP-CBS and PSP-P.
[g]Difference between PSP-SL and PSP-P.
[h]Difference between PSP-SL and PSP-PGF.

Abbreviations: MoCA, Montreal Cognitive Assessment; FAB, Frontal Assessment Battery; MDS-UPDRS III, Movement Disorder Society sponsored revision of the Unified Parkinson Disorder Scale; PSIS, PSP Saccadic Impairment Scale, TULIA, Test for Upper Limb Apraxia; ASRS, Apraxia of Speech Rating Scale; MSD, Motor Speech Disorder Functional Rating Scale; NVOA, Nonverbal Oral Apraxia; OTSS, Oral Total Sum score; PTSS, Pharyngeal Total Sum score; PAS, Penetration-Aspiration Scale; FOIS, Functional Oral Intake Scale; PmaxA, anterior lingual strength; PmaxP, posterior lingual strength.

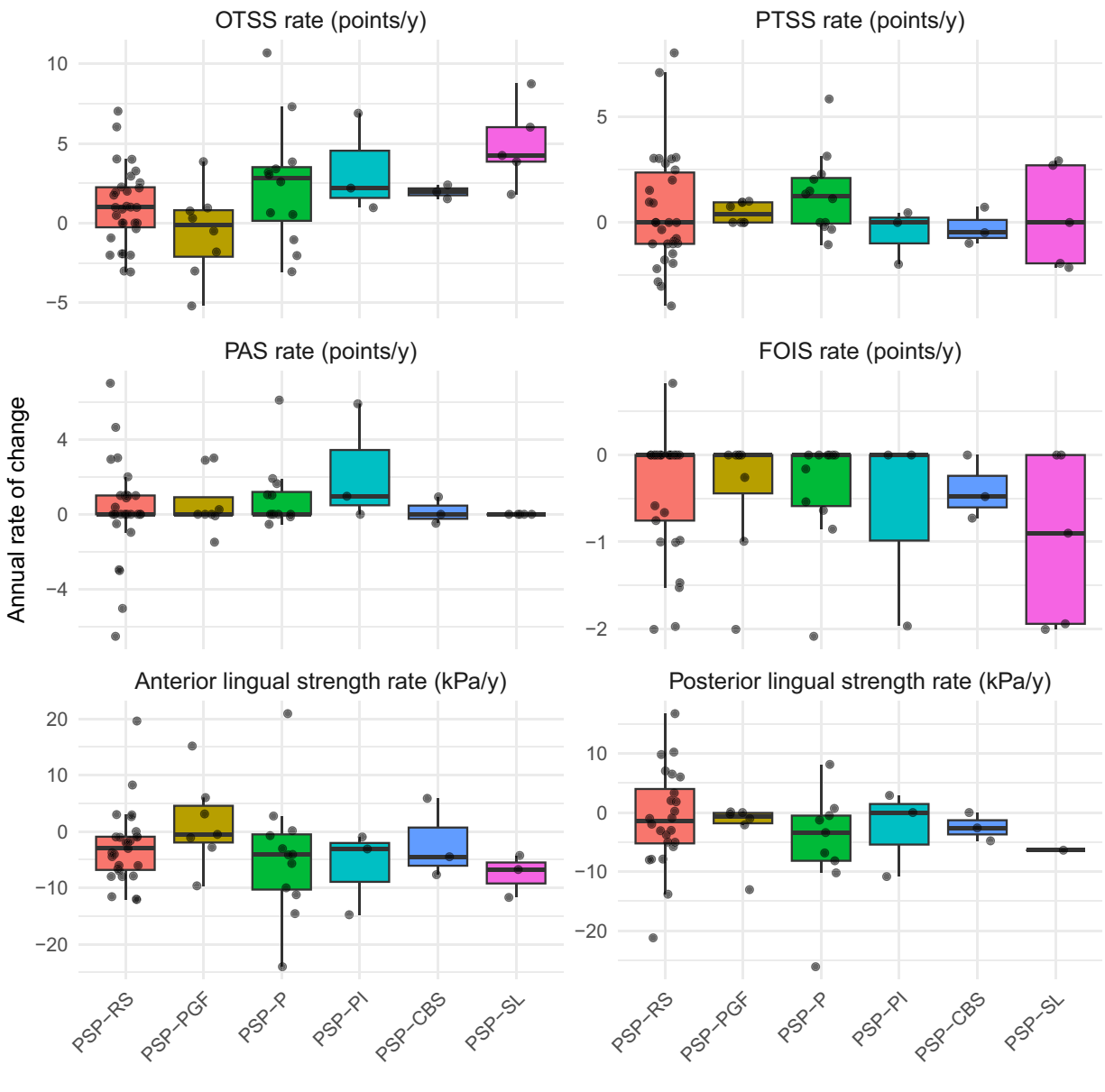


Figure 1. Boxplots showing annual rates of change in Oral Total Sum score (OTSS) and Pharyngeal Total Sum score (PTSS), PAS score, Functional Oral Intake Scale (FOIS), Anterior Lingual pressure, and Posterior Lingual pressure across the PSP groups. Boxes represent 25th, 50th and 75th percentiles, with whiskers extending to 1.5× interquartile range (IQR).

observed in OTSS and both anterior and posterior lingual strength. Although baseline severity of dysphagia did not differ across PSP variants, more variability was observed longitudinally with faster rates of decline in the PSP-SL variant. There was evidence that the rate of change in quantitative dysphagia measures was related to functional diet changes and disease severity. Lastly, the quantitative dysphagia measures related to rates of atrophy in key PSP-related regions, including the cerebellar dentate, midbrain and precentral cortex.

Mild impairment on baseline scores of dysphagia measures was present across our cohort, suggesting that dysphagia develops regardless of the PSP variant. There was no evidence that the severity of dysphagia differed across PSP variants at the baseline visit. Over time, worsening was observed across the quantitative dysphagia measures, although change was most evident in OTSS and the lingual strength measures, compared to PTSS and PAS. The more marked changes in OTSS versus PTSS concurs with baseline studies that have shown that oral phase impairments are more pronounced than pharyngeal impairments in PSP[6]. The reason for this dissociation has not been clearly established. The oral phase is traditionally thought to be more volitional and driven by cortical pathways.[17] In contrast, pharyngeal phase

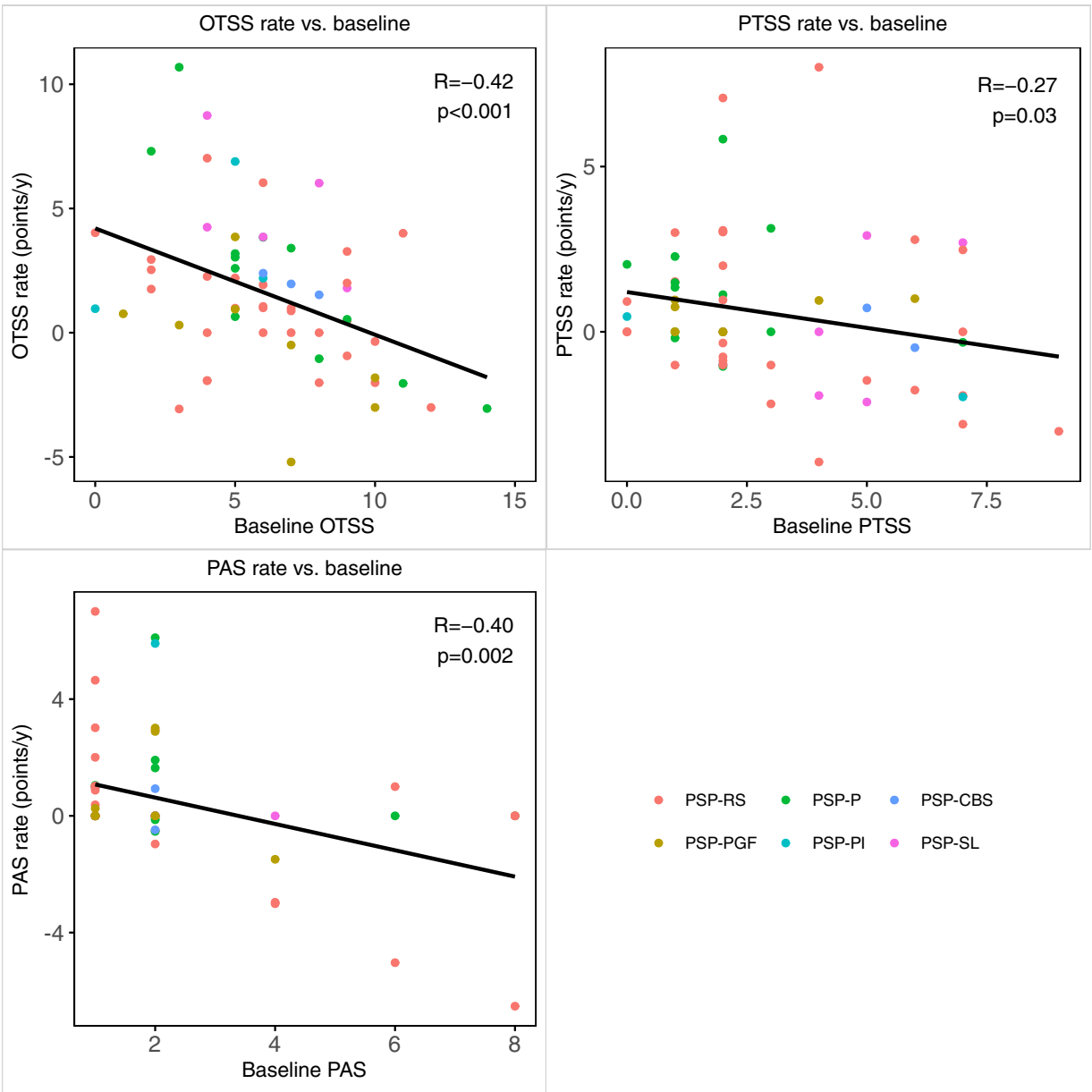


Figure 2. Scatterplots showing significant relationships between rates of change in the dysphagia measures and baseline performance. R denotes Spearman rank-order partial correlation after partialling out the effect of disease duration.

components are relatively more reflex- and brainstem driven. PSP is associated with both cortical and subcortical changes. We speculate that the cortical changes associated with PSP impact control centers influencing the oral phase of the swallow early. We speculate that subcortical changes in PSP have minimal impact on the key brainstem control centers, leaving the pharyngeal phase less susceptible to functional impairment.[16,39] Tongue strength has been shown to be reduced in PSP cross-sectionally,[8] and we further these studies by showing that both the anterior and posterior lingual strength progressively worsens over time across all PSP variants marking their importance in profiling swallowing impairments in PSP. Although strong association between tongue strength and oral phase swallow function have yet to be established in PSP,[40] studies in healthy aging adults and in those with neurologic conditions demonstrate that tongue weakness predicts effectiveness of bolus containment, manipulation, and propulsion to the oropharynx, duration of the oral phase, and degree of oral residue.[41,42] The rate of change in the OTSS varied across the PSP variants, with the fastest rates of worsening observed in PSP-SL and the slowest rates observed in

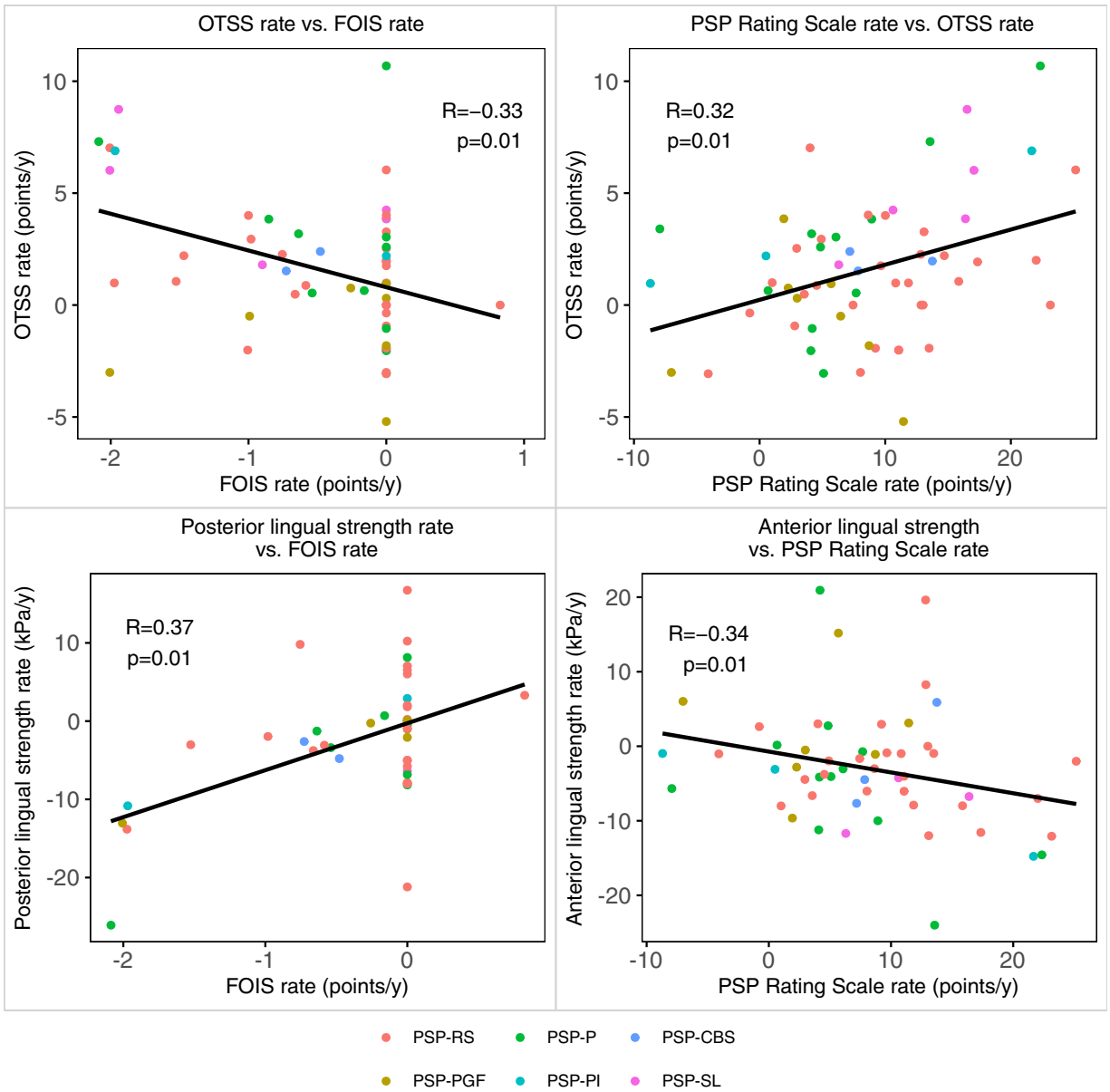
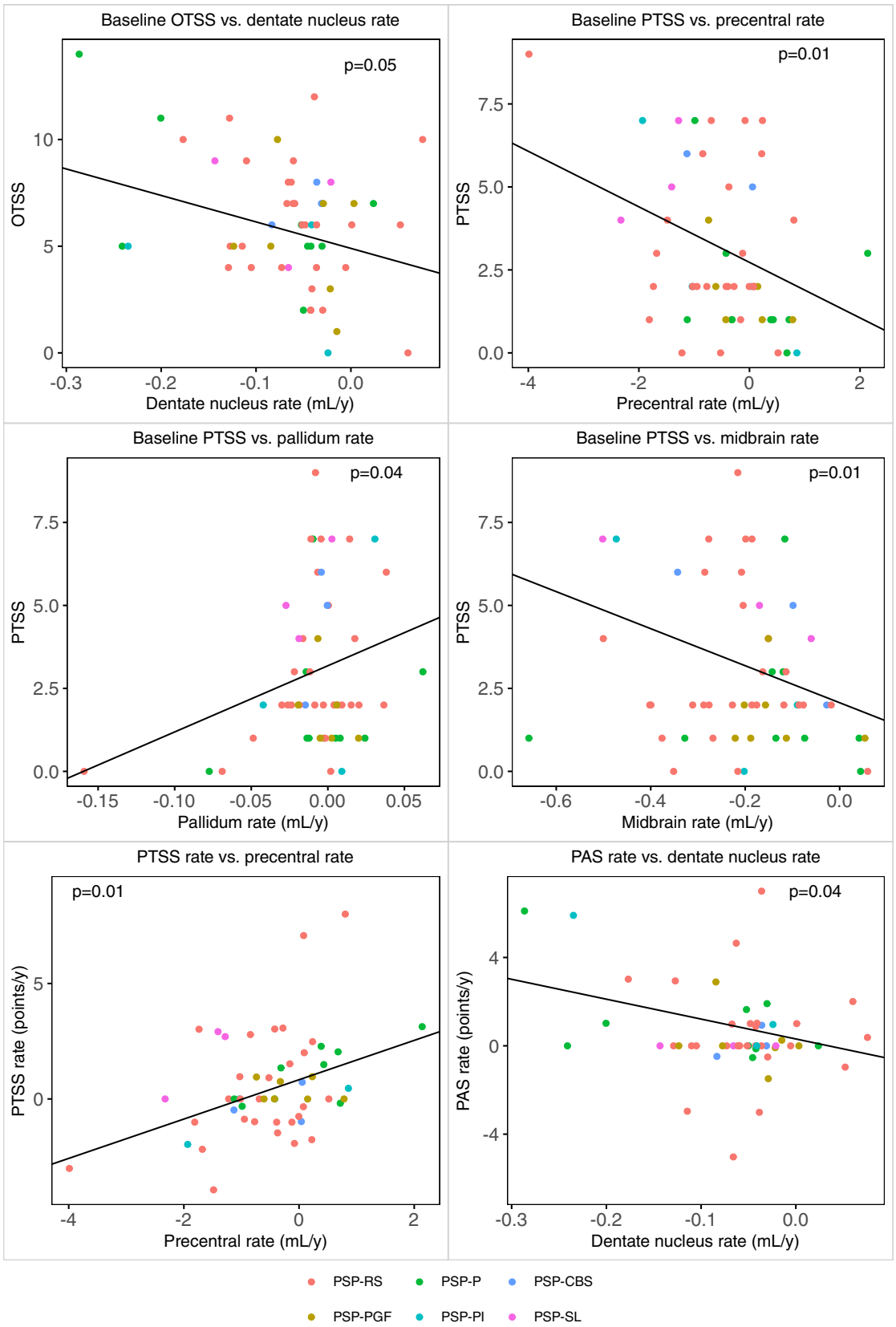


Figure 3. Scatterplots showing significant relationships between rates of change in the dysphagia measures and rates of change in the FOIS and PSP Rating Scale. R denotes Spearman rank-order partial correlation after partialling out the effect of disease duration.

PSP-PGF. This finding could be explained by the fact that the cortical variants of PSP, including PSP-SL, tend to show faster rates of general disease progression than the subcortical variants of PSP.[9] Indeed, the PSP-SL patients in our cohort showed the highest baseline scores and fastest rate of change on the PSP Rating Scale, concurring with previous studies[43,44] However, the PSP-SL group also had the longest disease duration at the baseline visit. It was difficult to disentangle the influence of syndrome versus disease duration. Typically, delay in PSP diagnosis in these patients is influenced by the later onset of PSP symptoms compared to speech and language impairments.[21] It could, therefore, be possible that we are capturing the PSP-SL patients in a later and more rapid phase of the disease. We did not, however, find any relationship between rate of change in OTSS and disease duration, suggesting that rates are not speeding up as the disease progresses. Regardless of the underlying reason for faster OTSS rates in PSP-SL, it will be important for these findings to be considered when counseling patients on what to expect as the disease progresses and it will be important for swallowing function to be monitored to improve disease management. Earlier diagnosis of PSP-SL is also important to allow earlier management.



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The associations between worse baseline scores and slower worsening in OTSS, PTSS, and PAS were not predicted. Multiple reasons could explain this phenomenon. One possible explanation could be that dysphagia measures reach a ceiling effect once achieving high scores. Therefore, patients with lower baseline scores may have more capacity to progress on these scales. This hypothesis could be more relevant to the OTSS, in which some patients achieved severe scores[10–15] at baseline, than the PTSS, which was milder at baseline. It is also possible that the rate of change in dysphagia measures is not linear over time, displaying faster progression earlier in the disease and slower progression during the final stages of the disease. Importantly, these relationships were observed after correcting for disease duration. The collection of more serial data across patients will be important to better understand the relationships between baseline performance and rate of change.

Faster worsening on the FOIS functional scale was associated with faster worsening in OTSS and posterior lingual strength, suggesting that impairments in the oral phase of the swallow and posterior tongue strength most strongly relate to restrictions in diet over time. However, it is important to point out that no actual change in FOIS was witnessed over time in a large proportion of cases. Among patients who demonstrated change, the relationships were in the predicted direction. This data supports the use of the FOIS as a simple and reliable tool for documenting eating habits in PSP. Faster worsening in the OTSS and anterior lingual pressure were also associated with faster worsening on the PSP Rating Scale, suggesting that dysphagia worsening is related to worsening in disease severity, as one may expect. The lack of a relationship between rate of change in PTSS and the PSP Rating Scale may reflect the milder worsening observed in the pharyngeal phase across the cohort. Questions regarding swallowing function are included in the PSP Rating scale (max 8 points) but would be unlikely to drive the findings since the patients were scoring on average 20–44 points on the PSP Rating Scale already at baseline, and the FOIS scores showed little evidence of dietary changes in the cohort.

Lastly, we found evidence that rates of brain atrophy in key PSP-related regions were associated with dysphagia scores at baseline. Specifically, worse performance on OTSS at baseline was related to a faster rate of atrophy in the cerebellar dentate, and worse performance on PTSS at baseline was associated with faster rates of midbrain and precentral atrophy. The reason that different regions were associated with OTSS and PTSS is unclear. It could suggest different anatomical underpinnings of the oral and pharyngeal phase, as we previously concluded,[16] perhaps with atrophy of the dentatorubrothalamic tract related to the oral phase and connections between the midbrain and cortex related to the pharyngeal phase. It is likely not this straightforward, however, with cortical regions implicated in both the oral and pharyngeal phase in our baseline study. A network-level approach may be needed to identify key parts of the PSP network related to dysphagia. The findings in the current study may suggest more broadly that faster rates of atrophy within the PSP network are observed in patients with worse dysphagia at baseline. Worse baseline pharyngeal scores were also associated with a slower rate of change in pallidum. However, this could be explained by the fact that pallidum rates are mainly distributed around zero, impairing the reliability of this result. A slower rate of change in PTSS was associated with faster rates of precentral atrophy. This finding may reflect the ceiling effect in the dysphagia scores hypothesized earlier or may suggest that the patients with a more subcortical pattern of atrophy (with relative sparing of the cortex) are the patients that are changing most on the PTSS. Contrarily, a faster rate of change in the PAS score related with faster rate of atrophy of the cerebellar dentate, suggesting that PAS may be less impacted by the ceiling effect, and more accurately relates to underlying atrophy. In fact, PAS is considered to be a global rating that can reflect oral and pharyngeal physiology as well as cognitive components such as attention and impulsiveness that also impact an individual's ability to protect the airway.[45]

Strengths of our study include the fact that our cohort is composed of a variety of PSP variants and that patients had longitudinal neurological and videofluorographic examinations. However, considering the heterogeneity displayed by PSP patients, it is possible that patients were captured at different stages, we had a small number of patients with some of the PSP variants and no patients with the frontal or oculomotor variants of PSP. Quantitative assessments of other features that could contribute to dysphagia, such as apraxia of mouth opening/closure and overstuffing, were lacking and would serve as useful variables in future work. The study also lacked pathological confirmation of diagnosis. Additionally, we included only PSP-related regions in our imaging analysis to minimize the number of comparisons. Future studies assessing more fine-grained relationships with anatomy or brain networks would be needed to further explore the anatomical and functional correlates of dysphagia.

In summary, dysphagia is a common finding across PSP variants and shows decline over time that can be measured using videofluoroscopic examinations, PAS, and the FOIS. Lingual weakness also worsens over time across PSP variants. These findings highlight the importance of dysphagia and lingual strength assessments in PSP as critical tools to aid patient management and prognosis. Further exploration of lingual strength as well as

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Figure 4. Scatterplots showing significant relationships between baseline and rate of change in dysphagia measures and rate of change in volumes of PSP-related regions. The regression line corresponds to a Siemens scanner, 70 years as age at baseline, 1500 mL as the total intracranial volume, and a disease duration of 3 years.

other measures, such as timing of airway closure and degree of airway invasion, will be needed to help fully characterize swallowing abnormalities in PSP.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique; (4) Funding.

A.C.C.: 1B, 1C, 2A, 2B, 3A
J.G.B.: 2B, 2C, 3B
F.A.: 1C, 3B
J.S.: 1C, 3B
F.A.: 3B, 4
M.F.: 3B, 4
K.A.J.: 1A, 1C, 3B, 4
H.M.C.: 1B, 1C, 3B
J.L.W.: 1A, 1B, 1C, 2C, 3B, 4

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Disclosures

Ethical Compliance Statement: The study was approved by the Mayo Clinic IRB (IRB #15–004618) and written informed consent was obtained from all participants. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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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 Information

Supporting information may be found in the online version of this article.

TABLE S1. Relationship between rates of regional brain atrophy and dysphagia measures. Data in each cell represents B (Standard Error), p value from the models

Figure S1. Boxplots showing baseline Oral Total Sum score (OTSS) and Pharyngeal Total Sum score (PTSS), PAS score, Anterior Lingual pressure and Posterior Lingual pressure, and Functional Oral Intake Scale (FOIS) across the PSP groups. Boxes represent 25th, 50th and 75th percentiles, with whiskers extending to 1.5× interquartile range (IQR).