RESEARCH ARTICLE

Sensorimotor Cough Dysfunction Is Prevalent and Pervasive in Progressive Supranuclear Palsy

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ABSTRACT: Background: Pneumonia, a leading cause of death in progressive supranuclear palsy (PSP), results from progressive and pervasive deficits of airway protection, including both cough and swallowing dysfunction. Cough protects the airway by expelling aspirate and may be an important therapeutic target to protect against pneumonia in the presence of dysphagia. However, cough has not been objectively characterized in PSP or compared to other common forms of parkinsonism, such as Parkinson's disease (PD).
Objective: The purpose of this study was to examine voluntary and reflex cough function in PSP, as compared to patients with PD matched for disease duration.
Methods: Twenty-six patients with PSP and 26 with PD completed voluntary and reflex cough testing via spirometry. Linear mixed effects models examined comparisons between groups and within cough types across cough sensory and motor outcomes.
Results: Patients with PSP demonstrated significantly reduced cough motor function compared to PD, specifically reduced peak expiratory flow rate ($P < 0.001$), cough expiratory volume ($P < 0.001$), and cough inspiratory volume ($P = 0.008$). Both groups showed similar reflex cough thresholds ($P = 0.694$), but PSP demonstrated an increased perception of cough stimuli ($P = 0.041$).
Conclusions: These findings suggest that sensorimotor cough dysfunction is prevalent in PSP, and cough motor deficits, in particular, are worse in PSP than in PD. These deficits likely contribute to the pathogenesis of pneumonia in PSP. Therefore, cough should be integrated into assessments of airway protection and considered as a therapeutic target to potentially reduce adverse health events and improve quality of life in this population.

Key Words: progressive supranuclear palsy; cough; Parkinson's disease; dystussia; airway protection

Pneumonia is a leading cause of death among patients with neurodegenerative conditions.[1-5] Although swallowing dysfunction, or dysphagia, contributes to pneumonia, the development of pneumonia cannot be solely explained by its presence.[6,7] Instead, it is likely that progressive and pervasive deficits of airway protection, including both swallowing and cough (dystussia) dysfunction, collectively result in uncompensated aspiration that cannot be cleared from the airway, thereby increasing the risk for pneumonia and mortality. Therefore, it is imperative that if we are to reduce the risk for pneumonia and associated mortality, we not only understand dysphagia but also the reflexive and voluntary cough deficits that occur in a given population. This understanding is key because reflex cough forms the first line of defense in the presence of aspiration, while voluntary coughs initiated on command may serve as a compensatory approach to prophylactically protect the airway and expel aspirate among individuals with chronic dysphagia.[8,9]

The characterization and rehabilitation of cough deficits has garnered significant research and clinical interest in recent years, particularly in Parkinson's disease (PD).[10-14] However, much less is known about cough

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dysfunction in atypical parkinsonism. Progressive supranuclear palsy (PSP) is the most common atypical parkinsonian syndrome and tauopathy that presents with high rates of dysphagia and aspiration pneumonia[1,15] and with an earlier dysphagia onset associated with increased mortality as compared to PD.[16,17] Although studies have examined swallowing function in PSP,[15,18-21] research characterizing cough is limited and based on subjective reports[18] with limited quantification of cough characteristics. Understanding sensory and motor aspects of reflexive and voluntary cough is essential to promote a significant advancement in the management of airway-protective deficits in PSP.

An objective and comprehensive examination of cough dysfunction in PSP may improve the screening and evaluation of deficits in airway protection and elucidate important therapeutic targets to improve function and quality of life. Preliminary evidence suggests that integrating cough testing into clinical practice increases the sensitivity and specificity of screening tools[13,22,23] and improves long-term health outcomes, such as a reduction in the prevalence of aspiration pneumonia.[24] In addition, there is a growing body of literature suggesting that upregulating voluntary and reflex cough is feasible and effective for cough rehabilitation,[12,25] supporting its role as a clinically relevant therapeutic target in individuals with neurodegenerative disease and concomitant dysphagia and dystussia. Lastly, cough may also provide a deeper understanding of the underlying disease process and distinct neuropathological features of PSP, serving as a potential biomarker to differentiate between parkinsonian disorders and PD, to facilitate more timely and accurate diagnoses.

Therefore, the aim of this study was to characterize voluntary and reflex cough dysfunction in PSP. Secondarily, we aimed to compare cough dysfunction between PSP and PD, given that PSP is often misdiagnosed as PD, a population also found to have swallowing and cough deficits.[12,26] We hypothesized that individuals with PSP would demonstrate reduced motor and somatosensory cough responses compared to PD, and that reflex cough airflow would be reduced compared to voluntary cough.

Patients and Methods

Participants

The Institutional Review Board approved study procedures, and informed consents were obtained. Participants with PSP and idiopathic PD were prospectively recruited and diagnosed by a fellowship-trained movement disorders neurologist based on current Movement Disorder Society clinical diagnostic criteria for PSP[27] and the UK Brain Bank criteria for PD.[28] Participants were matched based on disease duration from PD or PSP symptom onset. Participants with PSP were classified into particular PSP subtypes based on disease features. Exclusion criteria included a history of other neurological disorders, head and neck cancer, respiratory disease, or smoking within 5 years. To understand baseline characteristics between groups, the following demographic factors were collected: age, sex, disease duration from symptom onset and diagnosis, Schwab and England activities of daily living,[29] cognition,[30] and severity of swallowing deficits.[31]

Procedures

Reflex cough testing was performed with a face mask coupled to a pneumotachograph with a side port and inspiratory valve for a nebulizer connection. The nebulizer connected to a dosimeter that delivered single doses of capsaicin during inhalation for a duration of 2 seconds. Participants were presented three randomized blocks of 0, 50, 100, and 200 μM capsaicin. The capsaicin was dissolved in a vehicle solution consisting of 80% physiological saline, 20% ethanol. If no cough response was reliably elicited with 200 μM capsaicin, then 500 μM was provided. Participants were instructed to "cough if you need to" before each trial. A minimum 30-second interval was provided between trials during which participants were provided with water. Participants also performed sequential voluntary coughs with an identical spirometric setup. They were instructed to "cough as if something went down the wrong tube," after which a model of a three-cough epoch was performed for the participant by the examiner. Both voluntary and reflex cough airflow were inputted into the PowerLab Data Acquisition system, digitized, and recorded on a computer through LabChart software. Each sample was low pass filtered at 50 Hz.

Data Analysis and Outcomes

Cough airflow outcomes were measured from both voluntary and reflex cough types and included peak expiratory flow rate (PEFR; L/s), cough expiratory volume (CEV; liters), inspiratory volume (IV; liters), compression phase duration (CPD; seconds), peak expiratory flow rise time (PEFRT; seconds), and cough volume acceleration (CVA; L/s/s) (Fig. 1). The first cough from the epoch of each trial was used for analyses. All trials of voluntary cough and reflex cough at 200 μM were included for airflow statistical analyses. The capsaicin concentration of 200 μM was selected from reflex coughs because it has been previously identified as a suprathreshold concentration for eliciting a cough response in healthy adults.[25,32] The coefficient of variation (standard deviation [SD] divided by the mean of three trials) was calculated for cough airflow outcomes to examine within-subject variability. Interrater and intrarater reliability were performed on 20% of coughs.

Sensory outcomes during reflex cough included cough threshold and urge to cough. The total number of coughs was counted for each cough epoch (CrTot). The lowest concentration of capsaicin that elicited at least two

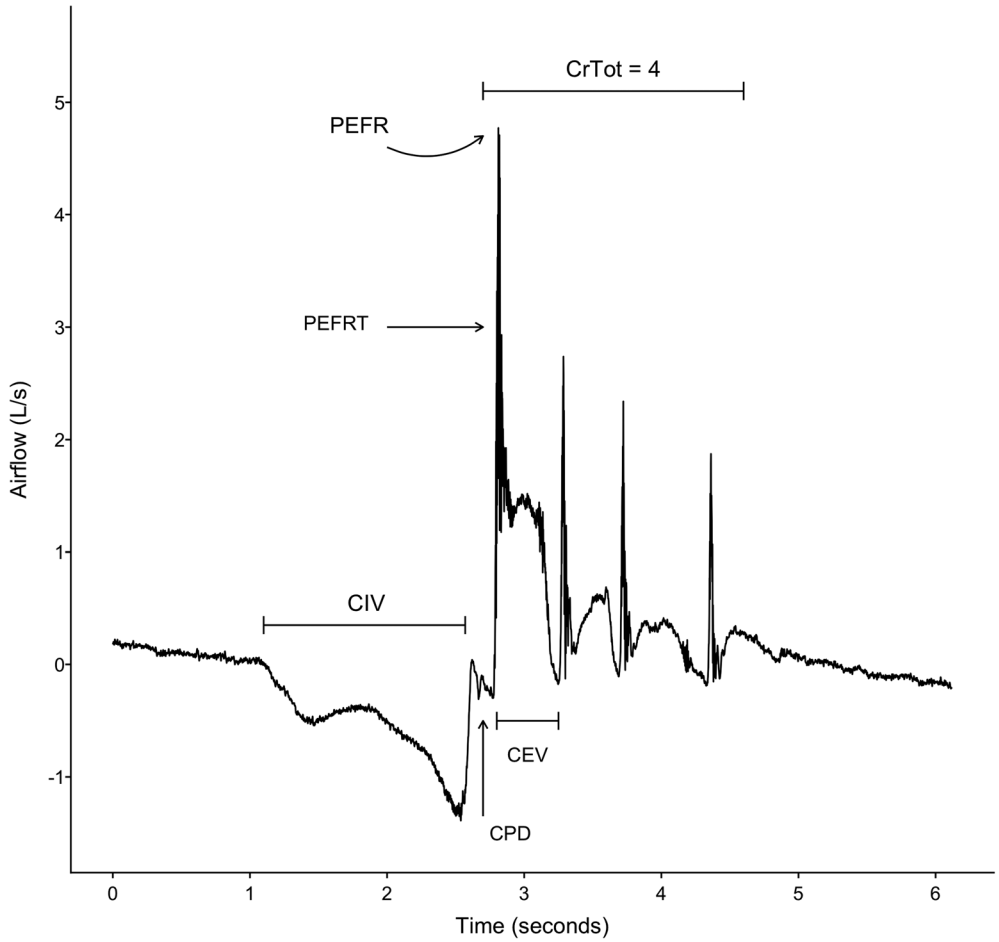

FIG. 1. Cough airflow diagram. CEV, cough expired volume (L); CIV, cough inspiratory volume (L); CPD, compression phase duration (seconds); CrTot, total number of coughs; PEFR, peak expiratory flow rate (L/s); PEFRT, peak expiratory flow rise time (seconds).

consecutive coughs within 30 seconds of the stimulus on two out of three trials was recorded as the cough threshold.[33] Participants self-reported their urge to cough immediately after each capsaicin stimulus presentation using a modified Borg scale ranging from 0 (no urge to cough) to 10 (maximal urge to cough) during reflex cough.[34]

Statistical Analysis

A simulation-based sensitivity analysis showed that our data had 80% power to detect a mean PEFR difference between PSP and PD of 0.48 L/s ($d = 0.46$) in voluntary cough and 0.50 L/s ($d = 0.48$) in reflex cough at 200 μM[35] (Table S1). Welch's t tests and chi-square tests compared demographic characteristics between groups. Two-way random effects intraclass correlation coefficients (single measure, absolute agreement) were used for reliability estimates.

Linear mixed effects models were performed for each cough airflow outcome. Group (PD/PSP), cough type (voluntary/reflex), and their two-way interaction were included as fixed effects, and participant was a random effect. CrTot was included as a covariate in the PEFR, CEV, and CVA models given prior research demonstrating a relationship between expiratory airflow and number of coughs.[36] The Akaike information criterion determined the appropriate covariance structure for each model. Welch's t tests explored cough airflow variability (coefficient of variation) between groups.

To examine reflex cough sensitivity and urge to cough, we performed separate mixed effects models for these outcome variables with fixed effects of capsaicin concentration and group and a random effect of participant. First- and second-order polynomials were used with capsaicin concentration in separate models. Likelihood ratio tests compared models to determine best fit. Given that a second-order polynomial did not significantly improve model fit for urge to cough ($\chi^2 = 0.36$, $P = 0.549$) or CrTot ($\chi^2 = 0.45$, $P = 0.501$), a log–log scale was used in subsequent analyses. Urge-to-cough sensitivity slopes were then calculated for each participant by performing a linear regression of urge to cough and capsaicin concentration on a log–log scale within each participant, resulting in sensitivity slopes for analysis between groups.[37] Similarly, reflex cough motor slopes were calculated with a regression of log CrTot and log capsaicin. To examine

TABLE 1 *Demographic Characteristics*

	PSP ($n = 26$)	PD ($n = 26$)
Age, mean (SD), y	72.08 (7.47)	71.37 (6.63)
Sex (n)		
Male	16	20
Female	10	6
MoCA, mean (SD)	20.21 (7.00)	25.75 (3.12)
Disease duration from symptom onset, mean (SD), y	5.01 (2.14)	5.39 (2.57)
Schwab and England activities of daily living, mean (SD)	47.69 (23.38)	78.46 (16.42)
Swallowing severity[a]	3 (2–6)	3 (1–5)

[a]Penetration-aspiration scale scores obtained from trials of 90 mL thin liquid during flexible endoscopic evaluation of swallowing. Median scores and interquartile ranges are provided.
PSP, progressive supranuclear palsy; PD, Parkinson's disease; SD, standard deviation; MoCA, Montreal Cognitive Assessment.

differences in urge-to-cough or reflex cough sensitivity, we used mixed models assuming a compound symmetry covariance structure with fixed effects of capsaicin concentration and group and a random effect of participant. To examine differences in urge-to-cough sensitivity slopes and reflex cough motor slopes between groups, we performed Welch's *t* tests. Fisher's exact test compared cough thresholds between groups.

Inspection of standardized residual plots indicated that assumptions were met. Fixed effects were deemed appropriate based on an a priori threshold (ie, variance inflation factor < 3). Marginal R^2 for the fixed effects in each model provided an overall measure of effect size,[38] and Cohen's d[39] was used for post hoc comparisons. Alpha was set at <0.05. A Holm-Bonferroni correction was applied for four planned post hoc comparisons within models reaching statistical significance, and adjusted *P* values are reported for these comparisons. Analyses were performed in R version 4.0.1.[40]

Results

Demographics

Twenty-six individuals with PSP and 26 with PD matched for disease duration met inclusion criteria. Voluntary cough included 65 trials for PSP and 77 trials for PD, and reflex cough included 290 trials (73 for 200 μM) for PSP and 318 trials (78 for 200 μM) for PD. Four participants with PSP-Richardson Syndrome (PSP-RS) were unable to

TABLE 2 *Descriptive Statistics*

		Airflow, Mean (SD)		Trial-by-Trial Variability, CoV (%)	
Outcome	**Cough Type**	**PSP**	**PD**	**PSP**	**PD**
PEFR (L/s)	Voluntary	1.82 (0.93)	2.74 (0.81)	19.00	14.40
	Reflex	1.89 (0.62)	2.42 (0.64)	18.70	14.30
CEV (L)	Voluntary	0.37 (0.39)	0.54 (0.44)	34.60	29.20
	Reflex	0.38 (0.27)	0.49 (0.21)	29.60	25.10
CVA (L/s/s)	Voluntary	28.20 (24.20)	50.10 (24.50)	38.20	25.80
	Reflex	39.0 (20.70)	48.0 (24.50)	35.50	28.90
CIV (L/s)	Voluntary	0.75 (0.47)	1.04 (0.59)	31.80	30.20
	Reflex	0.29 (0.19)	0.47 (0.30)	43.10	43.60
CPD (s)	Voluntary	0.38 (0.40)	0.34 (0.32)	43.10	39.70
	Reflex	0.45 (0.63)	0.29 (0.21)	62.10	41.00
PEFRT (s)	Voluntary	0.11 (0.13)	0.07 (0.08)	32.90	24.90
	Reflex	0.08 (0.08)	0.06 (0.03)	24.40	23.40
CrTot	Voluntary	3.46 (2.29)	4.27 (2.62)	30.90	28.00
	Reflex	2.33 (1.65)	2.90 (2.00)	60.30	55.00
Urge to cough	Reflex	3.00 (0–5)	3.00 (1–5)		

Reflex airflow reported from 200 μM capsaicin. Median is reported for urge to cough.
SD, standard deviation; CoV, coefficient of variation; PSP, progressive supranuclear palsy; PD, Parkinson's disease; PEFR, peak expiratory flow rate; CEV, cough expired volume; CVA, cough volume acceleration; CIV, cough inspiratory volume; CPD, compression phase duration; PEFRT, peak expiratory flow rate; CrTot, total number of coughs; PAS, penetration-aspiration scale.

perform a voluntary cough. One participant with PSP with predominant frontal presentation (PSP-F) and one participant with PD were unable to complete any voluntary cough trials. One participant with PSP-RS was unable to tolerate reflex cough testing. Two participants with PSP-Parkinsonism (PSP-P) and PSP-RS completed only two trials of 200 μM.

There were no significant differences between groups in age, sex, disease duration from symptom onset, maximum inspiratory pressure, or maximum expiratory pressure ($P > 0.05$). Individuals with PSP demonstrated lower scores on the Schwab and England activities of daily living compared to PD ($P < 0.001$; Table 1). Descriptive statistics of cough airflow are provided by

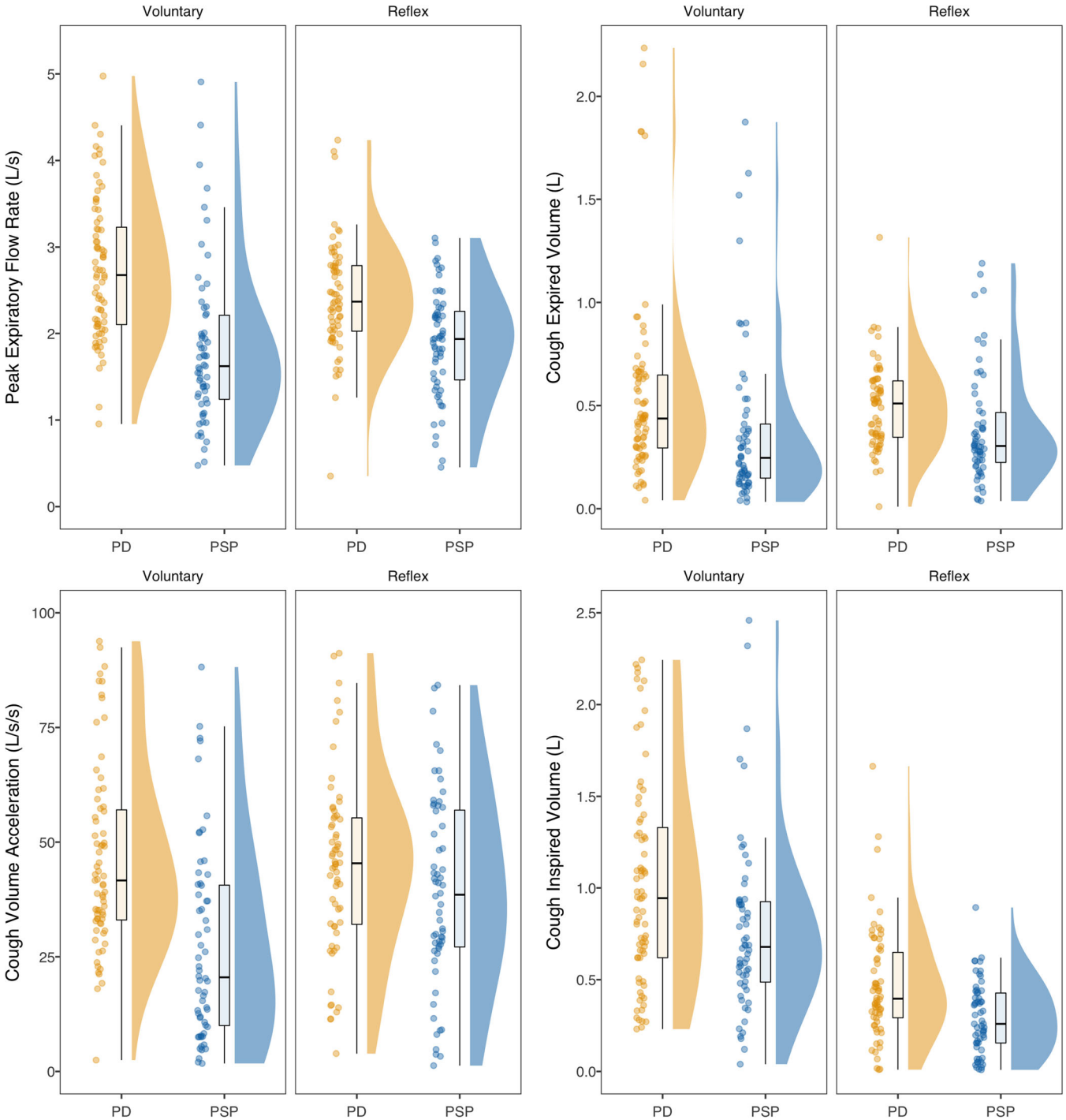

FIG. 2. Cough airflow outcomes in Parkinson's disease (PD) and progressive supranuclear palsy (PSP) across cough tasks. [Color figure can be viewed at wileyonlinelibrary.com]

group (Table 2) and PSP subtype (Table S2). There were no significant differences in trial-by-trial variability between groups across cough outcomes ($P > 0.05$).

Peak Expiratory Flow Rate

Random and fixed effects estimates are provided in Table S2. A significant interaction of group and cough type was found for PEFR ($P = 0.015$, $R^2 = 0.17$; Fig. 2) while controlling for CrTot. Post hoc comparisons revealed increased PEFR for PD compared to PSP for voluntary ($P < 0.001$, $d = 1.11$) and reflex ($P = 0.041$, $d = 0.57$) cough. Comparisons between cough tasks showed increased PEFR for voluntary compared to reflex cough in PD ($P = 0.007$, $d = 0.45$), but no significant differences between voluntary and reflex in PSP ($P = 0.583$, $d = 0.09$).

Cough Expired Volume

There was a significant interaction effect of group and cough type for CEV ($P = 0.014$, $R^2 = 0.26$) controlling for CrTot. Post hoc comparisons revealed increased CEV for PD compared to PSP for voluntary ($P < 0.001$, $d = 1.46$) and reflex cough ($P < 0.001$, $d = 1.01$). Comparisons between cough tasks showed increased CEV for reflex compared to voluntary cough in PSP ($P = 0.002$, $d = 0.44$), but no significant differences between voluntary and reflex in PD ($P = 0.884$, $d = 0.03$).

Cough Volume Acceleration

There was a significant main effect of group ($P = 0.001$, $R^2 = 0.14$) such that individuals with PD demonstrated increased CVA compared to individuals with PSP across cough types. There was no statistically significant effect of cough type ($P = 0.750$) or interaction between group and cough type ($P = 0.062$).

Cough Inspiratory Volume

There was a significant interaction effect of group and cough type ($P = 0.007$, $R^2 = 0.15$). Post hoc comparisons revealed increased CIV for PD compared to PSP for voluntary cough ($P = 0.008$, $d = 0.31$), but not

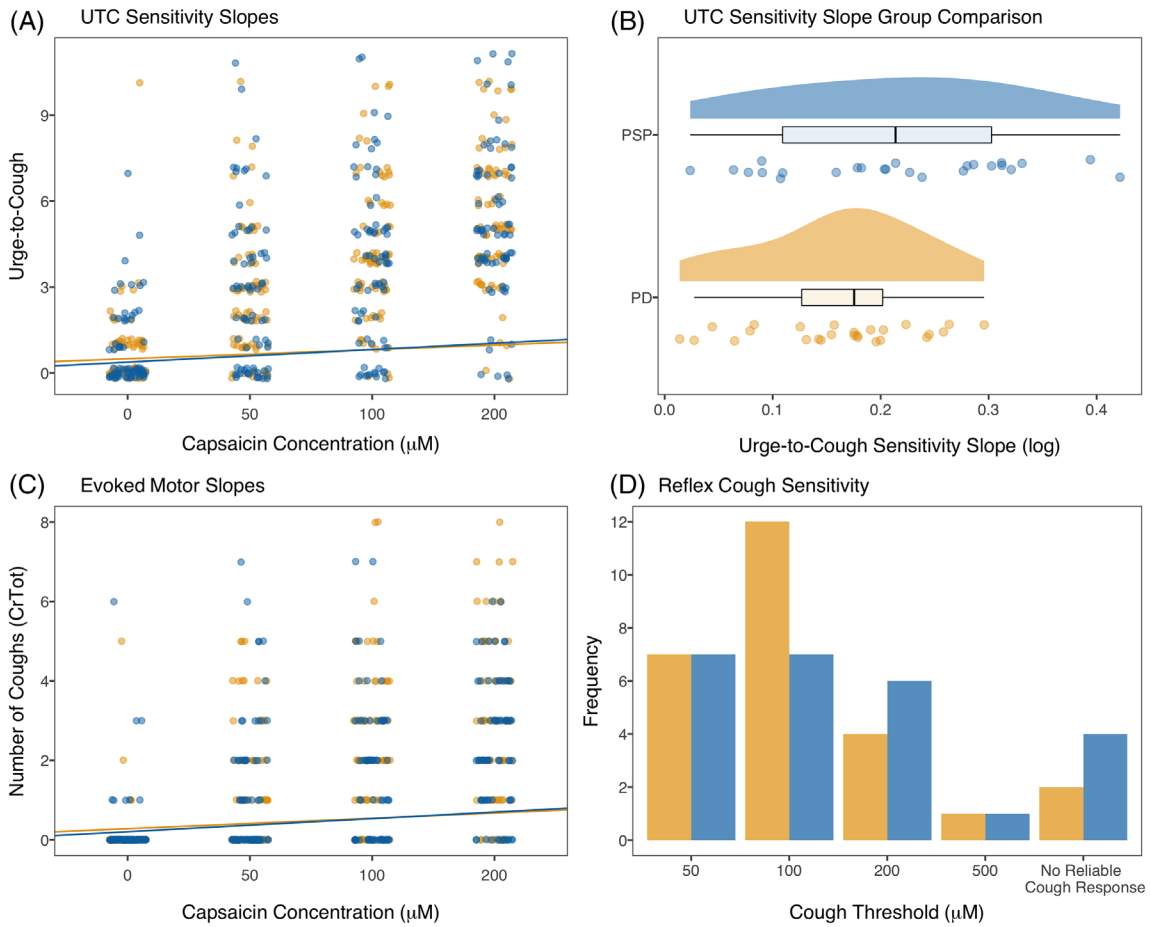

FIG. 3. Cough sensory responses between groups. (**A**) Unadjusted urge-to-cough (UTC) sensitivity slopes between groups. (**B**) Group comparison of adjusted (log–log transformed) UTC sensitivity slopes. (**C**) Unadjusted motor slopes for number of coughs (CrTot) during reflex cough. (**D**) Distribution of cough thresholds between groups. Data for (**A**) sensitivity and (**C**) motor slopes are presented before log–log transformation. PD, Parkinson's disease; PSP, progressive supranuclear palsy. [Color figure can be viewed at wileyonlinelibrary.com]

reflex cough ($P = 0.684$, $d = 0.04$). Comparisons between cough tasks showed increased CIV for voluntary compared to reflex cough in PD ($P < 0.001$, $d = 0.92$) and PSP ($P < 0.001$, $d = 0.66$).

Compression Phase Duration and Peak Expiratory Flow Rise Time

There were no significant main effects for CPD by group ($P = 0.085$), cough type ($P = 0.415$), or an interaction between group and cough type ($P = 0.497$). In addition, there were no significant main effects of PEFRT by group ($P = 0.138$), cough type ($P = 0.631$), or an interaction between group and cough type ($P = 0.702$).

Urge to Cough

Urge to cough significantly increased across capsaicin concentrations in both groups ($P < 0.001$; Fig. 3A). Individuals with PSP ($M = 0.22$, SD = 0.11) showed significantly higher urge-to-cough sensitivity slopes ($P = 0.041$, $d = 0.59$) compared to PD ($M = 0.16$, SD = 0.08; Fig. 3B). All participants with PSP and PD demonstrated reduced urge-to-cough sensitivity slopes compared to healthy adults from prior research.[37]

Reflex Cough Sensitivity

There was a significant main effect of cough type ($P < 0.001$, $R^2 = 0.10$) showing increased number of coughs for voluntary compared to reflex cough. There were no statistically significant effects of group ($P = 0.122$) or interaction between group and cough type ($P = 0.695$). Number of evoked reflex coughs significantly increased across capsaicin concentrations in both groups ($P < 0.001$; Fig. 3C). Reflex cough motor slopes were not significantly different ($P = 0.194$, $d = 0.38$) between PD ($M = 0.13$, SD = 0.09) and PSP ($M = 0.17$, SD = 0.08). Cough thresholds were also not significantly different between PD and PSP ($P = 0.694$; Fig. 3D). Three participants with PSP-RS, two with PSP-P, and three with PD did not demonstrate a reliable cough response to 200 μM; however, one participant with PSP-RS and one with PD did cough in response to 500 μM. Two participants with PSP-RS, two with PSP-P, and two with PD did not demonstrate a reliable cough response across all capsaicin concentrations. One participant with PSP-P, one with PSP-F, and two with PD coughed in response to saline (0 μM) on at least one trial.

Interrater and Intrarater Reliability

Interrater reliability was 1.00 for PEFR, 0.97 for CEV, 0.97 for CPD, 0.96 for CVA, 0.85 for CrTot, and 0.82 for CIV and 0.82 for PEFRT. Intrarater reliability was 1.00 for PEFR, 0.98 for PEFRT, 0.95 for CEV and CPD, 0.94 for CIV, 0.90 for CVA, and 0.80 for CrTot.

Discussion

The development of pneumonia, a leading cause of death in PSP,[1] is multifactorial and likely precipitated by uncompensated aspiration secondary to cough and swallowing dysfunction. There have been no prior published studies examining dystussia in PSP.[15,18] Thus, this study sought to characterize voluntary and reflex cough dysfunction across sensory and motor outcomes in PSP. Comparisons were made with PD, a population with known cough and swallowing dysfunction.[12,26] Both PSP and PD were matched for disease duration to control for effects of disease severity. Results showed reduced PSP cough motor performance compared to PD, blunted motor response to cough stimuli (ie, reflex cough thresholds) in both groups, but increased perception of cough stimuli (ie, urge to cough) in PSP. Overall, these findings suggest that both motor and sensory cough dysfunction are prevalent and pervasive in PSP.

Cough Sensorimotor Outcomes

Individuals with PSP demonstrated reduced cough expiratory (PEFR, CEV, CVA) airflow, as compared to PD. These motor measures provide insight into the shearing forces necessary to clear the airway of secretions or aspirate material to maintain a homeostatic pulmonary environment.[11,36] Importantly, these deficits in both PSP and PD are substantially altered compared to prior research in healthy control subjects.[41] Patients with PSP demonstrated clinically important differences compared to patients with PD. For example, average PEFR was 0.92 and 0.53 L/s lower for voluntary and reflex cough, reflecting substantial impairments in cough performance in PSP compared to PD.

Detection of a sensory stimulus is an important component of cough, which is mediated from peripheral mechanoreceptors and chemoreceptors, as well as neural substrates from ascending vagal pathways.[42,43] Blunted reflex cough sensitivity (ie, the inability to cough in response to a sensory stimulus, such as capsaicin) has been previously associated with dysphagia in PD.[44-46] Our findings suggest that PSP demonstrates similar blunted cough thresholds, with nearly half of participants demonstrating impaired reflex cough sensitivity compared to normative data from healthy adults.[25,37] This finding is in contrast with reports of pyramidal signs, including hyperreflexia, in individuals with PSP.[47] However, it is interesting to note that although both groups exhibited blunted urge-to-cough slopes compared to prior research in healthy adults,[37] patients with PSP demonstrated increased urge to cough compared to PD. This means that even though the

participants with PSP were perceiving the increasing cough stimulus more than patients with PD, they were not coughing more to that stimulus. In the presence of dysphagia, these sensorimotor cough deficits may result in an inability to detect and identify a sensory stimulus, such as aspirate material, as threatening and insufficient generation of expulsive airflow to clear the airway, leading to clinical profiles of progressive and pervasive impairments in airway protection commonly seen in both PSP and PD. The increased urge-to-cough slopes in PSP may be leveraged to improve cough strength through a treatment approach focused on a more effective motor response to the cough stimuli they are perceiving. This may explain, in part, recent findings demonstrating improved cough upregulation using a sensorimotor rehabilitation approach in PSP.[48]

Cough Airflow Between Reflex and Voluntary Cough

Cough airflow patterns can vary based on the type of cough elicited. Specifically, lower inspiratory volumes and reduced expiratory airflow have been noted in reflex cough compared to voluntary cough.[36] In PD, voluntary cough testing also has been shown to overestimate expiratory airflow during reflex cough.[14,22] Understanding these differences is important to guide interpretation of clinical cough outcomes in PSP. In this study, both groups demonstrated increased CIV for voluntary compared to reflex cough, likely because of the volitional, unevoked nature of voluntary cough. In PSP, increased CEV was appreciated in reflex compared to voluntary cough, although no differences were found in any other expiratory airflow parameters (PEFR, CVA). The absence of an effect for PEFR between cough types is likely due to more severe deficits in voluntary cough motor control compared to PD and healthy control subjects. Participants with PD demonstrated reduced PEFR in reflex compared to voluntary cough, replicating prior findings.[14,22] However, increased CEV in voluntary compared to reflex cough was not replicated in PD. This discrepancy may be because of our decision to statistically control for the number of coughs given prior research demonstrating a relationship with the volume of expiratory airflow.[36] This study provides additional evidence that evaluations of voluntary cough may overestimate PEFR during reflex cough in PD; however, PEFR from voluntary cough may serve as an adequate proxy for reflex cough motor function in PSP.

Cough Dysfunction as a Neuropathological Feature of PSP

The sensorimotor cough deficits identified in PSP and the differences with PD may be explained by several neural and peripheral mechanisms. Dysfunction of the basal ganglia, brainstem, and cortical structures involved in discriminative and affective processing have all been described in PSP and have potential to impair cough function.[49,50] The increased atrophy of brainstem regions in PSP versus PD[51,52] is likely the main cause of the more severe deficits of cough in PSP given that the brainstem houses the central pattern generator controlling cough. In addition, the more severe cortical impairments in PSP, including attention and executive function, may also contribute to more severe cough dysfunction, resulting in reduced somatosensation and motor planning. Although basal ganglia dysfunction most certainly plays a role in the dysfunctional cough in PSP, our results showed similar cough variability between PSP and PD, with both groups descriptively demonstrating increased variability compared to healthy adults.[53,54] Similarly blunted cough sensory function in both groups could indicate that PSP and PD pathology affect some similar sensory afferent pathways; however, the severity of basal ganglia dysfunction, presence of pyramidal signs, and varying degrees of brainstem pathology cannot be excluded as potential contributors to sensory cough dysfunction.

Accurate diagnosis of PSP currently depends on clinical acumen based on symptomatology, often resulting in delayed or incorrect diagnoses.[55] Given the variable and atypical presentation of PSP and the absence of a reliable diagnostic biomarker, cough may serve as an additional symptom to improve the diagnostic accuracy of clinical examinations. Profound deficits in voluntary or reflex cough combined with other common clinical features may better differentiate PSP from similar parkinsonian disorders, such as PD. Future research will be necessary to confirm the diagnostic utility of cough as biomarker of PSP in longitudinal studies.

Limitations and Future Considerations

There are several limitations to address. This study is unable to directly address the neural and peripheral mechanisms underlying reduced cough function seen in PSP compared to PD. It is unclear whether this may be unique to the disease process of PSP or a result of a more rapid disease progression compared to PD. We chose to match both cohorts based on duration from symptom onset given that scales of clinical severity for PSP and PD are not equivalent. For example, gait and balance are more likely to be compromised early on in PSP cases, confounding comparisons of clinical severity. In addition, this approach was fundamental to our primary aim examining differences in cough presentation between groups when disease duration was comparable. However, we acknowledge that reports of disease duration may be subject to recall bias. Future studies should investigate the impact of other disease-specific factors on cough outcomes in PSP. Capsaicin was administered in a randomized block design, which has

the benefit of reducing potential order effects across doses. However, the use of discrete capsaicin presentations with limited gradation between doses may have limited our ability to detect differences in reflex cough outcomes. Although we provide a description of cough function across three PSP subtypes, our distribution favored Richardson's syndrome, which prohibited statistical comparisons. This is an important limitation because substantial variability in pathological profiles has been documented in PSP,[52] and some subtypes may have cough presentations that are more similar or different compared to PD. However, pervasive deficits of cough dysfunction were identified across all PSP subtypes.

Clinical Implications and Future Directions

Sensorimotor cough dysfunction is prevalent in PSP, and cough motor deficits, in particular, are worse in PSP than in PD. Cough dysfunction may contribute to the pathogenesis of pneumonia, a leading cause of death in PSP. These findings provide support for the integration of cough testing into screening and assessments of airway protection in this population. Expiratory cough airflow can be easily obtained from low-cost peak flow meters, facilitating the integration of voluntary cough testing into clinical practice to better characterize and differentiate parkinsonian syndromes, such as PSP and PD. Swallowing treatment in this population is limited to compensatory strategies in the absence of efficacious rehabilitation approaches, and this study suggests that cough is a necessary treatment target. Indeed, sensorimotor cough paradigms have shown preliminary efficacy to upregulate cough,[48] which may prevent adverse health outcomes and improve quality of life. Overall, cough is an important component of progressive and pervasive deficits of airway protection in PSP, which may improve clinical management and reduce adverse health outcomes, such as pneumonia and mortality.

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Ethical Approval

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval was obtained from the Institutional Review Board.

Informed Consent

Informed consent was obtained from all participants before enrollment in this research study.

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Supporting Data

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