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Short Communications

Distinct sensorimotor cough features in a cohort of Progressive Supranuclear Palsy

Michela J. Mir [a,b,*], Justin Childers [c], Yuhan Mou [a,d], Bryn Taylor [d], Karen Wheeler-Hegland [a,b,d]

[a] Department of Speech, Language, and Hearing Sciences, University of Florida, Gainesville, United States
[b] Breathing Research and Therapeutics Center & Department of Physical Therapy, University of Florida, Gainesville, United States
[c] College of Medicine, Florida Atlantic University, Boca Raton, United States
[d] Upper Airway Dysfunction Lab, University of Florida, Gainesville, United States

A B S T R A C T

Background: Progressive Supranuclear Palsy (PSP) and Parkinson's disease (PD) similarly affect many neural substrates; however, some brain regions may be more impacted by PSP vs PD, giving rise to distinct cough features that could facilitate earlier differential diagnosis and inform airway protection therapies to prevent fatal lung infections, since patients may not effectively sense and clear irritants from their airways.
Methods: Thirteen individuals with PSP participated and were age- and sex-matched to persons with PD and healthy, unaffected adults. Using a cross-sectional study design this study aimed to 1) compare cough function in PSP using voluntary and induced reflex cough testing, and 2) compare cough airflow and sensation metrics to PD and healthy adult groups.
Results: Voluntary cough function, particularly cough effectiveness during the expiratory phase, was most impaired in the PSP group ($P = 0.047$), while expiratory phase timing outcomes only differed between PSP and healthy controls ($P = 0.03$) during reflex cough. There were no significant differences between groups regarding cough sensation to a cough-inducing stimulus (capsaicin), yet there were more cough responders in PSP vs. PD group.
Conclusions: Degeneration of distinct neural substrates in PSP versus PD may give rise to differentiating sensorimotor cough deficits. Future directions should focus on cough interventions that maintain respiratory health.

1. Introduction

Swallow and cough disorders often coexist in neurological diseases [1]. Importantly, disordered cough can compound the effects of a disordered swallow, such that individuals may ineffectively clear aspirate material [2], leading to increased risk of fatal respiratory complications—a primary cause of death in persons with Parkinson's disease (PD) and forms of atypical Parkinsonism (Progressive Supranuclear Palsy (PSP)) [3,4]. PSP is characterized by tau deposits causing neurofibrillary tangles, tufted astrocytes, and coiled bodies of oligodendrocytes that primarily localize to brainstem and subcortical structures such as the pons, substantia nigra, locus coeruleus, basal ganglia, and thalamus [4–6]. These areas are also impacted by PD [7]; thus, PSP and PD have similar phenotypes that may lead to misdiagnosis. Life expectancy with PSP is shorter than PD, therefore, accurate and early diagnosis is essential for establishing appropriate care [4].

PSP tau deposits and subsequent degeneration of the frontal cortex, dentate nucleus of the cerebellum, corticopontocerebellar pathways, and inferior olives of the medulla [4–6] may differentially impact control of cough resulting in distinguishing cough metrics from PD and facilitate differential diagnosis and individualized symptom management of airway protection deficits. These are regions highly involved with voluntary motor control; thus, voluntary cough production may be distinctly impacted in PSP versus PD.

Our understanding of cough in PSP is limited [8]; thus, the aim of this study was to further characterize and identify distinct cough metrics in PSP. Given the PSP-related degeneration in areas important for volitional motor control, we first hypothesized that voluntary cough would be more impaired than reflex cough, within the PSP cohort and compared to PD and an age-matched control group. We also hypothesized that the PSP group would have the greatest reflex cough motor impairments but that sensation to a cough-inducing stimulus would be intact since sensory pathways may be less impacted by PSP compared to PD.

* Corresponding author.
E-mail address: michela.mir@ufl.edu (M.J. Mir).

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2. Methods

Participants were recruited from the university-affiliated movement disorders clinic and provided informed consent (IRB202101196 and IRB201700959) between November 2021 and May 2022. Diagnoses were given by neurologists with fellowship training in movement disorders and based on Hoglinger et al. criteria [6] and the UK brain bank criteria, respectively. Participants with PSP or PD were excluded if disease duration exceeded five years; they were unable to ambulate at least 10 feet with assistance; had moderate or severe cognitive-linguistic deficits; or another neurological diagnosis. Healthy controls (HC) were age- and biological sex-matched to patients and were excluded if they had a history of neurological disease or injury. All participants were excluded with history of head, neck, or lung cancer; current respiratory infection or disease; cigarette smoking within five years; allergy to capsaicin; severe or profound depression risk [9]. All participants who reported taking carbidopa-levodopa were tested in the "on" state.

2.1. Voluntary & induced-reflex cough testing

Voluntary cough measures were collected using a pneumotachograph (MLT1000L, ADInstruments) and pressure transducer (FE141, ADInstruments) coupled to a disposable facemask (Ambu, 000252055). LabChart8 (ADInstruments) recorded cough airflows for offline analysis. Spirometry volume was calibrated using a 3L syringe. The facemask was placed over the nose and mouth and participants completed one-minute of quiet breathing, followed by instructions to cough into the facemask "as if something went down the wrong pipe".

Induced-reflex cough testing was completed using a capsaicin (IND #76866) dose–response method [10]. The same data acquisition setup from voluntary cough testing was used. Saline, or one of four capsaicin doses (50, 100, 150, and 200 μM dissolved in 80 % physiologic saline and 20 % ethanol) was delivered with a nebulizer (DeVilbiss Healthcare, LLC, Model 646) and air compressor (PulmoMate, DeVilbiss Healthcare) connected to a dosimeter (KoKo Dosimeter, Ferraris 2004KD005) that delivered the aerosolized concentrations at a flow rate of 5 L/min for two seconds. Capsaicin and saline were randomly presented across three blocks and participants were instructed "cough if you need to." The facemask was removed after each cough, or after 10 s if there was no cough. Participants rated their perceived urge-to-cough (UtC) along the modified Borg Scale (0 = no urge; 10 = maximum urge) after each concentration.

Data from the first cough across three trials of voluntary and induced-reflex cough responses were averaged. Cough volume acceleration was the primary motor outcome, as it is a function of peak expiratory flow rate divided by the flow rise time –a composite metric of cough thought to reflect the summative forces that clear the airways. Secondary motor outcomes included inspiratory phase volume and flow rate, compression phase duration, peak expiratory flow rate, expiratory flow rise time, and cough expired volume. All metrics were extracted by one rater, who also re-analyzed a randomly selected 20 % of the data for intra-rater reliability. For inter-rater reliability, a second rater analyzed a random selection of 20 % of the data. During reliability ratings, if discrepancies were greater than 0.1 L/s in airflow and.02 s in timing, consensus meetings were held to collectively re-examine de-identified data, including blinding to diagnoses, until agreed upon values were achieved.

Cough dose–response threshold (lowest capsaicin dose that elicited a 2-cough response in 2/3 trials) and UtC sensation slope (regression of UtC ratings per capsaicin dose) were the primary sensory outcomes for reflex cough. Secondary sensory outcomes were number of cough responders per capsaicin dose and the UtC dose–response threshold (lowest dose that induced UtC 2/3 times).

2.2. Statistical analyses

SPSS v. 27 and Prism 9 were used for statistical analyses and figures. Descriptive statistics summarized demographics and outcomes. Wilcoxon matched-pairs signed-rank test compared voluntary versus induced-reflex cough airflows within the PSP group. Kruskal Wallis analysis of variance assessed PSP, PD, and HC group differences with Dunn's correction for multiple comparisons. Cohen's D effect sizes were calculated using nonparametric formulas [11] and a priori significance was $P < 0.05$.

3. Results

Thirteen individuals with PSP (aged 71-years ± 5) volunteered and were matched to those with PD and HC. There were no differences between groups in age ($H(2) = 0.81$; $P = 0.668$), disease duration since diagnosis (1.92 ± 1 vs. 2.77 ± 1-year; $H(2) = 2.70$; $P = 0.100$), or symptom onset ($H(2) = 0.003$; $P = 0.956$). PSP variants included 1 Speech-Language, 1 Progressive Gait Freezing, and 11 Richardson Syndrome. Additional participant characteristics are included in Supplementary Table 1.

3.1. PSP within group comparisons

Voluntary cough data are from 10 individuals, since three could not produce voluntary coughs. Supplementary Table 2 summarize voluntary cough data. Results revealed cough volume acceleration was significantly lower ($Z(1) = 1.99$; $P = 0.047$; $d = 0.43$), inspiratory volume was greater ($Z(1) = 1.89$; $P = 0.042$; $d = 0.41$), and peak expiratory flow rate was almost 1 L/s lower in voluntary (1.26 L/s) versus reflex cough (2.23 L/s) although not statistically different ($Z(1) = 1.99$; $P = 0.282$; $d = 0.43$).

3.2. Voluntary cough between group comparisons

Cough volume acceleration was significantly different between PSP, PD, and HC ($H(2) = 19.08$; $P < 0.001$). There was lower cough volume acceleration in PSP compared to PD ($Z(2) = 2.77$; $P = 0.017$; $d = 0.47$) and HC ($Z(2) = 4.35$; $P < 0.0001$; $d = 0.90$) (Fig. 1a).

There were differences across groups for voluntary peak expiratory flow rate ($H(2) = 13.94$; $P = 0.001$), expiratory flow rise time ($H(2) = 2.84$; $P = 0.013$), and cough expired volume ($H(2) = 9.20$; $P = 0.01$). Multiple comparisons indicated lower peak expiratory flow rates in PSP versus PD ($Z(2) = 2.56$; $P = 0.031$; $d = 0.43$) and HC ($Z(2) = 3.69$; $P < 0.01$; $d = 0.69$). The PSP group had prolonged expiratory flow rise times and lower cough expired volumes compared to HC (Fig. 1b-1d).

3.3. Induced reflex cough differences between groups

Metrics from coughs produced at 200 μM of capsaicin were used for data analysis. Descriptive data are summarized in Supplementary Table 1. Reflex cough volume acceleration was significantly different between groups ($H(2) = 8.75$; $P = 0.013$), such that it was lower in PD compared to HC ($Z(2) = 8.16$; $P = 0.015$; $d = 0.48$). Compression phase duration ($H(2) = 8.20$; $P = 0.016$) and expiratory flow rise time ($H(2) = 10.48$; $P = 0.03$) were different between PSP and HC. There were no differences between PSP and PD in any reflex cough outcomes (Fig. 2).

3.4. Cough sensation measures

Since not all achieved a 2-cough dose–response threshold, a 1-cough response threshold was compared across groups, revealing no differences (150uM capsaicin for each group). UtC sensation slopes were not different either (PSP = 0.27; PD = 0.25; HC = 0.29). The number of responders to 100 and 200uM capsaicin was similar in each group, although more individuals with PSP coughed at 50 (15 % vs. 1 %) and

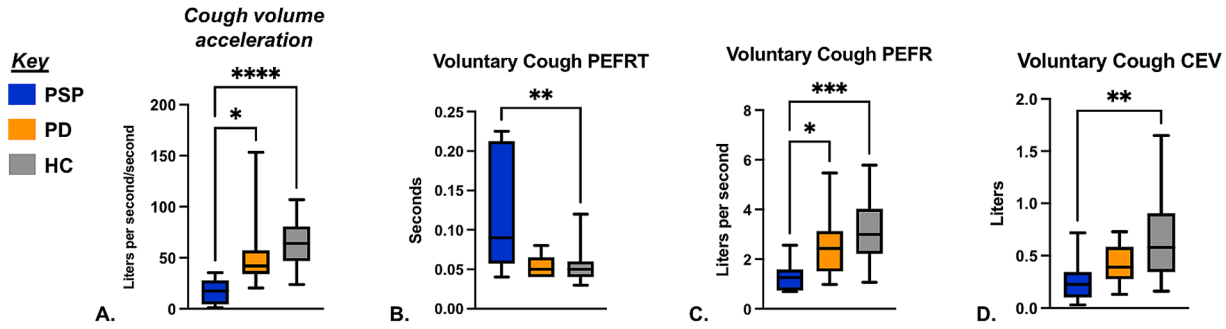

Fig. 1. Comparison of voluntary cough (VC) airflow metrics between PSP, PD, and HC groups. Multiple comparisons indicated significantly lower cough volume acceleration (A) and peak expiratory flow rate (C) in PSP versus PD and HC. Expiratory flow rise time (B) and cough expired volume was only more impaired in PSP versus HC. *denotes $p < 0.05$; **$p < 0.01$; ***$p < 0.001$;****$p < 0.0001$.

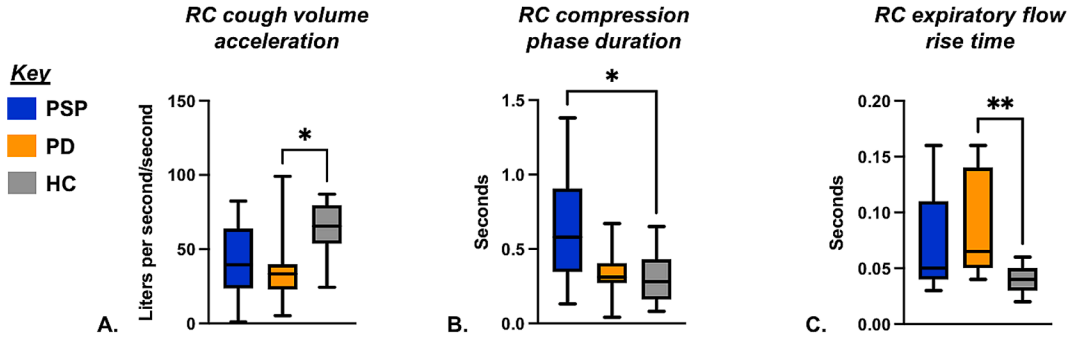

Fig. 2. Comparison of reflex cough (RC) airflow metrics between PSP, PD, and HC groups. The PSP group had longer compression phase duration than the HC group (B) and the PD group had lower cough volume acceleration (A) and longer expiratory flow rise time (C) compared to HC. *denotes $p < 0.05$; **$p < 0.01$.

150 μM of capsaicin (100 % vs. 85 %) versus PD.

3.5. Inter- and Intra-Rater reliability

Intraclass correlational analyses revealed excellent inter- and intra-rater reliability (0.90–1.00) for cough airflow assessments.

4. Discussion

Findings from this study largely support the hypothesis that persons with PSP have greater impairments in voluntary versus reflex cough function, specifically in the expiratory phase, which supports work from another group [8]. However, this present study uniquely described PSP vs. PD vs. healthy controls and found that reflexive cough responses were only distinctly different in PSP *and* PD compared to healthy controls, suggesting that brainstem-mediated reflex cough regions are similarly impacted by PSP and PD-related pathology.

Although voluntary cough expiratory phase metrics were more impaired in PSP, both compared to reflex cough and to voluntary cough in PD and HC, the inspiratory and compression phase outcomes were not statistically different. Essentially, people with PSP produced inadequate, volitional expiratory airflows, despite what appeared to be a sufficient volume of air in the lungs. These findings may be explained by differences in disease pathophysiology and severity of progression affecting critical areas for cortical control of volitional movements. PSP-related pathology implicates the basal ganglia, cerebellum, and frontal cortex [4–6]; important regions for voluntary motor control. Although volitional control of inspiration and expiration share neural substrates, voluntary expiration and coughing differentially activate the subthalamic nucleus, the pontomesencephalic junction, and a larger volume of the supplementary motor area [12–14]. These regions of the brain are not implicated as much in PD, nor are they activated during capsaicin-induced cough challenges [13].

Interestingly, PSP reflex cough airflows were not distinct from PD. Instead, there were only differences in PSP and PD groups when compared to HC. Specifically, cough volume acceleration was worse in PD and timing outcomes (e.g., compression phase duration and expiratory flow rise time) were worse in PSP. Deficits in both patient groups may be due to generalized dysfunction from parkinsonian-related pathology that impact these reflexive cough metrics.

Finally, cough sensation outcomes did not differ between groups, supporting the hypothesis that these would be intact for the PSP group. UtC sensation slopes were not different between PSP and PD in the Borders et al. study either [8]; however, the authors of that paper indicated that some individuals did not tolerate higher levels of capsaicin and that some PSP UtC ratings were higher than PD ratings. Interestingly, in this current study, there was a higher percentage of cough responders in the PSP group at 50 and 150 μM capsaicin compared to PD and HC. Taken together, this may suggest that sensitivity to cough stimuli may be higher, but variable in PSP.

Because voluntary cough is significantly impaired compared to PD counterparts, evaluating voluntary cough in persons suspected to have, or diagnosed with, PSP, may be a useful clinical marker to facilitate differential diagnosis. Moreover, collecting voluntary cough data using clinical devices, such as a peak flow meter, will provide baseline data to incorporate into plans of care for cough rehabilitation.

5. Limitations

There were 39 participants in all, which led to small group sizes and less robust statistical analyses. Furthermore, a definitive diagnosis of PSP or PD is only obtained through post-mortem pathological assessment and it is possible that clinical diagnoses could evolve and should be considered when interpreting the data. Future research should control for factors that can impact cough sensation and aim to collect longitudinal data in a larger cohort so that the group can be stratified according

to type of PSP variant, disease duration, and severity for more thorough understanding of cough in this rare patient population.

6. Conclusion

PSP causes rapid functional decline and a shorter lifespan. Respiratory infections are leading causes of mortality and impaired cough may contribute to those complications. Findings from this study suggest there are distinct voluntary expiratory phase cough metrics that could distinguish PSP from PD in the context of a thorough neurological evaluation. Early identification of impaired cough could differentiate PSP and lead to earlier implementation of appropriate medical management, support teams, and rehabilitation plans. These findings support the need for future research to develop better diagnostic tools and interventions for cough dysfunction to improve and maintain pulmonary health and quality of life.

7. Author Roles

Michela J. Mir: conception, organization, execution of research project—design, execution, review and critique of statistical analyses—writing of all drafts, review and critique of manuscript. **Justin Childers, Yuhan Mou, and Bryn Taylor:** execution of research project—review and critique of statistical analyses—review and critique of manuscript preparation. **Karen W. Hegland:** conception and organization of research project—design and review and critique of statistical analyses—review and critique of manuscript preparation.

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CRediT authorship contribution statement

Michela J. Mir: Writing – original draft, Visualization, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Justin Childers:** Writing – review & editing, Project administration, Investigation, Data curation. **Yuhan Mou:** Writing – review & editing, Resources, Project administration, Investigation, Data curation. **Bryn Taylor:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation. **Karen Wheeler-Hegland:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Conceptualization.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2025.100305.

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