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ORIGINAL ARTICLE

Comparison of Two Methods for Inducing Reflex Cough in Patients With Parkinson's Disease, With and Without Dysphagia

Karen W. Hegland[1] · Michelle S. Troche[2] · Alexandra Brandimore[1] · Michael S. Okun[3] · Paul W. Davenport[4]

Abstract Aspiration pneumonia is a common cause of death in people with Parkinson's disease (PD). Dysfunctional swallowing occurs in the majority of people with PD, and research has shown that cough function is also impaired. Previous studies suggest that testing reflex cough by having participants inhale a cough-inducing stimulus through a nebulizer may be a reliable indicator of swallowing dysfunction, or dysphagia. The primary goal of this study was to determine the cough response to two different cough-inducing stimuli in people with and without PD. The second goal of this study was to compare the cough response to the two different stimuli in people with PD, with and without swallowing dysfunction. Seventy adults (49 healthy and 21 with PD) participated in the study. Aerosolized water (fog) and 200 μM capsaicin were used to induce cough. Each substance was placed in a small, hand-held nebulizer, and presented to the participant. Each cough stimulus was presented three times. The total number of coughs produced to each stimulus trial was recorded. All participants coughed more to capsaicin versus fog ($p < 0.001$). A categorical 'responder' and 'non-responder' variable for the fog stimulus, defined as whether or not the participant coughed at least two times to two of three presentations of the stimulus, yields sensitivity of 77.8 % and a specificity of 90.9 % for identifying PD participants with and without dysphagia. The data show a differential response of the PD participants to the capsaicin versus fog stimuli. Clinically, this finding may allow for earlier identification of people with PD who are in need of a swallowing evaluation. As well, there are implications for the neural control of cough in this patient population.

Keywords Cough · Parkinson's disease · Deglutition · Deglutition disorders · Dysphagia · Screening

Background

Reflexive, or induced, cough is a complex sensorimotor behavior that is essential to the maintenance of pulmonary health. Induction of reflex cough occurs as a result of stimulation of multiple afferent receptor types, including mechanoreceptors, chemoreceptors, and nociceptors. A myriad of stimuli can readily elicit cough, including aspiration of foreign or endogenous material, various tactile or punctate stimuli [1, 2], aerosolized water ("fog") [3], capsaicin [4–6], citric acid [7–9], and tartaric acid [10]. Several of these cough-inducing, or tussigenic, stimuli have been used to study cough in patient populations with airway protective deficits. The results of these studies highlight the potential utility of reflex cough sensitivity as an indicator of swallowing dysfunction [7, 11, 12] or risk for developing aspiration pneumonia [10].

The functionality of airway protective behaviors (i.e., swallowing and cough) is of particular importance in Parkinson's disease (PD), where aspiration pneumonia is a leading cause of mortality [13, 14]. The development of

✉ Karen W. Hegland
  kwheeler@ufl.edu

1 Department of Speech Language and Hearing Sciences, University of Florida, Box 117420, 336 Dauer Hall, Gainesville, FL 32611, USA

2 Department of Biobehavioral Sciences, Teacher's College, Columbia University, New York, USA

3 Department of Neurology, University of Florida, Gainesville, USA

4 Department of Physiological Sciences, University of Florida, Gainesville, USA

Table 1 Hoehn and Yahr staging description

Stage	Description
1	Unilateral involvement only
1.5	Unilateral and axial involvement
2	Bilateral involvement without impairment of balance
2.5	Mild bilateral disease with recovery on pull test
3	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severe disability; still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided

Table 2 Exclusionary criteria for the Healthy and PD participant groups

Healthy	PD
• History of neurologic disease	• Acute respiratory illness
• Acute respiratory illness	• History of chronic cough or other chronic respiratory illnesses
• History of chronic cough or other chronic respiratory illnesses	• History of cancer in the head, neck, or lungs
• History of cancer in the head, neck, or lungs	• Current tracheostomy
• Current tracheostomy	• Current intubation
• Currently intubation	

aspiration pneumonia is multifactorial; yet, it is known that aspiration of material secondary to disordered swallowing (dysphagia) is a precipitating factor. Additionally, the presence of dysphagia is largely underestimated via self-report in the PD population [15, 16]. Further, the severity of dysphagia does not directly correlate to Hoehn and Yahr stage (Table 1), so the stage of PD alone cannot be used as a predictor of swallowing dysfunction [17]. Thus, the question of when to evaluate swallowing is difficult to answer, yet critically important to the effective management of these patients.

Studies have shown that the peak airflow produced during voluntary cough (cough on command) is reduced in people with both PD and dysphagia as compared to those with PD and without dysphagia [18, 19]. Reflex cough can be considered more ecologically valid than voluntary cough given that it, like a cough in response to aspirate material, is induced by a sensory stimulus. However, it is not known whether measures of reflex cough may serve in a predictive capacity for identifying those at increased risk of airway compromise during swallowing for these patients. Additionally, tussigenic stimuli act on different sensory receptors, and it is unknown whether any given stimulus type is a better indicator of airway protective deficits. Therefore, the first goal of this study was to determine whether there were differences in number of coughs produced between two different, commonly used tussigenic stimuli. We aimed to determine whether responses to these stimuli would be different in healthy adults versus adults with PD with and without airway protective deficits (i.e., dysphagia). Second, we aimed to determine whether either of the stimuli would be sensitive and specific predictors of disordered swallowing. Our overarching hypothesis was that capsaicin, a stronger tussigenic stimulus, would result in more coughs produced across participant groups versus the less intense fog stimulus. Further, we hypothesized that the PD group would respond less (produce fewer coughs) as compared to the healthy group, and that the response would be further reduced in the PD group with dysphagia.

Materials and Methods

Participants were recruited via the University of Florida (UF) Center for Movement Disorders and Neurorestoration, and among patients referred to the speech pathology service for swallowing evaluation. This study received ethical approval by the UF Institutional review board (study # 506-2010), and all participants provided verbal and written informed consent prior to initiation of any study procedures. Healthy adults met inclusion criterion if they were between 18 and 60 years of age. Inclusion criterion for the patients with neurologic disease was referral to the speech pathology service for swallowing evaluation. Exclusionary criteria for both groups are summarized in Table 2.

There were a total of 70 study participants. There were 49 healthy younger adults (mean 20.43 ± 2.5 years; Table 3) and 22 adults with PD; however, due to changes in diagnosis, three of the PD participants were later excluded from the study. The diagnosis of PD was made by a fellowship-trained movement disorders neurologist according to the United Kingdom (UK) brain bank criteria. The remaining participants with PD were further subdivided into a group without deficits in airway protection, and those with deficits in airway protection. Airway protective deficits were identified based on clinical videofluoroscopic swallowing evaluations and defined using the penetration–aspiration scale (PAS) [20]. The swallowing data were analyzed by three clinically certified speech-language pathologists, with at least 5 years of experience rating swallows using the penetration–aspiration scale, and who all had expertise working with this patient population. For all swallows, two of the three raters independently analyzed the swallowing data. In cases where there was disagreement, the data were reviewed during a consensus meeting with all three raters present, and a final score was assigned. The group with airway protective deficits ("PD-PA") exhibited the presence of laryngeal penetration of bolus material to the level of the vocal cords, or tracheal

Table 3 Participant demographic information

Group	Participants	Age (years; mean ±1 SD)*	Sex*	Hoehn & Yahr	PAS
Non-PD group	N = 49	20.43 (±2.50)	46 female; 3 male	NA	NA
PD No PA	1	78	F	1.5	1
	2	64	F	2.5	1
	3	64	M	2	1
	4	73	F	3	1
	5	71	M	2.5	1
	6	69	M	1.5	1
	7	61	F	2	1
	8	66	M	2	2
	9	69	F	2	1
	10	68	M	3	3
PD No PA group data	N = 10	68.3 (±4.94)	5 female, 5 male		
PD-PA	11	74	M	3	5
	12	56	F	2.5	5
	13	67	F	2.5	5
	14	66	M	2	5
	15	64	M	2.5	7
	16	64	M	2.5	5
	17	79	M	4	5
	18	73	M	2.5	5
	19	65	F	2.5	5
PD No PA group data	N = 9	67.56 (±6.80)	3 female; 6 male		

PAS penetration–aspiration scale, SD standard deviation

* Indicates significant difference between the PD and healthy group ($p < 0.001$) in terms of both mean age and sex distribution

aspiration (PAS >4). There were 9 in the PD-PA group, and 10 in the PD without PA group ("PD no PA"). Further participant information is summarized in Table 2.

Cough Testing

Cough testing was performed using two hand-held nebulizers (Omron Micro-Air NE U22 V). One of the nebulizers was filled with capsaicin dissolved in a vehicle solution (80 % physiologic saline and 20 % ethanol), diluted to a concentration of 200 μM, and the other filled with distilled water (referred to as *fog*). For the capsaicin-filled nebulizer, participants placed the mouthpiece in the mouth, inhaled one time, and then removed the mouthpiece from the mouth. For the fog nebulizer, participants placed the mouthpiece in the mouth and breathed continuously on the mouthpiece until they coughed, or up to 1 min. Each nebulizer stimulus was presented 3 times, for a total of 6 stimuli delivered per participant. These protocols were chosen based on methods previously reported in the literature for capsaicin [4, 6, 21] and fog [3].

Outcome Measures

The primary outcome measure for both stimuli was total number of coughs produced in the first 30 s following stimulus delivery. The total number of coughs produced was recorded for each of the three presentations per stimulus type, and the median was calculated for the 3 trials of each stimulus. As well, a binary categorical responder/non-responder variable was computed based on the total number of coughs produced. Specifically, participants were categorized as 'responders' if they produced at least 2 coughs, in 2/3 trials of each stimulus type. This categorization was based on the 2-cough (C2) method for determining reflex cough threshold [4, 5], adapted for the presentation of single concentrations [12] of the stimuli.

Statistical Analysis

A repeated measures analysis of variance (RM ANOVA) with between-subject factor group (healthy and PD) and within subject factor stimulus type (capsaicin, fog) was

used to determine whether there were significant differences between healthy adults and those with PD in terms of their overall cough response to the two stimuli. A second RM ANOVA with between-subject factor group (healthy, PD no PA, PD-PA) and within subject factor stimulus type (capsaicin, fog) was used to determine whether differences existed for total number of coughs produced between PA and no-PA subgroups in the PD cohort. Tukey's HSD was used for post hoc testing of differences between the groups according to stimulus type. Chi-square analyses were used to test the sensitivity and specificity of the capsaicin and fog stimuli for identifying the group identity of participants (healthy, PD or PD-PA) according to the binary responder/non-responder variable. Statistical significance levels were set at $p < 0.05$.

Results

Participant demographic information is presented in Table 3. There were statistically significant differences between the healthy and PD groups in terms of age $(F_{(1,73)} = 1811.65; p < 0.001)$ and gender $(F_{(1,73)} =$

Table 4 Means and standard deviation for the Total coughs produced across three trials to each stimulus type according to participant group

	Capsaicin	Fog
Healthy	3.94 (1.90)	1.73 (1.48)
PD (all)	3.26 (2.77)	2.11 (1.91)
PD no PA	4.50 (2.99)	3.31 (1.85)
PD-PA	1.89 (1.76)	1.00 (1.75)

PD no PA is Parkinson's disease with penetration–aspiration score less than 4; PD-PA is Parkinson's disease with penetration–aspiration score greater than 4

36.00; $p < 0.001$), with the healthy participants being younger and consisting of primarily female participants. There were no significant differences in terms of age $(p = 0.899)$ or gender $(p = 0.529)$ between the PD no PA and PD-PA groups.

Mean values for total number of coughs produced are presented in Table 4. Results of the first RM ANOVA failed to show a main effect for group (healthy or PD), or a group x stimulus interaction, but did show a significant main effect for stimulus $(F_{(1,66)} = 39.821; p < 0.001)$. These results show that all participants produce more coughs to capsaicin compared to fog (Fig. 1). Results of the second RM ANOVA, which compared the PD no PA, PD-PA, and healthy groups, showed a main effect for stimulus type $(F_{(2, 65)} = 22.204, p = 0.00001)$ and group $(F_{(2)} = 6.887, p = 0.002$; Fig. 2). There was no significant interaction between stimulus type and group $(F_{(2, 65)} = 2.066, p = 0.135)$. Results of post hoc testing showed that the PD-PA group produced significantly fewer coughs across both stimulus types as compared to the healthy and PD no PA groups. There were no significant differences in terms of the total number of coughs produced between the healthy and PD no PA groups (Table 5).

Results of the Chi-square analysis are shown in Fig. 3. The categorical responder/non-responder response to fog did not differentiate the healthy versus PD (inclusive of both PD no PA and PD-PA) groups $(\chi^2_{(1)} = 0.004, p = 0.950)$. The categorical responder/non-responder response to capsaicin is significantly different between the two groups $(\chi^2_{(1)} = 4.533, p = 0.033)$; however, this yields only 20 % sensitivity with 95.9 % specificity. Within just the PD cohort, when PD-PA group is compared to the PD no PA group, both the fog and capsaicin responder categories are statistically significant (fog: $(\chi^2_{(1)} = 9.731, p = 0.002$; capsaicin: $(\chi^2_{(1)} = 6.111,$
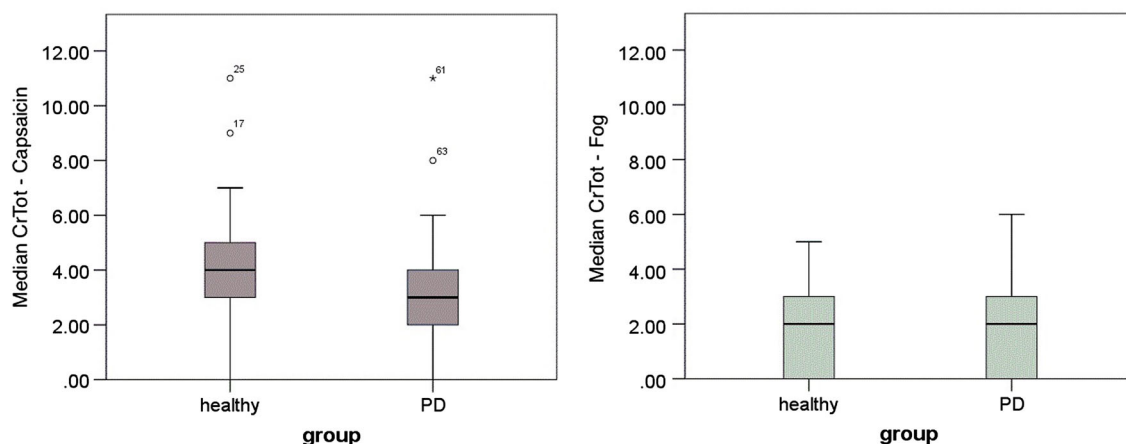

Fig. 1 Median of the total coughs produced (CrTot) according to stimulus type for the healthy versus PD cohort (inclusive of PD no PA, and PD-PA). Outliers are more than 1.5 times the interquartile range above the third quartile
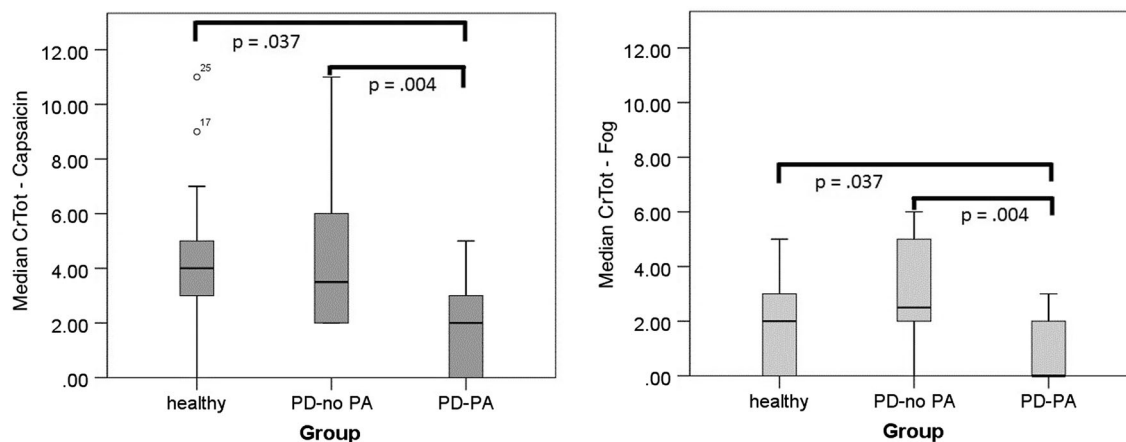
Fig. 2 Median of the total coughs produced (CrTot) according to stimulus type for the healthy, PD no PA, and PD-PA cohorts. Significant differences exist between the PD-PA and healthy groups, as well as between the PD-PA and PD no PA groups, but not between the PD no PA and healthy groups. Outliers are more than 1.5 times the interquartile range above the third quartile

$p = 0.013$). For the capsaicin stimulus, sensitivity is 44.4 %, while specificity is 100 %. Sensitivity and specificity are optimized for the categorical fog responder/non-responder variable, where the non-responder designation yields a sensitivity of 77.8 % and a specificity of 90.9 %.

Discussion

The first goal of this study was to determine whether total number of coughs produced across two different cough-inducing stimuli would be different in healthy adults versus those with PD, and also different within the PD group; those with and without airway protective deficits (i.e., dysphagia). Our results show that people with PD as compared with healthy younger adults do not produce fewer coughs overall to either the capsaicin or fog stimulus. A more detailed look at the PD group showed that the PD-PA group produced fewer coughs to both stimuli versus people with PD and no PA, and compared to the healthy group. Interestingly, when only the PD (no PA) group was compared to the healthy adults, they actually produced slightly more coughs to both stimuli. When the data were

Table 5 Results of post hoc analysis for the main effect of group (Healthy, PD-PA, and PD No PA) on total coughs produced across stimulus types

Contrast pair	Mean difference	p value
Healthy–PD no PA	−0.963	0.170
Healthy–PD-PA	1.39	0.037
PD no PA—PD-PA	2.35	0.004

PD no PA is Parkinson's disease with penetration–aspiration score less than 4; PD-PA is Parkinson's disease with penetration–aspiration score greater than 4

coded into binary 'responder' and 'non-responder' categories, the less intense fog stimulus showed very good sensitivity (77.8 %) and specificity (90.9 %) for detecting membership to the PD and PD-PA groups. The capsaicin stimulus had excellent specificity (95.9 %), but poor sensitivity (20 %), as it failed to identify those with PD from healthy controls and those with PD-PA from PD no PA. Thus, identifying airway protective deficits using a single-breath inhalation method for capsaicin presentation had an unacceptably high false negative rate.

To our knowledge, this is the first study to directly compare the cough response to two different tussigenic stimuli in PD. These results suggest differences in the neural control of cough in PD, and in PD with and without dysphagia. The framework (Fig. 4) proposed by Troche and colleagues [22], which was modified from Eccles [23], identified two pathways for irritant induced cough: a brainstem reflex pathway and a cortical pathway that includes the perception of an urge-to-cough (for review, see Davenport [24]). The implication of the framework is that when a cough stimulus is sufficiently strong, brainstem pathways are capable of producing the cough response independent of, or with minimal cortical modulation. However, for less intense stimuli, the cortex may either modulate the cough motor response based on the perceived urge-to-cough, or fail to detect the biological need to cough altogether and therefore not trigger a cough.

Troche and colleagues [25] recently published a study reporting a blunted urge-to-cough sensation for lower capsaicin concentrations (i.e., less intense capsaicin) in people with PD who had dysphagia versus those who did not. In light of current and previous findings, a possible hypothesis is that the less intense stimuli resulted in a reduced urge-to-cough, and thus, a reduced likelihood of reflex cough response across the groups. When cough was produced in response to
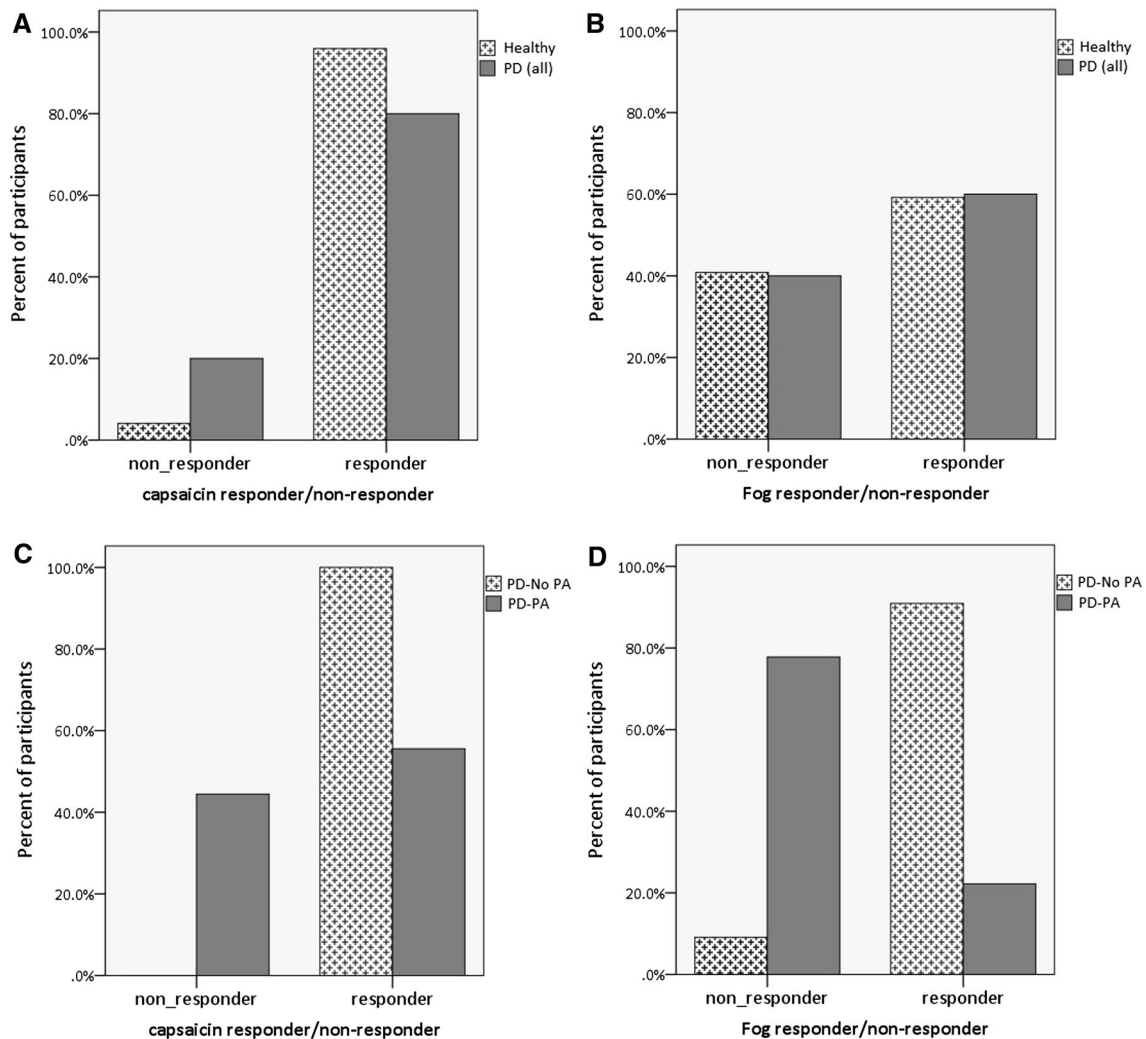
Fig. 3 Categorical responder and non-responder variables according to stimulus type. **a** Percent of healthy and PD cohort (inclusive of PD no PA, and PD-PA) in non-responder and responder categories to capsaicin. **b** Percent of healthy and PD cohort (inclusive of PD no PA, and PD-PA) in non-responder and responder categories to fog. **c** Percent of PD no PA and PD-PA in non-responder and responder categories to capsaicin. **d** Percent of PD no PA and PD-PA in non-responder and responder categories to fog

the continuous-breathing fog stimulus, it is possible that prolonged sensory stimulation and processing by higher cortical structures result in an increased urge-to-cough (Fig. 4, path 1). In contrast, the single-breath method directly activated brainstem cough control mechanisms (Fig. 4, path 2). This hypothesis is supported by the data showing that the majority of these participants, inclusive of 96 % of the healthy cohort, 100 % of the PD no PA cohort, and 60 % of the PD-PA cohort, *did* respond to the capsaicin stimulus. The stimulus was sufficiently intense enough such that cortical drive was not necessary to initiate the brainstem response.

On the other hand, 59 % of the healthy cohort versus 82 % of the PD no PA cohort responded to the fog stimulus. Leow and colleagues found that people with less severe PD (defined as less than or equal to H&Y II) showed decreased ability to volitionally suppress their cough compared with both young and age-matched control participants [8].

Similarly, in this study, the PD no PA cohort may have detected the fog stimulus cortically, experienced an urge-to-cough, and been unable to suppress cough to the same degree that the healthy cohort did, resulting in more coughs produced for that stimulus compared with the healthy cohort. This is in contrast to the PD-PA group that may not have detected an urge-to-cough at all to this stimulus. Clearly, there is a need for further research in this group of patients.

Limitations

There are limitations to this study. The healthy and PD participant groups were not matched for either age or gender distribution (however, within the PD cohort, the PD-PA and PD No PA groups were well matched). In the future, a healthy age- and sex-matched control group
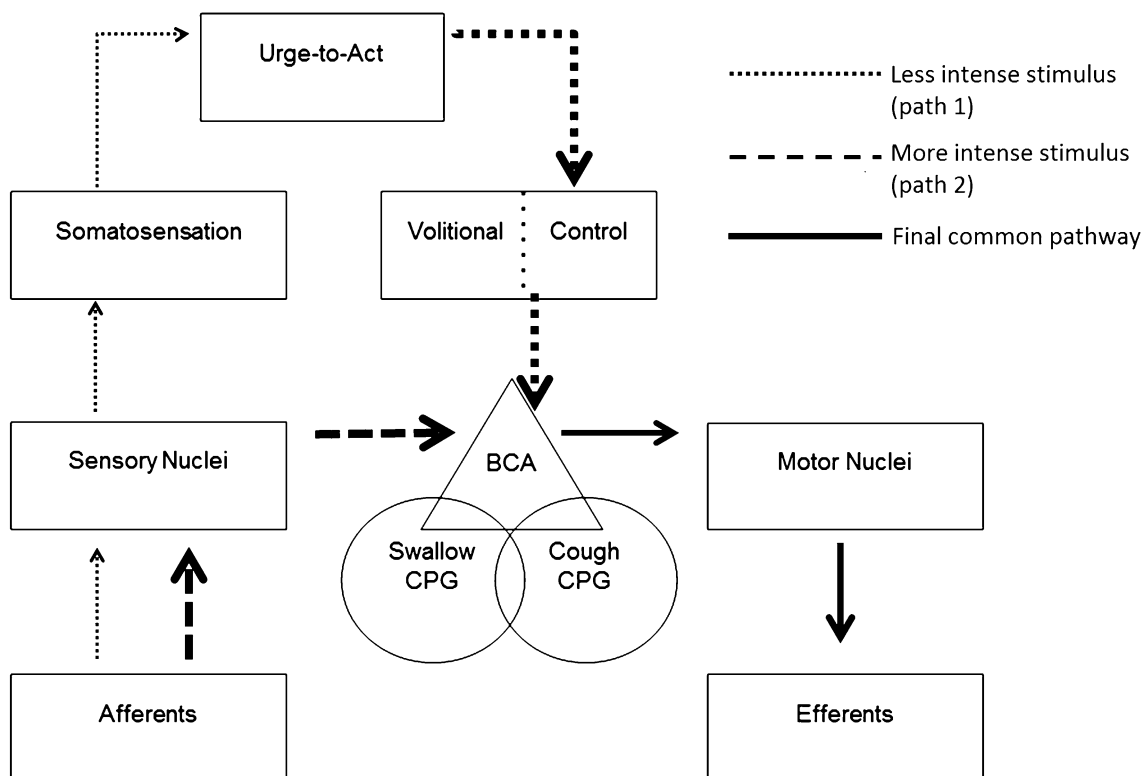
Fig. 4 Framework of cough neural control adapted from Troche et al. [22]. Path 1 is the hypothesized path for fog, or other less intense cough stimuli. Path 2 is the hypothesized path for high concentrations of capsaicin or other more intense stimuli. The solid arrows represent a final common pathway once the motor command for cough exits the behavioral control assembly (BCA) within the brainstem. *CPG* central pattern generator, *BCA* behavioral control assembly

should be included. Additionally, participants were not screened for whether they currently were taking an ACE inhibitor, which is known to affect the frequency of cough to a stimulus. Next, we did not include a measure of the urge-to-cough, and certainly, this is necessary in future study to enhance our interpretation of the data. Regarding the experimental protocol, the fog and capsaicin stimuli differed in terms of not only the method of delivery, but also the mechanism of action (i.e., the types of sensory receptors responding to each stimulant). Future studies should better control for the intensity, amount and duration of stimulus applied in order to identify whether differences found between fog and capsaicin in this preliminary study were due to delivery method, stimulus type, or intensity.

Conclusions

To our knowledge, this is the first study to directly compare two tussigenic stimuli, fog, and capsaicin, for inducing cough in people with PD. These results have implications not only for the neural control of cough, but also for detecting airway protective deficits in PD. These results show that lower-intensity stimuli may be better for

differentiating groups of PD subjects with and without airway protection deficits. Clinically, this finding is promising in terms of improving early detection for people with PD who are in need of evaluation and treatment for swallowing dysfunction. This study provides the framework for future studies which should focus on larger cohorts of PD patients with and without dysphagia with the goal of developing a valid and reliable method to identify risk for airway protection deficits in this population.

Compliance with Ethical Standards

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Karen W. Hegland   PhD

Michelle S. Troche   PhD

Alexandra Brandimore   MA

Michael S. Okun   MD

Paul W. Davenport   PhD