Dysphagia
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ORIGINAL ARTICLE

The Role of Aspiration Amount on Airway Protective Responses in People with Neurogenic Dysphagia

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Abstract

The aim of this study was to examine relationships between the presence vs. absence of an aspiration-related airway protective response (i.e., coughing or throat clearing) with aspiration amount, trial volume, disease diagnosis, and disease duration in people with neurologic disease. A secondary analysis was completed of flexible endoscopic evaluations of swallowing (FEES) in people with neurologic disease. Thin liquid boluses with endoscopically confirmed aspiration were included. Aspiration amount was measured for each trial using the visual analysis of swallowing efficiency and safety (VASES). Statistical analyses were used to (1) compare aspiration amount between swallows with vs. without an airway protective response and (2) examine if trial volume, disease duration, and disease diagnosis were related to the presence of airway protective responses when controlling for aspiration amount. 422 aspirated swallows across 86 FEES were analyzed. Of the 59 people who aspirated more than once, 66.1% exhibited variability in the presence vs. absence of an airway protective response. Statistical analyses revealed airway protective responses were significantly related to aspiration amount ($p < 0.001$; Marginal $R^2 = 0.46$) and disease duration ($p = 0.036$, L.R. = 4.35) but not trial volume ($p = 0.428$) or disease diagnosis ($p = 0.103$). The participants in this study were less likely to cough or throat clear when having smaller amounts of aspiration or longer disease durations. Future research is needed to examine if aspiration amount is related to airway protective responses in healthy adults and across other patient populations.

Keywords Aspiration amount · Silent aspiration · Dysphagia · Swallowing · Cough · FEES

Introduction

Pneumonia is a highly prevalent medical morbidity [1–4] that is significantly associated with aspiration of foods, liquids, and secretions during swallowing [5–12] and is a leading cause of death in many neurologic diseases [3, 4, 13–16]. When aspiration does occur, airway protective behaviors such as coughs and throat clears are often elicited to clear aspirate material out of the lower airway [17] in order to maintain a healthy and homeostatic pulmonary environment [18]. Ineffective or absent airway protective behaviors are significantly associated with the development of pneumonia and pneumonia-related mortalities in people with neurologic disease [8, 19–24]—highlighting the importance of having robust sensorimotor responses following aspiration events.

Silent aspiration occurs when foods, liquids, or secretions enter the subglottis and do not elicit an airway protective response. Silent aspiration is common in people with neurologic disease and accounts for more than half of all aspiration events [25–29]. Recent work by Miles and colleagues found that silent aspiration accounted for 60% of all aspirated swallows within a heterogenous sampling of hospitalized dysphagic adults, and that the presence of an airway protective response in this patient population varied from trial to trial within individuals [25]. This finding suggests that swallowing-specific factors (e.g., bolus consistency, bolus temperature, chemical composition, speed of bolus transit, etc.) may influence the presence or absence of a cough response across trials and within individuals. In this same study, Miles found that the presence of silent

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vs. non-silent aspiration was significantly affected by bolus viscosity, such that aspiration of thick liquids was less likely to elicit a cough compared to thin liquids.

Aspiration is thought to be relatively rare in healthy adults [30–37]. When aspiration does occur it tends to be of a trace amount, and typically does not elicit an airway protective response [30, 31, 34, 38–41]. Conventional thinking would suggest that aspiration of any amount should elicit an airway protective response. This is because the subglottis is innervated by the recurrent laryngeal nerve, which when stimulated produces an airway protective response such as a cough or throat clear [42]. However, musculoskeletal structures containing sensory receptors on their mucosal surfaces are known to become more sensitive as the size of the stimulated surface area increases. This relationship between size of surface area stimulated and sensory sensitivity is known as the theory of spatial summation [43]. Translating this theory to swallowing, it would stand to reason that larger amounts of aspiration would be more likely to elicit an airway protective response when compared to smaller amounts of aspiration. Conversely, smaller amounts of aspiration would be less likely to elicit an airway protective response compared to larger amounts of aspiration. While this has not been empirically tested in swallowing research, findings in the reflex cough testing literature have demonstrated that increasing intensity of cough stimuli results in a higher likelihood of a cough response being present, as well as a greater number of coughs and a greater urge-to-cough, in both healthy adults [44–48] and disordered populations [45, 49, 50].

Other factors that may influence the presence of an airway protective response include trial volume, disease diagnosis, and disease duration. Leder and colleagues found that silent aspiration risk increased with larger trial volumes (i.e., the amount of liquid given to an individual to sip and swallow) when comparing 5 and 90 mL liquid bolus trials [51]. In contrast, Miles and colleagues found that silent aspiration risk was not influenced by trial volume in a study comparing 5 and 50 mL liquid bolus trials [25]. Therefore, it remains unclear if and what trial volumes influence airway protective responsiveness. Additionally, it should be noted the trial volume does not necessarily equate to sip size (the amount of liquid dispensed from a cup into the oral cavity during a drinking task), bolus volume (the amount of bolus propelled from the oral cavity into the pharynx during a single swallow), or aspiration amount (the amount of bolus passing below the level of the vocal folds and into the subglottic space, trachea, and lungs). Therefore, if a relationship does exist between trial volume and airway protective responsiveness, then it is important to discern if this is due to trial volume or is explained by other factors such as aspiration amount.

Disease factors such as disease diagnosis and disease duration could also influence the presence of airway protective behaviors in response to cough-inducing stimuli such as aspiration. For example, recent research has demonstrated that people with progressive supranuclear palsy exhibit increased perception of cough stimuli than people with Parkinson's disease during reflex cough testing [52]. Therefore, understanding how factors such as disease diagnosis and disease duration influence the presence of aspiration-related coughs and throat clears is critical for identifying mechanisms of silent aspiration in people with dysphagia. This in turn is important for ultimately developing targeted cough and swallowing screeners, evaluations, and treatments.

The primary aim of this study was to assess the relationship between aspiration amount with the presence of airway protective responses, specifically coughing and throat clearing, in people with progressive neurologic disease. It is important to understand if a relationship exists between aspiration amount and airway protective responses in people with progressive neurologic disease given the high prevalence of silent aspiration in this patient population [25–29] and its impact on long-term health outcomes [9, 10, 53]. We hypothesized that the presence of an airway protective response would be associated with greater amounts of aspiration. If this hypothesis holds true, then this would provide clinical evidence for the need to routinely report aspiration amount when observing the presence of aspiration on endoscopic and fluoroscopic swallowing assessments. As a secondary aim, we sought to explore the relationship between trial volume, disease diagnosis, and disease duration with the presence of aspiration-related airway protective responses. We hypothesized that, after controlling for aspiration amount, trial volume would not be related to the presence of an airway protective response. We also hypothesized that disease diagnosis and disease duration would be related to the presence of an airway protective response, but the directionality of this relationship was unknown given the paucity of current research.

Methods

A secondary analysis was completed of data originally collected for prospective research purposes. The university's institutional review board approved study procedures and informed consent was obtained for all the participant records included in this secondary analysis. Records were of outpatient adults with neurologic disease undergoing a flexible endoscopic evaluation of swallowing (FEES) for suspected dysphagia. FEES was used to address the current research question given that current literature suggests FEES is more sensitive at visualizing aspiration when compared to videofluoroscopy [54]. Only swallowing trials demonstrating aspiration on thin liquids were included in the present

study. Furthermore, records were included if participants had a neurologic medical diagnosis from a licensed neurologist. Records available for this analysis included people with a diagnosis of Parkinson's disease (PD), progressive supranuclear palsy (PSP), multiple systems atrophy, and SCA, though other neurodegenerative diagnoses (e.g., amyotrophic lateral sclerosis, stroke) would have been included if available. Records were excluded if participants had multiple co-existing neurologic diseases; a history of head and neck cancer; chronic obstructive pulmonary disease; lung cancer; or surgeries of the head, neck, thorax, or spine.

Procedures

FEES was completed with participants seated comfortably in an upright position. FEES equipment consisted of a 3.0 mm diameter flexible distal chip laryngoscope (ENT-5000; Cogentix Medical, New York, USA) and video system with integrated LED light source LCD display (Cogentix Medical, DPU-7000A). The flexible laryngoscope was passed transnasally without the use of topical anesthetic or vasoconstrictor. Swallowing trials began 1–2 min following scope insertion to allow for acclimation to the endoscopic procedure. Swallowing tasks varied across participants depending on the study-specific FEES protocol for which the participant was being examined. Thin liquids were the only consistency included in the present analysis since previous research has demonstrated that bolus consistency can influence cough response [25]. Trial volumes included 5 mL, 10 mL, 15 mL, patient preferred volume (PPV), and 90 mL. Only boluses with endoscopically observed aspiration were included. Trials requiring compensatory strategies (e.g., chin tuck, breath hold, supraglottic swallow) were excluded.

Data Analysis and Outcomes

The amount of aspiration seen during FEES was rated using the visual analysis of swallowing efficiency and safety (VASES) [55, 56]. VASES is a standardized, reliable, and valid method for estimating the presence and amount of pharyngeal residue, penetration, and aspiration during FEES. VASES ratings of aspiration involve using a 100-point scale to estimate the amount of subglottic surface area covered with aspirate residue, expressed as a percentage (%) of the subglottic shelf surface area. Aspiration amount was rated according to the VASES methodology. Specifically, aspiration amount was judged prior to coughs or throat clears (if visualized) or during VASES' 'after the swallow' temporal boundary. Aspiration had to be directly visualized (i.e., no inferences) below the glottis. Penetration-aspiration scale (PAS) [57] scores were used to characterize the presence/absence of airway protective response (coughs and/or throat clears), with PAS 6 and PAS 7 indicating the presence of an airway protective behavior in response to aspiration, and with a PAS 8 indicating the absence of an airway protective behavior in response to aspiration. Swallows with PAS scores 1–5 were not included in the present analysis.

Video clips were de-identified and blindly analyzed by a pair of raters trained in VASES. All videos were viewed in real time with audio, with additional slow-motion frame-by-frame analysis as needed. Rating discrepancies were resolved by a third expert rater. Discrepant ratings for aspiration amount were defined as paired ratings that differed by > 10%, or when one rating indicated the absence of subglottic residue (0/100), while the other rating indicated the presence of subglottic residue (> 0/100). Discrepant ratings were defined as PAS score that did not match.

Statistical Analysis

A binomial multilevel model was used to assess the relationship of aspiration amount on the presence/absence of an airway protective response. Airway protective response was treated as the outcome variable, with silent aspiration (PAS 8) treated as the referent group. Aspiration amount was treated as a fixed effect and participant as a random effect. Marginal R^2 was used as a measure of effect size for aspiration amount [58].

A second binomial multilevel effects model was used to assess the relationship of trial volume on the presence/absence of an airway protective response after controlling for aspiration amount. Only 5 mL, 10 mL, 15 mL, and 90 mL volumes were included in this sub-analysis. Trial volume and aspiration amount were treated as fixed effects and participant was a random effect. Likelihood ratio tests compared this full model to a model containing aspiration amount as the only fixed effect to determine if trial volume significantly predicted the presence of an airway protective response above and beyond aspiration amount. Likelihood ratios were used as a measure of effect size from the model comparison.

Lastly, binomial multilevel models were used to assess the relationship of disease diagnosis and disease duration on the presence of an airway protective response, after controlling for aspiration amount. This sub-analysis was originally limited to records containing information on disease duration from symptom onset and records for participants with a singular diagnosis of either PD, PSP, multiple systems atrophy, or SCA. However, because statistical models would not converge when including people with multiple systems atrophy due to a limited sample size ($n = 4$), people with multiple systems atrophy were ultimately excluded in this sub-analysis. Disease diagnosis, disease duration, and aspiration amount were treated as fixed effects with participant as a random effect. Three model comparisons were made. First, a full model containing disease duration and aspiration

amount fixed effects was compared to a model containing only aspiration amount. Second, a full model containing disease diagnosis and aspiration amount fixed effects was compared to a model containing only aspiration amount. And lastly, a full model containing disease duration, disease diagnosis, and aspiration amount fixed effects was compared to a model containing only aspiration amount. Likelihood ratios were used as a measure of effect size from each model comparison.

All analyses were performed in R version 3.6.3 [59]. All multilevel models were run using the *lme4* package. A familywise alpha was set at $p < 0.05$. A Holm-Bonferroni adjustment was used to correct for three model comparisons. Unadjusted p values are reported, with text denoting which comparisons reached statistical significance after correcting for multiple comparisons. As a soft interpretation guideline, likelihood ratio (LR) effect sizes were considered "small" if $|2| \leq LR < |5|$, "moderate" if $|5| \leq LR < |10|$, and "large" if $\geq |10|$ [60]. Predicted probabilities were calculated for each significant statistical model using the *ggmeans* function. Predicted probabilities were used to estimate the probability of having an airway protective response as a function of each predictor variable. Predicted probabilities for trial volume were completed by adjusting for mean aspiration amount. Predicted probabilities for disease diagnosis were calculated by adjusting for mean aspiration amount and mean disease duration. Predicted probabilities for disease duration were calculated by adjusting for mean aspiration amount and the weighted average for each disease diagnosis.

Results

Demographics

A total of 422 swallowing trials with aspiration from 86 participants were included in the analysis (Tables 1, 2). One hundred fifty-one swallows exhibited an airway protective response and 271 swallows exhibited no airway protective response. Of the 86 participants who aspirated, 59 (68.6%) aspirated more than once. Of the 59 participants who aspirated more than once, four (6.7%) exhibited an airway protective response for all aspiration events, 16 (27.1%) never exhibited an airway protective response, and 39 (66.1%) exhibited airway protective responses on some but not all aspiration events.

Table 2 Descriptive Statistics of Participant Demographics

	Sex (count)	Age (years)	Disease duration (months)
PD ($n = 59$)	Males = 45 Females = 14	Mean = 70.0 SD = 8.9 Range = 48–88	Mean = 112.2 SD = 81.6 Range = 6–368
PSP ($n = 13$)	Males = 10 Females = 3	Mean = 70.2 SD = 6.5 Range = 53–81	Mean = 58.3 SD = 45.1 Range = 12–138
MSA ($n = 4$)	Males = 3 Females = 1	Mean = 58.5 SD = 2.9 Range = 56–65	Mean = 67.5 SD = 20.6 Range = 37–82
Ataxia ($n = 10$)	Males = 6 Females = 4	Mean = 53.6 SD = 11.0 Range = 36–67	Mean = 186.6 SD = 130.4 Range = 92–468

PD Parkinson's disease, *PSP* Progressive Supranuclear Palsy, *MSA* Multiple Systems Atrophy, *Ataxia* Cerebellar Ataxia, SD standard deviation

Aspiration Amount

Aspirated swallows with no airway protective response exhibited a median aspiration amount of 9% (interquartile range: 6–16), indicating that 9% of the subglottic shelf was covered with subglottic (aspirate) residue. Aspirated swallows with an airway protective response had a median aspiration amount of 22% (interquartile range: 12–45) (Fig. 1). This difference in aspiration amount represented a large, significant relationship between aspiration amount and the presence of an airway protective response ($p < 0.001$, marginal $R^2 = 0.467$; L.R. = 116.7), such that swallows with a greater amount of aspiration were more likely to have an airway protective response compared to swallows with a smaller amount of aspiration (Table 3). There was a 19% probability (95% CI 0.13–0.27) that an aspiration amount of 10% would elicit an airway protective response, a 70% probability (95% CI 0.56–0.80) that an aspiration amount of 30% would elicit an airway protective response, an 88% probability (95% CI 0.75–0.94) that an aspiration amount of 40% would elicit

Table 1 Descriptive statistics of VASES rating of aspiration amount

	VASES rating of aspiration amount (%)					
	Min	25th percentile	50th percentile	Mean (SD)	75th percentile	Max
All swallows ($n = 422$)	1	7	13	18.7 (17.9)	23	92
Response ($n = 151$)	4	12	22	29.8 (22.1)	45	92
No response ($n = 271$)	1	6	9	12.5 (11.2)	16	45

min minimum, *SD* standard deviation, *max* maximum

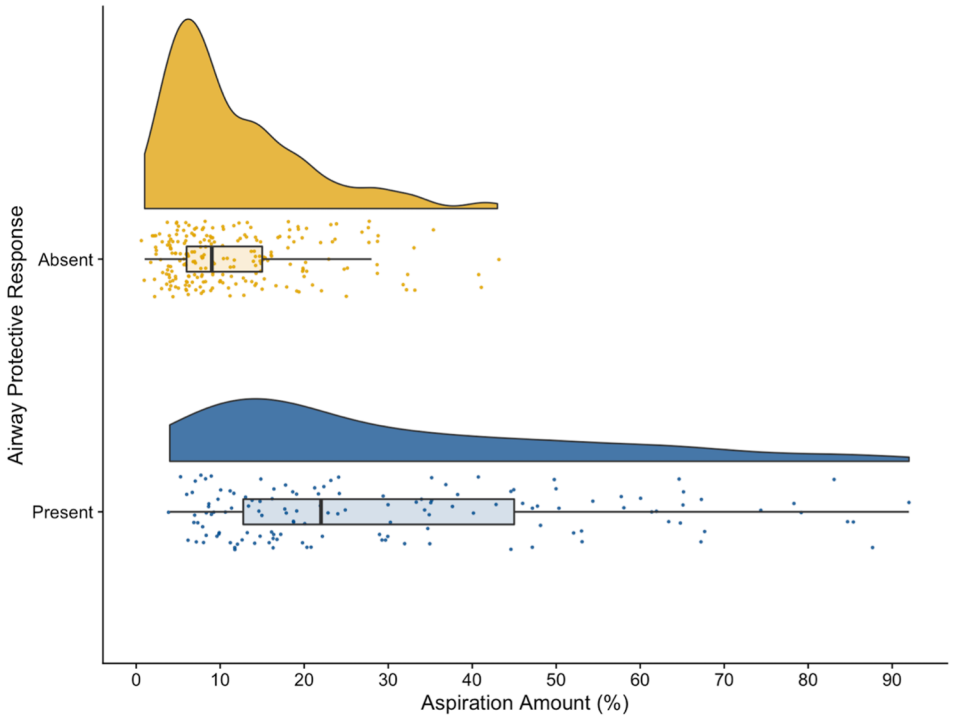

Fig. 1 Differences in aspiration amount, expressed as a percentage of the subglottis shelf surface area, between swallows with (bottom; PAS 6 and 7) and without (top; PAS 8) an airway protective response

Table 3 Effects of Aspiration Amount on Airway Protective Response

Predictors	Odds ratios	95% CI	*p*
Airway protective response			
(intercept)	0.08	0.04–0.15	<0.001
Aspiration amount (%)	1.12	1.09–1.16	<0.001*
Random effects			
σ^2	3.29		
$\tau_{00\ participant}$	1.21		
ICC	0.27		
$N_{participant}$	84		
Observations	364		
Effect size			
Marginal R^2	0.467		
Conditional R^2	0.610		

Unadjusted *p* values are presented in the table above, with "*" denoting a significant *p* value after correcting for multiple comparisons; σ^2 is the within-person residual variance; $\tau_{00\ participant}$ is the between-person variance in intercepts; intraclass correlation coefficient (ICC) is the proportion of variance explained by between-person differences; marginal R^2 is the variance explained only by the fixed effects (i.e., aspiration amount); conditional R^2 is the variance explained by both the fixed and random effects

an airway protective response, a 96% probability (95% CI 0.88–0.99) that an aspiration amount of 50% would elicit an airway protective response, and a 99% probability (95% CI 0.94–1.00) that an aspiration amount of 60% would elicit an airway protective response (Fig. 2).

Trial Volume

Eighty-five 5 mL trials, fifty-seven 10-mL trials, thirty-two 15 mL trials, and eighty-three 90 mL trials were analyzed. Median aspiration amount for 5 mL trial volumes was 13% (range: 4%–92%), for 10 mL trial volumes was 10% (range: 2%–88%), for 15 mL trial volumes was 15% (range: 2%–83%), and for 90 mL trial volumes was 11% (range: 1%–65%). Trial volume was not significantly related to the presence of an airway protective response after controlling for aspiration amount, $p = 0.428$, L.R. = 2.770 (Table 4).

Neurologic Disease Diagnosis and Duration

There was a small, significant relationship between disease duration and the presence of an airway protective response after controlling for aspiration amount, $p = 0.036$, L.R. = 4.351. For every month of having a neurologic diagnosis (i.e., having longer disease durations), people were 1% less likely to have airway protective response ($p = 0.040$; O.R. = 0.99; Table 5). When adjusting for this sub-analysis' mean aspiration amount of 18.9%, there was a 48% probability (95% CI 0.32–0.65) that a person with a disease duration of 60 months would exhibit an airway protective response, a 42% probability (95% CI 0.29–0.57) that a person with a disease duration of 120 months would exhibit an airway protective response, and a 30% probability (95% CI 0.29–0.57) that a person with a disease duration of 240 months would exhibit an airway protective response (Fig. 3).

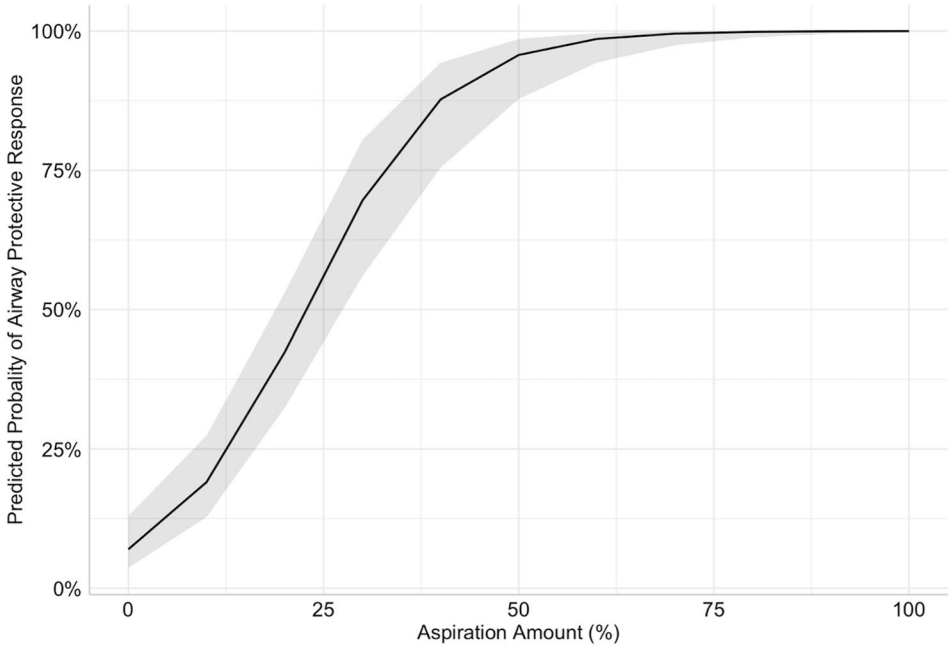

Fig. 2 Predicted probability slope of airway protective response as a function of aspiration amount

Disease diagnosis was not significantly related to the presence of an airway protective response, $p = 0.103$, L.R. = 4.535 (Table 6). Furthermore, the combination of disease duration and disease diagnosis was not significantly related to the presence of an airway protective response after controlling for aspiration amount, $p = 0.081$, L.R. = 6.782 (Table 7).

Discussion

This study examined how aspiration amount, trial volume, disease duration, and disease diagnosis were related to the presence of an aspirated-related airway protective response in people with neurologic disease. Results from this study found that the presence of an aspiration-related airway protective response (cough or throat clear) was significantly related to aspiration amount and disease duration, but not trial volume or disease diagnosis. Specifically, the probability of the presence of a cough or throat clear increased as aspiration amount increased or with shorter duration of their neurologic diagnosis. The presence of a cough or throat clear in response to aspiration was found to be variable within the majority of people who aspirated on more than one swallow—a finding consistent with previous work by Miles and colleagues in hospitalized patients with dysphagia [25].

The large, significant relationship between aspiration amount and the presence of an airway protective response following aspiration is a clinically important finding for both evaluation and treatment purposes. From an evaluation standpoint, knowing that aspiration amount is significantly related to the presence of a cough or throat clear provides valuable insight regarding when silent versus non-silent aspiration may be expected. For example, the present data suggest that a cough response would not be typically expected in a person with PD, SCA, or PSP if aspiration of a thin liquid trial covered less than 10% of the subglottic shelf. This is because an aspiration amount of 9% or less has less than a 19% probability of triggering a cough response. However, a cough response would be typically expected in these patient populations if 40% or more of the subglottic shelf was covered with aspirate residue. This is because an aspiration amount of 40% has at least an 88% probability of triggering an airway protective response. Understanding that the presence of a cough or throat clear is highly dependent on aspiration amount in people with neurologic disease may assist clinicians in determining if sensory dysfunction is impaired and contributing to compromised airway protection. However, future research is needed to more comprehensively determine how aspiration amount and airway protective responses relate to each other in healthy adults, in other populations with dysphagia, and across a variety of bolus properties.

Understanding that the presence of an airway protective response is related in part to aspiration amount is also important for accurately tracking therapeutic changes over time. In practice, clinicians and researchers often use maximum PAS scores to characterize level of swallowing impairment. The PAS describes the depth of and reaction to penetration and aspiration but does not provide information related to the amount of penetration and aspiration. Higher PAS scores typically suggest worse airway protective function. However, without supplementing the PAS with ratings of aspiration amount, clinicians and researchers could be misguided in

Table 4 Effects of trial volume and aspiration amount on airway protective responses

Airway protective response			
Comparison between full model and aspiration-amount only model			
Significance test p value			0.428
Likelihood ratio			2.770
Predictors	Odds ratios	95% CI	p
Full model (intercept; 5 mL)	0.17	0.07–0.45	< 0.001
Aspiration amount (%)	1.11	1.11–1.16	< 0.001*
10 mL	0.52	0.18–1.47	0.217
15 mL	0.48	0.15–1.51	0.212
90 mL	0.52	0.20–1.36	0.183
Random effects			
σ^2	3.29		
$\tau_{00\ participant}$	0.78		
ICC	0.19		
$N_{participant}$	74		
Observations	231		
Effect size			
Marginal R^2	0.469		
Conditional R^2	0.571		
Predictors	Odds ratios	95% CI	p
Pairwise comparisons			
5 mL–10 mL	1.91	1.13–3.25	0.217
5 mL–15 mL	2.06	1.15–3.69	0.212
5 mL–90 mL	1.93	1.17–3.17	0.182
10 mL–15 mL	1.07	0.55–2.06	0.911
10 mL–90 mL	1.00	0.61–1.66	0.988
15 mL–90 mL	0.93	0.51–1.70	0.912

5 mL trial volume reference group in the full model; unadjusted p values are presented in the table above, with "*" denoting a significant p value after correcting for multiple comparisons; σ^2 is the within-person residual variance; $\tau_{00\ participant}$ is the between-person variance in intercepts; intraclass correlation coefficient (ICC) is the proportion of variance explained by between-person differences; marginal R^2 is the variance explained only by the fixed effects (i.e., aspiration amount); conditional R^2 is the variance explained by both the fixed and random effects

their diagnostic impressions when tracking changes over time. For example, if a patient's maximum PAS score increased from a seven (aspiration with an ineffective cough response) to an eight (silent aspiration) over the course of therapy, then a patient's airway protective function may appear to have worsened. However, this change in PAS may represent an improvement in swallow function due in part to decreases in aspiration amount. For example, the aspiration amount may have decreased from 40% pre-therapy (which has a high likelihood of eliciting a cough response/PAS 7) to 5% post-therapy (which has a low likelihood of eliciting a cough response/PAS 8). This post-therapy reduction in aspiration amount would be a significant marker for improved swallow function and would likely explain why the patient had an absent cough response.

The present study also examined how trial volume, disease duration, and disease diagnosis were related to airway protective response. As hypothesized, no significant relationship was observed between the presence of an airway protective response and trial volume after adjusting for aspiration amount in these participants with neurologic disease. Disease duration was found to have a small but significant relationship with the presence of an airway protective response after controlling for aspiration amount. Specifically, as disease duration increased, the likelihood of producing a cough or throat clear in response to aspiration decreased. The cause for this decline in airway protective responsiveness is unknown, but may be related to sensory changes at both the peripheral [61, 62] and central [63] nervous system levels.

Contrary to our original hypothesis, disease diagnosis was not found to be significantly related to aspiration-related airway protective responsiveness. Descriptively, the median predicted probability of having an airway protective response was nearly double that for people with progressive

Table 5 Effects of disease duration and aspiration amount on airway protective response

Airway protective response			
Model comparison between full model and aspiration-amount only model			
Significance test p value			0.036*
Likelihood ratio			4.351
Predictors (full model)	Odds ratios	95% CI	p
Full model			
(intercept)	0.16	0.07–0.40	< 0.001
Aspiration amount (%)	1.12	1.08–1.16	< 0.001*
Disease duration (months)	0.99	0.99–1.00	0.040*
Random effects			
σ^2	3.29		
$\tau_{00\ participant}$	0.85		
ICC	0.21		
$N_{participant}$	73		
Observations	323		
Effect size			
Marginal R^2	0.516		
Conditional R^2	0.615		

Unadjusted p values are presented in the table above, with "*" denoting a significant p value after correcting for multiple comparisons; σ^2 is the within-person residual variance; $\tau_{00\ participant}$ is the between-person variance in intercepts; intraclass correlation coefficient (ICC) is the proportion of variance explained by between-person differences; marginal R^2 is the variance explained only by the fixed effects (i.e., aspiration amount); conditional R^2 is the variance explained by both the fixed and random effects

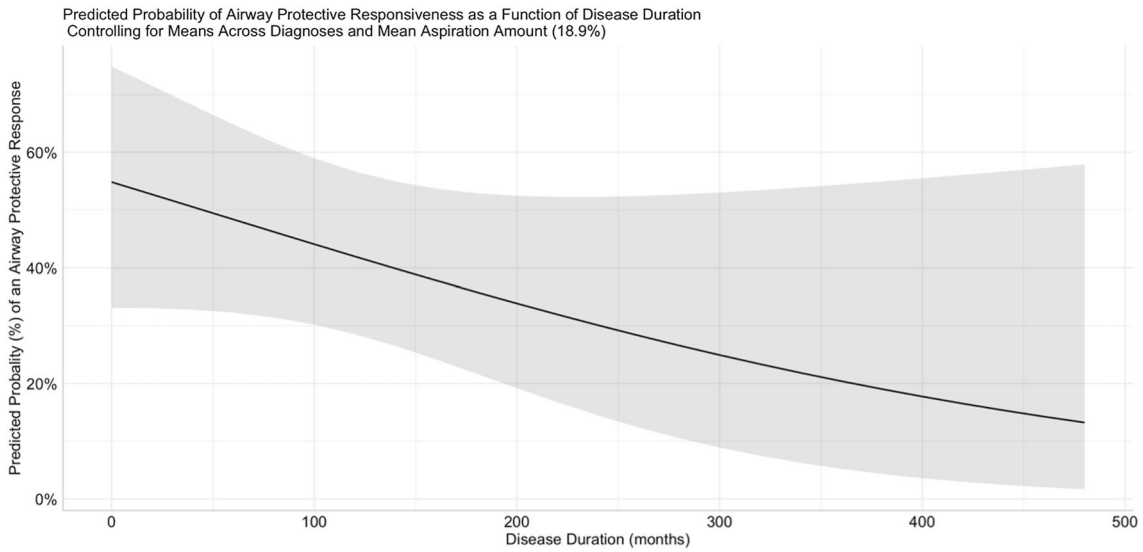

Fig. 3 Predicted probability of airway protective response across disease diagnoses adjusting for a mean disease duration of 10.5 years and a mean aspiration amount of 18.9%

supranuclear palsy compared to people with Parkinson's disease. While it is possible that the lack of a statistically significant finding related to disease diagnosis may be a true negative finding, this finding may also be due to a lack of statistical power in the presence of heightened heterogeneity, as well as small sample sizes for participants with spinocerebellar ataxia and progressive supranuclear palsy. Therefore, a sensitivity power analysis was performed to estimate the smallest effect size detectable with 80% power an alpha of 0.05, and the data from this study. This revealed the present study was powered to detect a minimum effect size of ≥ 5.98 between the SCA and PD groups, ≥ 10.27

Table 6 Effects of disease diagnosis, and aspiration amount on airway protective response

Airway protective response			
Model comparison between full model and aspiration-amount only model			
Significance test p value			0.103
Likelihood ratio			4.535
Predictors (full model)	Odds ratios	95% CI	p
Full model (intercept; ataxia)	0.04	0.01–0.16	< 0.001
Aspiration amount (%)	1.12	1.08–1.15	< 0.001*
Parkinson's disease (PD)	2.14	0.54–8.59	0.281
Progressive supranuclear palsy (PSP)	6.55	1.15–37.44	0.035
Random effects			
σ^2	3.29		
$\tau_{00\ participant}$	0.71		
ICC	0.18		
$N_{participant}$	73		
Observations	323		
Effect size			
Marginal R^2	0.510		
Conditional R^2	0.597		

Predictors	Odds ratios	95% CI	p
Pairwise comparisons			
Ataxia–PD	2.14	0.54–8.59	0.281
Ataxia–PSP	6.55	1.15–37.44	0.035
PD–PSP	3.05	1.63–5.72	0.074

Cerebellar ataxia is the referent group for disease diagnosis in the full model; unadjusted p values are presented in the table above, with "*" denoting a significant p value after correcting for multiple comparisons; σ^2 is the within-person residual variance; $\tau_{00\ participant}$ is the between-person variance in intercepts; intraclass correlation coefficient (ICC) is the proportion of variance explained by between-person differences; marginal R^2 is the variance explained only by the fixed effects (i.e., aspiration amount); conditional R^2 is the variance explained by both the fixed and random effects

between the SCA and PSP groups, and ≥ 5.52 between the PD and PSP groups. Therefore, this sensitivity power analysis revealed that our data and study design was underpowered to detect smaller effects of medical diagnosis on airway protective response. Therefore, additional research is needed with larger sample sizes across diagnoses to determine whether an effect exists with high certainty.

This study used FEES to estimate aspiration amount, which presents unique advantages and limitations. First, FEES has been found to be the most sensitive assessment technique to evaluate pharyngeal functional swallowing outcomes (pharyngeal residue, penetration, and aspiration) [54]. This makes it an ideal imaging exam to answer the present research question. However, the potential influence of transnasal laryngoscopy on the up- or down-regulation of airway protective responses is unknown. We attempted to mitigate this by not using topical nasal anesthetics or vasoconstrictors. Despite this, it is possible the present findings may not generalize to swallowing conditions without a flexible endoscope in place. Furthermore, the axial viewing plane of FEES is such that some amount of aspiration along the posterior edge of the subglottis or deep within the trachea may have been missed. Additionally, because endoscopic whiteout typically obliterates visualization of a portion of the pharyngeal phase of swallowing, some aspiration events may have been missed 'during' the swallow. Therefore, future research may consider exploring how aspiration amount is related to airway protective response using other imaging techniques such as videofluoroscopy whereby the posterior and inferior tracheal margins, and the entire pharyngeal phase of swallowing, are visualized. However, prior to completing such research, it would be important to first examine how bolus area as measured during videofluoroscopy relates to stimulated subglottic surface area. It would also be important to examine the effect of liquid type (water vs. barium/radiopaque liquids) on airway protective response, given that the chemosensory properties of liquids may differentially elicit airway protective responses. For example, capsaicin, citric acid, and fog activate different sensory receptors during reflex cough testing [64], and differences in the frequency of silent aspiration have been observed when swallowing water vs. milk (without

Table 7 Effects of disease duration, disease diagnosis, and aspiration amount on airway protective response

Airway protective response			
Model comparison between full model and aspiration-amount only model			
Significance test p value			0.081
Likelihood ratio			6.782
Predictors	Odds ratios	95% CI	p
Full model (intercept; ataxia)	0.08	0.01–0.46	0.005
Aspiration amount (%)	1.12	1.08–1.15	< 0.001*
Symptom duration (months)	1	0.99–1.00	0.145
Parkinson's disease (PD)	1.67	0.40–6.92	0.478
Progressive supranuclear palsy (PSP)	4.02	0.64–25.40	0.139
Random effects			
σ^2	3.29		
$\tau_{00\ participant}$	0.65		
ICC	0.16		
$N_{participant}$	73		
Observations	323		
Effect size			
Marginal R^2	0.520		
Conditional R^2	0.599		
Predictors	Odds ratios	95% CI	p
Pairwise comparison			
Ataxia–PD	1.67	0.81–3.44	0.477
Ataxia–PSP	4.02	2.12–7.60	0.138
PD–PSP	2.40	1.27–4.54	0.168

Cerebellar ataxia is the referent group for disease diagnosis in the full model; σ^2 is the within-person residual variance; unadjusted p values are presented in the table above, with "*" denoting a significant p value after correcting for multiple comparisons; $\tau_{00\ participant}$ is the between-person variance in intercepts; intraclass correlation coefficient (ICC) is the proportion of variance explained by between-person differences; marginal R^2 is the variance explained only by the fixed effects (i.e., aspiration amount); conditional R^2 is the variance explained by both the fixed and random effects

controlling for aspiration amount) [34]. The present study also only examined the effects of aspiration amount on aspiration-related coughs and throat clears using thin liquid boluses. Therefore, future research should expand on the present findings by determining if similar relationships exist with boluses of other consistencies (e.g., purees and solid boluses), chemical compositions, and temperatures. Future research may also examine how speed of bolus transit and central sensory processing influence the presence or absence of a cough or throat clear.

Conclusions

Silent aspiration and the presence of an airway protective response were found to be highly dependent on the amount of liquid aspirated in participants with neurologic disease. Silent aspiration also appears to be influenced, albeit to a lesser extent, by the duration that a person has been living with a neurologic disease. Therefore, clinicians and researchers should consider including measures of aspiration amount and disease duration when documenting the presence of aspiration and when using other validated scales such as the PAS. Future research is needed to examine how the present findings generalize to healthy adults and other patient populations.

Declarations

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 prior to enrollment in this research study.

References

1. Won JH, Byun SJ, Oh BM, Kim HJ, Park SJ, Seo HG. Pneumonia risk and its associated factors in Parkinson's disease: a national database study. J Neurol Sci. 2020. https://doi.org/10.1016/j.jns.2020.116949.
2. Takizawa C, Gemmell E, Kenworthy J, Speyer R. A systematic review of the prevalence of oropharyngeal dysphagia in stroke, Parkinson's disease, Alzheimer's disease, head injury, and pneumonia. Dysphagia. 2016;31(3):433–41. https://doi.org/10.1007/s00455-016-9695-9.
3. Tomita S, Oeda T, Umemura A, et al. Impact of aspiration pneumonia on the clinical course of progressive supranuclear palsy: a retrospective cohort study. PLoS ONE. 2015. https://doi.org/10.1371/journal.pone.0135823.
4. Nath U, Thomson R, Wood R, et al. Population based mortality and quality of death certification in progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome). J Neurol Neurosurg Psychiatry. 2005;76:498–502. https://doi.org/10.1136/jnnp.2004.039370.
5. Takahashi N, Kikutani T, Tamura F, Groher M, Kuboki T. Videoendoscopic assessment of swallowing function to predict the future incidence of pneumonia of the elderly. J Oral Rehabil. 2012;39(6):429–37. https://doi.org/10.1111/j.1365-2842.2011.02286.x.
6. Marik PE. Aspiration pneumonitis and aspiration pneumonia. N Engl J Med. 2001;344(9):665–71.
7. Langmore SE, Terpenning MS, Schork A, et al. Predictors of aspiration pneumonia: how important is dysphagia? Dysphagia. 1998;13:69–81. https://doi.org/10.1007/PL00009559.
8. Bock JM, Varadarajan V, Brawley MC, Blumin JH. Evaluation of the natural history of patients who aspirate. Laryngoscope. 2017;127:S1–10. https://doi.org/10.1002/lary.26854.
9. Tomita S, Oeda T, Umemura A, et al. Video-fluoroscopic swallowing study scale for predicting aspiration pneumonia in Parkinson's disease. PLoS ONE. 2018;13(6): e0197608. https://doi.org/10.1371/journal.pone.0197608.
10. Seo ZW, Min JH, Huh S, Shin Y-I, Ko H-Y, Ko S-H. Prevalence and severity of dysphagia using videofluoroscopic swallowing study in patients with aspiration pneumonia. Lung. 2021;199(1):55–61. https://doi.org/10.1007/s00408-020-00413-7.
11. Kim JW, Choi H, Jung J, Kim HJ. Risk factors for aspiration pneumonia in patients with dysphagia undergoing videofluoroscopic swallowing studies: a retrospective cohort study. Medicine (Baltimore). 2020;99(46): e23177. https://doi.org/10.1097/MD.0000000000023177.
12. Hollaar VRY, van der Putten GJ, van der Maarel-Wierink CD, et al. Nursing home-acquired pneumonia, dysphagia and associated diseases in nursing home residents: a retrospective, cross-sectional study. Geriatr Nurs (Minneap). 2017;38(5):437–41. https://doi.org/10.1016/j.gerinurse.2017.02.007.
13. Akbar U, Dham B, He Y, et al. Incidence and mortality trends of aspiration pneumonia in Parkinson's disease in the United States, 1979–2010. Park Relat Disord. 2015;21(9):1082–6. https://doi.org/10.1016/j.parkreldis.2015.06.020.
14. Mehanna R, Jankovic J. Respiratory problems in neurologic movement disorders. Park Relat Disord. 2010;16(10):628–38. https://doi.org/10.1016/j.parkreldis.2010.07.004.
15. Rüb U, Brunt ER, Petrasch-Parwez E, et al. Degeneration of ingestion-related brainstem nuclei in spinocerebellar ataxia type 2, 3, 6 and 7. Neuropathol Appl Neurobiol. 2006;32(6):635–49. https://doi.org/10.1111/j.1365-2990.2006.00772.x.
16. Beach TG, Russell A, Sue LI, et al. Increased risk of autopsy-proven pneumonia with sex, season and neurodegenerative disease. medRxiv Prepr Serv Health Sci. 2021. https://doi.org/10.1101/2021.01.07.21249410.
17. Borders JC, Troche MS. Voluntary cough effectiveness and airway clearance in neurodegenerative disease. J Speech Lang Hear Res. 2021. https://doi.org/10.1044/2021_JSLHR-21-00308.
18. Troche MS, Brandimore AE, Godoy J, Hegland KW. A framework for understanding shared substrates of airway protection. J Appl Oral Sci. 2014;22(4):251–60. https://doi.org/10.1590/1678-775720140132.
19. Perry SE, Huckabee ML, Tompkins G, Milne T. The association between oral bacteria, the cough reflex and pneumonia in patients with acute stroke and suspected dysphagia. J Oral Rehabil. 2020;47(3):386–94. https://doi.org/10.1111/joor.12903.
20. Nakamori M, Imamura E, Kuwabara M, et al. Simplified cough test can predict the risk for pneumonia in patients with acute stroke. PLoS ONE. 2020;15(9): e0239590. https://doi.org/10.1371/journal.pone.0239590.
21. Bianchi C, Baiardi P, Khirani S, Cantarella G. Cough peak flow as a predictor of pulmonary morbidity in patients with dysphagia. Am J Phys Med Rehabil. 2012;91(9):783–8. https://doi.org/10.1097/PHM.0b013e3182556701.
22. Yamanda S, Ebihara S, Ebihara T, et al. Impaired urge-to-cough in elderly patients with aspiration pneumonia. Cough. 2008. https://doi.org/10.1186/1745-9974-4-11.
23. Niimi A, Matsumoto H, Ueda T, et al. Impaired cough reflex in patients with recurrent pneumonia. Thorax. 2003;58:152–3.
24. Nakashima T, Maeda K, Tahira K, et al. Silent aspiration predicts mortality in older adults with aspiration pneumonia admitted to acute hospitals. Geriatr Gerontol Int. 2018;18(6):828–32. https://doi.org/10.1111/ggi.13250.
25. Miles A, Mcfarlane M, Scott S, Hunting A. Cough response to aspiration in thin and thick fluids during FEES in hospitalized inpatients. Int J Lang Commun Disord. 2018;53(5):909–18. https://doi.org/10.1111/1460-6984.12401.
26. Donzelli J, Brady S, Wesling M, Craney M. Predictive value of accumulated oropharyngeal secretions for aspiration during video nasal endoscopic evaluation of the swallow. Ann Otol Rhinol Laryngol. 2003;112(5):469–75. https://doi.org/10.1177/000348940311200515.
27. Hafner G, Neuhuber A, Hirtenfelder S, Schmedler B, Eckel HE. Fiberoptic endoscopic evaluation of swallowing in intensive care unit patients. Eur Arch Oto-Rhino-Laryngol. 2008;265(4):441–6. https://doi.org/10.1007/s00405-007-0507-6.
28. Miles A, Moore S, McFarlane M, Lee F, Allen J, Huckabee ML. Comparison of cough reflex test against instrumental assessment of aspiration. Physiol Behav. 2013;118:25–31. https://doi.org/10.1016/j.physbeh.2013.05.004.
29. Garon BR, Sierzant T, Ormiston C. Silent aspiration: results of 2,000 video fluoroscopic evaluations. J Neurosci Nurs. 2009;41(4):178–85.
30. Humbert IA, Sunday KL, Karagiorgos E, et al. Swallowing kinematic differences across frozen, mixed, and ultrathin liquid boluses in healthy adults: age, sex, and normal variability. J Speech Lang Hear Res. 2018;61(7):1544–59. https://doi.org/10.1044/2018_JSLHR-S-17-0417.
31. Allen JE, White CJ, Leonard RJ, Belafsky PC. Prevalence of penetration and aspiration on videofluoroscopy in normal individuals without dysphagia. Otolaryngol Head Neck Surg. 2010;142(2):208–13. https://doi.org/10.1016/j.otohns.2009.11.008.
32. Steele CM, Peladeau-Pigeon M, Barbon CAE, et al. Reference values for healthy swallowing across the range from thin to extremely thick liquids. J Speech Lang Hear Res. 2019;62(5):1338–63. https://doi.org/10.1044/2019_JSLHR-S-18-0448.
33. Mancopes R, Gandhi P, Smaoui S, Steele CM. Which physiological swallowing parameters change with healthy aging? OBM Geriatr. 2021. https://doi.org/10.21926/obm.geriatr.2101153.
34. Butler SG, Stuart A, Markley L, Feng X, Kritchevsky SB. Aspiration as a function of age, sex, liquid type, bolus volume, and bolus

delivery across the healthy adult life span. Ann Otol Rhinol Laryngol. 2018;127(1):21–32. https://doi.org/10.1177/0003489417742161.
35. Jardine M, Miles A, Allen J, Leonard R. Quantifying post-swallow residue in healthy aging. Perspect ASHA Spec Interes Groups. 2020;5(6):1657–65. https://doi.org/10.1044/2020_PERSP-20-00087.
36. Molfenter SM, Lenell C, Lazarus CL. Volumetric changes to the pharynx in healthy aging: consequence for pharyngeal swallow mechanics and function. Dysphagia. 2019;34(1):129–37. https://doi.org/10.1007/s00455-018-9924-5.
37. Garand KL, Hill EG, Amella E, Armeson K, Brown A, Martin-Harris B. Bolus airway invasion observed during videofluoroscopy in healthy, non-dysphagic community-dwelling adults. Ann Otol Rhinol Laryngol. 2019. https://doi.org/10.1177/0003489419826141.
38. Butler SG, Stuart A, Kemp S. Flexible endoscopic evaluation of swallowing in healthy young and older adults. Ann Otol Rhinol Laryngol. 2009;118(2):99–106.
39. Butler SG, Clark H, Baginski SG, Todd JT, Lintzenich C, Leng X. Computed tomography pulmonary findings in healthy older adult aspirators versus nonaspirators. Laryngoscope. 2014;124:494–7. https://doi.org/10.1002/lary.24284.
40. Butler SG, Stuart A, Case LD, Rees C, Vitolins M, Kritchevsky SB. Effects of liquid type, delivery method, and bolus volume on penetration-aspiration scores in healthy older adults during flexible endoscopic evaluation of swallowing. Ann Otol Rhinol Laryngol. 2011;120(5):288–95. https://doi.org/10.1177/000348941112000502.
41. Butler SG, Stuart A, Leng X, Rees C, Williamson J, Kritchevsky SB. Factors influencing aspiration during swallowing in healthy older adults. Laryngoscope. 2010;120:2147–52. https://doi.org/10.1002/lary.21116.
42. Foote AG, Thibeault SL. Sensory innervation of the larynx and the search for mucosal mechanoreceptors. J Speech Lang Hear Res. 2021;64(2):371–91. https://doi.org/10.1044/2020_JSLHR-20-00350.
43. Gescheider GA, Güçlü B, Sexton JL, Karalunas S, Fontana A. Spatial summation in the tactile sensory system: probability summation and neural integration. Somatosens Mot Res. 2005;22(4):255–68. https://doi.org/10.1080/08990220500420236.
44. Perry SE, Troche MS. Dual tasking influences cough sensorimotor outcomes in healthy young adults. J Speech Lang Hear Res. 2019;62(9):3596–606. https://doi.org/10.1044/2019_JSLHR-H-19-0122.
45. Perry SE, Troche MS. Dual tasking influences cough reflex outcomes in adults with Parkinson's disease: a controlled study. Dysphagia. 2021;36(6):959–73. https://doi.org/10.1007/s00455-020-10223-x.
46. Rajappa AT. Psychophysical Evaluation of Descriptors and Tools for Measurement of Urge-to-Cough Sensation in Healthy Young Adults (HYA). 2019.
47. Monroe MD, Manco K, Bennett R, Huckabee ML. Citric acid cough reflex test: Establishing normative data. Speech Lang Hear. 2014;17(4):216–24. https://doi.org/10.1179/2050572814Y.0000000041.
48. Vovk A, Bolser DC, Hey JA, et al. Capsaicin exposure elicits complex airway defensive motor patterns in normal humans in a concentration-dependent manner. Pulm Pharmacol Ther. 2007;20(4):423–32. https://doi.org/10.1016/j.pupt.2006.11.006.
49. Imoto Y, Koji MAA, Osawa Y, Sunaga H, Fujieda S. Cough reflex induced by capsaicin inhalation in patients with dysphagia. Acta Otolaryngol. 2010;131(1):96–100. https://doi.org/10.3109/00016489.2010.516013.
50. Ebihara S, Saito H, Kanda A, et al. Impaired efficacy of cough in patients with Parkinson disease. Chest. 2003;124(3):1009–15. https://doi.org/10.1378/chest.124.3.1009.
51. Leder SB, Suiter DM, Green BG. Silent aspiration risk is volume-dependent. Dysphagia. 2011;26:304–9. https://doi.org/10.1007/s00455-010-9312-2.
52. Borders JC, Sevitz JS, Curtis JA, Vanegas-Arroyave N, Troche MS. Sensorimotor cough dysfunction is prevalent and pervasive in progressive supranuclear palsy. Mov Disord. 2021;36(11):2624–33. https://doi.org/10.1002/mds.28707.
53. Nóbrega AC, Rodrigues B, Melo A. Is silent aspiration a risk factor for respiratory infection in Parkinson's disease patients? Park Relat Disord. 2008;14(8):646–8. https://doi.org/10.1016/j.parkreldis.2007.12.007.
54. Giraldo-Cadavid LF, Leal-Leaño LR, Leon-Basantes GA, et al. Accuracy of endoscopic and videofluoroscopic evaluations of swallowing for oropharyngeal dysphagia. Laryngoscope. 2017;127(9):2002–10. https://doi.org/10.1002/lary.26419.
55. Curtis JA, Borders JC, Perry SE, Dakin AE, Seikaly ZN, Troche MS. Visual Analysis of Swallowing Efficiency and Safety (VASES): a standardized approach to rating pharyngeal residue, penetration, and aspiration during FEES. Dysphagia. 2021. https://doi.org/10.1007/s00455-021-10293-5.
56. Curtis JA, Borders JC, Troche MS. Visual Analysis of Swallowing Efficiency and Safety (VASES): Establishing criterion-referenced validity and concurrent validity. Am J Speech-Lang Pathol. 2022. https://doi.org/10.1044/2021_ajslp-21-00116.
57. Rosenbek JC, Robbins J, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11(2):93–8.
58. Lorah J. Effect size measures for multilevel models: definition, interpretation, and TIMSS example. Large-Scale Assess Educ. 2018. https://doi.org/10.1186/s40536-018-0061-2.
59. R Core Team. R: A language and environment for statistical computing. *R Found Stat Comput*. 2019:115–124. https://doi.org/10.1016/j.dendro.2008.01.002
60. McGee S. Simplifying likelihood ratios. J Gen Intern Med. 2002;17(8):647–50.
61. Mu L, Sobotka S, Chen J, et al. Alpha-synuclein pathology and axonal degeneration of the peripheral motor nerves innervating pharyngeal muscles in Parkinson disease. J Neuropathol Exp Neurol. 2013;72(2):119–29.
62. Mu L, Sobotka S, Chen J, et al. Altered pharyngeal muscles in Parkinson disease. J Neuropathol Exp Neurol. 2012;71(6):520–30. https://doi.org/10.1097/NEN.0b013e318258381b.
63. Conte A, Khan N, Defazio G, Rothwell JC, Berardelli A. Pathophysiology of somatosensory abnormalities in Parkinson disease. Nat Rev Neurol. 2013;9(12):687–97. https://doi.org/10.1038/nrneurol.2013.224.
64. Mazzone SB. An overview of the sensory receptors regulating cough. Cough. 2005;1(2):1–9. https://doi.org/10.1186/1745-9974-1-2.

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