RESEARCH ARTICLE

Rehabilitating Cough Dysfunction in Parkinson's Disease: A Randomized Controlled Trial

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ABSTRACT: Background: Disorders of airway protection (cough and swallowing) are pervasive in Parkinson's disease (PD) resulting in a high incidence of aspiration pneumonia and death. However, there are no randomized controlled trials comparing strength and skill-based approaches to improve airway protection in PD.
Objectives: The aim of this study was to compare expiratory muscle strength training (EMST) and sensorimotor training for airway protection (smTAP) to improve cough-related outcomes in people with PD.
Methods: Participants with PD and dysphagia were recruited for this prospective phase II randomized-blinded controlled clinical trial. Participants completed baseline assessment, 5 weeks of EMST or smTAP, and a post-training assessment. Primary outcome measures included maximum expiratory pressure (MEP) and voluntary cough peak expiratory flow rate (PEFR). Mixed effects models were used to assess the effects of EMST and smTAP on outcomes.
Results: A total of 65 participants received either EMST ($n = 34$) or smTAP ($n = 31$). MEP improved from pre- to post-treatment for smTAP ($P < 0.001$, $d = 0.19$) and EMST ($P < 0.001$, $d = 0.53$). Voluntary PEFR increased from pre- to post-treatment for smTAP ($P < 0.001$, $d = 0.19$) and EMST ($P < 0.001$, $d = 0.06$). Moreover, reflex cough PEFR ($P < 0.001$, $d = 0.64$), reflex cough expired volume ($P < 0.001$, $d = 0.74$), and urge to cough ($P = 0.018$, $OR = 2.70$) improved for the smTAP group but not for the EMST group.
Conclusions: This clinical trial confirmed the efficacy of smTAP to improve reflex and voluntary cough function, above and beyond EMST, the current gold standard. © 2022 International Parkinson and Movement Disorder Society.

Key Words: dysphagia; dystussia; rehabilitation; Parkinson's disease; cough

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By 2030 Parkinson's disease (PD) is projected to affect 9 million people globally.[1] Airway protective disorders, including swallowing (dysphagia) and cough (dystussia) disorders, are a pervasive consequence of PD and result in severe health consequences, including malnutrition, dehydration, and aspiration pneumonia,[2-5] negatively impacting quality of life[2,3] and increasing caregiver burden.[6-8] In fact, aspiration pneumonia is the leading cause of death in individuals with PD,[4,5,9-11] and this

cannot be explained by disordered swallowing alone.[12-14] People with PD have multifactorial deficits of airway protection, including the need for more intense cough stimuli to trigger a cough,[14,15] reductions in the perception of cough stimuli (ie, urge to cough [UTC]),[15,16] disordered voluntary control of cough,[17-19] and peripheral respiratory muscle weakness.[20-22] Furthermore, these cough impairments are often worse when patients have dysphagia.[14,16-18,23] Therefore, reducing adverse health effects and improving quality of life in PD should involve a comprehensive approach to rehabilitating airway protection, which includes targeting sensorimotor cough dysfunction.

Only expiratory muscle strength training (EMST) has been found to improve airway protection via randomized controlled trials (RCTs) in individuals with PD.[24,25] EMST is an exercise-based, treatment approach that uses a calibrated device with a one-way, spring-loaded valve to primarily overload the expiratory muscles. In PD, studies have shown that EMST improves maximum expiratory pressure, voluntary cough effectiveness,[26] swallowing safety and efficiency,[24,25] and swallowing-related quality of life.[24] Although PD can result in decreased muscle strength, the primary deficits are often in the motor organization for airway protection and a blunted perception of cough-inducing stimuli,[27] leading to reduced cough effectiveness to clear aspirated material.[14,28] Despite these deficits, people with PD can volitionally upregulate both reflex and voluntary cough functions.[29,30] These data led to the development of a cough training approach, namely sensorimotor training for airway protection (smTAP), that targets three key components to improve cough coordination for improved airway protection: (1) a cue for immediate enhancement of peak expiratory flow rate (PEFR) and (2) visual biofeedback in the presence of (3) a subthreshold level of a cough-inducing stimulus (ie, capsaicin). Several studies have started to define the feasibility and effect of cough skill training approaches in PD and related disorders.[26,31,32]

There are no RCTs comparing the efficacy of strength and skill-based approaches for improving airway protection in PD. Therefore, the aim of this study was to compare the efficacy of EMST and smTAP for improved airway protection in individuals with PD and dysphagia. We hypothesized that both treatments would result in improvements in cough, with more robust improvements after smTAP.

Patients and Methods

Participants

Procedures were performed in accordance with ethical standards approved by the institutional review boards of the two study sites: Teachers College, Columbia University (no.: 16-098) and the University of Florida (no.: IRB201601082); and the trial was registered with Clinicaltrials.gov (NCT02927691). Informed consent was obtained from all participants before enrollment in this study. Participants were recruited from Teachers College and the Columbia University Movement Disorders Division and the University of Florida Norman Fixel Institute for Neurological Diseases between November 2016 and March 2020. Participants were diagnosed with PD by a Movement Disorders Fellowship–trained neurologist using strict UK Brain Bank criteria.[33] Participants also met the following criteria: (1) dysphagia—defined as a Penetration-Aspiration Scale score >2 on at least one bolus trial seen during endoscopic and/or fluoroscopic swallowing assessments,[34] (2) dystussia—defined as a maximal voluntary cough PEFR <5 L/s, and (3) not actively receiving swallowing therapy. Exclusion criteria included (1) other neurological disorders, (2) head and neck cancer, (3) breathing disorders or diseases, (4) smoking in the past 5 years, (5) uncontrolled hypertension, and (6) difficulty complying due to neuropsychological dysfunction (ie, severe depression, dementia with a score of less than 23 on the Montreal Cognitive Assessment[35]). The target sample size of 60 participants (30 in each group) was determined based on a power analysis guided by data from an RCT investigating the effects of EMST to improve airway invasion in PD.[24] Specific to cough outcomes, assuming between-subject (SD [standard deviation] = 0.59) and within-subject (SD = 0.38) variability, based on pilot data on 16 individuals with PD,[36] a simulation-based power analysis showed that a sample size of 65 would provide 80% power to detect a post-treatment difference of 0.22 L/s between EMST and smTAP groups.

Study Design

Participants in this prospective phase II RCT were randomly assigned with allocation concealment to either the EMST or smTAP groups (Fig. 1). A simple computer-generated random allocation sequence was completed before study initiation, and allocation sequence was concealed from the investigators enrolling and assessing eligibility. Randomization was revealed sequentially after enrollment. No comment was made to participants about whether better outcomes were expected with either treatment. Participants were further randomly assigned to receive immediate or delayed training, where there was a 5-week wait-to-start followed by a second baseline. The delayed training group served to identify whether there were any potential improvements in primary outcomes with repeated assessment, which would confound treatment effects. Once treatment commenced, all participants received 5 weeks of intensive training, including weekly meetings with a trained study clinician, and 4 days of home

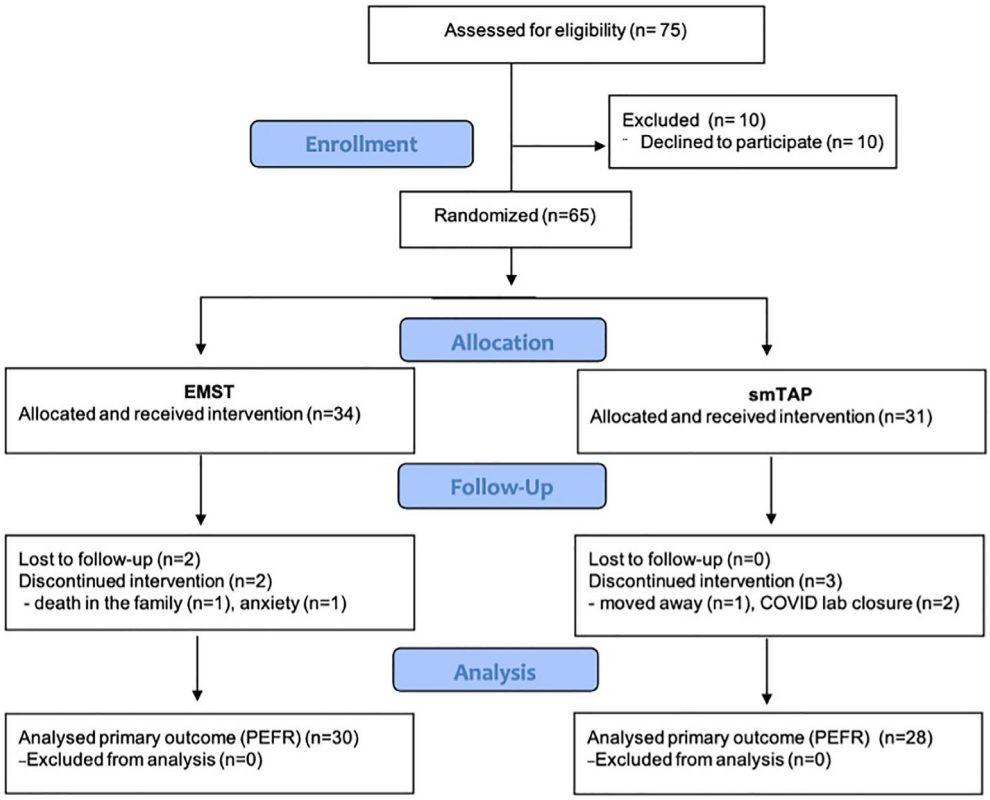

FIG. 1. CONSORT diagram outlining the flow of study participant recruitment, allocation, and follow-up for this randomized controlled trial. [Color figure can be viewed at wileyonlinelibrary.com]

practice each week. After the treatment, participants were seen for a post-training assessment.

Assessment Visits

The same assessment protocol was completed at pre- and post-treatment visits. Participants were tested 1 hour after the intake of their dopaminergic medications to ensure they were in a practically defined *on* state. The first assessment visit was also used to screen for inclusion criteria. Assessment visits were completed by trained research speech-language pathologists (SLPs) who were blinded to participant treatment group assignment and did not participate in treatment visits.

To assess voluntary and reflex cough function, participants were outfitted with a facemask covering the nose and mouth. The facemask was coupled to a pneumotachograph, a differential pressure transducer, and a side port with a one-way inspiratory valve for nebulizer connection. The nebulizer was a DeVilbuss T-piece connected to a dosimeter that delivered aerosolized solution during inspiration with a delivery duration of 2 seconds. The cough airflow signal was digitized (Power Lab Data Acquisition System, Colorado Springs, USA) and recorded (LabChart 8, ADInstruments, Inc.) to a computer.

Participants were seated for an initial 45 seconds of quiet breathing. They then completed a capsaicin challenge with three randomized blocks of 0, 50, 100, and 200 μM dissolved in a vehicle solution (80% physiological saline, 20% ethanol). They were instructed to "cough if you need to" before capsaicin or placebo (0 μM) delivery. The solution was administered upon detection of an inspired breath with at least 1-minute rest between each trial. After each trial, participants rated their UTC on a modified Borg rating scale, where 0 was no UTC and 10 was maximal UTC and provided information regarding participants' perceived magnitude of the cough-inducing stimuli. Participants were provided water to drink between trials. To assess voluntary cough function, participants were asked to "cough as if something went down the wrong pipe" without the presentation of any stimulus.

MEPs were obtained using a pressure manometer coupled to a mouthpiece. Nose clips were used to prevent nasal air escape. The participants were then instructed to inhale as deeply as possible, seal their lips and teeth around the mouthpiece, and blow into the manometer with maximal effort. Verbal encouragement was provided to the participants.

Treatments

All treatment visits were completed by trained research SLPs who were not involved in the assessment visits (Video S1; Fig. 2).

EMST

Participants in the EMST group used a calibrated EMST150 device (Fig. 2) with a one-way, spring-loaded pressure relief valve. The adjustable spring allowed for discrete changes in the valve blocking the flow of air until sufficient expiratory pressure was produced, thus modifying the physiologic load placed on the muscles. Once opened, air flowed through the device. Training targets were set at 75% of the participant's MEP. The pressure range of the device was from 30 to 150 cm H_2O. Participants were instructed to (1) occlude their nose with nose clips, (2) take a big breath in, and (3) blow as forcefully as possible into the device to open the valve. Participants completed 25 repetitions (5 sets of 5 repetitions) with the clinician.

smTAP

Participants in the smTAP group were seated at a computer with the same spirometry setup used for reflex cough testing. Given that the ultimate goal of treatment was to improve cough effectiveness during airway invasion, participants were presented with a background dose of subthreshold capsaicin, defined as a concentration that was half that of their baseline reflex cough threshold, to allow for training in the context of a sensation similar to airway invasion. After the presentation of the subthreshold sensory stimulus, participants were instructed to direct their attention to their UTC and "cough hard" to elicit a cough with sufficient intensity to hit a target line provided via real-time cough airflow visual biofeedback. The target line was set 25% above the maximum PEFR based on baseline reflex cough testing. Participants completed 25 repetitions (5 sets of 5 repetitions) of sequential volitional coughs with the clinician.

Home practice (Video S2): in addition to one therapy session per week with a research clinician, all participants completed 4 days of home practice, totaling 5 days of training per week. The home practice protocol was identical to the protocol described earlier for EMST (at 75% MEP). For smTAP, participants completed 25 repetitions (5 sets of 5 repetitions) of single volitional coughs using an analog peak flow meter and a target set 25% above baseline PEFR (Fig. 2). No capsaicin and no visual cough airflow biofeedback were used for the smTAP home practice. However, participants were able to visualize their PEFR at the conclusion of each cough using the analog peak flow meter to assess whether they had met their target PEFR. Participants were provided with written home practice instructions and a practice log to track adherence.

Data Analyses and Outcome Measures

All data analyses were completed by trained raters with experience in cough analysis who were blinded to participant identity, time point, and training group. Inter- and intra-rater reliability was completed on 20% of the data. Voluntary cough PEFR and MEP were selected as the primary treatment outcomes given that each was the central target of treatment for smTAP and EMST, respectively. In addition, voluntary cough PEFR served as the primary treatment outcome measure of cough effectiveness given that it has been found to be related to the ability to clear aspirate material from the airway.[37] PEFR was derived from cough waveforms obtained via voluntary cough spirometry and was

	EMST	smTAP
Primary Tx Target	Maximum Expiratory Pressure (MEP)	Voluntary Cough Peak Expiratory Flow Rate (PEFR)
Type of Training	Primarily strength-based	Primarily skill-based
Treatment Dose	5 sets of 5 breaths = 25 breaths	5 sets of 5 coughs = 25 coughs
Treatment Intensity	EMST @ 75% MEP	Voluntary coughs @ 25% above PEFR
Time Period	5 days a week – with clinician once per week and four days of independent home practice (both tx)	
Tx with Clinician	25 repetitions of EMST	25 coughs via spirometry with sub-threshold capsaicin and real-time visual biofeedback.
Home Program	25 repetitions of EMST (a)	25 coughs using a handheld peak flow meter (b)

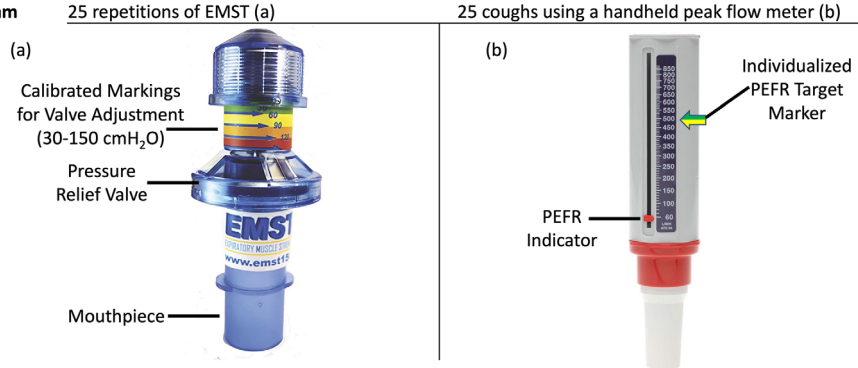

FIG. 2. Comparison of the two treatment (tx) approaches. Exercise devices used for home practice, including the expiratory muscle strength training (EMST) (left) and sensorimotor treatment for airway protection (smTAP [sensorimotor training for airway protection]) peak flow meter (right). [Color figure can be viewed at wileyonlinelibrary.com]

measured from the first cough in each cough epoch. MEP served as the primary treatment outcome measure of respiratory strength.[24,26,38] Three values within 10% of each other were targeted to achieve a representative sample of MEP scores.

Secondary outcomes included other measures of voluntary and reflex cough function and effectiveness. All cough airflow measures were derived from cough waveforms obtained via voluntary or reflex cough spirometry. The total number of coughs was counted for each cough epoch (CrTot) for both reflex and voluntary coughs and was used as a covariate and outcome measure. Reflex cough PEFR and voluntary and reflex cough expired volume (CEV) were measured from the first cough in each cough epoch. Reflex cough airflow measures were made from each trial of 200 μM capsaicin. The concentration of capsaicin that elicited the reliable two-cough response (Cr2) was recorded as the reflex cough threshold.[14,16] A reliable Cr2 was defined as at least two coughs produced within 30 seconds after the presentation of the stimulus in two of three trials of that concentration. UTC ratings were collected for each trial of capsaicin across concentrations.

Statistical Analyses

Multilevel models with main effects of treatment, time, and their two-way interaction were used. A random effect of participant was used to include multiple trials (eg, three trials of MEP at each time point). In the presence of an interaction, differences in the magnitude of change between groups, as well as changes within each group, were examined. For primary outcomes, separate models were performed for delayed to pre-training and pre-training to post-training cohorts. More specifically, for participants randomized to the delayed treatment group, MEP and voluntary cough PEFR were tested between delayed (first baseline) and pre-training (second baseline). For the active treatment phase, all outcomes were tested between pre-training (which was the second baseline for those in the delayed treatment group) and post-training. α was set at 0.05, and multiple pairwise comparisons were adjusted via Holm–Bonferroni corrections. Unadjusted *P*-values are presented in the text. Standardized effect sizes were computed by dividing mean difference by the error and random effect variance.[39] Single measure, absolute agreement intraclass correlation coefficients and weighted Cohen's kappa were used for cough airflow and number of coughs, respectively, for reliability.[40] Analyses were performed in R.[41]

Data Sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Participants

Seventy-five participants were recruited and screened (Fig. 1). Ten participants declined to participate in the study; therefore, 65 participants were randomly assigned to either the EMST ($n = 34$) or smTAP ($n = 31$) group. Fifteen and 13 participants were randomly allocated to the delayed baseline in EMST and smTAP groups, respectively. A total of 30 participants completed the study in the EMST group and 28 in the smTAP group. The participants were recruited between January 2017 and February 2020, and the last participant completed the study in March 2020. Dropout rate was calculated at 11%, including participants who discontinued due to COVID-19 laboratory closure (Fig. 1). A decision was made to close the study several months into the COVID-19 pandemic given the proximity to the target sample and to avoid confounding factors introduced through recruitment of participants after the pandemic. After closure of participant enrollment and blind rating of airway invasion utilizing strict criteria to maximize reliability of visuo-perceptual measures (ie, VASES42 [visual analysis of swallowing efficiency and safety]), three participants were found to have maximum Penetration-Aspiration Scale scores of 1 or 2 (Table 1). A review of additional measures (swallowing-related quality of life[43] [SWAL-QOL], functional oral intake scale (FOIS),[44] residue,[42] and cough outcomes) was completed to confirm the participants had dysphagia. All three participants had PEFR values well below inclusion cutoff (range: 3.06–3.44) and SWAL-QOL scores, indicating complaints of dysphagia and significant impact of swallowing symptoms on their quality of life. One of the participants was on a modified diet. Therefore, the determination was made to include them in this analysis that focuses on cough outcomes. Return rates for home training logs were similar between the two training groups, and treatment adherence rates were high (Table 1). No adverse events, including laryngeal pathology, were reported or endoscopically observed during the study. Both groups demonstrated similar demographic characteristics, including age, duration from symptom onset, and disease severity (Table 1). All 65 participants were analyzed with intent-to-treat statistical analyses.

Reliability

For inter-rater reliability, estimates were 0.90 for voluntary cough PEFR (95% CI [confidence interval]: 0.85–0.93), 0.82 for reflex cough PEFR (95% CI: 0.77–0.86), 0.93 for voluntary cough CEV (95% CI: 0.90–0.95), 0.81 for reflex cough CEV (95% CI: 0.975–0.85), 0.99 for voluntary CrTot (95% CI: 0.99–0.99), and 0.93 for reflex CrTot (95% CI: 0.93–0.93).

TABLE 1 *Participant demographics*

Measure	EMST (n = 34)	smTAP (n = 31)
Age (y)[a]	70.5 (53.0, 87.0)	69.1 (53.0, 81.0)
Disease duration (y)[a]	8.0 (1.3, 21.8)	7.6 (0.2, 24.7)
Missing	1	0
Hoehn & Yahr[b]		
1	0 (0%)	2 (6.5%)
2	26 (79%)	20 (65%)
2.5	1 (3.0%)	1 (3.2%)
3	4 (12%)	5 (16%)
4	2 (6.1%)	3 (9.7%)
Missing	1	0
Location[b]		
Teachers College	28 (82%)	26 (84%)
University of Florida	6 (18%)	5 (16%)
Sex[b]		
Female	13 (38%)	9 (29%)
Male	21 (62%)	22 (71%)
Maximum PAS at baseline[b]		
1	1	1
2	1	0
3	5	6
4	0	0
5	11	5
6	3	3
7	3	4
8	10	12
Reflex cough threshold at baseline		
50 μM	5 (15%)	3 (10%)
100 μM	8 (23%)	5 (16%)
200 μM	7 (21%)	6 (19%)
>200 μM	13 (38%)	16 (52%)
Missing	1 (3%)	1 (3%)
Treatment adherence		
Percentage home practice logs returned	78%	80%
Treatment adherence (% of exercise completed)	96.9% (6.5%)	96.7% (6.6%)

[a]Mean (range).
[b]Frequency (%).
Abbreviations: EMST, expiratory muscle strength training; smTAP, sensorimotor training for airway protection; PAS, Penetration-Aspiration Scale (maximum).

For intra-rater reliability, estimates were 0.99 for voluntary cough PEFR (95% CI: 0.99–1.00), 0.98 for reflex cough PEFR (95% CI: 0.97–0.98), 0.85 for voluntary cough CEV (95% CI: 0.76–0.91), 0.87 for reflex cough CEV (95% CI: 0.82–0.90), 0.82 for voluntary CrTot (95% CI: 0.82–0.82), and 0.77 for reflex CrTot (95% CI: 0.77–0.77).

Primary Outcomes

Delayed (No-Treatment) Effects—Primary Outcomes (MEP and Voluntary PEFR)

Voluntary cough peak flow decreased by 0.30 L/s after 5 weeks of no treatment ($P < 0.001$, $d = 0.34$), whereas there was no change in MEP ($P = 0.79$, $d = -0.01$) (Supplementary Tables).

Treatment Effects—Primary Outcomes (MEP and Voluntary PEFR)

MEP increased from pre- to post-treatment for smTAP by 8 cmH_2O ($P < 0.001$, $d = 0.19$) and for EMST by 22 cmH_2O ($P < 0.001$, $d = 0.53$). EMST showed greater improvements in MEP compared to smTAP ($P < 0.001$, $d = -0.34$) (Table 2).

Voluntary PEFR increased from pre- to post-treatment for smTAP by 0.51 L/s ($P < 0.001$, $d = 0.19$) and for EMST by 0.17 L/s ($P < 0.001$, $d = 0.06$). smTAP showed greater improvements in PEFR compared to EMST ($P < 0.001$, $d = 0.12$).

Secondary Outcomes

Voluntary Cough (CEV and CrTot)

Voluntary CEV increased from pre- to post-treatment for smTAP by 0.18 liter ($P < 0.001$, $d = 0.16$) and for EMST by 0.07 liter ($P = 0.001$, $d = 0.06$). smTAP showed greater improvements in CEV compared to EMST ($P < 0.001$, $d = 0.10$) (Table 2).

The number of voluntary coughs (CrTot) decreased from pre- to post-treatment for smTAP ($P < 0.001$, $OR = 0.68$) and EMST ($P < 0.001$, $OR = 0.69$). There were no between-group differences in the magnitude of change ($P = 0.846$).

Reflex Cough (PEFR, CEV, CrTot, Reflex Cough Threshold, and UTC)

Reflex cough PEFR at 200 μM increased for smTAP from pre- to post-treatment by 0.53 L/s ($P < 0.001$, $d = 0.64$), whereas EMST decreased by 0.23 L/s ($P < 0.001$, $d = -0.28$). smTAP showed greater improvements in PEFR compared to EMST ($P = 0.022$, $d = 0.93$) (Table 2).

Reflex CEV improved for smTAP from pre- to post-treatment by 0.22 liter ($P < 0.001$, $d = 0.74$) but was unchanged for EMST ($P = 0.48$, $d = -0.10$). smTAP

TABLE 2 *Descriptive statistics for cough outcomes*

	Treatment	Time	Estimate	95% CI
Primary outcomes				
Voluntary PEFR (L/s)	EMST	Pre	2.98	2.71–3.25
		Post	3.10	2.8–3.5
	smTAP	Pre	3.05	2.77–3.34
		Post	3.60	3.1–4
Maximum expiratory pressures (cmH_2O)	EMST	Pre	97	81.8–111
		Post	119	102–134
	smTAP	Pre	112	96.5–126.6
		Post	120	103–136
Secondary outcomes				
Reflex PEFR (L/s)	EMST	Pre	2.63	2.33–2.94
		Post	2.40	1.9–2.9
	smTAP	Pre	2.48	2.17–2.78
		Post	3.00	2.5–3.5
Reflex CEV (liter)	EMST	Pre	0.66	0.55–0.71
		Post	0.63	0.43–0.83
	smTAP	Pre	0.57	0.46–0.68
		Post	0.79	0.59–1
Voluntary CEV (liter)	EMST	Pre	0.53	0.43–0.64
		Post	0.60	0.46–0.75
	smTAP	Pre	0.54	0.43–0.64
		Post	0.72	0.58–0.86

All estimates were obtained from statistical models and included a covariate of number of coughs (except for maximum expiratory pressures).
Abbreviations: CI, confidence interval; PEFR, peak expiratory flow rate; EMST, expiratory muscle strength training; smTAP, sensorimotor training for airway protection; CEV, cough expired volume.

showed greater improvements in CEV compared to EMST ($P < 0.001$, $d = 0.84$).

There were no significant differences in the total number of reflex coughs (CrTot) at 200 μM ($P = 0.20$) or in the reflex cough thresholds ($P = 0.147$).

UTC at 50 μM capsaicin increased for smTAP ($P = 0.018$, $OR = 2.70$) but not for EMST ($P = 0.102$, $OR = 0.58$). smTAP showed greater improvements in UTC compared to EMST ($P = 0.018$, $OR = 4.70$). At 100 and 200 μM capsaicin, there were no significant differences in UTC ($P > 0.05$; Fig. 3; Supplementary Material).

Discussion

The results of this first RCT comparing a strength- and skill-based approach to rehabilitation for airway protection demonstrated that EMST and smTAP for 5 weeks are safe and efficacious for the rehabilitation of critical aspects of airway protection, specifically cough effectiveness, in PD. More specifically, both EMST and smTAP resulted in significant improvements in MEP and voluntary cough PEFR. However, only smTAP improved reflex cough effectiveness. These findings are particularly impactful given that the delayed-treatment group demonstrated a significant worsening of voluntary cough effectiveness with no treatment over 5 weeks.

Voluntary cough PEFR improved in both the EMST and smTAP groups, though the smTAP group demonstrated a significantly larger improvement. On average, the EMST group improved PEFR from 2.98 to 3.15 L/s (6% improvement), and the smTAP group improved PEFR from 3.05 to 3.60 L/s (18% improvement). These values remain below those seen in healthy older adults where voluntary cough PEFR is estimated at 4.16 L/s.[29] However, these improvements are of particular clinical importance given recent findings indicating that voluntary

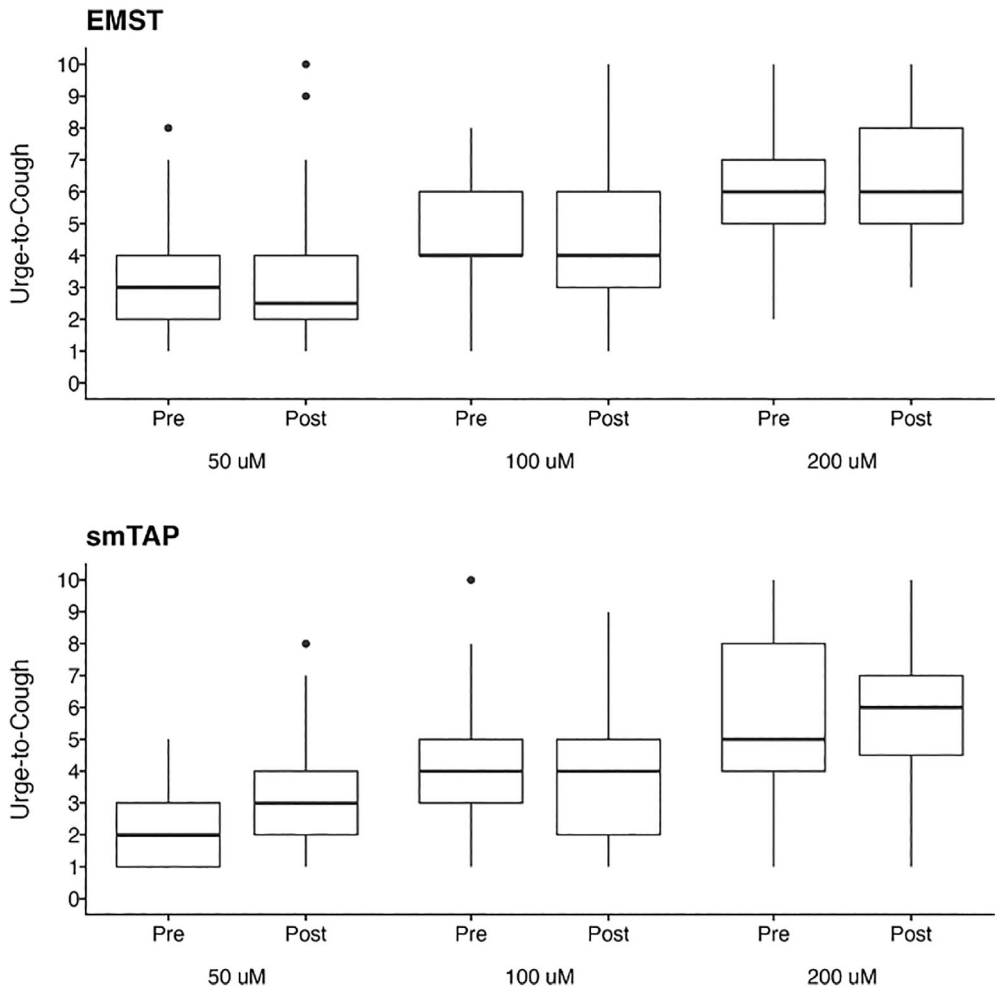

FIG. 3. Following each trial of capsaicin, participants rated their urge to cough (UTC) on a modified Borg rating scale, indicating their perceived magnitude of the cough-inducing stimuli. UTC at 50 μM capsaicin increased for the sensorimotor for airway protection group (smTAP [sensorimotor training for airway protection], $P = 0.018$, $OR = 2.70$) but not the expiratory muscle strength training group (EMST [expiratory muscle strength training], $P = 0.102$, $OR = 0.58$). smTAP showed greater improvements in UTC compared to EMST ($P = 0.018$, $OR = 4.70$). At 100 and 200 μM capsaicin, there were no significant differences in UTC.

cough PEFR values of 3.41 L/s differentiate between "effective" and "ineffective" airway clearance for ≥80% of subglottic residue (aspirate material).[37] Therefore, smTAP improved PEFR to levels that are associated with 80% of aspirate material expelled after a voluntary cough. CEV, another measure of cough effectiveness, also increased significantly in both groups, though significantly more for the smTAP group. On average, voluntary cough CEV increased from 0.53 to 0.60 liter (13% increase) for the EMST group and increased from 0.54 to 0.72 liter (33% increase) for the smTAP group. This is the first RCT demonstrating the efficacy of a sensorimotor skill-based approach (ie, smTAP) to improve voluntary cough effectiveness (ie, PEFR and CEV) in PD, having led to greater improvements in voluntary cough outcomes than those observed in the EMST group.

EMST has as its primary treatment target an increase in MEP to improve expiratory force generation. In PD specifically, the average increase in MEP has been around 24%.[24,45] The findings of this study are consistent with those of prior EMST studies. Participants in the EMST group increased MEP from 97 to 118 cmH_2O (22% improvement) on average. Interestingly, the smTAP group also had an improvement in MEP, with an increase from 112 to 120 cmH_2O (7% improvement) on average; however, the EMST group had a larger magnitude of change in MEP. Though an increase in MEP is favorable, the translation of these improvements to airway protective function is more critical.

Another key contribution of this work was to test the efficacy of these treatments for improving reflex cough function given the need for patients with dysphagia to detect aspirate material and cough effectively to clear aspirate from the airway. The EMST group did not show any changes in reflex cough outcomes. In contrast, the smTAP group showed a significant improvement in both reflex cough PEFR and CEV. On average,

reflex cough PEFR increased from 2.48 to 3.01 L/s (21%), and CEV increased from 0.57 to 0.79 liter (39%). Of note, after training, the smTAP group demonstrated higher reflex cough PEFR and CEV than what has been found in healthy older adults, 2.85 L/s and 0.19 liter, respectively.[29] We also sought to understand whether EMST or smTAP would improve the perception of cough stimuli in PD. We found that UTC significantly increased at 50 μM capsaicin for the smTAP group, but not the EMST group, post-training. These data support the notion that the blunted perception of subthreshold cough stimuli in PD can be upregulated with rehabilitation. This is the first RCT to identify an improvement in reflex cough function and detection of cough stimuli in PD after a behavioral therapeutic approach.

Beyond the positive treatment effects identified in both groups, both treatments also appear to be safe and feasible for participants. This study included a wide range of patients with mild to severe PD, all of whom had dysphagia. In this study there were no adverse events, supporting the safety of these treatment approaches in PD. Though both treatments were intensive, requiring one weekly visit to the laboratory and 4 days of home practice, there was low dropout related to issues other than COVID-19 lab closure. In addition, most participants returned their home treatment logs, and most participants reported completion of all of their home practice. Therefore, these findings indicate that this type of treatment approach is well tolerated and accepted by patients with dysphagia and various severity levels of PD.

This RCT is not without limitation. Treatment adherence to the home program was measured via patient logs, which have potential to be unreliable. Another limitation is that capsaicin is not immediately available to clinicians, which can limit translation of our findings to clinical settings. Capsaicin, a cough-inducing stimulus derived from hot peppers, was selected for this study and treatment approach because of its superior reliability versus acid-based cough-inducing agents on multiple cough tests and because the affective sensations associated with capsaicin as compared to acid-based agents have been reported to be more pleasant.[46] However, other tussive agents that are more readily available can be considered.[47,48] In addition, studies have identified that cough skill training without capsaicin still translates to improvements in reflex cough function, and that this can be completed via telehealth, further supporting the clinical translation.[31] Finally, though this study included patients with mild to severe PD and dysphagia, it will be necessary to study whether these findings are replicated in a larger cohort of patients with severe PD and dysphagia.

Overall, this clinical trial has confirmed the safety and efficacy of a novel sensorimotor approach to cough skill training (smTAP) for improvement in both motor and sensory aspects of voluntary and reflex cough function, above and beyond the changes seen with EMST, the current gold standard for treatment of airway protection in PD. These differences in airway-protective treatment outcomes between the EMST and smTAP groups point to differences in the mechanistic targets of treatment (ie, strength- vs. skill-based training), with EMST leading to greater improvements in MEP but smTAP resulting in greater improvements in voluntary and reflex cough function. The value of skill-based training for individuals with PD is further supported by studies demonstrating improvement in speech and gait.[49,50] For the smTAP group, the improvements in voluntary and reflex cough function to levels indicative of improved airway clearance are of clear health impact, especially given that these individuals have dysphagia. This study supports the consideration of skill-based training approaches for cough rehabilitation in individuals with PD and dysphagia. Future studies should test the combined strength- and skill-based approaches for the rehabilitation of airway-protective disorders in PD and should assess the long-term health outcomes associated with these approaches.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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1. Research project:
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2. Statistical analysis:
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f. Review and critique

3. Manuscript preparation:
g. Writing of the first draft
h. Review and critique

M.S.T.: 1a, 1b, 1c, 2a, 2c, 3a.
J.A.C.: 1b, 1c, 2c, 3b.
J.S.S.: 1b, 1c, 2c, 3b.
A.E.D.: 1b, 1c, 2c, 3b.
S.E.P.: 1b, 1c, 3b.
J.C.B.: 1c, 2a, 2b, 3b.
A.A.G.: 2a, 2b, 3b.
N.V.-A.: 1b, 1c, 3b.
K.W.H.: 1a, 1b, 1c, 2a, 2c, 3b.
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