

RESEARCH ARTICLE

Immediate and long-term effects of speech treatment targets and intensive dosage on Parkinson's disease dysphonia and the speech motor network: Randomized controlled trial

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Abstract

This study compared acoustic and neural changes accompanying two treatments matched for intensive dosage but having two different treatment targets (voice or articulation) to dissociate the effects of treatment target and intensive dosage in speech therapies. Nineteen participants with Parkinsonian dysphonia (11 F) were randomized to three groups: intensive treatment targeting voice (voice group, $n = 6$), targeting articulation (articulation group, $n = 7$), or an untreated group (no treatment, $n = 6$). The severity of dysphonia was assessed by the smoothed cepstral peak prominence (CPPS) and neuronal changes were evaluated by cerebral blood flow (CBF) recorded at baseline, posttreatment, and 7-month follow-up. Only the voice treatment resulted in significant posttreatment improvement in CPPS, which was maintained at 7 months. Following voice treatment, increased activity in left premotor and bilateral auditory cortices was observed at posttreatment, and in the left motor and auditory cortices at 7-month follow-up. Articulation treatment resulted in increased activity in bilateral premotor and left insular cortices that were sustained at a 7-month follow-up. Activation in the auditory cortices and a significant correlation between the CPPS and CBF in motor and auditory cortices was observed only in the voice group. The intensive dosage resulted in long-lasting behavioral and neural effects as the no-treatment group showed a progressive decrease in activity in areas of the speech motor network out to a 7-month follow-up. These results indicate that dysphonia and the speech motor network can be differentially modified by treatment targets, while intensive dosage contributes to long-lasting effects of speech treatments.

KEYWORDS

articulation, dysphonia, hypokinetic dysarthria, LSVT LOUD, Positron Emission Tomography, smoothed cepstral peak prominence, speech motor network

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1 | INTRODUCTION

Nearly 90% of the over 6 million individuals with Parkinson's disease (PD; Dorsey et al., 2018) develop speech and voice signs (Hartelius & Svensson, 1994; Ho, Iansek, Marigliani, Bradshaw, & Gates, 1999; Logemann, Fisher, Benjamin, & Richard, 1978; Miller et al., 2007; Schalling, Johansson, & Hartelius, 2017). These signs include disorders of voice (harsh, breathy voice quality, reduced loudness, and monotone; Baumgartner, Sapir, & Ramig, 2001; Fox & Ramig, 1997; Lazarus et al., 2012; Midi et al., 2007), articulation (imprecise consonants, vowel centralization; Ackermann & Ziegler, 1991; Forrest, Weismer, & Turner, 1989; Ruzs et al., 2013; Sapir, Spielman, Ramig, Story, & Fox, 2007; Skodda, Grönheit, & Schlegel, 2012; Skodda, Visser, & Schlegel, 2011; Tjaden, Lam, & Wilding, 2013) and rate (increased, decreased or variable; Hammen & Yorkston, 1996; Skodda & Schlegel, 2008). Disordered voice (dysphonia) is considered one of the earliest, most debilitating, and pervasive signs (Pinto, Ghio, Teston, & Viallet, 2010; Sewall, Jiang, & Ford, 2006). These speech signs, collectively termed hypokinetic dysarthria (HKD), have been associated with an overall decreased excitatory input to the cortex from the basal ganglia (Duffy, 2005; Sapir, 2014). The decreased excitatory input to the cortex gives rise to physiological deficits at the periphery (i.e., laryngeal, articulatory, and respiratory apparatus) as well as decreased cortical activity in the regions of speech production network (Cannito et al., 2012; Mahler, Ramig, & Fox, 2015; Narayana et al., 2010, 2020; Pinto et al., 2004; Smith, Ramig, Dromey, Perez, & Samandari, 1995).

In individuals with PD, HKD results in greatly decreased communication that worsens an already compromised quality of life and further contributes to lowered productivity and financial burdens (Miller, Noble, Jones, Allcock, & Burn, 2008; Miller, Noble, Jones, & Burn, 2006; Schenkman, Wei Zhu, Cutson, & Whetten-Goldstein, 2001). Hence, effective treatment of HKD in individuals with PD is as important as developing optimal control of limb motor symptoms. The pharmacological and surgical interventions that improve limb motor symptoms in individuals with PD are generally ineffective in treating HKD (D'Alatri et al., 2008; Pinto, Ozsancak, et al., 2004; Pinto et al., 2005; Sapir, 2014; Schulz & Grant, 2000; Tripoliti et al., 2008). Presently, the most effective treatment for speech and voice disorders in individuals with PD is the behavioral treatment known as LSVT LOUD® (Lee Silverman Voice Treatment, henceforth voice treatment). This voice treatment is based on principles of motor learning and neural plasticity (Kleim & Jones, 2008) and its therapeutic principle is that increasing vocal intensity in individuals with PD together with training sensory feedback and internal cueing will re-train the motor and sensory processes involved in disordered speech and voice (Fox &

Boliek, 2012; Fox, Morrison, Ramig, & Sapir, 2002; Mahler et al., 2015; Ramig, Halpern, Spielman, Fox, & Freeman, 2018). Consistent with experience-dependent skill learning principles, the voice treatment is intensive and takes place over 4 weeks, with patients receiving 1 hr of clinician treatment for 4 days a week and performing practice and carryover (generalization) exercises on their own every day. Research has documented that intensive treatment targeting voice significantly improves many voices and speech symptoms (Levy et al., 2020; Ramig et al., 2018; Ramig, Sapir, Fox, & Countryman, 2001; Schulz et al., 2021). Clinical trials of voice treatment that were randomized, blinded, and controlled (Ramig et al., 2001; Ramig et al., 2018; Ramig, Countryman, O'Brien, Hoehn, & Thompson, 1996; Ramig, Countryman, Thompson, & Horii, 1995; Ramig, Sapir, Fox, & Countryman, 2001), have shown increases in vocal intensity and quality with improvements lasting up to 24 months posttreatment. The therapeutic effects of voice therapy have been shown to also extend beyond the treatment target indicating a network-wide effect. Intensive voice treatment has been shown to improve dysphonia, respiratory physiology, orofacial movements, articulation, intonation, rate, facial expression, swallowing, overall speech intelligibility, and patient-reported outcomes (Alharbi, Cannito, Buder, & Awan, 2019; Baumgartner et al., 2001; Cannito et al., 2012; Dumer et al., 2014; El Sharkawi et al., 2002; Fox & Boliek, 2012; Levy et al., 2020; Mahler et al., 2015; Ramig et al., 2018; Ramig, Sapir, Fox, & Countryman, 2001; Sapir et al., 2007; Schulz et al., 2021; Spielman, Borod, & Ramig, 2003).

While the perceptual and acoustic characteristics in individuals with HKD have been extensively characterized (Darley, Aronson, & Brown, 1975; Duffy, 2005), only few neuroimaging studies have examined the nature of cortical alterations in individuals with PD with HKD. Alterations in cortical activation in individuals with HKD during phonation and reading have been reported using both Positron Emission Tomography (PET; Liotti et al., 2003; Narayana et al., 2020; Pinto et al., 2004) and functional MRI (fMRI; Arnold, Gehrig, Gispert, Seifried, & Kell, 2014; Baumann et al., 2018; Maillet et al., 2012; Narayana et al., 2020; Rektorova, Barrett, Mikl, Rektor, & Paus, 2007; Saxena, Behari, Kumaran, Goyal, & Narang, 2014). These studies have shown both increases and decreases in activity in critical regions of the speech motor network including primary orofacial sensorimotor cortices, the supplementary motor area (SMA), dorsal premotor cortex, prefrontal cortex, somatosensory, and auditory cortices in individuals with HKD when compared to typical speakers. While the increased activity in individuals with HKD has been interpreted as compensatory changes in the speech motor network (Liotti et al., 2003; Rektorova et al., 2007), the reduced activity in these regions has been attributed to an overall decreased excitatory input

to the cortex from the basal ganglia. The discrepancy in the imaging findings is also likely to be a result of differing levels of HKD severity, different tasks used (phonation vs. speech and overt vs. covert), and the imaging modalities (PET vs. fMRI) across these studies.

Even fewer studies have examined the effects of voice treatment on the speech motor network of individuals with PD (Baumann et al., 2018; Liotti et al., 2003; Narayana et al., 2010). These studies have shown that intensive voice treatment increases activity in motor and auditory regions of the speech motor network. Specifically, the increase in vocal intensity and intelligibility following the voice treatment strongly correlated with increased activity in right temporal and supramarginal cortices (Baumann et al., 2018; Narayana et al., 2010) as well as motor and somatosensory cortices (Narayana et al., 2010). However, it is not clear whether the observed behavioral and neural changes are a result of the treatment target, that is, vocal intensity or the intense nature of treatment delivery. In order to dissociate the effects of treatment target and intensive dosage on ameliorating the symptoms of HKD, a randomized controlled trial was carried out to evaluate two speech treatments matched in dosage and high-effort mode of delivery, that targeted two significant signs in HKD, disordered voice or articulation (Ramig et al., 2018). In Ramig et al.'s (2018) study, PD participants were randomized to receive voice treatment, articulation treatment, or no treatment. Primary outcome was sound pressure level (SPL) in reading and spontaneous speech evaluated at baseline, posttreatment, and 7-month follow-up. The study found that at posttreatment and at 7-month follow-up, the voice treatment group showed the greatest improvement in SPL when compared to both articulation treatment and no treatment groups. The articulation treatment resulted in a small but significant increase in posttreatment SPL that was not maintained at a 7-month follow-up. In contrast, the posttreatment increases in SPL following voice treatment was significantly greater than that following articulation treatment and remained significant at 7-month follow-up. Thus, the study demonstrated that the treatment target and not the intensive dosage of treatment was a critical factor in treating HKD. Of the two targets evaluated, voice was found to be more effective in treating HKD than articulation (Ramig et al., 2018).

In order to further isolate the neural effects of the treatment target of voice contributing to successful speech rehabilitation in PD, we evaluated the effects of voice treatment with the comparison articulation treatment on the speech motor network. Particularly, we examined changes in cerebral blood flow in the dorsal premotor cortex, articulatory and laryngeal motor cortices, and the auditory cortices. These regions are engaged during speech initiation and articulation including control of orofacial and laryngeal muscles and breathing and monitoring feedback. In the context of voice treatment, the observed changes in different brain areas can be explained as synergistic changes in these brain regions. We hypothesized that consistent with previous studies (Narayana et al., 2010), at posttreatment, the voice treatment would result in greater activation in primary laryngeal motor and auditory cortices. However, due to the specific effects of the articulatory system, we expected that articulation treatment would increase the activity primarily within the primary articulatory motor, dorsal premotor, superior

temporal, and insular cortices (Basilakos, Smith, Fillmore, Fridriksson, & Fedorenko, 2018; Correia, Caballero-Gaudes, Guediche, & Carreiras, 2020; Dronkers, 1996; Woolnough, Forseth, Rollo, & Tandon, 2019; Zacà et al., 2018). Furthermore, we hypothesized that consistent with the previously reported behavioral findings (Ramig et al., 2018), the alterations in the brain areas observed at posttreatment would be sustained more in the voice treatment group than the articulation group at 7-month follow-up.

In this study, we sought to objectively evaluate voice quality by using the acoustic measure of Cepstral Peak Prominence (CPP). CPP is increasingly being recognized for quantifying harmonic spectral dominance in individuals with dysphonia (Burk & Watts, 2019; Hillenbrand, Getty, Clark, & Wheeler, 1995; Jannetts & Lowit, 2014; Maryn, Corthals, Van Cauwenberge, Roy, & De Bodt, 2010; Murton, Hillman, & Mehta, 2020). CPP is an automated measure that is independent of fundamental frequency (F0), indicates harmonic dominance, and has been shown to be equally applicable to sustained vowels and connected speech for both dysphonic and nondysphonic voices (Awan, Novaleski, & Yingling, 2013; da Silva Antonetti, Siqueira, de Gobbo, Brasolotto, & Silverio, 2020; Murton et al., 2020). Furthermore, it has also been observed that CPP correlates better than vocal intensity with both visual analog scales of overall voice quality made by experienced voice clinicians and single word intelligibility (SWIT) measures (da Silva Antonetti et al., 2020; Gaskill, Awan, Watts, & Awan, 2017; Watts & Awan, 2011). In fact, CPP is well suited to confirm the previously found LSVT LOUD-induced augmentation of laryngeal function including increase of glottal closure (Smith et al., 1995) and subglottal pressure (Ramig & Dromey, 1996). Indeed, a recent study found that following LSVT LOUD, speakers with PD showed significantly increased CPP when compared to baseline, indicating improved harmonic structure and reduced dysphonia following treatment (Alharbi et al., 2019). A derivative of CPP, referred to as Smoothed Central Peak Prominence (CPPS), added smoothing operations in temporal and cepstral domains which show slightly higher correlation with breathiness (Hillenbrand & Houde, 1996) and reduced variability in analysis (Skowronski, Shrivastav, & Hunter, 2015). We expected to find the CPPS measures to be in line with the changes in SPL previously noted in a similar study cohort (Ramig et al., 2018) with significant increases in CPPS observed in the voice treatment group at posttreatment and at 7-month follow-up. Finally, we sought to evaluate more directly the relationship between the changes in CPPS and changes in the speech motor network activation following the two treatments. For this, we choose to correlate the changes CPPS with the changes in cerebral blood flow in the regions of the speech motor network.

2 | METHODS

2.1 | Trial design

The study design was an unblinded randomized controlled trial with PD participants using two behavioral speech treatments relative to

TABLE 1 Demographic and clinical characteristics at baseline for participants by group

Characteristics	Voice	Articulation	No treatment
<i>N</i>	6	7	6
Males (0.5)			
<i>N</i>	3	3	2
%	50.0	42.9	33.3
Females (0.5)			
<i>N</i>	3	4	4
%	50.0	57.1	66.7
Age in years (0.5)			
Mean	63.8	67.7	62.0
<i>SD</i>	10.0	4.3	5.8
Years since diagnosis (0.5)			
Mean	4.3	5.3	3.8
<i>SD</i>	3.1	1.5	3.4
Hoehn and Yahr stage with medication (0.5)			
Mean	2.3	1.4	1.8
<i>SD</i>	0.8	0.8	0.8
Voice severity (1)			
Mean	2.4	2.1	1.6
<i>SD</i>	1.0	0.8	0.6
Articulation severity (1)			
Mean	0.3	0.6	0.2
<i>SD</i>	0.6	0.7	0.3
BDI-II (0.25)			
Mean	8.5	4.4	9.0
<i>SD</i>	5.7	3.7	5.5
MMSE (0.25)			
Mean	28.3	28.6	27.8
<i>SD</i>	0.5	1.1	1.0
CPPS			
Mean	9.9	11.3	11.1
<i>SD</i>	0.6	1.5	0.8

Note: Numbers in parentheses represent weights. Voice and articulation severities were measured on a scale from 0 to 5, where 0 = no disorder and 5 = severe disorder. Randomization ratio was 1:1:1 performed using a minimization algorithm based on variables and weights chosen a priori. There were no significant between-group differences at baseline for any variables. Abbreviations: BDI-II, Beck Depression Inventory-II; MMSE, Mini-Mental Status Exam; CPPS, smoothed cepstral peak prominence.

untreated PD control participants. The clinician delivering treatment could not be blinded. Participants were aware they were receiving one of two possible treatments, but specific treatment names were never provided. Participants in the no-treatment group were offered complimentary treatment at the conclusion of the study.

Acoustic and imaging data collection and treatment sessions occurred at the University of Texas Health Science Center at San Antonio, Research Imaging Institute. Additional screening and inclusionary data were collected from neurology and otolaryngology offices in the San Antonio area.

2.2 | Participants

Individuals with PD were recruited from support groups, outpatient clinics, and physicians. Recruitment through follow-up appointments took place during a 2-year period. To be included in this study, participants were required to be within Hoehn and Yahr severity scale stages I–IV (Hoehn & Yahr, 1967) demonstrate stability on their antiparkinsonian medication (as judged by their referring neurologist), exhibit mild to severe voice symptoms (as confirmed by two speech-language pathologists), not have had

intensive speech treatment in the prior 2 years or LSVT LOUD at any time, have no greater than moderate depression as measured by the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996), and have no greater than mild dementia as determined by the Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975). Initial eligibility screening occurred via telephone. Individuals who passed the telephone screening then completed an in-person screening of speech, voice, hearing, depression (assessed by BDI-II), and cognition (assessed by MMSE).

Twenty-two participants passed the in-person screening and were enrolled in the study. One participant withdrew due to personal issues, and two participants were unable to complete PET scans (one due to scheduling issues and one due to inability to tolerate position in the PET scanner). Therefore, 19 participants (11 F) with idiopathic PD (confirmed by a neurologist) were enrolled and participated in the study. All participants underwent a laryngeal examination by a licensed, board-certified otolaryngologist of the structure and function of the musculoskeletal anatomy of the vocal tract and were cleared for participation in the study. They were then stratified and randomized into three groups: voice group ($n = 6$), articulation group ($n = 7$), or no treatment group ($n = 6$), using a statistician-derived minimization algorithm to balance baseline characteristics such as age, disease duration and severity, dementia, depression, and voice severity. The statistician informed the treating clinician of each participant's group assignment. The clinical and demographic information used for randomization is listed in Table 1. The study design and allocation of participants can be seen in Figure 1. Written informed consent was obtained from all participants, and all procedures were approved by the Institutional Review Board at the University of

Texas Health Science Center at San Antonio. The study was listed in clinicaltrials.gov (trial #NCT00123084).

2.3 | Speech and voice assessments

All participants underwent speech and voice assessments at three time points, namely baseline (pretreatment), posttreatment, and 7-month follow-up. To assure that treatment-related changes exceeded day-to-day variability of participants with PD, acoustic recordings of speech were collected at each of the three time points on 2 different days within 1 week. The speech and voice assessments included a range of tasks, as part of a larger protocol. In the current study, we analyzed data from the oral reading of the standard "Rainbow Passage" (Fairbanks, 1960). Recordings were made in an IAC sound isolation booth using a head-mounted microphone (Shure, Model SM10A) positioned 8 cm from participants' mouths and digitized at a sampling rate of 44.1 kHz using Audacity. For the purpose of this research to match the reading task that was completed during imaging data collection, CPPS was estimated from the oral reading of the "Rainbow Passage" collected in the sound isolation booth.

2.4 | Treatments

Participants in the voice group and articulation group underwent daily training (4 days per week for 4 weeks), targeting voice and articulation respectively. The treatments were delivered in-person and were

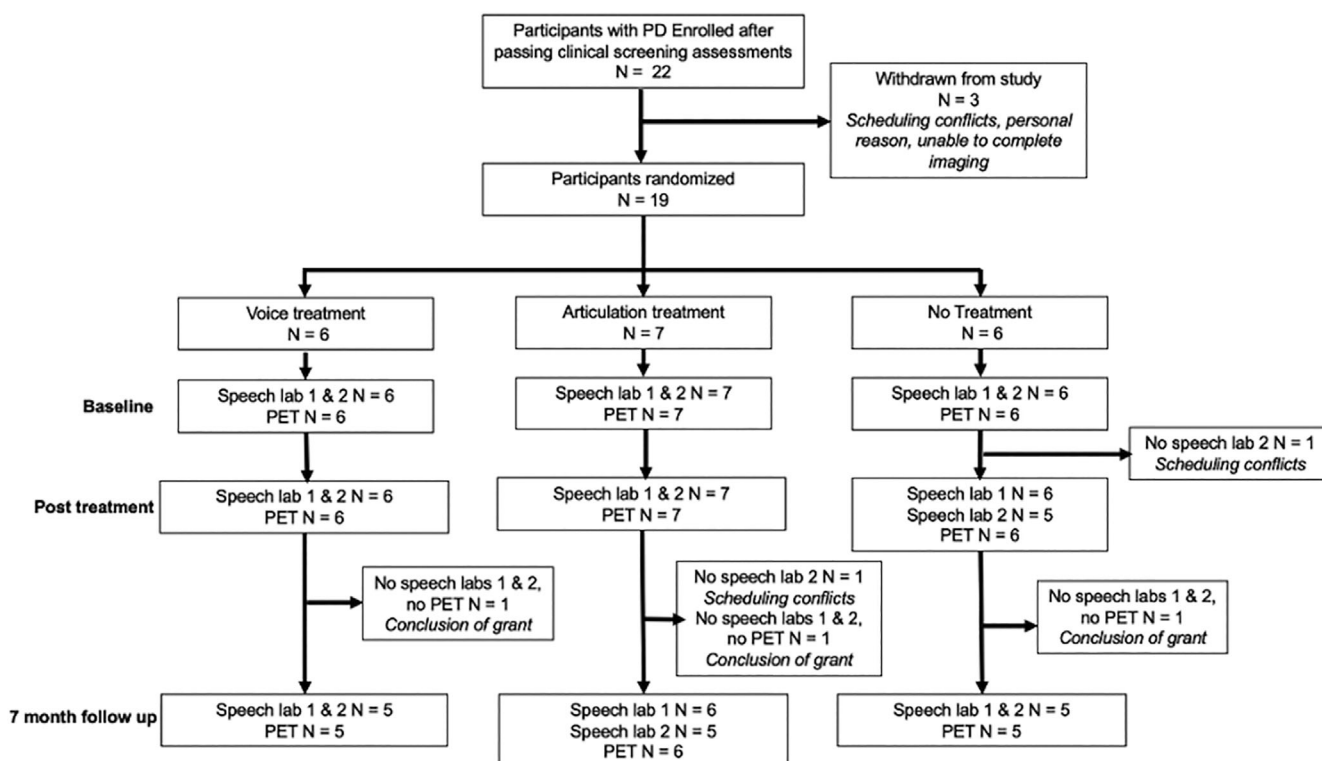


FIGURE 1 Consolidated Standards of Reporting Trials flow diagram

TABLE 2 Comparison of treatment targeting voice (Voice) and treatment targeting articulation (Articulation) for patients with Parkinson's disease

	Voice	Articulation
Focus of treatment	Loudness	Enunciation ^a
Dosage	Increased movement amplitude directed predominately to respiratory-laryngeal systems. Individual treatment session of 1 hr, 4 consecutive days per week over a 4-week period.	Increased movement amplitude directed predominately to the orofacial-articulatory system. Individual treatment session of 1 hr, 4 consecutive days per week over a 4-week period.
Effort	Push for maximum participant perceived effort.	Push for maximum participant perceived effort.
Daily exercises		
Maximum sustained movements completing multiple repetitions of tasks, 1–12 min	Sustain the vowel “ah” in a good quality, loud voice, for as long as possible.	Sustain articulatory placement for “p” (lips closed) and “t” (tongue tip behind upper teeth) with low Oral pressure instrument (IOP); hold for 4 s for each trial.
Directional movements completing multiple repetitions of tasks, 13–23 min	Say the vowel “ah” in a good quality, loud voice gliding high in pitch; hold for 5 s. Say the vowel “ah” in a good quality, loud voice gliding low in pitch; hold for 5 s.	Repeat as many as possible in 5 s trials, each of the following single consonants with precise articulation (voiceless productions): /p/ /t/ /k/ Repeat as many as possible in 5 s trials, each of the following minimal pair combinations with precise articulation: /t-k/, /n-g/, “oo-ee”, and “oo-ah”
Functional movements, 24–30 min	Participant reads 10 self-generated phrases he/she says daily in functional living (e.g., “good morning”) using the same effort and loudness as he/she did during the maximum sustained movements exercise.	Participant reads 10 self-generated phrases he/she says daily in functional living (e.g., “good morning”) using same effort for enunciation as he/she did during the maximum sustained movements exercise.
Hierarchy exercises, 31–55 min		
Purpose	Train rescaled vocal loudness achieved in the daily exercises into context-specific and variable speaking activities.	Train rescaled enunciation achieved in the daily exercises into context-specific and variable speaking activities.
Method	Incorporate multiple repetitions of reading and conversation tasks with a focus on vocal loudness.	Incorporate multiple repetitions of reading and conversation tasks with a focus on enunciate.
Tasks	Tasks increase in length of utterance and difficulty across weeks, progressing from words to phrases to sentences to reading to conversation, and can be tailored to each participant's goals (e.g., communicate at work or with caregivers) and interests (e.g., speak on topics of golf, cooking).	Tasks increase in length of utterance and difficulty across weeks, progressing from words to phrases to sentences to reading to conversation, and can be tailored to each participant's goals (e.g., communicate at work or with caregivers) and interests (e.g., speak on topics of golf, cooking).
Assign homework exercises to be completed outside of the therapy room, 56–60 min		
Duration and repetitions on treatment days (4 days/week)	Subset of the daily exercises and hierarchy exercises; 10 min, performed once per day.	Subset of the daily exercises and hierarchy exercises; 10 min, performed once per day.
Duration and repetitions on nontreatment days (3 days/week)	Subset of the daily exercises and hierarchy exercises; 15 min, performed twice per day.	Subset of the daily exercises and hierarchy exercises; 15 min, performed twice per day.
Conversational carryover assignment	Participant is to use the louder voice practiced in exercises in a real-world communication situation.	Participant is to use enunciated speech practiced in exercises in a real-world communication situation.
Difficulty level	Matched to the level of the hierarchy where the participant is in treatment.	Matched to the level of the hierarchy where the participant is in treatment.
Shaping techniques		
Purpose and approach	Train vocal loudness that is healthy (i.e., no unwanted vocal strain) through use of modeling (“do what I do”) or tactile/visual cues.	Train speech enunciation that is within normal limits (i.e., no excessive movements) through use of modeling (“do what I do”) or tactile/visual cues.
Sensory calibration	Focus attention on how it feels and sounds to talk with increased vocal loudness (self-monitoring) and to internally cue (self-generate) new loudness effort in speech	Focus attention on how it feels and sounds to talk with increased enunciation (self-monitoring) and to internally cue (self-generate) new enunciation effort in speech
Objective and subjective clinical data collected during each treatment session	Measures of duration, frequency, and sound pressure level. Documentation of percentage of cueing required to implement vocal loudness strategy. Observations of perceptual voice quality. Participant's self-reported comments about the successful use of the improved loudness in daily communication Participant self-reported perceived effort.	Measures of oral pressure and precise articulatory productions. Documentation of percentage of cueing required to implement enunciation strategy. Observations of perceptual speech intelligibility. Participant's self-reported comments about the successful use of the improved enunciation in daily communication. Participant self-reported perceived effort.

Note: Both therapies are standardized with respect to intensive dosage. Effort in treatment targeting voice and treatment targeting articulation are based on the participant's self-perceived effort during treatment tasks, on a scale of 1–10, with 10 being the highest perceived effort. Reproduced from Ramig et al. (2018, table 1) with permission from the publisher Wiley. Comparison of LSVT LOUD and LSVT ARTIC speech therapy for PD.

^aThe instruction “Enunciate” is used to train articulatory effort and “Speak loud” is used to train healthy vocal effort.

matched on all variables except for the training target. Both treatments included three elements: (a) a single training target, (b) intensive dosage with daily homework practice and carryover exercises, and (c) a focus on retraining the sensory feedback system and internal cueing. Refer to Table 2 for a detailed comparison of the voice and articulation treatments. Participants in the no-treatment group did not receive any intervention.

Treatment began within 2 weeks of group randomization. Participant adherence to either treatment protocol was assessed by their attendance at all 16 treatment sessions and submission of daily homework to the treating clinician. To assess generalization of treatment effects, on treatment days the clinician asked the participant how others responded to their voice and speech outside of the treatment room, and mid-way through treatment, the clinician phoned a family member or close friend of each participant to ask questions regarding changes in voice and speech that they noted from the participant since beginning treatment. Participants and their family members or close friends also completed rating scales at baseline and post-treatment to provide information on the impact of treatment on the participants' communication outside of treatment. Adherence by participants was comparable across both treatment groups.

2.5 | Treating speech clinician

Both treatments were delivered by a licensed and certified speech-language pathologist, with experience treating individuals with PD and certified in LSVT LOUD treatment delivery. The clinician followed the established protocols for both treatments and provided the same level of encouragement and positive reinforcement when delivering both treatments. The principal investigator provided oversight to the clinician to ensure fidelity of treatment delivery across both treatment protocols. The clinician complied with IRB requirements and was trained according to the University's required standards of clinical research.

2.6 | Control of bias

To control for bias when delivering treatment, the speech clinician focused on delivering both treatment protocols with equipoise (Djulbegovic, Cantor, & Clarke, 2003) and reported equal investment in both treatments. Data collection at all timepoints followed scripted protocols and interview and experimental data were collected by trained research staff and the treating clinician. The treating clinician did not collect posttreatment or 7-month follow-up data from participants in the treatment groups during speech and voice assessments or PET imaging data collection sessions. The trained research staff were blinded to the treatment group when collecting speech and voice and imaging data.

2.7 | PET imaging

PET data were acquired with a CTI EXACT HR. scanner (Knoxville, TN). Sixty-three contiguous slices (2.5-mm thick) in a transaxial field

of view of 15.5 cm were acquired. Images were corrected by measured attenuation using $^{68}\text{Ge}/^{68}\text{Ga}$ transmission scans and reconstructed at an in-plane resolution of 7-mm full width at half maximum (FWHM) and an axial resolution of 6.5-mm FWHM. Water labeled with oxygen-15 (H_2^{15}O , half-life 122 s) was administered intravenously (555 MBq H_2^{15}O dose/scan) and cerebral blood flow (CBF) was measured using a bolus technique (Fox et al., 2000, 2006). Participants' heads were immobilized in the PET scanner using individually fitted, thermally molded, plastic face masks (Fox & Raichle, 1984). Each participant was studied in three sessions: baseline, posttreatment, and 7-month follow-up. During each session, the participants underwent a total of eight measurements of CBF during different tasks each repeated twice. As part of a larger protocol, data from different reading tasks and no reading with eyes open at rest were collected. To be consistent with the speech and voice data that was collected at the habitual conversational voice, and for the proposed correlational analyses of imaging and behavioral data, the imaging data from reading at habitual voice and enunciation level contrasted with no reading with eyes open at rest are reported here. The participants read standard passages used in speech and voice assessments, "The Rainbow" (Fairbanks, 1960) and "The Grandfather" (Darley et al., 1975). The passages were displayed on a computer monitor screen placed in front of participants' eyes. The order of presentation for the passages was randomized, and the passages were presented alternatively (i.e., if Rainbow was randomly selected to be presented first, then the participant would be presented with Rainbow first, followed by Grandfather). In the eyes open rest condition, participants were asked to lie still while looking at a crosshair on the monitor and maintain a relaxed state.

2.8 | MRI imaging

An anatomical MRI was acquired for each subject for the purposes of spatial transformation of the PET data to the standard brain template and for overlay of parametric images. A high-resolution anatomical MRI (3T-TIM, Siemens, Germany) was acquired for all participants with 1 mm³ isotropic resolution, using a 3D Turbo-FLASH sequence with an adiabatic inversion contrast pulse (TE/TR/TI = 3.04/2100/785 ms, and flip angle = 13°).

3 | DATA ANALYSIS

3.1 | Analysis of voice and speech data

3.1.1 | Smoothed cepstral peak prominence

Speech recordings collected in the sound isolation booth were edited to remove nonspeech sounds such as coughs, microphone pops, throat clears, and heavy breathing before further analysis. For analysis, the initial 34 syllables of the Rainbow Passage were extracted (about 45 s of running speech). Analysis of all samples was conducted using custom MATLAB scripts (MathWorks, Natick, MA) which also used PRAAT 5.4.17 (Boersma & Weenik, 1996) to estimate CPPS

using published routines (Maryn et al., 2010). In this case, the CPPS data presented were from voice-concatenated versions (pauses and silences removed) of the speech.

Single factor analysis of variance was conducted to compare between-group baseline values of CPPS, with an overall α -level of .05. Descriptive statistics for CPPS are presented as means and SDs. Test-retest reliability (Days 1 and 2) for CPPS was derived using intraclass correlation coefficients (ICC) for baseline, posttreatment, and 7-month follow-up measures. Additionally, *t* tests were performed to compare Day 1 and Day 2 values of CPPS at all timepoints. A two-way repeated-measures analysis of variance was conducted to compare within- and between-group changes in CPPS from baseline to posttreatment and 7-month follow-up, with an overall α -level of .05. Power analysis for CPPS values was performed in SPSS (Version 27.0., IBM Corp, Armonk, NY).

3.2 | Analysis of PET imaging data

3.2.1 | Image preprocessing

Image preprocessing was performed using previously validated methods and in-house software. PET images were corrected for head motion using the MCFLIRT tool in FSL 4.0 (<http://www.fmrib.ox.ac.uk/fsl/>), and PET and MRI images were spatially transformed relative to the stereotaxic atlas of Talairach and Tournoux (Lancaster et al., 1995, 2000; Talairach & Tournoux, 1988). Regional tissue uptake of ^{15}O -water was globally normalized to whole rCBF brain mean value with images scaled to a mean of 1,000 counts. These value and spatially normalized images were tri-linearly interpolated, re-sampled (60 slices, 8 mm^3 voxels), and Gaussian filtered to a final resolution of 9.9 mm (FWHM). Further data analyses were performed using MIPS, a previously validated in house image analysis software (Medical Image Processing Station, Research Imaging Center, UT Health Science Center at San Antonio, TX) and MANGO (Multi Analysis GUI, Research Imaging Center, UT Health Science Center at San Antonio, TX).

3.2.2 | Conditional contrast analysis

For each participant and session, voxel-by-voxel pairwise contrasts were generated to identify regional changes present during reading using habitual loudness and enunciation relative to rest. Task-specific, within-subject regional changes were then averaged across individuals. A maxima and minima search (Fox & Mintun, 1989; Fox, Mintun, Reiman, & Raichle, 1988; Mintun, Fox, & Raichle, 1989) was then used to identify local extrema within a search volume measuring $1,000\text{ mm}^3$. A gamma 1 statistic measuring skewness and gamma 2 statistic measuring kurtosis of the distribution of the extrema established before post hoc analysis were used as an omnibus test to assess overall significance. We confirmed that for all task versus rest contrasts, the gamma 2 statistic for all the masked voxels and for the

extrema set were significant. The group-mean subtraction images from all sessions were then converted to statistical parametric images of *z* scores (SP $\{z\}$). Additionally, in order to identify significant CBF changes in speech motor regions induced by each type of intensive treatment and no treatment, the SP $\{z\}$ images at posttreatment and 7-month follow-up were contrasted against those derived at baseline using the processing methods described above. The Bonferroni correction was applied to correct for the number of extrema locations that were reported to have a *p*-value $<.05$.

3.2.3 | Correlation analysis

To evaluate the relationship between the hemodynamic changes and the change in CPPS in the three groups, we performed a voxel-wise correlation analysis. A statistical parametric image of *r* values (SP $\{r\}$) was computed as a whole-brain voxel-wise correlation of value normalized PET counts (VNC) in the habitual reading contrasted with rest image with the corresponding CPPS value for each individual and an average derived for each group using previously described method (Fox et al., 2000). For each treatment group, the conditional contrasts (habitual reading–rest) derived at baseline, posttreatment, and at a 7-month follow-up were correlated with respective measure of CPPS. SP $\{r\}$ was analyzed for speech performance effects first by an omnibus (whole brain) test and, if omnibus significance was proven, then a post hoc (regional) test was done and local extrema were identified. The SP $\{r\}$ was converted to SP $\{z\}$, and *p* values were assigned from the *Z* distribution and corrected for the number of positive extrema. To further confirm the relationship between brain activity and CPPS, the value normalized PET counts were extracted from brain regions that were found to be significantly changed in the conditional contrast analysis. Cubic volumes of interests (VOIs) with a side of 10 mm were placed at the center-of-mass of bilateral primary laryngeal motor cortices (M1), supplementary motor areas (SMA), dorsal premotor cortices (PMd), and superior and middle temporal gyri. The mean VNC were derived for the above locations during rest and reading conditions, at baseline, posttreatment and 7-month follow-up time points from each subject. Change in VNC between reading and rest was calculated in each participant at the three time points. The relationship between the CPPS and VNC in each of these regions for each group was assessed using Pearson's correlation.

4 | RESULTS

4.1 | Participants

There were no significant between-group differences in baseline characteristics of gender, age, time since diagnosis, Hoehn and Yahr stage with medications, perceptual voice and speech severity, depression, and dementia, as revealed by single factor analysis of variance ($p > .05$). All participants with PD were stable with their anti-Parkinson medications throughout the duration of the study.

	Voice treatment	Articulation treatment	No treatment
Baseline ^a	9.9 ± 0.6	11.3 ± 1.5	11.1 ± 0.8
Baseline range	9.2–10.8	9.8–14.5	9.4–11.7
Posttreatment	11.7 ± 1.4	11.5 ± 1.5	11.3 ± 0.8
7-month follow-up	11.4 ± 0.7	10.9 ± 0.8	11.5 ± 0.9

Note: Between-group comparisons of changes in CPPS from baseline to posttreatment and 7-month follow-up indicated that increases in the voice group were significantly larger than those for both the articulation group and the no treatment group ($p < .05$; $p < .05$). For the voice group, within-group increases in CPPS from baseline to posttreatment and baseline to 7-month follow-up were significant ($p < .05$).

^aAt baseline, there was no significant difference among the three groups ($p = .08$).

4.2 | Voice and speech data

4.2.1 | Reliability

No significant differences in test-retest reliability were observed between Day 1 and Day 2 measures of CPPS values as revealed by paired *t*-test, $t(51) = -0.11$, $p = .92$. Furthermore, intraclass correlation coefficients (ICCs) for Days 1 and 2 for CPPS within each group at baseline, posttreatment, and 7-month follow-up were between 0.53 and 0.99. The lack of significant differences between Day 1 and Day 2 indicate general consistency among subjects. To avoid bias attributed to practice effects, statistical analysis was performed on Day 1 measures.

4.2.2 | Smoothed cepstral peak prominence

At baseline, the range of CPPS in this study cohort ranged from 9.2 dB to 14.5 dB. There were no significant differences in CPPS at baseline between groups ($p = .08$), although the CPPS values were on average lower in the intensive voice treatment group. Furthermore, the perceptual voice severity in all the three groups was not significantly different. Descriptive statistics for between and within-group changes in CPPS from baseline to posttreatment and 7-month follow-up, are presented in Table 3. Between-group increases in CPPS from baseline to posttreatment and 7-month follow-up in the voice group were significantly larger than those for both the articulation group and the no treatment group ($p < .05$; $p < .05$). There were no significant differences between the articulation group and the no treatment group ($p > .05$). Within-group changes in CPPS from baseline to posttreatment and 7-month follow-up were significant following the voice treatment ($p < .05$). Within-group changes in CPPS from baseline to posttreatment and 7-month follow-up in both the articulation group and no treatment group were not significant. Power analysis confirmed that the CPPS data had sufficient power (time = 0.945, time × treatment group = 0.667). Compared to baseline, on average at posttreatment, the CPPS change per individual increased by 18% (range 2–39%) in the voice treatment when compared to 2% (range: 4–15%) in the articulation treatment group and 2% (range: 6–9%) in the untreated group. At 7-month follow-up, the mean CPPS change per individual in the voice treatment group remained

TABLE 3 CPPS values (mean ± SD) in the three groups during reading of the Rainbow passage at baseline, posttreatment, and 7-month follow-up

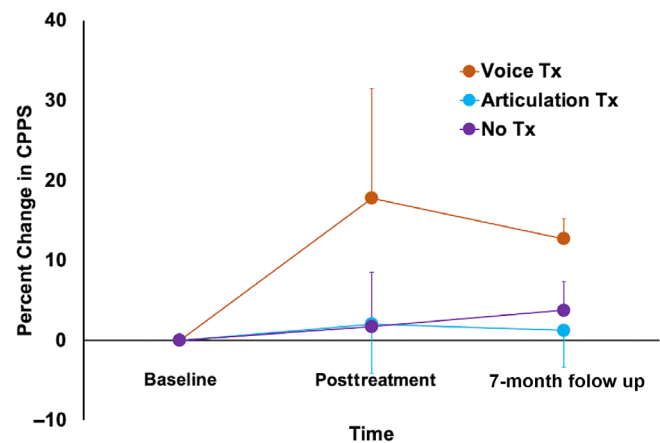


FIGURE 2 Mean of individual percent change in CPPS in the three groups during reading of the Rainbow passage at posttreatment and 7-month follow-up when compared to baseline. Error bars denote SD. CPPS, Smoothed cepstral peak prominence

15% higher than baseline where as the mean CPPS change per individual remained similar to baseline values in the other two groups. The mean (\pm SD) percent change in CPPS per individual in the three groups at posttreatment and 7-month follow-up when compared to baseline are shown in Figure 2.

4.3 | PET imaging

4.3.1 | Conditional contrast analysis

After correcting for multiple positive extrema, only maxima with *z*-score > 3.5, cluster volume > 150 mm³, and $p < .0001$, were identified as significant and are reported here. The brain regions identified in the conditional contrast analyses are listed along with their *x*, *y*, *z* coordinates (Talairach coordinates), Brodmann area, peak *z*-score and volume of activation in Tables 4–8. Brain regions showing a significant change during paragraph reading compared with rest at baseline averaged across all participants are listed in Table 4 and shown in Figure 3, left panel. Brain regions showing a significant change during paragraph reading compared with rest at posttreatment and 7-month follow-up following voice treatment and articulation treatment are

TABLE 4 Baseline activation during habitual reading contrasted with rest at baseline in the study cohort

Brain region	X	Y	Z	Brodmann area	Maximum z-score	Volume (mm ³)
Precentral gyrus	-46	-14	32	4/6	4.4	2,240
Cerebellum—declive	-6	-74	-14		5.3	3,864
Precentral gyrus	52	-10	26	4/6	3.7	1,064
Medial frontal gyrus—SMA	2	-6	56	6	3.5	200
Cerebellum—declive	14	-66	-20		4.7	2,056

Note: Only activations with z-score > 3.5, cluster volume > 150 mm³, and $p < .0001$ are reported here.

TABLE 5 Changes in brain activation following voice therapy at posttreatment and 7-month follow-up

Brain region	Voice treatment—post						Voice treatment—7 m follow-up					
	X	Y	Z	Brodmann area	Maximum z-score	Volume (mm ³)	X	Y	Z	Brodmann area	Maximum z-score	Volume (mm ³)
Precentral gyrus	-50	-14	32	4	6.0	4,024	-48	-14	30	6	5.6	5,048
Precentral gyrus	-34	-14	38	4	4.5	464	54	-8	24	4	4.5	448
Medial frontal gyrus—SMA	-4	-4	56	6	6.1	1,248	0	-4	58	6	5.0	2,512
Precuneus	-14	-40	52	7	5.8	216						
Paracentral lobule							0	-40	50	5	3.8	160
Middle temporal gyrus	-54	-32	2	22	4.0	528	-56	-34	4	22	3.8	280
Superior temporal gyrus							-54	-16	2	22	4.6	1,136
Transverse temporal gyrus	-34	-40	14	41	3.9	256	-32	-34	10	41	4.0	240
Superior temporal gyrus							-32	4	-30	38	4.1	464
Subcallosal gyrus							-2	0	-18	25	3.9	328
Caudate	-32	-32	4		4.1	224						
Cerebellum—uvula	-30	-62	-26		5.7	448	-14	-88	-26		5.2	432
Cerebellum—Declive	-28	-72	-22		5.2	304	-20	-64	-22		5.8	4,288
Cerebellar tonsil	-20	-42	-40		5.5	160						
Precentral gyrus	50	-12	30	4/6	5.3	3,016						
Transverse temporal gyrus	38	-34	8	41	3.7	248						
Inferior temporal gyrus	40	-2	-34	20	4.6	248						
Middle temporal gyrus	48	-30	2	22	5.3	1,656						
Superior temporal gyrus	56	-8	4	22	4.9	1,128	46	-20	6	41	3.5	168
Superior temporal gyrus	58	4	-2	22	4.0	224						
Superior temporal gyrus	62	-24	8	42	4.0	288						
Cerebellum—Declive	4	-80	-12		7.4	26,256	14	-62	-18		5.0	1,040
Cerebellum—tuber							34	-60	-28		4.6	872

Note: Only activations with z-score > 3.5, cluster volume > 150 mm³, and $p < .0001$ are reported here.

TABLE 6 Changes in brain activation following articulation therapy at posttreatment and 7-month follow-up

Brain regions	Articulation treatment—post						Articulation treatment—7 m follow-up					
	X	Y	Z	Brodman area	Maximum z-score	Volume (mm ³)	X	Y	Z	Brodman area	Maximum z-score	Volume (mm ³)
Precentral gyrus	-50	-14	30	4	7.4	6,272	-54	-14	26	4	5.9	6,400
Inferior frontal gyrus	-24	30	-22	11	4.6	192						
Superior frontal gyrus							-2	-4	58	6	5.3	1,384
Medial frontal gyrus/SMA	0	0	54	6	6.3	2,992	-2	12	56	6	4.0	264
Insula	-46	0	2	13	5.2	448						
Superior temporal gyrus	-54	-18	2	22	4.1	864	-44	-24	2	22	4.5	296
Transverse temporal gyrus	-40	-26	6	41	4.2	264	-34	-34	8	41	4.4	432
Middle temporal gyrus							-58	-22	-2	21	4.0	368
Uncus	-12	0	-22	34	4.4	408	-12	2	-24	34	3.9	312
Amygdala							-24	-10	-10		4.4	168
Lentiform nucleus—lat Globus pallidus							20	-8	8		4.1	208
Thalamus—Mammillary body	-10	-22	2		4.2	280						
Cerebellum—tonsil	-24	-56	-46		4.7	344	-6	-64	-44		5.2	1,504
Cerebellum—tuber	-42	-66	-26		4.1	5,288						
Cerebellum—dentate	-12	-64	-24		7.7	496						
Cerebellum—nodule	6	-50	-28		5.0	672						
Cerebellum—Declive							-6	-66	-22		8.6	7,816
Inferior semi-lunar lob							-38	-68	-42		4.9	200
Precentral gyrus	52	-8	28	6	5.8	4,304	52	-10	26	6	5.1	2,368
Inferior frontal gyrus	24	28	-22	11	4.5	208						
Superior temporal gyrus	48	-18	2	22	4.0	880	54	-12	2	22	4.1	344
Transverse temporal gyrus							42	-32	8	41	3.9	344
Cerebellum—tonsil	8	-44	-42		4.6	184	38	-54	-42		5.9	488
Cerebellum—Declive	16	-74	-14		8.9	8,472						
Inferior semilunar lobule	24	-62	-40		5.4	296	16	-72	-40		6.6	1,472
Cerebellum—tuber	32	-58	-28		4.0	168	34	-66	-28		4.3	248

Note: Only activations with z-score > 3.5, cluster volume > 150 mm³ and $p < .0001$ are reported here.

shown in Figure 3 and are tabulated in Tables 5 and 6. Figure 4 and Table 7 identify the brain regions showing a significant change during paragraph reading compared with rest at baseline and at 7-month follow-up in the untreated group.

At posttreatment, reading at habitual voice, articulation, and enunciation resulted in activations in bilateral primary and secondary motor cortices and left dorsal premotor region (PMd) in both the voice group and articulation group (Figure 3). Activation in the right PMd,

TABLE 7 Changes in brain activation following no therapy at 7-month follow-up

Brain regions	No treatment—7 m follow-up			Brodmann area	Maximum z-score	Volume (mm ³)
	X	Y	Z			
Precentral gyrus	-54	-12	26	4	3.5	336
Precentral gyrus	-42	-16	38	4	4.1	744
Medial frontal gyrus	-6	-12	58	6	4.0	160
Cingulate gyrus	-8	-10	44	31	4.6	536
Superior temporal gyrus	-60	-24	4	22	5.3	672
Uncus	-22	4	-22	28	4.6	152
Declive	-12	-60	-18		4.7	520
Precentral gyrus	30	-26	46	4	3.5	192
Precentral gyrus	50	-10	28	6	4.7	1,576
Medial frontal gyrus	8	-22	58	6	4.0	152
Superior temporal gyrus	52	8	2	22	4.2	216
Transverse temporal gyrus	58	-22	2	41	4.3	480

Note: Only activations with z-score > 3.5, cluster volume > 150 mm³, and $p < .0001$ are reported here.

TABLE 8 Significant activation in speech motor regions at posttreatment and at 7-month follow-up when contrasted with baseline in the three groups

Brain regions	x	y	z	Brodmann area	Maximum z-score	Volume (mm ³)
Voice treatment posttreatment > baseline						
Precentral gyrus	-30	-16	38	4	5.2	408
Middle temporal gyrus	-54	-36	0	22	4	168
Superior temporal gyrus	58	-12	6	22	4.2	248
Superior temporal gyrus	54	-32	6	41	4.6	200
Voice treatment follow-up > baseline						
Precentral gyrus	-52	-4	30	4/6	3	176
Middle temporal gyrus	-54	-36	2	22	3.66	200
Articulation treatment posttreatment > baseline						
Precentral gyrus	-50	-16	38	4	4.2	232
Precentral gyrus	56	-12	32	4	4.3	120
Superior temporal lobe	-38	-26	6	41	3.9	200
Insula	-44	0	-2	13	5.3	304
Articulation treatment follow-up > baseline						
Precentral gyrus	-50	-16	38	4/6	4.2	192
Precentral gyrus	56	-12	32	4/6	4.2	120
Precentral gyrus	-56	-20	26	4	3.8	120
Insula	-44	0	-2	13	5.3	304
Untreated follow-up > baseline						
Precentral gyrus	-48	-8	26	6	-4.6	328
Precentral gyrus	-42	0	18	6	-3.9	128
Superior temporal lobe	-46	-30	6	22	-4.4	144
Middle temporal gyrus	-50	-48	10	22	-3.5	272

Note: Only activations with z-score > 3.5, cluster volume > 150 mm³, and $p < .0001$ are reported here.

was also observed in both groups (Figure 3). However, only the voice treatment group demonstrated greater activation in the right auditory cortices (Figure 3). Of these activations, the activity in left PMd, right

superior temporal gyrus, and left middle temporal gyrus were found to be significantly higher at posttreatment, when compared to baseline in the voice treatment group (Figure 5, left panel; Table 8).

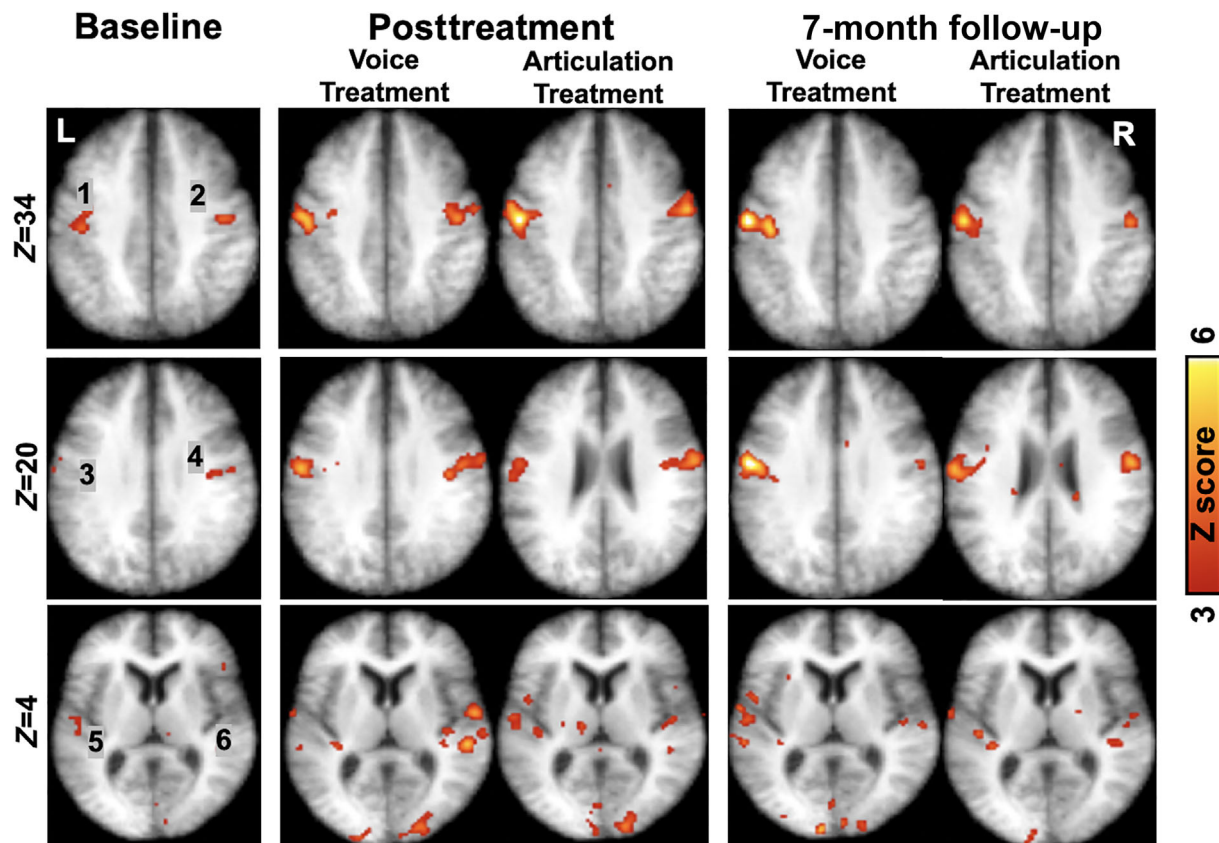


FIGURE 3 Changes in the speech network regions following voice and articulation treatments: (1) left dorsal premotor cortex; (2) right dorsal premotor cortex; (3) left primary laryngeal/mouth motor cortex; (4) right primary laryngeal/mouth motor cortex; (5) left auditory cortex; and (6) right auditory cortex. Note the increased activity in the right hemisphere motor/premotor areas at posttreatment following intensive articulation and intensive voice treatment. The right auditory cortex activation was increased at posttreatment only in the intensive voice treatment group. At follow-up, the intensive voice treatment group activation was normalized to the left hemisphere

Whereas, in the articulation treatment group, significantly increased activity was noted in bilateral PMd, left superior temporal gyrus, and left insula (Figure 5, left panel, Table 8). In the no-treatment group, compared to baseline, we noted no change in the activation pattern of any of the speech motor areas at posttreatment.

At 7-month follow-up, the articulation group exhibited activation in the regions of the primary and secondary motor cortices and dorsal premotor region bilaterally, but the activity in the auditory cortices was found to be reduced (Figure 3). Interestingly, in the voice treatment group, only the activations in the PMd and primary laryngeal/mouth motor cortex and auditory cortex in the left hemisphere remained significant (Figure 3). In the no-treatment group, progressive decrease in activity in the left hemisphere motor, premotor, and auditory cortices was noted when compared to baseline and post-treatment timepoints (Figures 4 and 5, right panel, Table 8). Of these activations, the activity in the left hemisphere primary mouth/laryngeal motor cortex and middle temporal gyrus were significantly higher at 7-month follow-up when compared to baseline in the voice treatment group (Figure 5, middle panel, Table 8). Activations in bilateral premotor cortex and left insula remained significant at 7-month follow-up following articulation treatment (Figure 5, middle panel, Table 8).

4.3.2 | Correlational analysis

From the whole-brain voxel-wise correlation analysis, the brain regions with an r -value $>.6$, z -score > 3 , and $p > .0025$ (Bonferroni corrected) are reported (Figure 6, bottom panel). In the voice treatment group, brain areas that showed a significant positive correlation between VNC and CPPS included primary laryngeal motor cortex in the right hemisphere and superior and middle temporal gyri and insula in the left hemisphere. Confirming these imaging findings, a significant correlation between the VNC counts extracted from left middle temporal gyrus and the right laryngeal motor cortex and the CPPS measures was observed only in the voice treatment group with an r -value of $.62$ and $.66$, respectively ($p < .05$; Figure 6, top panel). The correlation between VNC and CPPS in the articulation treatment and no treatment groups was low and not significant ($p > .05$). No other brain areas showed a significant correlation in any of the three groups.

5 | DISCUSSION

We report here for the first time, the short- and long-term effects of two speech treatments matched for intensive dosage with two

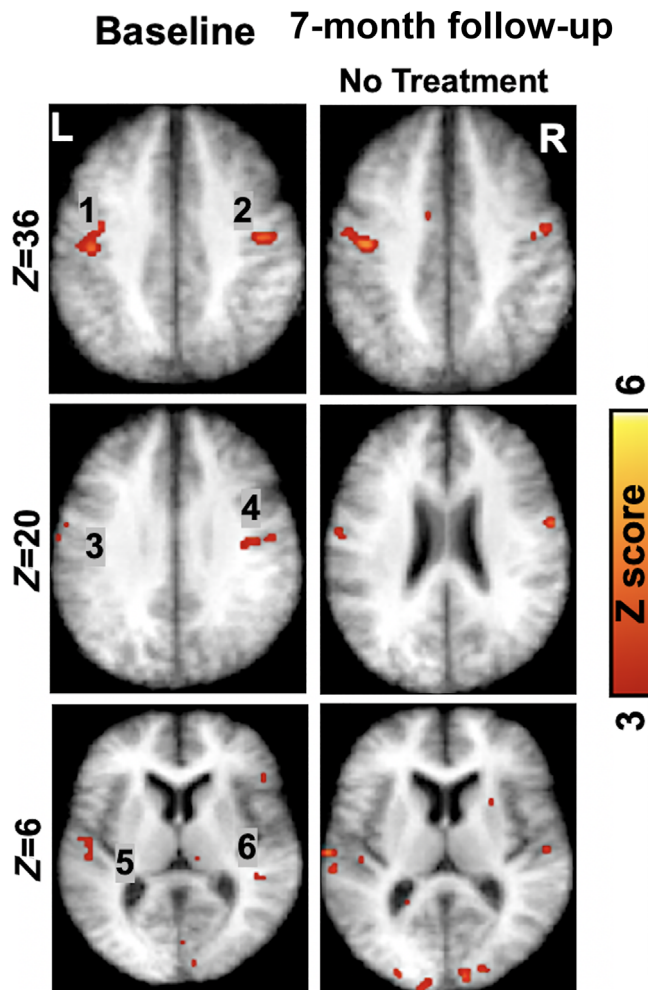


FIGURE 4 Changes in the speech motor system in no-treatment group. Progressive decrease in activity in left and right dorsal premotor cortex (1 and 2), left and right primary laryngeal/mouth motor cortices (3 and 4) were noted. In addition, continued weak activity in left auditory cortex (5) and progressive decrease in activity in right auditory cortex (6) were observed. These changes represent weakening speech motor system and unsuccessful compensatory mechanisms

different treatment targets: voice or articulation in individuals with Parkinsonian HKD on an acoustic measure of voice quality. When compared to articulation treatment and no treatment, voice treatment resulted in a significant improvement in CPPS at posttreatment that was maintained at 7-month follow-up (Figure 2). Additionally, the treating speech-language pathologist collected clinical dB SPL data for an uncued reading of the Grandfather passage on the initial and final day of treatment for participants in the voice treatment group. Within-group changes of dB SPL for passage reading in the voice treatment group (mean = 4.0; SD = 2.6) show significant improvement ($p < .05$), as revealed by a *t*-test, further confirming a positive treatment effect. These findings are consistent with the previous finding of SPL following the voice and articulation treatments (Ramig et al., 2018) and CPP changes immediately following voice therapy (Alharbi et al., 2019). While previous studies investigating effects of

intensive voice or articulation treatment have used dB SPL as a primary acoustic measurement, CPPS was chosen for this study due to its increasing use as an objective tool in research and clinical evaluation of voice disorders.

The significant changes in CPPS following voice treatment confirm that voice treatment results in improved harmonic structure and reduced dysphonia likely resulting from an increase of glottal closure and subglottal pressure (Ramig & Dromey, 1996; Smith et al., 1995). Although articulation treatment emphasized enunciation, increased movement amplitude of oro-facial muscles, and maximum effort by patients and was delivered with the same intensity as voice therapy, it did not result in any significant change in CPPS at posttreatment. The nonsignificant changes in CPPS following articulation treatment indicate that the treatment target of articulation does not alter laryngeal function in any acoustically measurable manner as detectable by CPPS. This study also independently confirms the previous finding (Ramig et al., 2018) that the treatment targeting voice intensity was more effective in treating HKD than that targeting articulation. Another unique feature of this study is the repeated measures of speech and voice data at each time point. Such repeated measures of voice and speech data allowed us to capture measurement stability. The inter-class correlation data support high test-retest reliability of our measures.

We also report here for the first time, the short- and long-term effects of two treatments matched for intensive dosage but having two different treatment targets (voice or articulation) on the speech motor network in individuals with Parkinsonian HKD. In the short-term, we observed treatment target specific changes in the cerebral blood flow in regions of the speech motor network resulting from both voice and articulation treatments. Voice treatment resulted in increased activity in left PMd while articulation treatment increased activity in right PMd. These changes in the premotor areas likely represent a treatment-induced increased control of movement execution with both treatments. In addition, these changes could represent the result of intensity of training and emphasis on maximum effort common to both treatments. These findings may appear to be contradictory to behavioral changes noted following the two treatments. In this study, CPPS was not significantly improved in the group receiving articulation treatment. In the previous study (Ramig et al., 2018), articulation treatment had a slight but significant improvement in SPL for reading and speaking. An explanation for this observation could be that both CPPS and SPL for reading and speaking are mediated by increased laryngeal activity, which was not the target of articulation treatment. Therefore, what could be the cause of increased activity in the premotor cortices in this group? One consideration for future research would be to quantify potential effects of articulation on running speech. In a preliminary analysis, we calculated the normalized spectral energy between 1 and 3.125 kHz (total energy between 1–3.125 kHz compared to overall spectral energy of the sample). This energy range has been shown to correlate with articulation changes when people move from “conversational” to “clear speech” (Krause & Braida, 2004). We found a significant increase in energy between 1 and 3.125 kHz at posttreatment when compared to baseline in both

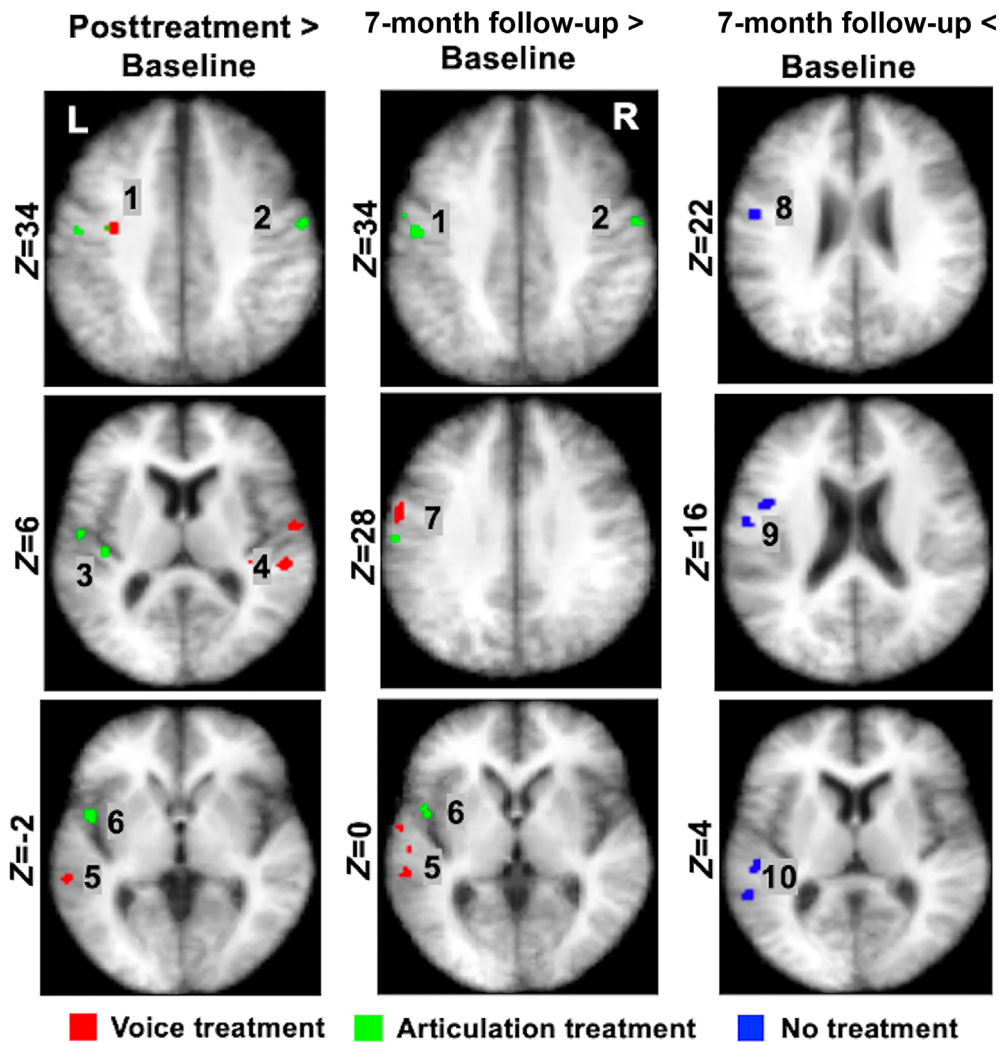


FIGURE 5 Changes in speech motor regions resulting from voice (red) and articulation (green) treatments, and no treatment (blue) at posttreatment and at 7-month follow-up. Only voxels with z-score > 3 are shown. Voice treatment resulted in significantly increased cerebral blood flow in left premotor cortex (1), right superior temporal gyrus (4), and left middle temporal gyrus (5) at posttreatment, and in left hemisphere primary mouth/laryngeal motor cortex (7) and middle temporal gyrus (5) at 7-month follow-up. Articulation treatment resulted in significantly increased cerebral blood flow in bilateral premotor cortex (1 and 2), left superior temporal gyrus (3), and left insula (6) at posttreatment. Activations in bilateral premotor cortex and left insula remained significant at 7-month follow-up following articulation treatment. No treatment resulted in decreased activity in premotor cortex (8), laryngeal motor cortex (9), and superior temporal gyrus (10)

voice and articulation groups, but not in the untreated group. These initial observations suggest that since the articulation treatment targeted enunciation, increased movement amplitude of oro-facial muscles, and maximum effort, it directly resulted in increased activity in premotor regions. However, the increase in normalized spectral energy was maintained only in the voice treatment group at 7-month follow-up, but not in the articulation group. Future research will continue to investigate this finding more systematically. Premotor cortex activation observed in the articulation group could also be attributed to improvement in intelligibility in this group. Previously, some forms of articulation treatment have been reported to improve overall intelligibility (Yorkston, Beukelman, & Traynor, 1988). Although intelligibility was not assessed in the current study, it has been studied by other investigators (Levy et al., 2020; Schulz et al., 2021) who reported significant improvements in intelligibility following intensive voice treatment.

Additionally, both treatments resulted in increased activity in auditory cortices, albeit in different parts of the temporal lobe. Voice treatment resulted in greater activity in the superior temporal gyrus in the right hemisphere and middle temporal gyrus in the left hemisphere. The bilateral increase with a rightward shift in auditory

activity following voice treatment is consistent with our previous reports (Narayana et al., 2010), and likely correlating with the improved internalization of voice cuing or recalibration observed with voice treatment. These changes in auditory cortex activity observed only in the voice treatment group likely indicate changes specific to the treatment target. Since the CPPS was also observed to improve only in the voice treatment group, we believe that the harmonic spectral dominance of connected speech may be mediated by the right hemisphere superior temporal gyrus. Another auditory area that showed treatment target-specific activation was the left superior temporal gyrus, observed only in the articulation group. The activity in this region has been shown previously to show strong selectivity to articulation (in contrast to nonspeech movements) indicating to its role in speech planning and speech production (Basilakos et al., 2018; Woolnough et al., 2019). Our findings provide additional evidence that activity in the left superior temporal gyrus is also modified by treatments that target articulation. We also observed significant increase in activity in left posterior insula in the articulation group at posttreatment. Engagement of insula during articulation is thought to support respiratory control and monitoring of speech production (Ackermann & Riecker, 2010; Dronkers, 1996; Oh et al., 2014;

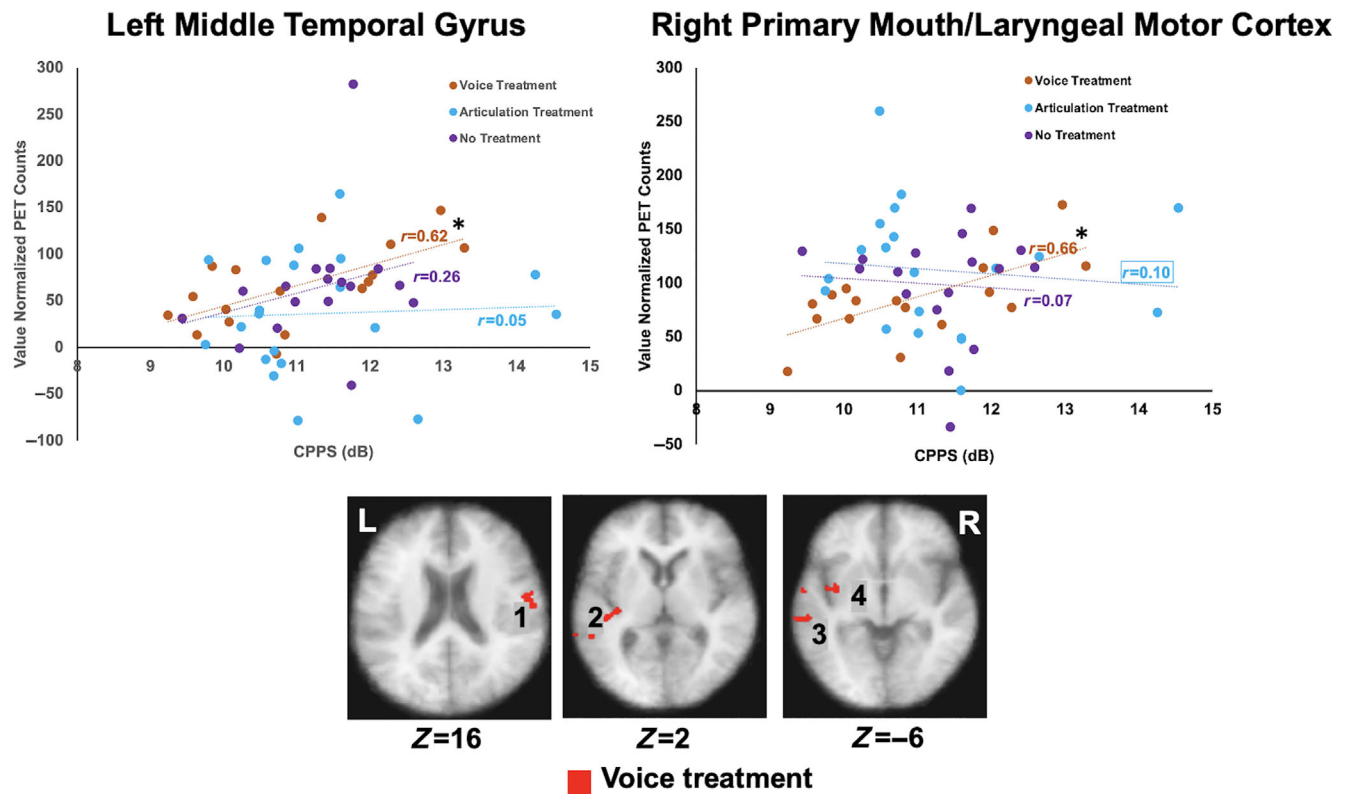


FIGURE 6 Correlation between CPPS and value normalized PET counts in reading contrasted with rest condition at baseline, posttreatment, and 7-month follow-up in the three groups in left middle temporal gyrus (top left) and right primary mouth/laryngeal motor cortex (top right). Significant ($p < .05$) relationship was observed between CPPS and PET Value normalized counts in these areas only in the intensive voice treatment group. A whole-brain voxel-wise correlation analysis re-demonstrated activity in these brain areas to significantly correlate with CPPS only in the voice treatment group (bottom panel). (1) Right primary mouth/laryngeal motor cortex, (2) left superior temporal gyrus, (3) left middle temporal gyrus, and (4) left insula. Only voxels with $r > .65$ are shown

Woolnough et al., 2019). While increased activity in insula and superior temporal gyrus during articulation has been previously shown in typical speakers, our study is the first to demonstrate direct modulation of these areas following treatment targeting articulation in individuals with dysphonia.

The present study is the first to examine the long-term effects of speech treatments on the speech motor network. At a 7-month follow-up, the voice treatment group demonstrated increased activity during reading in the laryngeal/mouth motor cortex and middle temporal gyrus only in the left hemisphere. The bilateral premotor and insular activation persisted in the articulation treatment group. Our results indicate that the right-sided activations in the auditory cortices observed at posttreatment likely indicate an intermediate phase in skill learning. In the long-term, the activity in the motor and auditory areas of the speech motor system reverted to the dominant hemisphere indexing successful skill retention. Similar patterns of increased activity in right and left hemisphere regions during skill acquisition and skill retention have been previously demonstrated in slow motor learning paradigms (Ma et al., 2011). These neuronal changes could be subserving the sustained improvement in vocal intensity and CPPS observed in this group. Such a phenomenon of continued change in speech motor network was not observed in articulation treatment, who also did not show any changes in speech and voice behaviors.

However, contrary to our expectation, increased activation in the brain areas subserving articulation was observed even at a 7-month follow-up in the articulation treatment group. We attribute this to be the result of intense dosage of treatment delivery. In the untreated group, we observed continued decrease in brain activity during reading in motor, premotor, and auditory cortices indicating further deterioration in HKD in this group (Figure 5, right panel). This is the first neuroimaging demonstration of progression of HKD in individuals with PD and highlights the need for early intervention in this group.

In order to examine the relationship between the CPPS changes observed in the study cohort and the cerebral blood flow in the speech motor network, we correlated the CPPS at baseline, posttreatment, and 7-month follow-up in the three groups with the value normalized counts in the reading contrasted with rest images at the same time points. Consistent with the behavioral findings, we found only voice group showed increased activity in the right primary laryngeal/mouth motor cortex and left middle temporal gyrus. These regions have been previously observed to correlate with change in voice intensity (SPL) following voice treatment (Narayana et al., 2010) confirming that the acoustic changes noted in this cohort were mediated by changes in activity of in the primary motor and auditory cortices. In particular, the correlation between CPPS and motor cortices in the right hemisphere confirms the rightward shift in voice control

following intensive voice treatment, reported in our previous study (Narayana et al., 2010). Since no significant changes in CPPS were observed in articulation treatment and no treatment groups, it is not surprising that we did not find a significant relationship between CPPS and any brain area in these two groups.

5.1 | Limitations

Because this is a behavioral intervention trial, neither the clinician providing treatment nor participants could be blinded. However, great care was taken to evaluate the reliability, ensure equipoise, implement standardized training, minimize bias in data collection and analysis, and maintain independence between the treating clinician and those recording data. The imaging data were limited by the number of subjects in each group. Due to the radiation exposure limitation of PET imaging, the number of repetitions of tasks at each visit was limited to two trials, which may have contributed to lower statistical power. However, the conditional contrast data were robust with significant activations persisting after correcting for multiple comparisons.

6 | CONCLUSIONS

This study compared acoustic and neural changes accompanying a treatment targeting voice with that targeting articulation, both matched on intensive dosage in order to dissociate the effects of treatment target and intensive dosage in speech treatments. This is the first neuroimaging study demonstrating a system-specific change in brain activity resulting from both voice and articulation treatments. The changes in the premotor regions of speech motor network likely represent a target-induced increased control of movement execution that was observed in both voice and articulation treatments. Such common activations indicate that the effects are mediated via the intensive dosage with which both treatments were delivered. However, the long-lasting alterations in the motor and auditory cortices of speech motor network were observed only in the voice treatment group, indicating to the specific effect of the treatment target of voice intensity. Additionally, these findings likely represent the improved internalization of voice training intensity-induced auditory recalibration. The right-sided increases in motor, premotor, and auditory cortices in the short-term observed in the voice treatment group may also indicate a critical phase in skill learning and a long-term normalization of the activity to the dominant hemisphere indexing successful skill retention. This study also reveals that CPPS, an acoustic measure of voice quality, serves as a good measure to evaluate speech and voice treatments. Specially, CPPS significantly increased at post-treatment and was maintained at 7-month follow-up only in the voice treatment group, confirming previous findings in SPL in a similar study. The CPPS changes were found to be correlated with brain activations in brain regions within the speech motor network suggesting a potential neural mechanism for mediating treatment-induced changes in voice quality. The long-term changes in speech motor network

observed in this study aid in dissociating the effects of targets and dosage of speech treatments in individuals with PD dysphonia. While treatment targets engage target-specific brain regions, the dosage of treatment helps in long-term maintenance of skills irrespective of treatment targets. Finally, this study documents the progressive changes in the speech motor networks in untreated individuals supporting the need for early intervention to treat of speech and voice symptoms in individuals with PD.

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CONFLICT OF INTEREST

Lorraine Ramig is employed as Chief Scientific Officer and has ownership interest in the for-profit company, LSVT Global, Inc. Elizabeth Peterson and Angela Halpern are employed by LSVT Global, Inc. Dr Ramig, Ms Peterson, and Ms Halpern have disclosed any conflict of interest and conflict of interest management plans have been approved by the Office of Conflict of Interest and Commitment at the University of Colorado, Boulder.

ETHICS STATEMENT

All study procedures were approved by the Institutional Review Board at the University of Texas Health Science Center at San Antonio.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all participants.

DATA AVAILABILITY STATEMENT

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

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