

Hypophonia in Parkinson's disease

Neural correlates of voice treatment revealed by PET

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Abstract—Objective: To investigate the neural correlates of hypophonia in individuals with idiopathic PD (IPD) before and after voice treatment with the Lee Silverman Voice Treatment method (VT) using $^{15}\text{O}\text{-H}_2\text{O}$ PET. **Methods:** Regional cerebral blood flow (rCBF) changes associated with overt speech–motor tasks relative to the resting state were measured in the IPD subjects before and after VT, and in a group of healthy control volunteers. **Results:** Behavioral measures of voice loudness significantly improved following treatment. Before VT, patients had strong speech-related activations in motor and premotor cortex (M1-mouth, supplementary motor cortex [SMA], and inferior lateral premotor cortex [ILPm]), which were significantly reduced post-VT. Similar to the post-treatment session, premotor activations were absent (SMA) or below statistical threshold (M1-mouth) in the healthy control group. In addition, following VT treatment, significant right-sided activations were present in anterior insular cortex, caudate head, putamen, and dorsolateral prefrontal cortex (DLPFC). Finally, the VT-induced neural changes were not present with transient experimenter-cued increases of loudness in VT-untreated patients. **Conclusions:** Effective improvement of IPD hypophonia following voice treatment with VT was accompanied by a reduction of cortical motor–premotor activations, resembling the functional pattern observed in healthy volunteers and suggesting normalization, and additional recruitment of right anterior insula, caudate head, putamen, and DLPFC. This treatment-dependent functional reorganization suggests a shift from an abnormally effortful (premotor cortex) to a more automatic (basal ganglia, anterior insula) implementation of speech–motor actions.

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Disordered communication is particularly prevalent in the 1.5 million individuals with idiopathic PD (IPD). Although 89% have speech and voice symptoms, only 3 to 4% receive speech treatment.¹ Pharmacologic and neurosurgical interventions improve rigidity, tremor, and akinesia in individuals with IPD,^{2–5} but speech and voice function appears largely unaffected.⁶ In contrast, clinical efficacy has been demonstrated for voice therapy (Lee Silverman Voice Treatment or LSVT^{7–9} [VT]), and associated changes in speech and voice measures^{10–12} as well as facial expression¹³ have been documented. VT is based on intensive voice and loudness training, including 16 sessions, four times a week, over a 1-month period. Each session consists of repetitions of tasks such as maximum duration sustained “ah” phonation and maximum pitch range. Increased loudness is implemented through a hierarchy of speech tasks including words/phrases (week 1), sentences (week 2), reading (week 3), and conversation (week 4).^{7–9}

At a phenomenological level, in addition to a low

volume and breathy voice, individuals with IPD have an inability to spontaneously maintain loudness, in spite of often being able to increase their loudness by at least 5 to 10 dB sound pressure level (SPL) when cued by a listener. They also complain of feeling too loud when trying to increase their voice level to improve speech intelligibility. In contrast, effective treatment with VT is followed by increased loudness in functional speech production, as well as improved awareness of loudness that is maintained over time, without cueing.^{5–7}

The widespread effects of VT strongly implicate a central origin for the neural mechanisms associated with voice improvement. However, to date, the central mechanisms of VT are basically unknown.

Over the last 10 years, several functional imaging studies have investigated limb–motor function in individuals with IPD, using a variety of simple or complex motor tasks.^{14–24} These studies have identified abnormalities in cortical premotor areas (particularly supplementary motor cortex [SMA]) and

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Table 1 Demographic and clinical characteristics of the individuals with IPD

Patient	Sex	Age, y	Duration, y	Hoehn-Yahr score	Medication	Dose
1	F	59	9	3	Sinemet CR	50/200 8 tabs/d
					L-Deprenyl	5 mg BID
					Amantadine	100 mg BID
2	M	72	3	2	Sinemet CR	50/200 BID
					Mirapex	0.25 mg BID
					Parlodel	2.5 mg BID
3	M	66	3	2	Sinemet CR	50/200 TID
					Eldepryl	5 mg BID
4	M	59	6	2	Sinemet	25/100 6 tabs/d
					Sinemet CR	50/200 at 10 AM/5 PM
					Amitriptyline	100 mg at 10 PM
					Mirapex	0.25 mg TID
5	M	55	7	2	Sinemet CR	50/200 TID
					Mirapex	1.5 TID
					Eldepryl	5 mg qam
					Tolcapone	200 mg TID

1 PD = idiopathic PD; BID = twice daily; TID = three times daily; qam = every morning.

cerebellum, and have reported changes in these and other regions associated with improved motor–limb function following treatment with apomorphine,¹⁹ levodopa,²⁰ pallidotomy,^{21,22} and pallidal²² and subthalamic^{24,25} stimulation. However, no functional imaging studies have been carried out using speech–motor tasks in individuals with IPD to investigate the neural correlates of hypophonia and their change with successful speech and voice treatment.

The aims of the current study were twofold. The first goal was to identify neural correlates of VT-induced voice improvement. The second goal was to single out the possibility that VT effects could be simply accounted for by increased post-VT loudness. ¹⁵O-H₂O PET was therefore employed during three tasks—overt paragraph reading, sustained phonation (ah), and eyes closed rest—in individuals with IPD with hypophonia, before and immediately after voice treatment with VT. The effect of loudness was tested by manipulating vocal loudness during the overt reading task before voice treatment (loud vs habitual voice). A control group of age-matched healthy volunteers performing the overt paragraph reading and eyes closed rest was included for comparison. PET was chosen over fMRI because of the susceptibility of the fMRI modality to speech-related motion artifacts.

Methods. *Subjects.* *Selection.* The experimental group included five patients (four men, one woman, all right-handed) with diagnosis of IPD and marked speech and voice disorder. Mean age was 61 ± 4 years. Symptom severity was mild to moderate (Hoehn and Yahr²⁶ scores 2 and 3). Mean onset of the illness was 5.6 ± 2.6 years (range 3 to 9 years). They were all on levodopa medication (table 1). Patients had no history of past or present additional neurologic or psychiatric disease. They were not depressed or sig-

nificantly cognitively impaired. All subjects were patients in the Medical Center Clinic and were referred by a neurologist (P.N.) as possible candidates for voice treatment with VT. Patients were considered for VT if they had significant hypophonia but could increase vocal loudness on command (5 to 10 dB at 30 cm SPL). VT was administered according to the usual schedule (1 hour per day 4 days per week for 4 weeks^{7,8}) by a speech-language pathologist trained and certified in VT (D.V.). Medication status was not changed throughout the period of voice treatment.

The control group included five right-handed healthy volunteers (two men, three women). Mean age was 58.6 ± 14 years (not statistically different from the IPD group). They had no history of current or past neurologic or psychiatric disease or substance abuse. They were part of a larger group of control volunteers in a PET study on developmental stuttering²⁷ (owing to their age, the data were not included in the published report focusing on young adult stutterers).

Written informed consent was obtained from all subjects, and all procedures were conducted as approved by the University of Texas Health Science Center Institutional Review Board.

Imaging methods. *PET acquisition.* PET scans were acquired on a GE/Scanditronix 4096 camera (Uppsala, Sweden) (15 parallel slices; 6.5 mm center-to-center interslice distance; transaxial field of view 10.0 cm) using measured attenuation correction (68 Ge/68 Ga transmission scans) and reconstructed with an in-plane resolution of 7 mm, full width at half-maximum (FWHM). Cerebral blood flow was measured using a bolus ¹⁵O-water technique (60 to 65 mCi H₂¹⁵O dose/scan; H₂¹⁵O half-life 123 seconds; scan duration 90 seconds). Subjects were immobilized within the PET scanner using individually fitted, thermally molded, plastic facial masks.²⁸ An antecubital venous catheter was placed for administration of the blood flow radiotracer. Each individual with IPD was studied in two sessions: before VT and immediately after VT. In the first session (pre-VT), patients underwent eight measurements of brain blood flow during the following tasks: paragraph reading—habitual voice level; paragraph reading—experimenter-cued loud voice level; sustained phonation—experimenter-cued loud voice level; and eyes closed rest (two repetitions each). In the second session (post-VT), there were six scans: paragraph reading and sustained phonation (both at spontaneous voice level) and eyes closed rest (two repetitions each).

In the sustained phonation task, patients were asked to take a deep breath, then sustain phonation ([a]) for as long as possible,

Table 2 Main results of the group average conditional contrasts of sustained phonation vs eyes closed rest, regional cerebral blood flow increases only

Area	x	y	z	CS	z-Score
Pre-VT					
Motor/premotor					
L infLPm6	-52	-10	20	240	3.8
R SMA	2	-6	60	193	3.5
R M1-mouth	37	-14	40	142	3.5
L M1-mouth	-42	-17	42	118	3.2
Insula					
L Ant Ins	-38	3	12	89	3.3
Auditory					
R GTm 21	48	-17	0	234	4.1
L GTs 22	-46	-16	6	209	3.6
Cerebellum					
R posterior vermis	5	-66	-14	196	3.8
L posterior vermis	-8	-58	-16	154	3.4
L postlateral crbll	-18	-56	-28	125	3.3
Post-VT					
Insula					
R Ant Ins	40	14	9	274	4.2
L Ant Ins	-36	0	7	176	3.8
Aud					
R GTs 22	55	-8	6	159	3.3
R GTs 42	48	-14	10	145	3.2
Cerebellum					
L anterior vermis	-2	-46	-21	136	3.8
R anterior vermis	10	-41	-18	155	3.7
Basal ganglia					
R putamen	25	10	12	170	3.6
	28	-4	6	206	3.3
R caudate	6	20	2	79	3.2
Prefrontal					
R DLPF9	26	43	36	146	3.9
L DLPF9	-34	38	36	61	3.2
Thalamus					
L MD Thal	-5	-20	11	143	3.6

Talairach coordinates are expressed in mm from the anterior commissure. Positive x values: right hemisphere. Positive y values: front. Positive z values: top. Criterion for inclusion in the table is a z-score > 2.9 , $p < 0.002$ in at least one session. In that case, activations for that region in the other session are reported when z-score > 1.96 , $p < 0.05$, uncorrected.

CS = cluster size; VT = voice treatment; infLPm = inferior lateral premotor cortex; SMA = supplementary motor cortex; Ant Ins = anterior insula; GTm = middle temporal gyrus; GTs = superior temporal gyrus; crbll = cerebellum; BA = Brodmann area; DLPF = dorsolateral prefrontal; MD Thal = mediodorsal nucleus of thalamus.

then take another deep breath, then again sustain phonation, and so on until the end of the scan (90 seconds). In the first session (pre-VT), patients first practiced the sustained phonation task at a habitual, comfortable loudness level. During the actual PET scans that followed, individuals with IPD were instructed "to say ([a]) as loud as possible" until they were told to stop. In the second session (post-VT) no instructions concerning loudness were provided.

The paragraph reading task employed the rainbow passage, a commonly used reading test in speech and voice assessment. The

passage was displayed on a 25-inch screen placed about 30 cm in front of patients' eyes. Patients were instructed to read aloud continuously for the duration of the task (90 seconds). At the end of the passage, they were told to start again from the beginning and continue to read aloud until completion of the 90-second period. In the first session (pre-VT), patients were scanned while reading at a habitual voice level (two repetitions), and again after instructions to read as loud as possible (two repetitions). In the second session (post-VT) no instructions concerning loudness were provided.

Table 3 Main results of the group average conditional contrasts of paragraph reading vs eyes closed rest, regional cerebral blood flow increases only

Area	IPD pre-VT					IPD post-VT					Healthy controls										
	Loud voice–cued			Habitual voice		Loud voice–spontaneous			Habitual voice					Habitual voice							
	x	y	z	CS	z-Score	x	y	z	CS	z-Score	x	y	z	CS	z-Score	x	y	z	CS	z-Score	
Premotor																					
R SMA		2	0	62	235	3.9	1	-3	62	171	3.5										
L M1-mouth	-44	-14	42	118	3.0	-40	-9	44	144	2.9	-41	-2	50	78	2.8	-46	-8	34	141	2.6	
R M1-mouth	50	-10	36	149	2.8	50	-8	34	145	2.9	52	-10	44	52	2.5	52	-6	34	97	2.5	
Cerebellum																					
L postlateral	-20	-58	-27	89	3.3						-18	-57	-18	167	3.4	-6	-76	-23	187	2.9	
											-19	-61	-5	75	3.2	-18	-61	-24	50	2.5	
R postlateral	14	-64	-20	250	4.0	6	-70	-10	315	4.2	2	-50	-22	205	3.8						
						24	-70	-18	140	3.1	7	-41	-20	55	3.3						
											-2	-64	-30	223	3.7						

Activations in visual cortex are not reported. Same conventions as in table 2. Criterion for inclusion in the table is a z-score > 2.9, $p < 0.002$ in at least one session. In that case, activations for that region in the other session or in the control group are reported when z-score > 1.96, $p < 0.05$, uncorrected.

IPD = idiopathic PD; VT = voice treatment; CS = cluster size; SMA = supplementary motor cortex.

In the eyes closed rest condition, patients were asked to lie still with eyes closed and maintain a relaxed state.

Subjects in the control group took part in a single session. Two tasks were employed: overt paragraph reading (two repetitions) and eyes closed rest (two repetitions). Reading was at a habitual voice level. No scans were acquired in the sustained phonation task.

An anatomic MRI scan was also acquired for each subject on the day of the first PET session, for the purposes of spatial transformation of the PET data, region-of-interest analysis, and parametric image display (Elscent Gyrex 1.9T-DLX; Haifa, Israel; three-dimensional–gradient recalled acquisition in a steady state [GRASS] sequence; repetition time = 33 msec; echo time = 12 msec; flip angle = 60 deg; $256 \times 256 \times 127$ volume; spatial resolution of 1 mm^3).

PET data analysis. All analyses were performed using previously validated methods and in-house software. Within-session task-related changes were detected using voxel-by-voxel statistical parametric mapping (change distribution analysis) and interpreted using atlas-based coordinates and Brodmann areas (BA). Between-session (pre- vs post-treatment) within-task regional effects were explored using a region of interest (ROI) method followed by repeated measures analyses of variance (ANOVA) (see below). Automatic alignment and reslicing of the PET images was first performed to correct for head motion. PET and MRI images were then spatially transformed into proportional bicommissural coordinate space²⁹ relative to the 1988 stereotaxic atlas of Talairach.³⁰ Regional tissue uptake of ^{15}O -water was globally normalized to whole regional cerebral blood flow (rCBF) brain mean with images scaled to an arbitrary mean of 1,000. Value and spatially normalized images were trilinearly interpolated, resampled (60 slices, 8 mm^3 voxels), and Gaussian filtered to a final resolution of 9.9 mm (FWHM) before statistical analysis.

For each subject and session, voxel-by-voxel pairwise contrasts were performed to identify regional changes present during overt paragraph reading relative to eyes closed rest (patients with IPD and controls) and sustained phonation relative to eyes closed rest (individuals with IPD only).

Task-specific, within-subject regional changes were then averaged across individuals in the three groups (IPD pre-VT, IPD post-VT, and controls). A maxima and minima search³¹ was then used to identify local extrema within a search volume measuring 125 mm^3 . A beta-1 statistic measuring skewness of the histogram of the distribution of the extrema (change distribution curve) was used as an omnibus test to assess overall significance. The beta-1 test was implemented in the MIPS software (Research Imaging

Center, San Antonio, TX) in a manner similar to the use of the gamma-1 statistic. The beta-1 improves on the gamma-1 by using a better estimate of the degrees of freedom in PET images.³² To facilitate visualization of the data, group-mean subtraction images were converted to statistical parametric images of z-scores and superimposed on group mean MR images for the subject group. Locations of focal maxima and minima exceeding a z-score of 2.9 ($p < 0.01$, two-tailed) in at least one session are listed in tables 2 and 3 with the peak voxel (search cube volume = 125 mm^3) of each extrema described in x-, y-, and z-coordinates as millimeters relative to the anterior commissure.

The ROI analysis explored effects of the voice treatment on each task (rest, reading, phonation) in the group with IPD only. It employed $3 \times 3 \times 3$ voxel regions (216 mm^3) centered on extrema of the average group maximal regional difference in the previous analysis. Mean counts in each ROI per subject, repetition, and task were entered in repeated measures ANOVAs, with within factors being treatment (pre- vs post-VT), task (rest, reading, phonation), and repetition (trial one vs trial two). Degrees of freedom were corrected with the Greenhouse-Geisser epsilon method.

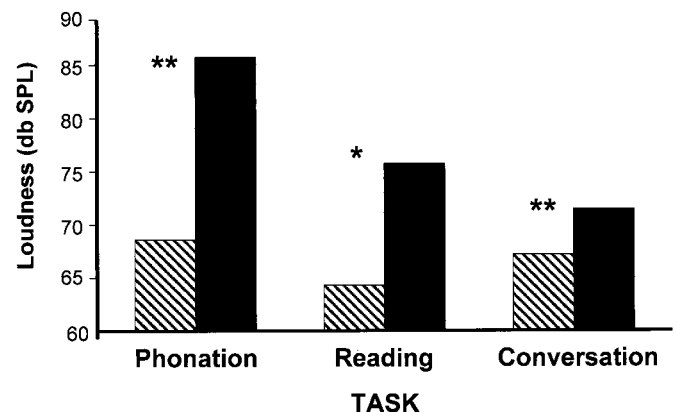


Figure 1. Changes in measured vocal loudness following voice treatment (VT) in sustained phonation, reading, and spontaneous conversation (* $p < 0.05$; ** $p < 0.005$). Pre-VT = hatched; post-VT = solid black.

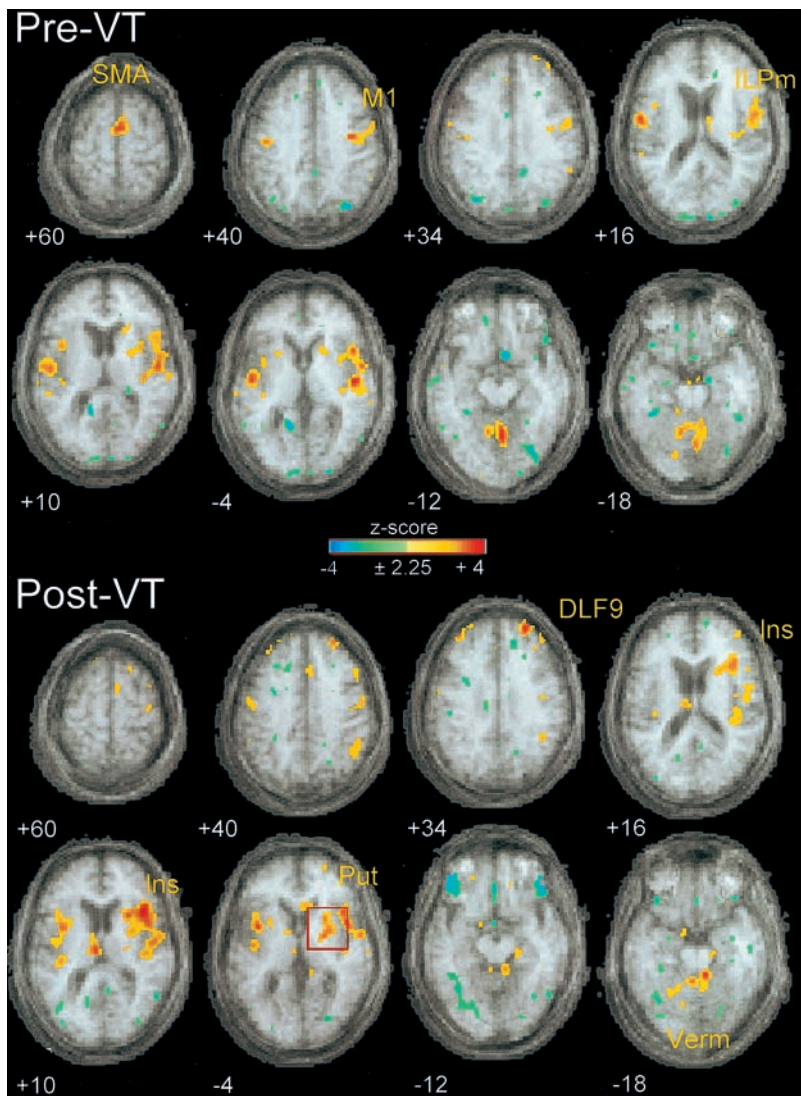


Figure 2. Sustained phonation vs eyes closed rest: Significant regional cerebral blood flow (rCBF) changes pre-voice treatment (VT) (top), post-VT (bottom). Axial slices. z-Score cut-off: ± 2.25 ($p < 0.01$). z-Score cut-off is lower than in table 2 to improve visualization of the effects. Right hemisphere is on the right; left hemisphere is on the left. SMA = supplementary motor area; M1 = primary motor cortex–mouth; ILPm = inferior lateral premotor cortex (Brodmann area [BA] 44/6); A2 = secondary auditory cortex (BA 22/21); Verm = cerebellar vermis; DLF9 = dorsolateral prefrontal cortex (BA 9); Ins = anterior insular cortex; Put = putamen/pallidum.

Results. Behavioral VT effects. Voice data acquired in the scanner were not suitable for analysis owing to technical artifacts in three patients. Data reported here pertain to a comparison between voice and speech measures acquired outside the PET suite, immediately before and after VT (at 30 cm SPL) (figure 1). The following measures were analyzed: loudness and duration of sustained phonation, loudness of paragraph reading, and loudness of spontaneous conversation (measured at 30 cm). Each variable was entered in a repeated measures ANOVA with factor being session (pre-VT vs post-VT). Post-VT loudness was higher during sustained phonation (68.2 ± 5.2 vs 85.6 ± 1.7 dB, $F[1,4] = 33.4$, $p < 0.005$), paragraph reading (64 ± 8.4 vs 75.8 ± 8.5 dB, $F[1,4] = 12.5$, $p = 0.02$), and spontaneous conversation (66.8 ± 3.7 vs 71.6 ± 4 , $F[1,4] = 31.1$, $p = 0.005$). Duration of sustained phonation did not significantly increase after VT (19 vs 23.1 seconds, $F[1,4] = 3.3$, NS). The increase in objective loudness across various tasks is consistent with previously published pre- to post-treatment data for VT^{7,8,11} and confirmed the overwhelming clinical impression of dramatic improvements of hypophonia and voice intelligibility. These outside the PET suite data were representative of the speech and voice behavior in the scanner.

PET results. Within session effects. Sustained phonation task. Figure 2 and table 2 show the significant rCBF changes for the sustained phonation vs rest contrasts in the IPD group. Only relative CBF increases will be discussed here, because relative rCBF decreases in speech–motor areas (more activation at rest than during the active speech–motor task) were considered unlikely.

Pre-VT. Before voice treatment, the conditional contrast of sustained phonation vs rest revealed rCBF changes (omnibus significance: $df = 2,180$, beta-1 z-score = 4.15, $p < 0.0001$). Activa-

tions were present in primary motor and premotor cortical regions, including SMA, the motor–mouth primary representation (M1), stronger on the right, and bilateral inferior lateral premotor cortex (ILPm) (including Broca area 44), the left anterior insula, bilateral auditory association cortex (BA 21 and 22), cerebellar vermis, and left posterior lateral cerebellum (see table 2 and figure 2).

Post-VT. Following voice treatment, the conditional contrast of sustained phonation vs rest showed rCBF changes (omnibus significance: $df = 2,180$, beta-1 z-score = 4.72, $p < 0.0001$). However, there were no significant activations in motor and premotor cortex. Phonation-related clusters were localized in anterior insular cortex (predominantly right), dorsolateral prefrontal (DLPF) cortex BA9 (much greater on the right), right putamen, right caudate nucleus, and left mediadorsal nucleus of the thalamus. Similarly activated were auditory association cortex and cerebellar vermis, although the extent of activation was somewhat reduced (by 32% and 39%) (see table 2 and figure 2).

Paragraph reading task. Table 3 and figure 3 show changes in the conditional contrast of paragraph reading vs rest in the IPD group before VT, after VT, and in the control group (z score threshold = ± 2.9 , $p < 0.002$). Activations in primary and secondary visual cortex associated to reading were present in both groups and sessions. They were similar in z-score level and extent, and are omitted here.

Pre-VT. Before voice treatment, individuals with IPD had rCBF changes in both conditional contrasts of habitual voice reading vs rest and loud voice reading vs rest (omnibus significance, $df = 2,180$, beta-1 z-score = 15.3 and 17.4; for both, $p < 0.0001$). There were robust activations in supplementary motor cortex

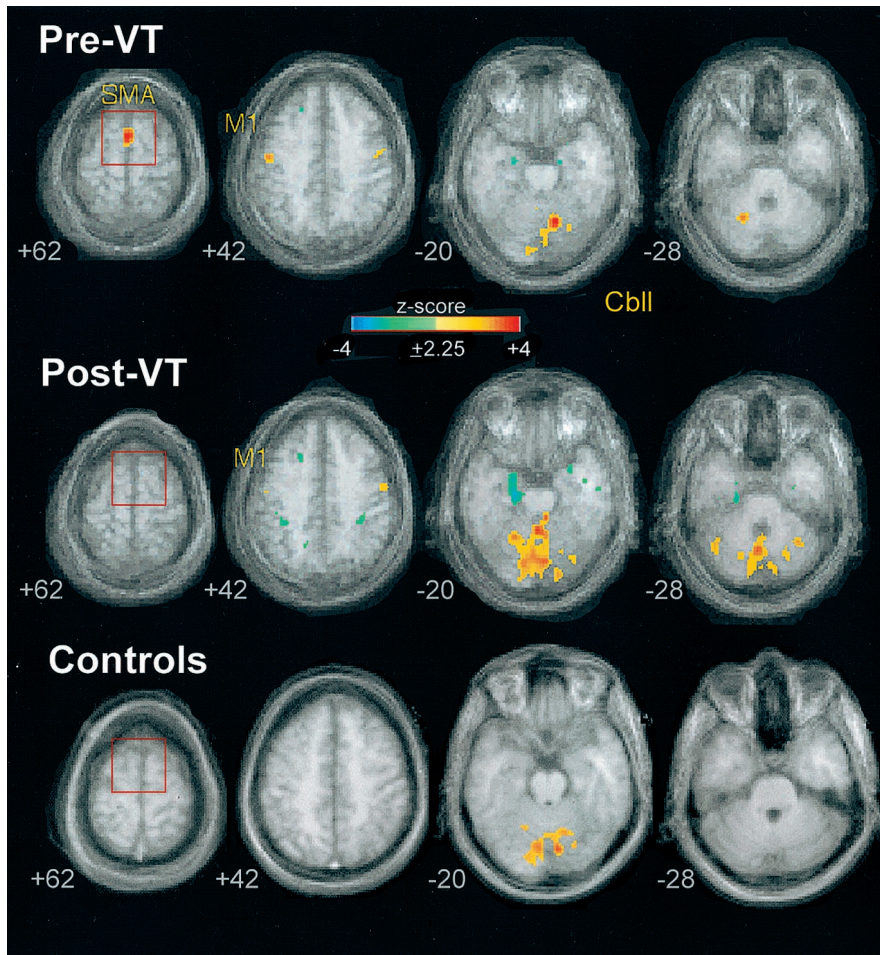


Figure 3. Paragraph reading vs eyes closed rest: Significant regional cerebral blood flow (rCBF) changes pre-voice treatment (VT) (top), post-VT (center), and in the healthy control group (bottom). Axial slices. z-Score cut-off: ± 2.25 ($p < 0.01$). z-Score cut-off is lower than in table 3 to improve visualization of the effects. Right hemisphere is on the right; left hemisphere is on the left. SMA = supplementary motor area; M1 = primary motor cortex-mouth; Cbll = cerebellum.

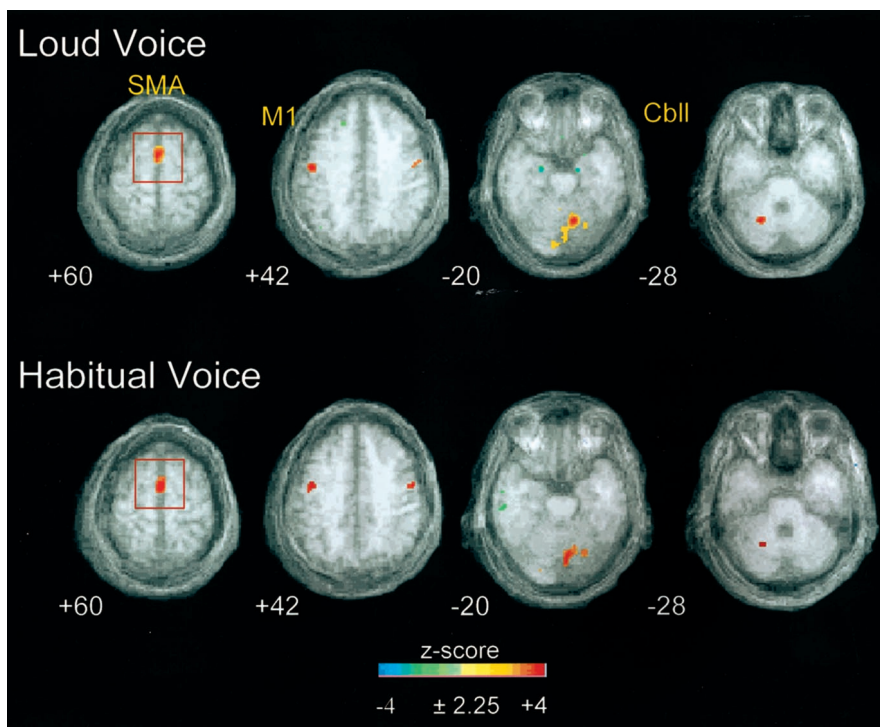


Figure 4. Paragraph reading vs eyes closed rest, pre-voice treatment (VT): Significant regional cerebral blood flow (rCBF) changes with experimenter-cued loud voice (top) and habitual voice (bottom). Axial slices. z-Score cut-off: ± 2.25 ($p < 0.01$). z-Score cut-off is lower than in table 3 to improve visualization of the effects. Red square highlights similar activation of SMA independent of voice level. SMA = supplementary motor area; M1 = primary motor cortex-mouth; Cbll = cerebellum.

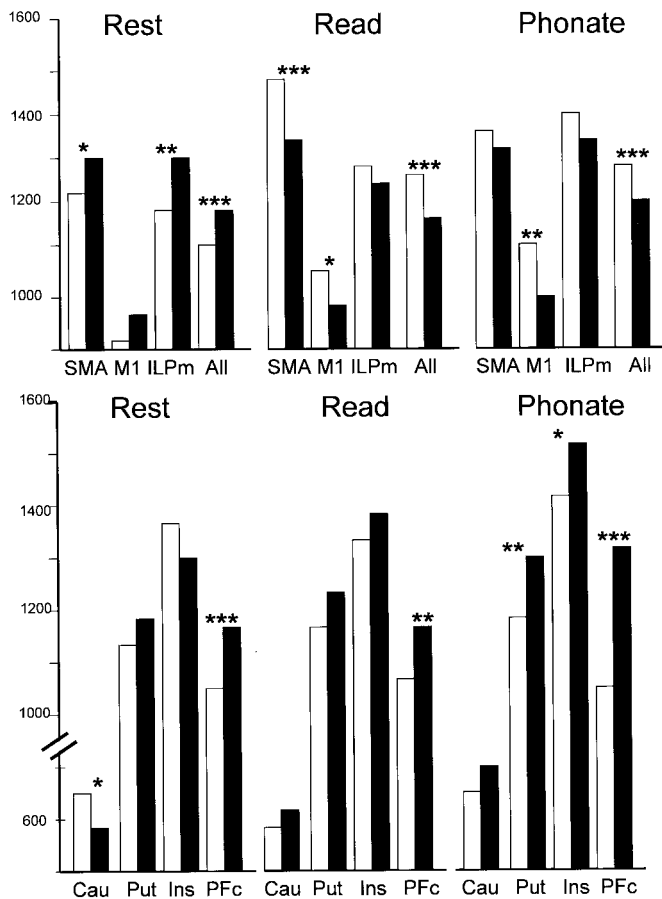


Figure 5. *Top:* Mean PET counts in supplementary motor area (SMA), primary motor-mouth (M1), inferior lateral premotor cortex (ILPm), and a combined region (all). *Bottom:* Mean PET counts in right caudate (Cau), right putamen (Put), right insula (Ins), and right prefrontal cortex (PFc) ($*0.05 < p < 0.01$; $**p < 0.05$; $***p < 0.01$). Rest = left; reading = center; phonation = right; white bars = pre-voice treatment (VT); black bars = post-VT.

(SMA), left primary motor cortex (M1-mouth), and lateral cerebellum (both sides).

Effect of loudness. In the conditional contrast of loud voice reading vs habitual voice reading, isolating the putative effects of experimenter-cued loudness, omnibus significance was not attained ($df = 2,180$, beta-1 z-score = 0.01, $p = 0.99$). As shown in figure 4 and table 3, activations in premotor/motor cortex and cerebellum were very similar independent of the voice level, habitual or loud.

Post-VT. After voice treatment in the IPD group, there were rCBF changes in the conditional contrast of paragraph reading vs rest (omnibus significance, $df = 2,180$, beta-1 z-score = 13.6, $p < 0.0001$). Cortical motor/premotor regions were much less activated, and none reached significance threshold. Activations in the cerebellum included a cluster in lateral cerebellum, present also pre-VT, and several more medial sites in the vermis not observed pre-VT (see figure 3 and table 3).

Control group. There were significant rCBF changes in the conditional contrast of paragraph reading vs rest (omnibus significance, $df = 2,180$, beta-1 z-score = 18.5, $p < 0.0001$). The only effect to exceed significance threshold (besides the reading-related effects in visual cortex) was an rCBF increase in left posterior cerebellum. Subthreshold clusters of activation were present in bilateral superior premotor cortex and left lateral cerebellum ($z = +34$, see table 3, bottom and figure 3, bottom). Importantly, no hint of activation was present in supplementary motor cortex (SMA) at any level of statistical threshold (above $z = 1.96$, $p < 0.05$, uncorrected).

ROI treatment effects. **VT-related rCBF increases.** The between-session ANOVA on the selected ROI revealed increases of mean PET counts post-VT compared to pre-VT in right caudate, right putamen, right anterior insula, and right DLPFC cortex in the phonation and reading tasks (see figure 5, bottom). For the right DLPFC region such increase was present also in the resting state.

VT-related rCBF decreases. In contrast, there were decreases of mean PET counts post-VT compared to pre-VT in all cortical motor-premotor areas, including SMA, right M1-mouth, left ILPm (Broca area), and a combined motor-premotor region in the phonation and reading tasks. Interestingly, the reverse was true for the resting state, in that activity was significantly greater post-VT than pre-VT (see figure 5, top).

Discussion. This is the first neuroimaging study focusing on the correlates of dysphonia in individuals with IPD, and on the correlates of speech and voice symptom remission after successful VT. Successful VT is accompanied by increases in activity in right anterior insula, right basal ganglia, and right DLPC during phonation, and decreases in activation in cortical motor/premotor regions during phonation and reading.

In the pretreatment session of the individuals with IPD, the voxel-by-voxel statistical contrasts revealed robust activations in SMA, the M1-mouth region, and in infero-lateral premotor cortex (both speech-motor tasks relative to rest). In the post-treatment session, the whole-brain statistical contrasts failed to reveal effects in any of the motor-premotor cortical areas activated pre-VT. VT-related changes were confirmed by the direct between-session comparison of PET activity with the ROI method, with significant reductions in activity post-VT relative to pre-VT in all motor-premotor cortical areas. In the control group, the voxel-by-voxel statistical contrast of paragraph reading vs rest revealed only subthreshold activations bilaterally in the M1-region, with no effect in the SMA region at any statistical threshold.

Based on these combined findings, we interpret the motor-premotor cortical effects in the group with IPD pre-VT as pretreatment abnormalities, and their absence in the post-VT session as treatment-induced normalization. This contention is supported by indirect evidence of similar increased cortical motor-premotor activity in untreated individuals with IPD compared to controls during complex sequential limb-motor tasks¹⁵⁻¹⁸ using both PET¹⁵⁻¹⁷ and, recently, fMRI,¹⁸ which reversed following treatment with pharmacologic agents^{19,20} and surgical interventions.²¹⁻²⁵ In individuals with IPD more cortical areas may be recruited to perform sequential finger movements as the result of increasing corticocortical activity to compensate for striatal dysfunction.¹⁸ Similarly, hypophonic individuals with IPD may recruit more strongly motor/premotor regions during speech-motor tasks. Other indirect evidence in support of a normalization of a baseline premotor dysfunction following VT comes from PET work in our laboratory showing a similar pattern of abnormal activation of SMA and M1-mouth in individuals with stuttering relative to healthy controls in a similar paragraph reading task in which they stuttered.²⁷ However, whereas the abnormalities in stutterers transiently subsided during fluency induc-

tion,²⁷ experimenter-cued increases in loudness in untreated individuals with IPD did not change the motor–premotor abnormalities. In contrast, such abnormalities only subsided in the post-VT session, indicating treatment-specific reorganization of speech–motor function developing in the course of VT.

Neuroimaging studies of limb–motor function in healthy volunteers have shown that the amount of activity in SMA depends on the complexity of the limb–motor task. In simple repetitive limb movements (such as finger tapping) SMA is active only at onset, whereas in limb–motor tasks involving new and changing sequences SMA remains active over time.^{14–24} This may help explain why SMA activity in individuals with IPD has been found either abnormally decreased or increased relative to healthy volunteers.^{14–24} Similarly, paragraph reading in healthy individuals may be expected to produce more integrated activity over time in the SMA region than the sustained phonation task owing to the need for reprogramming and reinitiation of new vocalizations in the former. However, paragraph reading did not yield significant activation in SMA in our small sample of aged adults, nor in a larger sample of young healthy subjects.²⁷ These combined results suggest that paragraph reading in healthy individuals may require less involvement of the SMA region. In contrast, in individuals with IPD, impaired vocal fluency with fragmented speech–motor output may require repetitive reinitiation of vocalization activity, resulting in elevated and protracted SMA activity both in the paragraph reading and the sustained phonation tasks, possibly as a compensatory mechanism to override impaired basal ganglia motor function.¹⁸

A treatment-specific effect was also found in right putamen and caudate nucleus in the phonation task. Increased signal in the basal ganglia is important in a disease whose primary pathology is in the basal ganglia. Electrophysiologic evidence in monkeys,³³ and PET data in healthy humans,³⁴ suggest new roles of the basal ganglia (the globus pallidus in particular) in the rescaling of movement dimensions in limb–motor tasks, including velocity, strength, and force.^{33,34} The right pallidus/putamen may play a similar role in speech–motor activities. Sustained phonation may require the ability to continuously rescale speech/motor output (loudness) based on incoming auditory feedback. Because a key component of VT is increased awareness of loudness, it is speculated that VT may restore function in the right basal ganglia during sustained phonation.

The largest and most significant treatment-specific effect was a predominantly right-sided activation in the anterior insula during sustained phonation, confirmed by both statistical methods.

In the monkey, the insular cortex connects reciprocally to premotor regions (premotor area 6),³⁵ and its role in humans as crucial speech–motor structure is becoming increasingly apparent by both functional imaging studies^{36,37} and lesion–behavior correlation studies.³⁸ Furthermore, in the monkey insula intero-

ceptive/autonomic signals also converge, yielding a global representation of body state.³⁵ Because of its role as convergence zone of widespread signals, the right anterior insula activation following VT may explain its multisystem effects, including enhanced facial expression and emotional expressive prosody.¹³ A crucial role of the right insula has been demonstrated in emotional and nonemotional expressive prosody³⁹ and singing.⁴⁰ Further evidence of a site of action of VT on substrates of emotion regulation and representation³⁹ comes from the right-sided predominance of treatment-specific effects during phonation (anterior insula, putamen, caudate, and DLPCF cortex) in the IPD group.

Increased activity in right DLPCF was found post-VT, with a significant increase in activity from the pre-VT level in all tasks, including rest. Several neuroimaging studies have shown relative right DLPCF hypoactivation in individuals with IPD compared to healthy individuals during limb–motor tasks,^{14,15,18} with a reversal following surgical treatment.^{22,25} DLPCF cortex receives projections from the basal ganglia and related thalamic nuclei. The defective signal in right DLPCF cortex in IPD may be explained by degeneration of mesofrontal dopaminergic afferents, or by a functional deafferentation of the prefrontal cortex from its basal ganglia–thalamic inputs.¹⁸ The treatment-specific activations of right DLPCF and the head of the caudate may be interpreted as normalization of a pretreatment abnormality, or the recruitment of an alternative fronto-striatal loop able to affect pallidal output.⁴¹

The results of the current study should be considered preliminary. Limitations are the small sample size, the lack of test-retest data in an untreated PD group, and the absence of performance data during the PET sessions. Because a control group of healthy volunteers was available only for the paragraph reading task, the results in the sustained phonation task should be considered exploratory.

Future studies should be carried out to confirm the robustness of the VT-related treatment effects, including larger sample sizes of individuals with IPD and healthy controls, and a group of untreated IPD patients, to single out confounds due to treatment specificity and test-retest reliability.

These limitations notwithstanding, the current study provides the first evidence linking voice treatment of hypophonia in IPD to specific neural correlates during speech–motor tasks. The improvement in speech and voice symptoms appears to entail a functional brain reorganization suggestive of a shift from an effortful implementation of speech–motor programs caused by the basal ganglia pathology to a more automatic, effortless instantiation of motor actions, and in part possibly relying on improved basal ganglia function.¹⁷ Such changes are similar in part to those observed with effective treatment of limb–motor symptoms with both pharmacologic and neurosurgical treatments.

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