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Functional Abnormalities in the Primary Orofacial Sensorimotor Cortex During Speech in Parkinson's Disease

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Abstract: Parkinson's disease (PD) affects speech, including respiration, phonation, and articulation. We measured the blood oxygen level-dependent (BOLD) response to overt sentence reading in: (1) 9 treated female patients with mild to moderate PD (age; mean 66.0 ± 11.6 years, mean levodopa equivalent 583.3 ± 397.9 mg) and (2) 8 age-matched healthy female controls (age; mean 62.2 years ± 12.3). Speech was recorded in the scanner to assess which brain regions underlie variations in the initiation and paralinguistic aspects (e.g., pitch, loudness, and rate) of speech production in the two groups. There were no differences in paralinguistic aspects of speech except for speech loudness; it was lower in PD patients compared with that in controls, when age was used as a covariate. In both groups, we observed increases in the BOLD response (reading-baseline) in brain regions involved in speech production and perception. In PD patients, as compared with controls, we found significantly higher BOLD signal in the right primary orofacial sensorimotor cortex and more robust correlations between the measured speech parameters and the BOLD response to reading, particularly, in the left primary orofacial sensorimotor cortex. These results might reflect compensatory mechanisms and/or treatment effects that take place in mild to moderately ill PD patients with quality of speech yet comparable with that of age-matched controls. © 2007 Movement Disorder Society

Key words: overt reading; paralinguistic aspects of speech; Parkinson's disease; functional magnetic resonance imaging.

Reading aloud requires many perceptual, cognitive and motor processes, including visual recognition of words, grapheme-to-phoneme conversion, planning of phonological output and articulation, and the actual vocalization. When comparing overt and covert reading directly, it appears that only the primary sensorimotor cortex (SM1), supplementary motor area (SMA), and the anterior insula show an additional increase in regional cerebral blood flow.[1] In terms of speech-related brain mechanisms, the SMA and anterior cingular cortex (ACC) have been shown to be involved in the initiation of speech,[2] the left anterior insular cortex (AIC) is thought to play a role in the planning of articulatory output,[3,4] and speech movements are generated in the SM1 corresponding mainly to the orofacial somatotopic areas.[4,5] With regard to motor speech function, the cortex-basal ganglia-cortex loop is tightly connected with the cortex-basal ganglia-cerebellum-cortex circuit.[5]

In Parkinson's disease (PD), the degeneration of dopaminergic nigrostriatal pathways results in functional disturbances of motor cortical areas and leads to the appearance of parkinsonian motor symptoms, including changes in speech. Speech in PD patients is characterized by decreased loudness and prosodic insufficiency.[6] Voice disorders appear to occur more frequently than articulation ones and can be present in the early phases of PD.[6] But any or all components of speech production, including respiration, phonation, and articulation may be affected.[7]Although pharmacological and surgical treatments are effective in treating motor symptoms of PD,

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the gains are not as significant for speech as they are for limb symptoms (e.g., Refs. [5, 8–12]).

So far, only two functional imaging studies have assessed the neural correlates of parkinsonian speech. Pinto and colleagues[13] used $H_2{}^{15}O$ PET to measure the effects of subthalamic nucleus (STN) stimulation on speech production and silent articulation of one sentence. In advanced PD patients OFF stimulation and OFF medication, when compared with healthy control subjects, they found a lack of involvement of the right orofacial primary motor area (M1) and the cerebellum, and increase in cerebral blood flow (CBF) in the SMA, dorsolateral prefrontal cortex (DLPFC), right superior premotor cortex and the left insula. In the ON stimulation condition, the pattern of CBF was similar to that of control subjects, notably for the orofacial M1, cerebellum, and SMA. Furthermore, these CBF changes were accompanied by behavioral changes: hypophonia in the OFF stimulation condition was significantly improved by STN stimulation. Liotti et al.[14] used the same PET technique and both paragraph reading and sustained phonation tasks to assess treatment with the Lee Silverman voice treatment (VT) on parkinsonian dysarthria. All PD patients had marked speech and voice disorder that improved after VT. Results revealed an increase in CBF post-VT compared with pre-VT in the right caudate, right putamen, right anterior insula, and right DLPFC in the phonation and reading tasks. In contrast, there were CBF decreases post-VT compared with pre-VT in all motor and premotor areas, including right orofacial M1, SMA, and left Broca area.

In our study, we used functional magnetic resonance imaging (fMRI) to assess the BOLD response to the overt reading of emotionally neutral sentences in pharmacologically treated female patients with mild to moderate PD; the patient data were compared with those acquired in age-matched healthy female controls. We hypothesized that the patients would show increased cortical activity necessary to compensate for striatocortical circuitry dysfunction. We also assessed which brain regions underlie variations in initiation and paralinguistic aspects of speech production known to be impaired in PD.

PATIENTS AND METHODS

Subjects

We recruited 9 right-handed female patients with PD classified according to the Parkinson's Disease Society Brain Bank criteria[15,16]; their mean age was 66.0 ± 11.6 years. The patients were outpatients at the Movement Disorder Centre at St. Anne's University Hospital in Brno. All PD patients had either normal speech or mild to moderate speech impairment, i.e., they scored 0–2 points according to the perceptual estimation of speech that corresponds to item 18 of the UPDRS, Part III (Unified Parkinson's Disease Rating Scale: Motor Examination [17]). The disease duration was 3.4 ± 1.7 years, Hoehn-Yahr stage[17] was 1 to 2.5 (2 ± 0.43), the mean UPDRS, Part III score was 17.8 ± 5.4 in the "off" state. All patients were treated with dopaminergic drugs (levodopa [L-dopa] and/or dopamine agonists); the mean L-dopa equivalent was equal to 583.3 ± 397.9 mg of L-dopa. Other drugs administered for PD: deprenyl 5 mg per day (2 patients) and entacapone 600 to 1000 mg per day (2 patients). All patients were scanned on medication in the "on" state, i.e., 1 to 2 hours after their morning dose to minimize motor artifacts during scanning.

We also enrolled 8 right-handed age-matched female control subjects (62.2 ± 12.3 years). They were examined and treated in our hospital for cervical and/or back pain syndrome and had no speech problems. At the time of the study, their symptoms were successfully managed and they had no analgesic treatment.

We recruited only women since men have a different mean fundamental voice frequency. None of the subjects had a history and/or presence of any psychiatric symptoms, cognitive impairment, and of any disease affecting the central nervous system (other than PD in the PD cohort). All subjects reported Czech as their first language. Prior to the fMRI session, subjects practiced the experimental tasks. All experimental protocols were approved by the Ethics Committee of the St Anne's Hospital in Brno, and all subjects provided informed consent prior to participating.

Speech Task

In the MRI scanner, subjects completed a speech task.[18] The presentation of all stimuli was controlled by a personal computer and was projected onto a screen at the back of the MRI scanner. Subjects were able to view the screen through a mirror attached to the head coil. The BOLD signal was measured in response to: (1) reading out loud emotionally neutral sentences; and (2) passively viewing a string of "x's" (baseline). Using an event-related design, 61 volume measurements were acquired during 12-min functional scans. A 12-second intermeasurement interval was used to minimize the effect of both scanner noise and head movement while reading aloud. Volume acquisition occurred 6 seconds after the onset of

stimulus presentation; the reading time for each sentence ranged from 2 to 4 seconds. All stimuli were displayed for 5 seconds. We acquired 40 measurements after sentence reading, 20 after viewing baseline stimuli, and 1 at the beginning of sequence for synchronization between MR scanner and presentation computer. The screen was black in between successive stimuli.

Speech Stimuli and Analyses

Sentence stimuli comprised 40 short sentences, matched for the number of syllables per sentence. Speech was recorded using a unidirectional analog computer microphone fixed to the head coil and stored on a personal computer. The microphone was MRI-compatible and did not contain any ferromagnetic material. For off-line analysis of the speech samples, a Matlab (Matlab 5.0; Mathworks, Natick, MA) platform was adapted to extract the following parameters from the sentences: initiation of sentence reading, duration of sentence reading, range of amplitude, root-mean-square (RMS) of amplitude, mean fundamental frequency (F_0), standard deviation (SD) of F_0 and range of F_0. The analysis of these paralinguistic aspects of speech was performed in the Montreal Neurological Institute, and details have been reported elsewhere.[19]

Fundamental frequency (F_0) is a major contributor to perceived vocal pitch. F_0 variation across a speech sample reflects the amount of intonation in speech, or prosody. An acoustical correlate of loudness is root-mean-square amplitude (RMS–amplitude). Range of amplitude provides information about the variability of loudness throughout an utterance.[19] Reading initiation (i.e., the reading onset latency) was measured by determining the time in seconds between the sentence presentation on the screen and the start of reading. Reading duration (in seconds) was measured by determining the period from the start of sentence reading to the end of sentence reading. For each speech parameter, means were calculated for each group (patients, controls). For comparing paralinguistic aspects of speech, the program Statistica (StatSoft, Inc., Tulsa, OK) was used.

Functional MRI

Subjects were scanned with a 1.5-T Siemens Symphony scanner (Siemens, Erlangen, Germany). Functional data were acquired with gradient-echo echoplanar T2*-weighted images (TE, 50 ms; TR, 191 ms; FA, 90°). The fMRI scan volume included 20 transversal slices parallel to an estimated line passing through the anterior and posterior commissures (matrix size, 128 by 80; in-plane resolution, 1.7×1.7 mm^2; slice thickness, 4 mm; 1 mm-gap between slices; acquisition of one measurement, 3.8 seconds; intermeasurement interval, 12 seconds). The imaged volume covered most of the brain excluding the cerebellum. After functional scans, a high-resolution T_1-weighted 3D volume was acquired for anatomical localization (TR = 1,700 ms, TE = 3.96 ms, FA, 15°, FOV, 246 mm; slice thickness 1.17 mm; 160 saggital slices; inplane resolution, 0.961×0.961 mm^2). Functional images were motion-corrected, normalized to standard stereotactic space (MNI305), and smoothed using a 6-mm full-width at half-maximum isotropic Gaussian kernel. The statistical analysis of the fMRI data was based on a general linear model implemented in SPM99 (Welcome Department of Cognitive Neurology, London, UK). For each subject, we first calculated the "reading effect" as a contrast between reading and baseline conditions. Next, using a random-effects model (one-sample t-test), the group analyses were performed (mean of patients, mean of controls). All group reading-effect statistics were thresholded to a *P*-value of 0.001 uncorrected for multiple comparisons with an extent threshold of 5 voxels.

Comparing Brain Activation in 14 Regions of Interest: Patients Versus Controls

We made use of a two-step approach in comparing data from volumes of interest between groups. First, we identified commonalities and differences in the patterns of activity observed for the two groups in regions of interest (ROI), namely in seven brain regions including the motor and premotor cortices, the SMA, anterior insula, anterior cingulate (ACC), thalamus, and putamen in each hemisphere (a total of 14 ROIs). These regions are likely involved in speech articulation and vocalization (e.g., Refs. [1, 4, 18, 20, 21]). Peak voxel-values were extracted from the group reading-effect *t*-images and, if a peak in one group was within 10 mm of a peak in the other group, the two peaks were considered to be equivalent (areas of common activation). This criterion has been used by others for identifying common areas of activation between groups.[22] Peaks that occur in one group, but have no equivalent in the other, were considered to be a site of unique activation. In the second step, the direct between-group analysis was performed at each pair of common or unique peaks using two-sample *t*-test (program Statistica [StatSoft]; $P < 0.05$ was corrected for multiple comparisons, which implies to $P < 0.00357$; [14 tests]). Rather than just comparing values at the peak voxels, we used mean "reading effect" in spheres (5-mm radius) centered about each peak in an effort to reduce the possible impact of interindividual variations in the exact position of the "peak."

TABLE 1. *Mean paralinguistic aspects of speech production in PD patients and controls*

Speech parameter	Patients		Controls			
	Mean	SD	Mean	SD	*t*-value	*P*-value
Reading initiation (s)	1.30	0.23	1.37	0.28	−0.795	0.442
Reading duration (s)	2.27	0.46	2.49	0.44	−1.843	0.090
Range of amplitude (absolute values)	1197.33	561.98	1634.00	495.92	−2.060	0.062
RMS of amplitude (absolute values)	93.00	39.58	131.00	51.39	−2.474	0.029
Mean pitch (F0) (Hz)	196.56	37.67	201.13	36.14	−0.037	0.971
SD of F0 (Hz)	65.33	8.28	67.50	11.94	−0.538	0.600
Range of F0 (Hz)	227.67	30.76	237.50	43.14	−0.526	0.608

The last two columns show between group comparisons using two sample *t*-tests.

Correlation Analysis

To evaluate the relationship between the various speech parameters and brain activity associated with overt reading, we calculated—-in each subject—the mean "reading effect" in volumes-of-interest (VOIs; 5-mm radius) centered at all significant "peaks" identified in the group analyses (patients and controls). These VOI values were then entered into a correlation analyses with speech parameters. For RMS amplitude, we used the partial correlation analysis to remove the effect of age, which correlated with RMS amplitude in the PD group ($r = 0.89$, $P = 0.007$). We did not use severity of symptoms as a covariate since our patients suffered from a very mild PD. For all correlation analyses, we used the program Statistica (StatSoft).

RESULTS

Paralinguistic Aspects of Speech Production in PD Patients and Controls

Even though PD patients tended to read less loudly, there were no statistical differences between the patients and controls in any of the paralinguistic aspects of speech production during scanning. When age was used as a covariate (see Methods), the RMS of amplitude was the only parameter of speech that was significantly lower in PD patients compared with that of controls (see Table 1).

Brain Regions Underlying Speech Production (Reading Effect) in PD Patients and Controls

In both groups, we observed increases in the BOLD signal in brain regions involved in speech production and perception, including particularly the anterior insula, SM1, SMA, basal ganglia, thalamus, and superior temporal gyrus, bilaterally (see Table 2).

Direct Comparison of BOLD Signal in 14 Regions of Interest: PD Patients Versus Controls

The direct between-group analysis from 14 regions of interest revealed increased BOLD signal in the right SM1 ($P = 0.004$, uncorrected) and decreased BOLD signal in the left SMA ($P = 0.05$, uncorrected) in PD patients compared with that of controls ($P < 0.05$). Only the difference in the right SM1 survived the Bonferroni correction (14 tests), see Table 3 and Figure 1.

The Results of the "Main Effect" Correlation Analysis Between the Reading Effect and Speech Parameters in Patients and Controls

In PD patients, as compared with controls, we found many more significant correlations between studied parameters of speech and the reading effect in various motor and nonmotor regions, particularly in the left SM1 (see Table 4 and Fig. 2).

DISCUSSION

Speech production engages a highly distributed system that includes the left insula and bilateral primary motor cortex involved, respectively, in articulatory planning and the control of vocal-tract musculature.[1,4,20,23] To produce speech, these regions must interact with other motor regions such as the SMA, basal ganglia, thalamus, and cerebellum.[1,4,18,20,24–26] To our knowledge, this is the first fMRI study that compares overt reading in mild-to-moderately ill, treated PD patients and age-matched controls.

When comparing the behavioral data in both groups, we did not find any significant differences between the PD patients and controls in any measured parameter of speech except for voice loudness as measured by the RMS-amplitude. This was lower in the patients compared with that in controls only when age was used as a covariate. As PD patients are known to have trouble initiating movements in general, it was reasonable to predict that they would also display difficulties in initiating speech.[27] This was not the case. But we demonstrated that all speech parameters, and the reading initiation in particular, were significantly correlated with involvement of many more cortical regions in the PD subgroup compared with controls (see Table 4). The left orofacial SM1, in particular, was significantly correlated

TABLE 2. *Brain regions underlying speech production (BOLD response to reading minus BOLD response to baseline stimuli) in healthy controls and in PD patients*

	Patients					Controls				
Region	X	Y	Z	*t*-stat	*z*-stat	X	Y	Z	*t*-stat	*z*-stat
BOLD increases										
L SMA	−4	12	60	16.08	5.18	−6	0	64	12.88	4.61
						−4	6	62	11.46	4.45
R SMA	4	8	62	15.64	5.14	2	10	56	9.01	4.09
L PAG	−2	−28	−8	14.38	5.01					
L AIC	−30	6	4	14.25	5.00	−26	20	2	13.77	4.71
	−40	26	2	9.21	4.32					
	−28	18	−2	9.15	4.31					
L STG	−46	−24	8	11.90	4.73	−62	−10	0	12.03	4.52
	−50	6	−8	9.81	4.42	−62	−30	2	8.58	4.02
	−64	−26	2	7.91	4.07	−52	10	−4	6.30	3.54
L SM1	−52	−14	44	11.43	4.66	−48	−10	48	11.58	4.46
	−58	−4	22	7.72	4.03	−60	−14	22	9.10	4.11
	−56	−16	16	5.74	3.52	−54	−6	16	6.01	3.46
L occipital cortex	−18	−96	−2	10.89	4.59	−24	−94	8	6.59	3.61
R STG	50	−14	4	10.50	4.53	62	−20	2	10.12	4.27
	66	−12	4	5.36	3.40	52	−10	4	7.70	3.85
R SM1	42	−14	48	10.19	4.48	58	−4	16	12.08	4.52
	46	−14	36	9.41	4.35	50	−14	40	11.60	4.47
R ACC	8	6	46	10.00	4.45	4	18	38	9.68	4.20
	6	20	40	6.44	3.72	4	−6	34	6.59	3.61
	4	−8	36	5.93	3.58					
L midbrain	−2	−32	−4	9.63	4.39					
R AIC	46	8	−4	8.93	4.27	42	20	10	9.36	4.15
	42	14	0	5.74	3.52					
R parietal cortex	26	−62	40	8.37	4.16	28	−74	46	8.27	3.96
L MTG	−50	−40	2	8.05	4.10					
	−50	−66	28	6.91	3.84					
L ACC	−6	22	44	7.95	4.08	−8	16	38	6.03	3.47
	−12	−18	42	6.98	3.86	−10	−12	42	5.68	3.37
L PMC	−46	−10	32	7.85	4.06	−54	−6	34	14.28	4.76
	−42	−6	56	7.76	4.04	−38	−6	52	6.59	3.61
R PMC	46	0	46	7.37	3.95	56	−4	36	11.81	4.49
	54	−6	34	6.47	3.73	44	−2	44	5.13	3.20
R MOG	26	−76	6	6.00	3.60	48	−72	−10	6.01	3.46
R SFG	34	−4	46	5.84	3.55	30	−6	48	7.67	3.85
R putamen	26	6	0	5.78	3.53					
L parietal cortex	−16	−56	56	5.70	3.51	−14	−64	52	12.43	4.56
R thalamus	16	−12	10	5.50	3.44	16	−18	8	7.50	3.81
						10	−18	6	6.52	3.59
L thalamus						−8	−18	6	14.71	4.80
L putamen						−20	10	−10	8.72	4.04
R LG						6	−76	−6	8.66	4.03
L Cuneus						−2	−78	6	6.38	3.56
L IFG						−44	30	8	6.15	3.50
BOLD decreases										
R MTG	46	−70	20	14.11	4.99					
	48	−56	10	11.32	4.65					
	50	−64	28	10.22	4.49					
L MTG						−50	−72	28	12.66	4.59
Parietal cortex	0	−62	36	10.84	4.58					
L parietal cortex						−10	−54	32	6.73	3.64
						−48	−64	46	6.17	3.50

MNI coordinates used; significance threshold $P < 0.001$ uncorrected, minimal spatial extent of 5 voxels.

L, left; R, right; SM1, primary sensorimotor cortex; PMC, premotor cortex; SMA, supplementary motor area; AIC, anterior insular cortex; ACC, anterior cingular cortex; STG, superior temporal gyrus; MTG, middle temporal gyrus; SFG, superior frontal gyrus; IFG, inferior frontal gyrus; LG, lingual gyrus; MOG, middle occipital gyrus; PAG, periaquaeductal grey matter.

TABLE 3. *Direct comparison of the BOLD signal in 14 regions of interest: PD patients versus controls*

			Coordinates for patients			Coordinates for controls		
ROI	*P*	*z*-stat	X	Y	Z	X	Y	Z
L SM1	0.808193	0.87	−52	−14	44	−48	−10	48
L PMC	0.619723	0.30	−46	−10	32	−54	−6	34
R SM1	0.002331	2.83	46	−14	36	50	−14	40
R PMC	0.775165	0.76	54	−6	34	56	−4	36
L SMA	0.032195	1.85	−4	12	60	−4	6	62
R SMA	0.107709	1.24	4	8	62	2	10	56
L AIC	0.125253	1.15	−28	18	−2	−26	20	2
R AIC	0.234803	0.72	42	14	0	42	20	10
L ACC	0.283172	0.57	−6	22	44	−8	16	38
R ACC	0.919782	1.40	6	20	40	4	18	38
L thalamus	0.289341	0.56	−8	−18	6	−8	−18	6
R thalamus	0.662353	0.42	16	−12	10	10	−18	6
L putamen	0.110940	1.22	−20	10	−10	−20	10	−10
R putamen	0.548821	0.12	26	6	0	26	6	0

MNI coordinates, statistical significance thresholded at $P < 0.00357$.

L, left; R, right; SM1, primary sensorimotor cortex; PMC, premotor cortex; SMA, supplementary motor area; AIC, anterior insular cortex; ACC, anterior cingulate cortex.

with all measured aspects of speech, including the reading initiation, duration, speech loudness and prosody (see Fig. 2). Taken together, these results may indicate a more efficient recruitment of the left SM1 and other relevant cortical regions during speech production in treated subjects with mild PD compared with controls. It is difficult to speculate about the pathophysiology of these phenomena, since we evaluated patients only on medication and thus both the role of dopaminergic therapy and/or compensatory mechanisms in PD could have been implicated. Interestingly, the importance of the left orofacial SM1 involvement has also been demonstrated in a recent study by Dias et al.[28] who reported that one session of high frequency (5Hz) repetitive transcranial magnetic stimulation (rTMS) applied over the left orofacial SM1 may lead to improvement of the fundamental frequency and voice intensity in PD patients.

The direct between-group analysis from regions engaged in articulation and vocalization revealed significantly higher BOLD signal in the right orofacial SM1 in PD patients, as compared with controls. One may speculate that this phenomenon could have occurred as a consequence of an impaired subcortical motor system and less efficient thalamic projections to the motor cortex.[29–31] SM1 overactivity in rather advanced PD patients was found by means of PET and fMRI while studying simple or complex motor hand tasks.[32,33] It is noteworthy that, unlike in our study, the patients were OFF medication and in the "OFF" state. Neurophysiological studies support the presence of "over-reactivity" in reporting excessive motor cortical output in the "OFF"

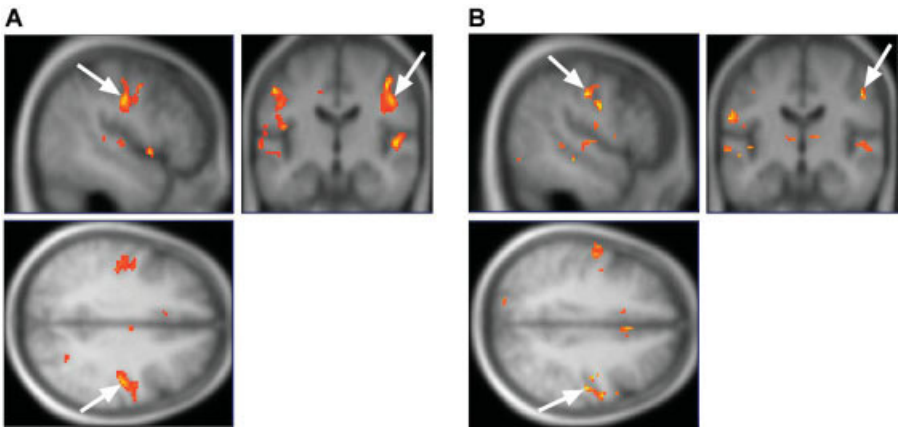

FIG. 1. BOLD signal increases in the right primary sensorimotor cortex (white arrow) during overt reading in PD patients (A) and controls (B); MNI coordinates for peak voxel values: 46, −14, 36 and 50, −14, 40 for patients and controls, respectively; significance threshold $P < 0.001$ uncorrected.

TABLE 4. *The results of the "main effect" correlation analysis: PD patients and controls*

			Patients				Controls			
		Structure	X	Y	Z	R	X	Y	Z	R
a. Reading initiation correlation: main effect	Negative covariation with increased BOLD signal	L SM1	−58	−4	22	−0.95				
		R SM1	46	−14	36	−0.87				
		L AIC	−30	6	4	−0.95				
		R AIC	46	8	−4	−0.78				
		L ACC	−6	22	44	−0.84				
		R ACC	6	20	40	−0.81				
		L PMC	−42	−6	56	−0.81				
		R thalamus	16	−12	10	−0.88				
		R putamen	26	6	0	−0.86				
		R STG	50	−14	4	−0.77				
b. Reading duration correlation: main effect	Negative covariation with increased BOLD signal	L SM1	−58	−4	22	−0.83				
		L primary occipital cortex	−18	−96	−2	−0.79				
		L STG	−64	−26	2	−0.77				
		R STG	66	−12	4	−0.76				
	Positive covariation with increased BOLD signal	L PMC					−38	−6	52	0.73
		L IFG					−44	30	8	0.79
c. RMS—amplitude correlation: Residuals after covarying out the effect of age	Negative covariation with increased BOLD signal	L SM1					−54	−6	16	−0.73
	Positive covariation with increased BOLD signal	L SM1	−52	−14	44	0.86				
		R thalamus	16	−12	10	0.71				
d. SD of F0 correlation: main effect	Negative covariation with increased BOLD signal	L SMA	−4	12	60	−0.76				
		R parietal cortex	26	−62	40	−0.83				
	Positive covariation with increased BOLD signal	L SM1	−52	−14	44	0.83				

The correlation analysis was performed to assess the significance of the relationship between the "reading effect" in VOIs centred at all significant "peaks" identified in the group analyses (MNI coordinates) and our speech parameters of interest ($P < 0.05$).

L, left; R, right; SM1, primary sensorimotor cortex; PMC, premotor cortex; SMA, supplementary motor area; AIC, anterior insular cortex; ACC, anterior cingulate cortex; STG, superior temporal gyrus; IFG, inferior frontal gyrus; PAG, periaquaeductal grey matter; R, correlation coefficient.

state PD patients at rest; this is coupled with a relative failure of volitional facilitation (e.g., Refs. [31, 34, 35]). Size of the motor evoked potential (MEP), duration of cortical silent period (CSP), and the magnitude of short-interval intracortical inhibition (SICI) are all reduced in PD. Taken together, these observations are consistent with an overactive corticospinal system.[31] In line with these results, neuroimaging studies have shown that STN stimulation acts through reduction of abnormal overactivity in the motor system at rest.[36,37]

But interestingly, results of imaging studies of speech production in PD do not parallel those of limb movements[13]; it has been suggested that the pathophysiology of PD dysarthria is, at least in part, different from that of limb dysfunction.[5] For example, a lack of activation in the right orofacial SM1 during speech was reported in PD patients scanned OFF medication and in the OFF stimulation condition.[13] But our patients were studied ON medication. Finding higher activity in the right SM1 is therefore consistent with the increases in the right SM1 activity after the STN stimulation,[13] and with robust activations in SM1 during paragraph reading vs. rest in patients on medication before voice treatment.[14] Taken together, this result might, at least in part, reflect changes that occur in response to treatment. What might be the behavioral consequences of such an "overactivity" of the right SM1 for the patient's speech? In our study, the correlation analysis revealed a significant negative correlation between the magnitude of the BOLD response in the right SM1 during reading and the reading onset latency in PD patients; such a correlation was not found in controls (see the identical VOI in Tables 3 and 4). It is tempting to speculate that the observed difference in the relationship between SM1 activity and speech initiation may play some role in the control of speech in PD patients. Specifically designed rTMS/functional imaging studies might bring further evidence for this notion.

Overall, our results indicate functional abnormalities in treated mild-to-moderately ill PD patients, as compared with controls during overt reading. Despite the quality of speech was comparable in both groups, the left orofacial SM1 and other cortical regions were more engaged in patients than in controls. In patients, as compared with controls, we found increased BOLD signal in

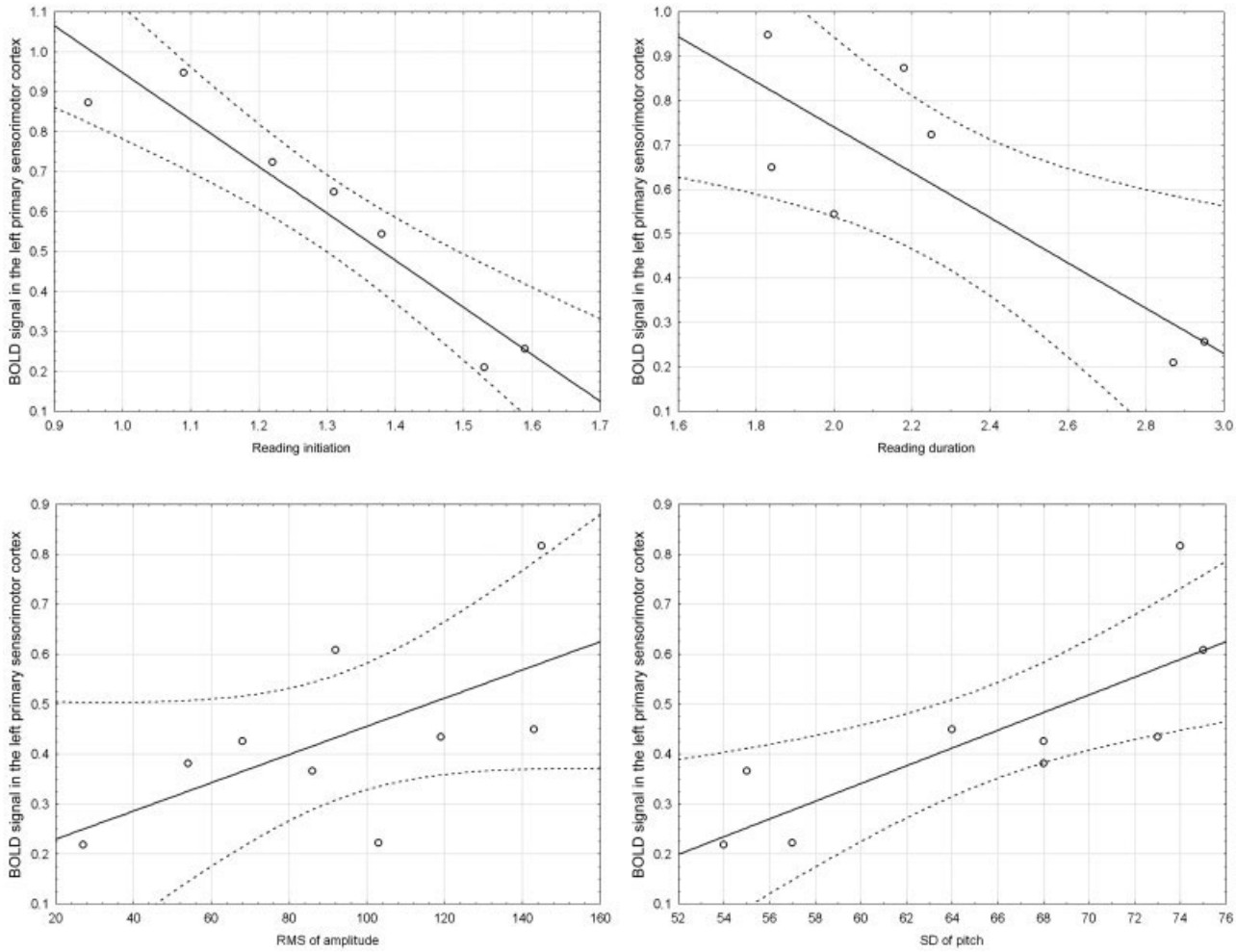

FIG. 2. PD patients; the results of the "main effect" correlation analysis between our speech parameters and increased BOLD signal in the left SM1.

the right SM1 which was correlated with reading initiation.

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REFERENCES

1. Sakurai Y, Momose T, Iwata M, Sudo Y, Ohtomo K, Kanazawa I. Cortical activity associated with vocalization and reading proper. Cogn Brain Res 2001;12:161–165.
2. McNeilage PF, Davis BL. Motor mechanisms in speech ontogeny: phylogenetic, neurobiological and linguistic implications. Curr Opin Neurobiol 2001;11:697–700.
3. Dronkers NF. A new brain region for coordinating speech articulation. Nature 1996;384:159–161.
4. Wise RJ, Greene J, Buchel C, Scott SK. Brain regions involved in articulation. Lancet 1999;353:1057–1061.
5. Pinto S, Ozsancak C, Tripoliti E, Thobois S, Limousin-Dowsey P, Auzou P. Treatments for dysarthria in Parkinson's disease. Lancet Neurol 2004;3:547–556.
6. Jimenez-Jimenez FJ, Gamboa J, Nieto A, et al. Acoustic voice analysis in untreated patients with Parkinson's disease. Parkinsonism Relat Disord 1997;3:111–116.
7. Pinto S, Gentil M, Fraix V, Benabid AL, Pollak P. Bilateral subthalamic stimulation effects on oral force control in Parkinson's disease. J Neurol 2003;250:179–187.
8. Gentil M, Chauvin P, Pinto S, Pollak P, Benabid AL. Effect of bilateral stimulation of the subthalamic nucleus on parkinsonian voice. Brain Lang 2001;78:233–240.
9. Wolfe VI, Garvin JS, Bacon M, Waldrop W. Speech changes in Parkinson's disease during treatment with L-dopa. J Commun Disord 1975;8:271–279.
10. Critchley EM. Speech disorders of Parkinsonism: a review. J Neurol Neurosurg Psychiatry 1981;44:751–758.
11. Dromney Ch, Kumar R, Lang AE, Lozano AM. An investigation of the effects of subthalamic nucleus stimulation on acoustic measures of voice. Mov Disord 2000;15:1132–1138.
12. Deuschl G, Herzog J, Kleiner-Fisman G, et al. Deep brain stimulation: Postoperative issues. Mov Disord 2006;21 (Suppl 14): S219–S237.
13. Pinto S, Thobois S, Costes N, et al. Subthalamic nucleus stimulation and dysarthria in Parkinson's disease: a PET study. Brain 2004;127:602–615.

14. Liotti M, Ramig LO, Vogel D, et al. Hypophonia in Parkinson's disease: neural correlates of voice treatment revealed by PET. Neurology 2003;60:432–440.
15. Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745–752.
16. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.
17. Fahn S, Elston RL, Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. Recent developments in Parkinson's disease. vol. 2. New York: MacMillan; 1987; p 153–163.
18. Barrett J, Pike GB, Paus T. The role of the anterior cingulate cortex in pitch variation during sad affect. Eur J Neurosci 2004;19:458–464.
19. Barrett J, Paus T. Affect-induced changes in speech production. Exp Brain Res 2002;146:531–537.
20. Ludlow CL. Stuttering: dysfunction in a complex and dynamic system. Brain 2000;123:1983–1984.
21. Murphy K, Corfield DR, Guz A, et al. Cerebral areas associated with motor control of speech in humans. J Appl Physiol 1997;83:1438–1447.
22. Milham MP, Erickson KI, Banich MT, et al. Attentional control in the aging brain: insights from an fMRI study of the Stroop task. Brain Cogn 2002;49:277–296.
23. Dronkers NF. A new brain region for coordinating speech articulation. Nature 1996;384:159–161.
24. McClean MD, Dostrovsky JO, Lee L, Tasker RR. Somatosensoryneurons in human thalamus respond to speech-induced orofacial movements. Brain Res 1990;513:343–347.
25. Riecker A, Mathiak K, Wildgruber D, et al. fMRI reveals two distinct cerebral networks subserving speech motor control. Neurology 2005;64:700–706.
26. Gitelman DR, Nobre AC, Sonty S, Parrish TB, Mesulam M. Language network specializations: an analysis with parallel task designs and functional magnetic resonance imaging. Neuroimage 2005;26:975–985.
27. Ravizza SM. Relating selective brain damage to impairments with voicing contrasts. Brain Lang 2001;77:95–118.
28. Dias AE, Barbosa ER, Coracini K, Maia F, Marcolin MA, Fregni F. Effects of repetitive transcranial magnetic stimulation on voice and speech in Parkinson's disease. Acta Neurol Scand 2006;113:92–99.
29. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 1990;13:266–271.
30. Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. Curr Opin Neurobiol 1996;6:751–758.
31. Lefaucheur JP. Motor cortex dysfunction revealed by cortical excitability studies in Parkinson's disease: influence of antiparkinsonian treatment and cortical stimulation. Clin Neurophysiol 2005;116:244–253.
32. Haslinger B, Erhard P, Kampfe N, et al. Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. Brain 2001;124:558–570.
33. Sabatini U, Boulanouar K, Fabre N, et al. Cortical motor reorganization in akinetic patients with Parkinson's disease: a functional MRI study. Brain 2000;123:394–403.
34. Ridding MC, Inzelberg R, Rothwell JC. Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. Ann Neurol 1995;37:181–188.
35. Cantello R. Applications of transcranial magnetic stimulation in movement disorders. J Clin Neurophysiol 2002;19:272–293.
36. Payoux P, Remy P, Damier P, et al. Subthalamic nucleus stimulation reduces abnormal motor cortical overactivity in Parkinson disease. Arch Neurol 2004;61:1307–1313.
37. Haslinger B, Kalteis K, Boecker H, Alesch F, Ceballos-Baumann AO. Frequency-correlated decreases of motor cortex activity associated with subthalamic nucus stimulation in Parkinson's disease. Neuroimage 2005;28:598–606.