

Functional neuroanatomy of vocalization in patients with Parkinson's disease[☆]

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ARTICLE INFO

Article history:

Received 29 March 2011

Received in revised form 14 June 2011

Accepted 17 October 2011

Available online 9 November 2011

Keywords:

Parkinson's disease

Hypokinetic dysarthria

Speech production

Vocalization

fMRI

Functional connectivity

Periaqueductal gray matter

Auditory feedback

ABSTRACT

In Parkinson's disease (PD) both speech production and self-monitoring of voiced speech are altered.

Methods: In our previous study we used functional magnetic resonance imaging (fMRI) to examine which brain areas are involved in overt reading in nine female PD patients (mean age 66.0 ± 11.6 years) compared with eight age-matched healthy female controls (mean age $62.2 \text{ years} \pm 12.3$). Here we performed the post-hoc seed-based functional connectivity analysis of our data to assess the functional connectivity between the periaqueductal gray matter (PAG; i.e. the core subcortical structure involved in human vocalization) and other brain regions in the same groups of PD patients and controls.

Results: In PD patients as compared with controls we observed increased connectivity between PAG and basal ganglia, posterior superior temporal gyrus, supramarginal and fusiform gyri and inferior parietal lobule on the right side. In the PD group, the connectivity strength in the right putamen and the right supramarginal gyrus was correlated with variability of pitch while the connectivity strength in the right posterior superior temporal gyrus and in the right inferior parietal lobule was correlated with speech loudness.

Conclusion: We observed functional reorganization in PD patients as compared with controls in both the motor basal ganglia-thalamo-cortical circuitry and cortical areas known to be engaged in auditory and somatosensory feedback control of voiced speech. These changes were hemisphere-specific and might either reflect effects of dopaminergic treatment or at least partially successful compensatory mechanisms involved in early-stage PD.

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1. Introduction

Human vocalization engages many cortical and subcortical structures including the midline structures centered upon the mesencephalic periaqueductal gray matter [PAG], neocortical motor and premotor areas, the basal ganglia thalamo-cortical circuitry, and cerebellum [1]. During speech production the supplementary motor area (SMA) and anterior cingulate 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 primary sensorimotor area (SM1) corresponding mainly to the orofacial somatotopic areas [4–6]. In the context of speech, “vocalization” specifically involves brain mechanisms that support the precise coordination of respiration (adjusting inspiration, expiration and subglottal air pressure) and laryngeal activity and adjustments of vocal fold length and tension (adjusting pitch).

Animal studies e.g. [7,8] reported a midline network of brain regions, with PAG at the core of this circuit, dedicated to the generation of species-specific calls. PAG regulates synchronous activity in visceromotor neurons of the lower brainstem that are known to control both the vocal fold tension and respiration [7,9]. Schulz et al. [1] contrasted voiced and whispered speech in healthy humans using H_2^{15}O PET and then evaluated functional connectivity of regions that significantly differentiated these conditions. The authors demonstrated for the first time that PAG was engaged also in human vocalization. During voiced but not whispered speech, activity in PAG was correlated not only with phylogenetically older paramedian cortices and neocortical motor brain regions but also with areas in the temporal lobes, namely bilateral posterior superior temporal gyri and supramarginal gyri. These temporal regions may support self monitoring and feedback regulation of human phonation [1].

In Parkinson's disease (PD), the degeneration of dopaminergic nigrostriatal pathways results in disturbances of motor cortical areas and leads to the appearance of parkinsonian motor symptoms, including changes in speech. The speech dysfunction resulting from PD is typically classified as hypokinetic dysarthria. It affects up to 90% of patients with PD during the course of their illness [10] and it is characterized by reduced loudness, monotonous pitch, hoarseness, a breathy voice quality, imprecise articulation and impaired speech rate and rhythm [e.g.

[☆] Originally submitted to the special issue “Proceedings of the 7th Congress of Mental and other Non-Motor Dysfunctions in Parkinson's Disease”.

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10–16]. It is thought that motor speech disorders may be present in the early phase of illness and include a reduced variability of pitch and loudness and reduced speech stress in particular [6]. In addition, abnormalities in the auditory system and abnormal auditory-motor integration in PD [17,18] may contribute both to disturbances of self-perception of voice and speech production in this patient population [14].

Although pharmacological and surgical treatments are effective in treating motor symptoms of PD, the gains are not as significant for speech as they are for limb symptoms and the results of studies are variable depending mostly on study parameters and subpopulations of PD patients involved [e.g. 6,11,19–28]. On the other hand, LSVT (Lee Silverman Voice Treatment), have been effective for the treatment of hypokinetic dysarthria [e.g. 10,14]. It targets increased amplitude of motor output during speech production by training increased vocal effort and loudness while training individuals to monitor their own vocal output [14]. Therefore, brain areas involved in the auditory and somatosensory feedback of voiced speech are of particular interest in PD.

So far only a few studies have assessed hypokinetic dysarthria in PD using functional imaging [29–34]. In our previous study we used functional magnetic resonance imaging (fMRI) to examine which brain areas are involved in speech production in PD patients compared with healthy controls and which regions underlie variations in speech initiation, sentence reading duration and paralinguistic aspects of speech production in both groups [31]. We demonstrated that despite a comparable quality of speech in the two groups, the left primary orofacial sensorimotor cortex (SM1) was more engaged in PD patients than in controls. In addition, we found increased blood-oxygen level-dependent (BOLD) signal in the right SM1 in patients, as compared with controls, which was correlated with reading initiation. Other studies specifically explored effects of LSVT [29,33] or deep brain stimulation of the subthalamic nucleus in PD [30,34]. Taken together, results of all mentioned studies show that brain changes in hypokinetic dysarthria do not parallel those of limb movements and it has been postulated that pathophysiology of PD dysarthria is, at least in part, different from that of limb dysfunction.

Since both speech production and self-monitoring of voiced speech are altered in PD, the aim of the present study was to perform the post-hoc analysis of our MRI data in order to assess the functional connectivity between PAG, the core subcortical visceromotor structure involved in human vocalization, and other cortical and subcortical regions in the same groups of PD patients and controls [31]. We hypothesized that patients would show increased functional connectivity between PAG and areas engaged both in motor speech output and monitoring of their own voice intensity and pitch in order to compensate for striato-cortical circuitry dysfunction. In case that was true, we also aimed at assessing whether or not the areas with altered connectivity underlie variations in paralinguistic aspects of speech production – and voice loudness and intonation in particular – since these parameters are known to be impaired already in early stages of PD.

2. Patients and methods

Data was analyzed in nine treated female patients with PD (age; mean 66.0 ± 11.6 years) and eight age-matched healthy female controls (age; mean 62.2 ± 12.3), see [31]. In the PD group, the disease duration was 3.4 ± 1.7 years. The mean daily levodopa equivalent dose was 583.3 ± 397.9 mg, patients were scanned on medication, for details see [31]. Only women were recruited since men and women differ with respect to the mean fundamental voice frequency. For paralinguistic aspects of speech, see Table 1. None of the participants 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 participants reported Czech as their first language. All

experimental protocols were approved by the Ethics Committee of the St Anne's Hospital in Brno, and all participants provided informed consent.

For the speech task and speech stimuli analysis, see [31]. Briefly, participants performed a speech task in the scanner. 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-minute functional scans (see below for details). Speech was recorded using a unidirectional analog computer microphone fixed to the head coil and stored on a personal computer. 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 (F0), standard deviation (SD) of F0 and range of F0. The analysis of these paralinguistic aspects of speech was performed in the Montreal Neurological Institute, and details have been reported elsewhere [35]. Fundamental frequency (F0) is a major contributor to perceived vocal pitch. F0 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.

2.1. Functional MRI

Participants 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 mm²; slice thickness, 4 mm; 1 mm-gap between slices; acquisition of one measurement 3.8 s; inter-measurement interval, 12 s). The imaged volume covered most of the brain excluding the cerebellum. After functional scans, a high resolution T1-weighted 3D volume was acquired for anatomical localization (TR = 1700 ms, TE = 3.96 ms, FA, 15°, FOV, 246 mm; slice thickness 1.17 mm; 160 sagittal slices; in-plane resolution, 0.961×0.961 mm²). Functional images were motion-corrected, normalized to standard stereotaxic space (MNI 305), and smoothed using a 6-mm full-width at half-maximum isotropic Gaussian kernel. While in our original report [31] the data was analyzed using SPM99, here we used SPM5 to analyze the functional connectivity.

Correlation analysis was performed between the seed reference centered in PAG and the whole brain in a voxel-wise manner. We chose PAG coordinates (−2, −28, −8) from the simple reading contrast results (i.e. reading minus baseline) in the PD group [31]. The seed time-series from PAG was extracted using the participant's

Table 1
Paralinguistic aspects of speech production in PD patients and healthy controls.

Speech parameter	Patients		Controls		t-value	p-Value
	Mean	SD	Mean	SD		
Range of amplitude [absolute values]	1197.3	562.0	1634.0	496.0	−2.06	0.06
RMS of amplitude [absolute values]	93.0	39.5	131.0	51.4	−2.47	0.03
Mean pitch (F0) [Hz]	196.6	37.7	201.1	36.1	−0.04	0.98
SD of F0 [Hz]	65.3	8.3	67.5	11.9	−0.54	0.60
Range of F0 [Hz]	227.7	30.8	237.5	43.1	−0.53	0.61

RMS of amplitude: root-mean-square of amplitude, F0: mean fundamental frequency or pitch, SD: standard deviation. The last two columns show between group comparisons using two sample t-tests.

individual nearest local maxima coordinates within PAG as a first eigenvariate from sphere with 6 mm radius. Second level analysis was performed in order to compare functional connectivity of the PAG between the PD patients and healthy controls. Subsequently, the mean connectivity strengths (regression slopes or beta values calculated within the seed-based functional connectivity analysis in each subject) were extracted from results using a sphere with a radius of 6 mm centered in 6 regions of interest, i.e. in the brain areas with observed between-groups differences in the magnitude of functional connectivity strength (Table 3). In order to assess whether the observed PAG functional connectivity with specific brain regions of PD patients are associated with their behavioral outcomes, we correlated the connectivity strength values with speech parameters of interest (i.e. SD of F0, range of amplitude, and RSM of A) using STATISTICA software (StatSoft, Inc., Tulsa, OK).

All group reading-effect statistics (basic analyses and seed correlation analyses) were thresholded to a p-value of 0.001 uncorrected for multiple comparisons with an extent threshold of 5 voxels.

3. Results

In both groups, increased BOLD signal in PAG was correlated with a number of regions, including SM1 and premotor cortices, SMA, anterior and posterior cingulate cortices, medial and superior temporal gyri, insula, middle occipital gyrus, precuneus, superior and inferior parietal sulci, temporal association areas and subcortical motor structures, see Fig. 1 and Table 2.

In PD patients as compared with controls, the increased strength of functional connectivity with the seed located in PAG was observed in basal ganglia (caudate head and putamen), posterior superior temporal gyrus, supramarginal and fusiform gyri and inferior parietal lobule on the right side, see Table 3. We found no significant increases of the functional connectivity in controls as compared with PD patients.

In the PD group, the magnitude of functional connectivity in the right putamen (coordinates 24, -10, 0) and the right supramarginal gyrus (coordinates 44, -46, 30) was correlated with SD of pitch ($r = 0.83$; $p = 0.02$ and $r = 0.78$; $p = 0.04$, respectively). The strength of functional connectivity in the right posterior superior temporal gyrus (coordinates 40, -38, 14) and in the right inferior parietal lobule (coordinates 42, -36, 28) was correlated with the RMS/range of A ($r = 0.8$; $p = 0.03$ and $r = 0.90$; $p = 0.01$, respectively), see Fig. 2a–c.

4. Discussion

Schulz et al. [1] have demonstrated that PAG, which is the subcortical visceromotor structure known to coordinate basic respiratory and laryngeal motor patterns that are necessary for speech, is functionally connected not only with cortical and subcortical areas

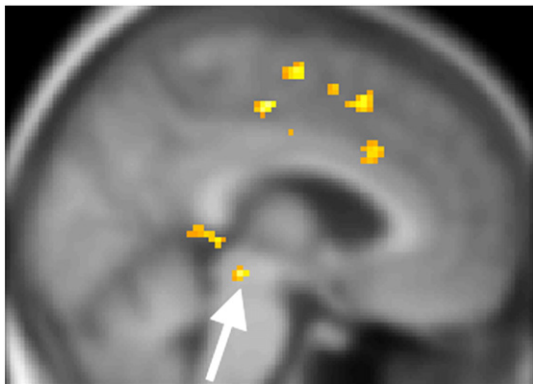


Fig. 1. Seed-based functional connectivity with the seed located in PAG (white arrow): group analysis results (data pooled from all participants).

Table 2

PAG-based functional connectivity: group analysis results (data pooled from all participants).

Region	X	Y	Z	K voxels	p corrected
L sensorimotor cortex (orofacial)	-54	-10	22	314	0.000
R anterior cingulate cortex/supplementary motor area	4	18	44	168	0.000
R premotor/sensorimotor cortex	52	-8	40	226	0.001
R midbrain	10	-24	-6	53	0.004
L occipital cortex	-28	-96	16	67	0.004
L inferior frontal gyrus	-44	26	-2	29	0.008
L cuneus	-24	-90	30	68	0.009
R putamen	22	10	-6	86	0.011
L anterior cingulate cortex	0	18	32	72	0.013
R putamen	28	-14	0	48	0.021
L superior temporal gyrus	-44	-34	8	25	0.022
R parietal cortex	26	-84	32	68	0.022
L insula	-30	16	-4	46	0.029
L superior temporal gyrus	-56	6	-14	13	0.037
L inferior frontal gyrus	-40	-2	32	18	0.039
R superior temporal gyrus/superior temporal sulcus	48	-36	4	36	0.046
L supplementary motor area	-4	-8	62	31	0.049

MNI coordinates used.

Reported areas are limited to those regions that were also present in the simple reading effect contrast (i.e. reading minus baseline) in the PD group and/or in the healthy controls group, and significant using cluster level inference $p > 0.05$; FWE corrected threshold.

L, left; R, right; K voxels, number of voxels in a cluster.

involved in speech production but also with areas involved in self-monitoring of voiced speech. Our results of seed-based functional connectivity in both healthy controls and PD participants are consistent with these notions. The second level analysis of our data revealed increased strength of functional connectivity in PD as compared with healthy controls specifically in the right striatum. The connectivity strength in the putamen positively correlated with speech intonation. The putamen is a central constituent of the dopaminergic nigrostriatal pathway which is known to be degenerated in PD, and part of the motor circuit which is connected through the ventral thalamus to the SMA [36,37]. The motor circuit might enable more precise voluntary control over the laryngeal, respiratory and articulatory activity during voiced speech [1,38]. In PD, the enhanced connectivity strength between PAG and putamen might reflect either successful compensatory changes in PD involved due to the dysfunction of the nigrostriatal circuitry or direct effects of dopaminergic therapy or combination of both.

In addition, there are areas in the temporal lobe and cerebellum that are functionally coupled to both visceromotor and neocortical systems during vocalization [e.g. 1,4,39]. We were not able to acquire data from cerebellum (see Patients and methods section) but we have demonstrated increased functional connectivity in various temporal regions in PD as compared with healthy controls. More specifically, the magnitude of connectivity in the posterior superior temporal

Table 3

Brain areas of increased PAG-based functional connectivity in PD patients as compared to healthy controls.

Region	X	Y	Z	t-stat	z-stat
R Caudate head	16	18	6	5.37	3.95
R Superior temporal gyrus	40	-38	14	4.80	3.68
R Supramarginal gyrus	44	-46	30	4.76	3.66
R Putamen	24	-10	0	4.74	3.65
R Fusiform gyrus	42	-66	0	4.61	3.58
R Inferior parietal lobule	42	-36	28	4.06	3.28

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

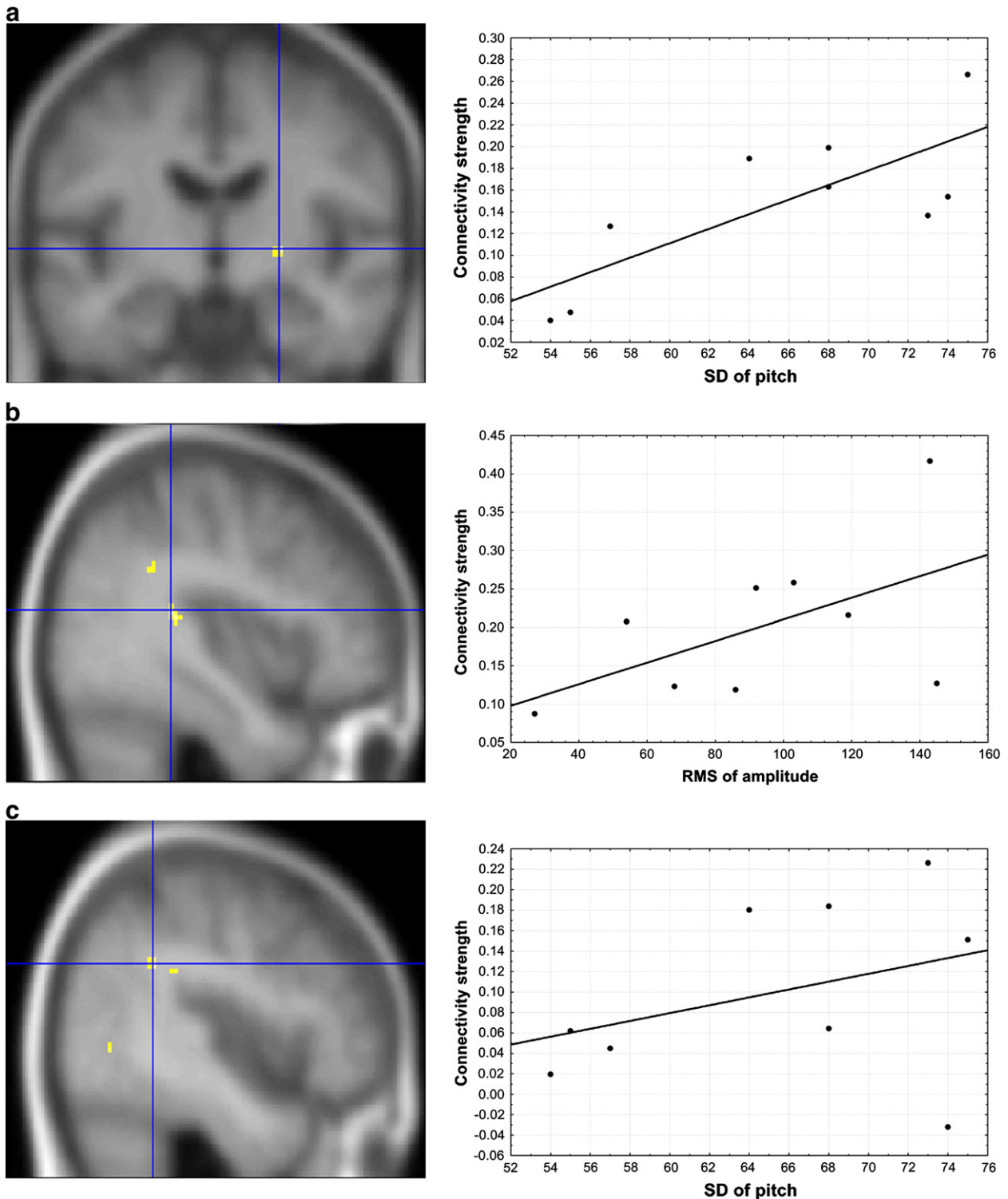


Fig. 2. a: Correlation between the magnitude of PAG-based functional connectivity in the right putamen and SD of pitch.2b: Correlation between the magnitude of PAG-based functional connectivity in the right posterior superior temporal gyrus and RMS of amplitude2c: Correlation between the magnitude of PAG-based functional connectivity in the right sylvian marginal gyrus and SD of pitch.

gyrus correlated with voice loudness and the strength of connectivity in the supramarginal gyrus correlated with intonation in speech. Thus we provided further evidence for the crucial role of these two regions in vocal and somatosensory self-monitoring respectively, and complex on-line adjustments of voice loudness and pitch [40,41]. In healthy humans, representation of the auditory control seems to be bilateral, usually with a right-sided preponderance [4,39,40] while the feedback control of pitch is mainly supported by the right

hemispheric network [e.g. 41,42]. Since abnormalities in the somatosensory [43] as well as in the auditory [18,44] systems have been documented in PD, we may again speculate that our results reflect compensatory mechanisms in early stage PD and/or treatment effects. These mechanisms were efficient for the control of speech intonation while they were not efficient enough for controlling the speech loudness. Our behavioral data showed that the voice loudness was significantly lower in the PD group as compared with healthy controls

while other studied acoustic parameters of speech were comparable in both groups.

Another interesting observation is the right-sided hemispheric lateralization with respect to all results of our between-groups analyses. Such a hemispheric lateralization in PD associated with successful vocalization and speech production has already been documented by others. For example Wang et al. [45] have shown that only right sided as opposed to left-sided STN DBS had positive effects on speaking rate and articulatory accuracy in PD. But in this paper acoustic parameters of speech were not specifically studied and therefore results of both studies cannot be directly compared. Santens et al. [46] have demonstrated that when left-sided STN stimulation is on and right-sided stimulation is off, this negatively influences speech including the prosody.

In our previous publication we demonstrated increased BOLD signal in the right SM1 in treated PD participants as compared with healthy controls [31]. Changes of regional cerebral blood flow (rCBF) between healthy controls and PD patients in the off stimulation condition were observed in the right motor and premotor areas and reversed by STN DBS. Furthermore, these changes as revealed by PET were accompanied by improvements in voiced speech production [30]. Positive effects of LSVT on paragraph reading and sustained phonation tasks were associated with significant rCBF increases in the right basal ganglia, and rCBF decreases in the right-sided SM1, SMA, and premotor areas [29]. Treatment-dependent shift to the right hemisphere with modification in the speech motor regions (orofacial SM1) as well as in prefrontal and temporal areas was also reported by Narayana et al. [33] in a recent H₂¹⁵O PET study. Taken together, the right-sided hemispheric lateralization seems to reflect specifically the successful treatment effects of both LSVT and STN DBS on voiced speech in PD. The hemispheric activation shift has also been described e.g. for affected upper limb movements in stroke patients. The previous work has shown that the worse the hand motor deficit, the greater the shift of primary motor cortex (M1) activation toward the contralesional hemisphere [e.g. 47,48]. In line with the functional imaging results, low-frequency (i.e. inhibitory) repetitive transcranial magnetic stimulation to the contralesional M1 improved the affected limb movements through modulating overactivity and brain connectivity of the contralesional primary and nonprimary motor areas [49,50]. Thus in contrast to PD dysarthria, the hemispheric activation shift in stroke patients seems to be associated with impaired rather than improved quality of hand movements. But it has already been shown by others that results of imaging studies of speech production in PD do not parallel those of limb movements [e.g. 30,31] and it has been suggested that the pathophysiology of PD dysarthria is, at least in part, different from that of limb dysfunction [6]. Studies examining functional connectivity in PD patients off and on dopaminergic medication should further explore whether our results were associated rather with effects of dopaminergic therapy or at least partially successful compensatory mechanisms in mild to moderate PD.

5. Conclusions

Using PAG centered seed-based functional connectivity analysis of MRI data acquired during overt reading, we observed functional reorganization in PD as compared with healthy controls that involved both the motor basal ganglia-thalamo-cortical circuitry and cortical areas known to be engaged particularly in auditory and somatosensory feedback control of voiced speech. These changes were hemisphere-specific and might either reflect effects of dopaminergic treatment or at least partially successful compensatory mechanisms involved in PD patients with early-stage PD.

Conflicts of interest

None.

Acknowledgment

Study was supported by a Research Project of the Czech Ministry of Education: MSM 0021622404.

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