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Articulatory network reorganization in Parkinson's disease as assessed by multimodal MRI and acoustic measures

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ABSTRACT

Introduction: Hypokinetic dysarthria (HD) is common in Parkinson's disease (PD). Our objective was to evaluate articulatory networks and their reorganization due to PD pathology in individuals without overt speech impairment using a multimodal MRI protocol and acoustic analysis of speech.

Methods: A total of 34 PD patients with no subjective HD complaints and 25 age-matched healthy controls (HC) underwent speech task recordings, structural MRI, and reading task-induced and resting-state fMRI. Grey matter probability maps, task-induced activations, and resting-state functional connectivity within the regions engaged in speech production (ROIs) were assessed and compared between groups. Correlation with acoustic parameters was also performed.

Results: PD patients as compared Tto HC displayed temporal decreases in speech loudness which were related to BOLD signal increases in the right-sided regions of the dorsal language pathway/articulatory network. Among those regions, activation of the right anterior cingulate was increased in PD as compared to HC. We also found bilateral posterior superior temporal gyrus (STG) GM loss in PD as compared to HC that was strongly associated with diadochokinetic (DDK) irregularity in the PD group. Task-induced activations of the left STG were increased in PD as compared to HC and were related to the DDK rate control.

Conclusions: The results provide insight into the neural correlates of speech production control and distinct articulatory network reorganization in PD apparent already in patients without subjective speech impairment.

1. Introduction

Hypokinetic dysarthria (HD) affects nearly 90% of Parkinson's disease (PD) patients during the course of their illness. It is characterized by several specific impairments such as monoloudness and monopitch, imprecise articulation of consonants, reduced stress, irregular pitch fluctuations, and aperiodicity (for a comprehensive review see Ref. [1]). Moreover, some features of HD such as altered speech rhythm, pausing, and rate have been related to axial PD motor symptoms such as freezing of gait [2], to non-motor symptoms of PD [3], and to progression of cognitive decline in one longitudinal study [4].

Regarding the neural substrates of speech production, complex neural networks have been implicated including both cortical and subcortical structures of the anterior components of the dorsal language pathway (inferior frontal gyrus/IFG, dorsolateral premotor cortex/PMC, supplementary motor area/SMA, anterior insula, and the orofacial region of primary motor cortex/OFM1), as well as the basal ganglia (particularly putamen), thalamus (ventral anterior/ventral lateral motor nuclei of thalamus), and cerebellum [5,6]. Moreover, an auditory feedback area within the posterior superior temporal gyrus (STG) also seems to play an important role in speech output modulation [7].

In PD, only a few functional imaging studies have explored the neural mechanisms of HD symptoms, with inconsistent results probably due to varied methodologies and patient populations [1]. In general,

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deficits in the basal ganglia and cerebellar activation and connectivity as well as altered functional connection of the STG have been described [8–15].

To shed further light on the neural mechanisms of motor speech in PD, we designed the first multimodal MRI study to explore and compare motor speech-related changes within the articulatory networks by comparing grey matter (GM) probability maps, speech task-induced activity, and intrinsic functional connectivity within the seeds of interest between a group of PD subjects and healthy age-matched controls (HC). In order to explore motor speech network reorganization due to PD pathology, we included only patients with intact speech intelligibility and without any subjective motor speech complaints whilst on dopaminergic medication. Since dopaminergic medication has a partial impact on both motor speech and the magnitude of BOLD signal increases in PD (e.g. Ref. [16]) we used daily levodopa equivalent dose (LED) as a co-variate in our patients' fMRI data. We expected grey matter volume (GMV) reductions and dorsal language network reorganization in PD as compared to HC within our speech production-related regions of interest (ROIs) due to PD pathology. Unlike previous studies, we used acoustic parameters to characterize articulation, prosody, and speech rhythmicity, as it has been shown that acoustic analysis is more precise than perceptive clinical assessment or self-evaluation of speech [1]. We hypothesized that structural and functional network changes in PD as compared to HC will be associated with variability of acoustic parameters quantifying phonetic aspects of the patients' speech production.

2. Methods

2.1. Participants

We included clinically diagnosed PD patients [17] who were well compensated on their stable dopaminergic medication with intelligible speech production and without subjective HD symptom complaints based on the self-evaluation voice handicap index questionnaire [18] and without major motor fluctuations or dyskinesias. The patients were longitudinally followed at the First Department of Neurology, Faculty of Medicine and St. Anne's University Hospital, Masaryk University, Brno, Czech Republic. Age-matched healthy subjects were recruited from our database at the Central European Institute of Technology (CEITEC), Masaryk University in Brno. Exclusion criteria for all subjects included alcohol/drug abuse, hallucinations or visual misperceptions, and any diagnosed psychiatric disorder. All participants were right-handed and reported Czech as their first language. PD patients were examined in the ON medication state without dyskinesias. The participants underwent clinical examination, a recording of speech using specific speech tasks for acoustic analysis of HD, and brain MRI examination using the 3T Siemens Prisma MR scanner (Siemens Corp., Erlangen, Germany). The MRI protocol consisted of structural scans, reading task fMRI scans (sentences were read aloud) and resting state fMRI (rs-fMRI). Each subject signed an informed consent form, and the study was approved by the local ethics committee.

2.2. Acoustic analysis of speech

The speech protocol was performed outside the MR scanner and contained reading (TSK1; reading a phonetically balanced paragraph containing 150 words; a patient could read the text for her-/himself in advance) and a diadochokinetic task (TSK2; rapid steady/pa/-/ta/-/ka/ syllable repetition as constantly and as long as possible, repeated at least 10 times; performed in one breath). These speech tasks are frequently used in the field of HD analysis [1]. HD symptoms were assessed with respect to articulation and prosody (see Table S1 in the Supplementary Materials). More specifically, we quantified rigidity of tongue and jaw (relF1SD and relF2SD), alternating motion/diadochokinetic rate (DDK rate), irregularity of the diadochokinetic task (DDK reg), monoloudness (relSEOSD), temporal changes in loudness (EEVOL), monopitch (relF0SD), and inappropriate silences (SPIR); for details see Supplementary Material and Table S1.

2.3. Speech production network: Regions of interest

Ten components of the speech production network were identified in both hemispheres based on a literature review [5,19], including supplementary motor area (SMA), premotor cortex (PMC), inferior frontal gyrus (IFG), superior temporal gyrus (STG), anterior insula, orofacial region of the precentral gyrus (OFM1), anterior cingulate cortex (ACC), putamen, thalamus, and cerebellum. The centre coordinates for ROIs were defined as maximum activations (peak voxel values, see Table S2 in the Supplementary Materials) in the fMRI reading task activation maps within the individual components of the speech production network for both the left and right hemispheres. Spheres with a 6 mm radius were created around the centre coordinates and intersected with fMRI group mask. The final masks then served as speech production network ROIs and were used in the subsequent analyses. SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running under Matlab 2014b (MathWorks, Inc.) was used for preprocessing of both anatomical T1-weighted and fMRI data. For details on specific MRI sequences and data processing including the GMV probability maps, reading task fMRI, and resting-state functional connectivity (rs-FC) within ROIs, see the Supplementary Materials.

2.4. Statistical analysis

In order to assess differences between HC and PD in acoustic parameters, GMV within ROIs, speech production network rs-FC, and reading task activations within ROIs, we employed the Mann-Whitney *U* test. Age, gender, and LED (in the PD group only) were included as covariates of no interest and were regressed out. In this exploratory study we report results without FDR correction and mark FDR corrected ones.

Spearman's partial correlations (controlling for the effects of age, gender, and LED) of GMV within ROIs with acoustic measures were calculated for both HC and PD groups separately. We also calculated Spearman's partial correlations between task-induced activations within the ROIs and the acoustic features of interest separately in both groups. Age, gender, GMV within ROIs, and LED in the PD group served as covariates of no interest. We further report and discuss only medium to strong correlations with $|R| > 0.4$ and $p < 0.05$.

3. Results

Our cohort consisted of 34 PD patients aged 69.02 ± 7.73 years (68% men; disease duration 5.69 ± 5.17 years; UPDRS III 14.03 ± 6.09; LED 857.31 ± 496.6 mg/day; 11 patients had right-sided PD symptom predominance, 17 had left-sided symptom predominance and 6 had bilateral PD) and 25 healthy controls (HC) aged 67.18 ± 5.54 years, 28% men. The groups did not significantly differ in age (Mann-Whitney *U* test, $p = 0.3$), but they differed in gender distribution (Pearson's Chi-Squared test, $\chi^2 = 9.0609$, $p = 0.003$).

3.1. Acoustic analysis results

The direct comparison between the PD and HC groups revealed only significant decreases of EEVOL (evaluated from TSK1) in the PD group (TSK1; 53% of PD patients as compared to 21% of HC below the 5th percentile interval, $p = 0.0364$), meaning that PD patients manifested loudness decreases with time. For all results of the acoustic analysis, see the Supplementary Materials, Table S3.

3.2. Results from GMV probability maps in ROIs and correlation with acoustic measures

PD patients were found to have significantly reduced GMV in both the left and right superior temporal gyrus (left STG: $p = 0.02$; right STG: $p = 0.04$), see Table S4 for all results in our ROIs.

The left and right STG volumes in PD patients revealed highly significant correlation with the diadochokinetic regularity (DDK reg, TSK2, $R = -0.61$, $p = 0.0008$ and -0.67, $p = 0.0001$, respectively, see Fig. 2). The direction of the correlation was negative, meaning that lower GMV were associated with increased irregularity during the diadochokinetic speech task. No such associations between the STG volume variability and acoustic parameters of speech were detected in the HC group. Of note, the DDK regularity was further related to the GMV variability of many other cortical and subcortical brain regions bilaterally, including the IFG, OFM1, anterior insula, ACC, and the left PMC and cerebellum in our PD group. Table 1 and Table S6 (Supplementary Materials) display all correlations between acoustic parameters from our speech tasks and our ROIs in the PD group and the HC group, respectively (medium to strong correlations are highlighted with $R > 0.4$ and $p < 0.05$).

3.3. Reading task-related activations in ROIs and correlation with acoustic measures

PD patients displayed increased activations as compared to HC, particularly in the left STG and right ACC (left STG: $p = 0.006$; right ACC: $p < 0.001$), although some other changes were also significant (see Fig. 1 and Table S5). The abovementioned results for the right ACC remained significant after FDR.

The left STG (TSK 2, $R = -0.51$, $p = 0.007$), but also the left thalamus and right IFG activations negatively correlated with DDK rate in the PD group. In the HC group there was only one negative correlation between left SMA activation and DDK rate.

The right ACC (TSK 1, $R = -0.42$, $p = 0.03$), but also the right SMA, right IFG, and left insula activations negatively correlated with EEVOL in PD patients whereas in the HC group there were no significant correlations for EEVOL. For detailed results see Table 2 and Table S7.

3.4. Resting-state functional connectivity (rs-FC) analysis results

The comparison of rs-FC of the left and right speech production network showed no significant differences between HC and PD. Because of the STG GMV differences between both groups we also tested the rs-FC between the left and right STG and other speech production-related ROIs. There were no differences between the PD and HC groups (results not shown).

4. Discussion

We used multimodal MRI to investigate PD pathology-induced changes in the GMV and functional reorganization within the articulatory brain networks in PD patients who were not yet experiencing subjective HD symptoms. We also used acoustic parameters of speech that precisely describe speech articulation, rhythm, and prosody in order to evaluate the relationship between variability of MRI findings, particularly in regions of between-group differences, and variability of speech parameters. Our PD participants were on stable dopaminergic medication and LED was used as a covariate for data analyses [16]. Results of previous functional studies have been inconsistent and difficult to compare since the authors used various study designs and usually enrolled PD patients with already manifested HD either OFF or ON dopaminergic medication [1]. The results therefore reflect the imaging correlates of specific motor speech deficits in those patients rather than brain reorganization due to PD brain pathology that is already present before full blown HD symptoms.

4.1. Behavioural results

Despite no subjective complaints of HD symptoms and speech intelligibility, using detailed acoustic analysis of speech, we observed

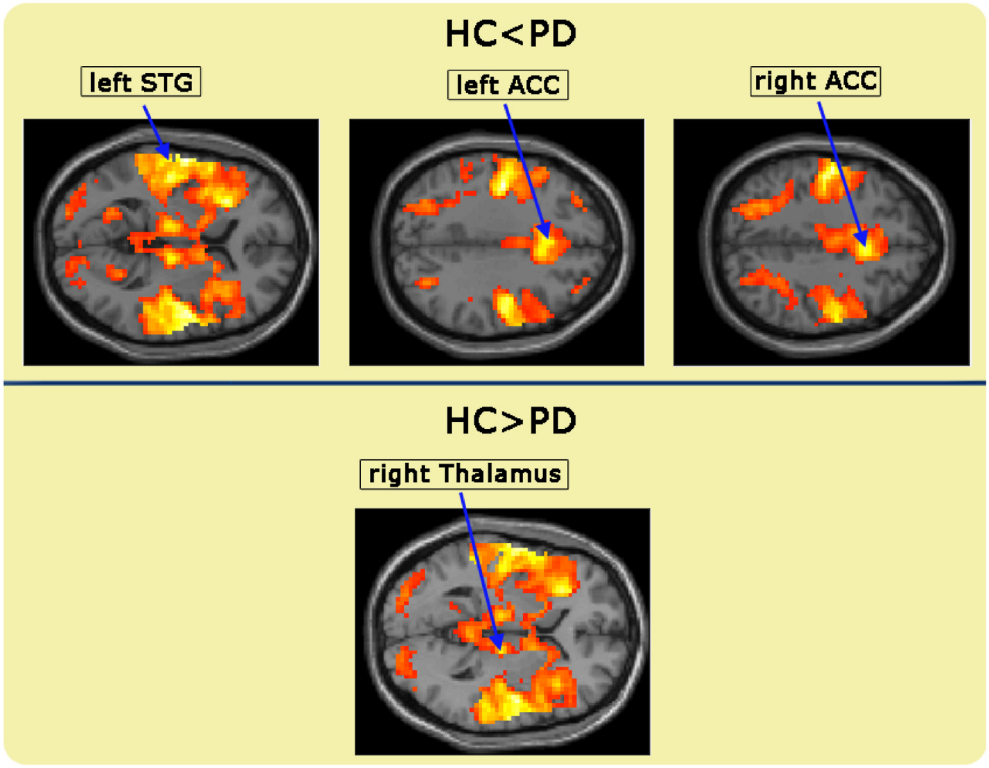

Fig. 1. Differences between speech task-related activations between groups.

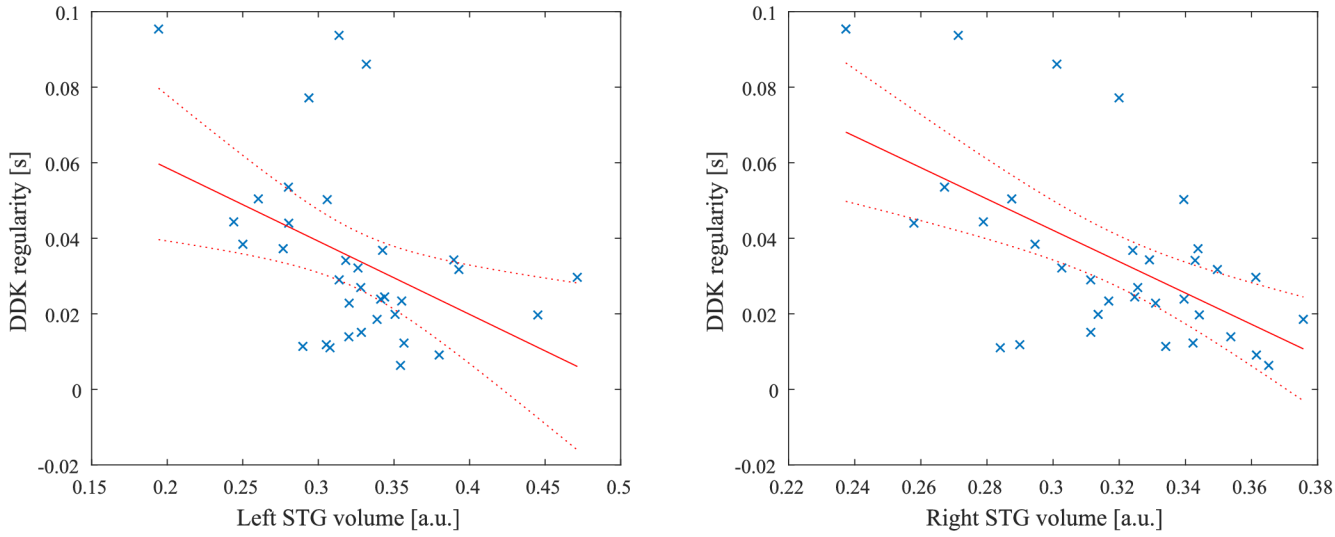

Fig. 2. Correlations of STG GMV with DDK regularity in PD group.

Table 1
Correlations between acoustic parameters from speech tasks and GMV within ROIs in the PD group.

PD	EEVOL	relF1SD	relF2SD	relF0SD	relSEOSD	SPIR	DDK rate	DDK reg
L_IFG	−0.28 (0.1335)	−0.06 (0.7545)	0.26 (0.1883)	0.23 (0.237)	0.36 (0.0619)	0.29 (0.1335)	0.36 (0.0572)	−0.47 (0.0115)
L_OFM1	−0.03 (0.8768)	−0.09 (0.6417)	0.29 (0.1374)	0.21 (0.2895)	0.04 (0.8335)	0.06 (0.7714)	0.5 (0.0077)	−0.52 (0.005)
L_Insula	−0.01 (0.9723)	−0.18 (0.3727)	0.29 (0.129)	−0.01 (0.9581)	0.07 (0.7419)	0.01 (0.9405)	0.39 (0.0431)	−0.49 (0.0094)
L_STG	−0.06 (0.7365)	−0.04 (0.8227)	0.3 (0.1195)	0.15 (0.4581)	−0.03 (0.8617)	−0.07 (0.7148)	0.39 (0.04)	−0.61 (0.0008)
L_Putamen	−0.17 (0.3494)	−0.09 (0.6557)	0.16 (0.4166)	0.15 (0.4581)	0.2 (0.3)	0.28 (0.1421)	0.23 (0.2451)	−0.2 (0.3162)
L_Thalamus	−0.31 (0.0939)	−0.06 (0.7588)	0.34 (0.0768)	0.09 (0.6397)	−0.03 (0.8813)	−0.04 (0.8574)	0.6 (0.0008)	−0.39 (0.0389)
R_Cerebellum	0.04 (0.8196)	−0.04 (0.8443)	0.07 (0.7066)	0.12 (0.5453)	0.19 (0.3373)	0.1 (0.6199)	0.35 (0.071)	−0.34 (0.0739)
L_SMA	0.01 (0.9598)	−0.19 (0.3246)	0.1 (0.5965)	0.04 (0.8443)	−0.25 (0.2064)	−0.05 (0.7842)	0.1 (0.6147)	0.03 (0.8618)
L_ACC	−0.02 (0.9275)	−0.06 (0.7461)	0.31 (0.112)	0.07 (0.7398)	−0.07 (0.7045)	−0.2 (0.2961)	0.2 (0.2973)	−0.45 (0.0181)
L_PMC	0.08 (0.6543)	−0.21 (0.2779)	0.24 (0.2268)	0.04 (0.8552)	−0.15 (0.4581)	0.16 (0.4166)	0.28 (0.1451)	−0.41 (0.0324)
R_IFG	0.05 (0.8014)	−0.22 (0.2593)	0.14 (0.4752)	0.19 (0.3274)	0.02 (0.9339)	0.26 (0.1731)	0.28 (0.1508)	−0.53 (0.0045)
R_OFM1	−0.01 (0.9594)	−0.17 (0.4006)	0.05 (0.812)	0.25 (0.2033)	−0.02 (0.9054)	0.13 (0.4945)	0.54 (0.0033)	−0.52 (0.0047)
R_Insula	−0.19 (0.3063)	−0.13 (0.4999)	0.29 (0.1374)	0.18 (0.3474)	0.07 (0.7357)	0.05 (0.8013)	0.26 (0.1876)	−0.48 (0.0107)
R_STG	0.08 (0.6804)	−0.07 (0.7231)	0.38 (0.0462)	0.18 (0.3651)	0.09 (0.6657)	0.29 (0.1366)	0.39 (0.0419)	−0.67 (0.0001)
R_Putamen	−0.36 (0.046)	0.07 (0.7419)	0.1 (0.5965)	0.09 (0.6317)	0.38 (0.0469)	0.33 (0.0814)	0.29 (0.1334)	−0.18 (0.3605)
R_Thalamus	−0.4 (0.0255)	−0.06 (0.744)	0.4 (0.0333)	0.04 (0.8314)	0.13 (0.5052)	0.09 (0.6476)	0.54 (0.0036)	−0.32 (0.1)
L_Cerebellum	0 (0.9898)	0.04 (0.8357)	0.1 (0.6023)	0.19 (0.3416)	0.31 (0.1048)	0.07 (0.7315)	0.39 (0.0437)	−0.5 (0.0069)
R_SMA	0.3 (0.0979)	−0.07 (0.7252)	−0.01 (0.9537)	0.02 (0.9317)	−0.15 (0.453)	−0.12 (0.5565)	0.09 (0.6505)	−0.11 (0.5683)
R_ACC	0.1 (0.5855)	−0.13 (0.5142)	0.28 (0.152)	0.14 (0.484)	−0.05 (0.812)	0.03 (0.8726)	0.34 (0.0734)	−0.41 (0.0322)
R_PMC	0.02 (0.8949)	−0.38 (0.0465)	0.16 (0.4022)	−0.02 (0.9383)	−0.15 (0.4429)	0.23 (0.2451)	0.16 (0.4263)	−0.29 (0.1327)

Correlations with $R > 0.4$ and $p < 0.05$ marked in red; L (prefix) – left; R (prefix) – right; IFG – inferior frontal gyrus, OFM1 – orofacial primary motor cortex, STG – superior temporal gyrus; SMA – supplementary motor area; ACC – anterior cingulate cortex, PMC – premotor cortex.

that PD patients as compared to HC displayed decreases of their speech intensity during the sentence reading task (as measured by EEVOL). Although HD in PD is known to be associated with reduced vocal loudness in general, decrements of speech intensity with time reflect a typical feature of bradykinesia, i.e. progressive reduction in amplitude of the movement, in this case of the vocal cords. This result suggests that EEVOL might be used as a potential marker for early HD associated with PD in future studies.

4.2. *fMRI results: Reading task-induced activations*

We found that the task-induced activation in the right ACC was significantly increased in the PD group as compared to HC. Moreover, BOLD signal increases in that region were associated with the above-mentioned decreases of EEVOL in the PD group. Engagement of other regions including the right SMA, right IFG, and left anterior insula was also related to EEVOL such that the more pronounced bradykinesia of vocal cords was associated with higher increases of the BOLD signal during sentence reading. Both the ACC and the SMA play a role in speech initiation; the left anterior insula is important for coordinating speech articulation and vocalization planning [20]. The abovementioned correlations and increased activation in the ACC mostly involved the right-sided hemispheric regions. This accords well with the described right-sided functional brain reorganization due to the successful LSVT [14,15]. However, it seems that the increased engagement of these regions did not fully compensate for vocal muscle bradykinesia in our patients.

Another finding concerns increased STG task-induced activation in PD as compared to HC and a negative correlation between the DDK rate and STG reading task-induced BOLD signal increases. It has been well documented [21] that patients with HD due to PD display significant difficulties in steadily executing a syllable repetition task, with a clear tendency to pace acceleration in the course of the performance. It is therefore plausible to speculate that the increased activation of the STG might have an underlying brain compensatory mechanism leading to normal speech rhythmicity (note that the acoustic parameter did not differ between our PD and HC groups) despite the brain neurodegeneration.

It has also been documented that laterality of PD motor symptoms could play a role in acceleration of syllable repetition in PD patients

Table 2
Correlations between acoustic parameters from speech tasks and speech-task related activations within ROIs in the PD group.

PD	EEVOL	relF1SD	relF2SD	relF0SD	relSEOSD	SPIR	DDK rate	DDK reg
L_IFG	−0.23 (0.2385)	−0.06 (0.7722)	−0.12 (0.5716)	−0.11 (0.5915)	0.35 (0.0807)	−0.07 (0.7258)	−0.13 (0.517)	−0.16 (0.4482)
L_Precentral	−0.14 (0.4801)	−0.11 (0.5898)	−0.09 (0.6688)	−0.13 (0.5229)	−0.13 (0.5289)	0.07 (0.7361)	−0.19 (0.3647)	0.15 (0.4665)
L_Insula	−0.5 (0.0077)	−0.18 (0.3922)	−0.22 (0.2875)	−0.17 (0.4065)	0.05 (0.815)	−0.12 (0.548)	−0.12 (0.5605)	0.13 (0.5259)
L_STG	−0.12 (0.5437)	−0.36 (0.0678)	0.17 (0.3954)	−0.15 (0.4678)	−0.33 (0.0961)	−0.05 (0.7937)	−0.51 (0.0072)	0 (0.9978)
L_Putamen	−0.31 (0.1168)	−0.03 (0.8836)	−0.04 (0.8544)	0.05 (0.7993)	0.12 (0.5749)	0.01 (0.9542)	−0.18 (0.369)	−0.04 (0.8489)
L_Thalamus	−0.06 (0.7586)	−0.13 (0.54)	−0.06 (0.7763)	−0.02 (0.925)	−0.06 (0.7798)	0.03 (0.899)	−0.43 (0.0273)	0.09 (0.6459)
R_Cerebellum	−0.08 (0.6797)	0.02 (0.9087)	−0.37 (0.065)	−0.02 (0.9286)	−0.1 (0.6233)	0.01 (0.9605)	−0.39 (0.0472)	0.29 (0.1536)
L_SMA	−0.31 (0.1179)	0.02 (0.9139)	−0.18 (0.3861)	−0.13 (0.512)	0.08 (0.7109)	−0.05 (0.7956)	−0.3 (0.1348)	0.19 (0.3455)
L_ACC	−0.37 (0.0604)	−0.05 (0.8171)	−0.32 (0.1075)	−0.17 (0.3947)	0.12 (0.5524)	−0.13 (0.5426)	−0.11 (0.5835)	0.17 (0.4103)
L_PMC	−0.28 (0.154)	0.06 (0.7835)	−0.02 (0.9371)	−0.39 (0.046)	0.05 (0.7899)	0.15 (0.4749)	−0.32 (0.1122)	0.09 (0.6618)
R_IFG	−0.44 (0.0222)	0.07 (0.7444)	−0.18 (0.3884)	−0.22 (0.2904)	−0.03 (0.8863)	−0.06 (0.7794)	−0.55 (0.0035)	0.5 (0.0099)
R_Precentral	−0.14 (0.4792)	0.07 (0.7245)	−0.06 (0.7713)	−0.18 (0.3688)	−0.09 (0.6727)	0.19 (0.3549)	−0.32 (0.1099)	0.16 (0.4211)
R_Insula	−0.2 (0.3053)	0.12 (0.5679)	−0.35 (0.0756)	−0.13 (0.5426)	0.14 (0.4946)	−0.01 (0.9441)	−0.13 (0.5419)	0.27 (0.1845)
R_STG	−0.24 (0.2252)	−0.05 (0.8136)	−0.16 (0.4376)	0.01 (0.9528)	0.1 (0.6178)	0.21 (0.2937)	−0.21 (0.293)	0.06 (0.7669)
R_Putamen	−0.39 (0.0463)	−0.19 (0.3603)	0 (0.992)	−0.17 (0.4133)	−0.05 (0.8135)	−0.02 (0.9399)	−0.08 (0.6847)	0.01 (0.9611)
R_Thalamus	−0.15 (0.459)	−0.15 (0.4652)	−0.07 (0.7445)	−0.09 (0.6478)	−0.14 (0.5036)	−0.18 (0.3824)	−0.34 (0.0938)	0.17 (0.4202)
L_Cerebellum	−0.04 (0.8605)	0 (0.983)	−0.37 (0.062)	0.01 (0.9773)	−0.19 (0.359)	−0.1 (0.6389)	−0.38 (0.0528)	0.24 (0.2473)
R_SMA	−0.42 (0.031)	−0.01 (0.966)	−0.27 (0.1815)	−0.17 (0.3953)	0.18 (0.3817)	−0.02 (0.9154)	−0.19 (0.3498)	0.19 (0.3465)
R_ACC	−0.42 (0.0295)	0.06 (0.7884)	−0.23 (0.2527)	−0.1 (0.6138)	0.14 (0.4891)	−0.18 (0.3758)	−0.15 (0.453)	0.28 (0.1677)
R_PMC	−0.27 (0.1717)	0.01 (0.96)	−0.1 (0.6172)	−0.34 (0.0935)	0.2 (0.3318)	0.33 (0.0976)	−0.32 (0.11)	0.44 (0.0255)

Correlations with $R > 0.4$ and $p < 0.05$ marked in red; L (prefix) – left; R (prefix) – right; IFG – inferior frontal gyrus, STG – superior temporal gyrus; SMA – supplementary motor area; ACC – anterior cingulate cortex, PMC – primary motor cortex.

[22]. However, our PD group was quite well balanced for PD symptom laterality and the fMRI results did not change even when the "laterality effect" was additionally added as a covariate in the second level analyses.

On the whole, fMRI may identify compensatory mechanisms recruited to overcome functional impairment associated with advancing pathology in neurodegenerative disease [23]. However, brain functional reorganization may also represent maladaptive changes that do not lead to enhanced performance [24]. In the only study that used reading task-induced activations in PD subjects without symptoms of HD [11], the authors observed increased activation of the left posterior STG in PD subjects as compared to HC. However, the authors interpreted this increased STG activation as diminished auditory cortex suppression during overt speaking, representing a maladaptive response within this brain region. Supporting our interpretation of the increased STG activation as compensatory, we previously demonstrated that manipulating the STG excitability with repetitive transcranial magnetic stimulation (rTMS) increases the reading task-induced activation of that region as well as total pause time and speech index of rhythmicity leading to more regular and intelligible speech in PD subjects with mild to moderate HD [12]. During the successful Lee Silverman Voice Treatment (LSVT) for HD in PD, increased loudness is achieved through increased speech effort and its subsequent automatization [25]. A recent fMRI study [14] showed increased STG activity as a neural correlate of effective LSVT. In that study, increased STG activations correlated with improved motor speech intelligibility. Taken together, we believe that increased engagement of the STG may represent the neural substrate of compensation for PD-related neurodegeneration in order to maintain successful syllable pace control in speech production.

It has to be mentioned that in addition to the STG, activation of other regions of the speech articulatory network such as the IFG and thalamus revealed significant association (negative correlations) with the DDK rate. In the HC group there was a negative correlation with the left SMA. These results are consistent with previous fMRI studies that found involvement of the motor basal ganglia circuitry and opercular IFG in the performance and maintenance of syllable sequence production in HC [26].

4.3. Intrinsic functional connectivity results

Although some previous studies found decreased rs-FC between subcortical (basal ganglia) structures and cortical regions engaged in overt vocalization in PD as compared to HC (e.g. Refs. [10,13]), in the current study we were not able to identify any abnormalities in the rs-FC of the left and right motor speech networks in PD subjects on dopaminergic medication even after regressing out the effects of LED.

4.4. Changes in GMV

Using GMV probability maps in ROIs, we observed only mild decreases in the GMV in both left and right STG in PD as compared to HC, however, the results did not survive the FDR correction and therefore have to be interpreted with caution. We are aware of only one study that explored brain morphological changes associated with HD [27]. The authors retrospectively used cortical thickness measures and a machine-learning model to predict HD severity in a PD group. HD was evaluated only subjectively by PD patients and its severity was found to be significantly positively associated with precentral and fusiform cortical atrophy. Our results cannot be directly compared with that study since the aims and methods of the two investigations differ. Of note, decreasing STG volume was strongly correlated with the increasing irregularity of syllable repetitions in the 'pa-ta-ka' task. The STG plays a critical role in representing phonological information that guides the motor system during speech production via the dorsal language pathway [28]. The STG also makes an important contribution to processing auditory feedback during speech production [7,29]. Although atrophy involving the STG and adjacent STS (superior temporal sulcus) with PD progression has been documented previously [30], here we show for the first time that the posterior part of the STG is engaged in motor speech control: the STG GMV decreases in PD were strongly associated with irregularity increases on the diadochokinetic speech task.

4.5. Study limitations

A limitation of this study is the fact that speech samples were not recorded inside the scanner, so we were conducting indirect correlations between MRI measures associated with a reading task in the scanner and acoustic measures derived from speech tasks performed outside the scanner. However, the pattern of pace disturbance during the 'pa-ta-ka' DDK task shows similarities with the findings of speech acceleration and rhythm irregularity in the course of reading [31], and it is therefore probable that speech rhythmicity control in both tasks shares the same pathophysiological mechanisms.

Another limitation is the fact that we report results without correction for multiple comparisons, which makes the study exploratory. Having said that, we have to underscore the task-related fMRI result for the right ACC that significantly differ between both groups even after the FDR correction and point to adaptive functional reorganization of the articulatory network already in pre-symptomatic or very early stages of HD in PD. Based on the literature [8,9,13,14,19,20], we expect more robust findings (deficits) in PD patients with full blown HD symptoms and future research should use a longitudinal study design to shed further light on brain compensation and deficits during the HD progression.

Since only right-handed PD patients were included in this study, the results cannot be generalized to left-handed individuals particularly in terms of MRI results.

Finally, current fMRI methods rely on the fact that task-induced cerebral blood flow changes more than the cerebral metabolic rate for oxygen, produce localized changes in tissue oxygen content (which is detected by fMRI and termed the blood oxygen level dependent (BOLD) signal) [32]. The changes in BOLD signal reflect the changes in neural activity. Despite the fact that we made attempts to regress out the effects of dopaminergic medication in the PD group in our second level statistical analyses (we used LED as a covariate of no interest in the PD group when comparing PD and HC groups), we cannot exclude the possibility that the dopaminergic medication might have influenced the baseline metabolic rate for oxygen in the PD group in a regionally specific manner which in turn might have partially impacted on the magnitude of task-induced BOLD signal increases. When inspecting the data thoroughly, we did not observe any significant effects of LED on BOLD signal increases in the PD group. To fully resolve this issue, future studies should include PD patients both in the ON and OFF dopaminergic medication state.

5. Conclusion

In conclusion, our work provides insight into the neural correlates of speech control and the neural underpinnings of altered motor speech in PD patients as well as brain compensatory mechanisms in PD without subjective HD symptoms. Our MRI results may help improve HD treatment strategies and select targets for non-invasive brain stimulation as a potential treatment of HD in PD.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.02.012.

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