CoBeN

Novel Network-Based Approaches for Studying Cognitive Dysfunction in Behavioural Neurology

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MARIE CURIE ACTIONS

D14: Neural substrates of speech prosody impairment in patients with different neurological diseases across three different languages

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1 Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons (Emamzadeh et al. 2018, Postuma et al. 2019). Besides typical motor symptoms such as bradykinesia, rigidity, postural instability and resting tremor, speech impairment is also very common and affects nearly 90 % of PD patients during the course of their illness (Ho et al., 1999). This motor speech disorder, typically classified as hypokinetic dysarthria (HD), is characterized by monoloudness and monopitch, imprecise consonants, reduced stress, airflow insufficiency, irregular pitch fluctuations, aperiodicity, and inappropriate silences (for a comprehensive review on HD we refer to Brabenec et al., 2017).

Among all of the abovementioned HD symptoms, impairment of rhythmicity of speech has been one of the alarming albeit less studied HD symptoms. It was described already in majority of subjects suffering from REM sleep behavioural disorder (Hlavnička et al., 2017), i.e. in a prodromal stage of degenerative syncleinopathies (Postuma et al., 2015), it has been related to other less favourable axial PD motor symptoms such as freezing of gait (Cantiniaux 2010, Ricciardi 2016, Mekyska 2018) and it may predict cognitive decline in PD population within the two years of follow-up (Rektorova, 2016). Speech rhythmicity alterations in PD usually manifest as abnormal pausing, speech rate and regularity, however, only few studies have addressed this topic in the PD literature with variable results (Skodda, 2011, Lowit, 2018, Tjaden 2003, Skodda+Flasskamp 2010, Rusz 2015, Ackermann 1997), and underlying mechanisms for this speech disorder are poorly understood.

On the whole, rhythmicity alterations in PD are manifested differently depending on a specific speech task. In the case of running speech, Skodda et al. (2008, 2009, 2011) described decreased articulatory rate with the disease progression. The authors suggested the role of particularly non-motor patophysiological mechanisms in speech timing and velocity (Skodda 2011). Others have focused on inter-word pausing (Skodda et al. 2008, Lowit 2018) or on the assessment of speech index of rhythmicity (SPIR) (Cantiniaux et al. 2010, Mekyska 2018, Rektorova 2016, Brabenec 2018), i.e. a parameter that evaluates the rhythmicity in terms of alternation between pauses and speech. SPIR was decreased in PD as compared to healthy age-matched controls (Cantiniaux 2010, Rektorova 2016). With respect to the diadichokinetic (DDK, syllable repetition) task, both decreased syllable repetition rates (Skodda 2011 – Aspects, Lowit 2018) and increased articulatory acceleration and unsteadiness during syllable repetition (Skodda MDS 2011, Rusz 2015, Skodda+Flasskamp 2010, 2011 MDS, Skodda+Gronheit 2010) have been reported in the literature.

Regarding the neural substrates of speech production, complex neural networks have been implicated including both cortical and subcortical structures, in particular dorsolateral premotor cortex (PMC), supplementary motor area (SMA), orofacial region of primary motor cortex (OFM1), inferior frontal gyrus (IFG), as well as the basal ganglia, thalamus, and cerebellum (Eickhoff et al., 2009; Fujii and Wan, 2014). Moreover, auditory feedback also plays a very important role and involves posterior superior temporal gyrus (STG) (Guenther and Hickok, 2016). In PD patients with HD, functional imaging studies have shown deficits in

basal ganglia and cerebellar activation and connectivity (New 2015, Pinto 2004b), as well as abnormal connection between the posterior STG and motor cortices and subcortical structures involved in speech production (New, 2015, Rektorova, 2012), for review, see Brabenec et al., 2017. It has been proposed that the fundamental cause of rhythm changes in PD reflect disruption of basal ganglia-thalamo-cortical motor networks (Fujii and Wan, 2014, Schmitz-Hubsch 2012). While no imaging study has specifically focused on neural underpinnings of speech rhythmicity alterations in PD, we have shown that one session of low-frequency repetitive transcranial magnetic stimulation applied over the right posterior superior temporal gyrus (X=40, Y=−38, Z=14) led to significant increase of the total pause time of pauses longer than 50ms with a medium effect size (r=− 0.411), and there was an additional trend towards increased values of the speech index of rhythmicity with a medium effect size (r=−0.319) (Brabenec et al., 2018). The result suggests that a voice feedback area in the posterior superior temporal gyrus is causally engaged in planning and control of speech rhythmicity and that intact voice feedback is important for correct pausing and speech rate and rhythm adjustments during the overt speech in PD. In line with this notion, rehabilitation approaches have been designed to compensate defective internal rhythm generation by the basal ganglia, and to overcome gait problems in PD. Rhythm-related interventions (such as external sensory cueing or music) have been extensively used in motor rehabilitation. Most studies showed that gait impairment in PD could be significantly improved by rhythmic (auditory) stimulation or musically cued gait training (for review, see Avanzino 2016). Rhythmic external cueing was also found to assist motor learning (Nieuwboer et al., 2009) and the Lee Silvermann Voice Treatment enhances speech voice intensity and intelligibility through modulation of voice feedback (Atkinson-Clement 2015, Brabenec et al., 2017).

In the current study, we specifically explore rhythmicity alterations in speech samples collected from PD patients using four associated acoustic features: speech index of rhythmicity, articulatory rate, diadochokinetic regularity, and diadochokinetic rate, for detailed description of these parameters, see Table II. Our aim was to identify the neural correlates of altered speech rhythmicity in PD in terms of both structural and functional changes within the speech production network.

2 Methods

Participants

Our cohort consisted of 25 healthy controls (HC) with age of (mean ± std) 66.48 ± 5.51 years (females 65.89 ± 5.60, and males 68.00 ± 5.35), and 34 PD patients with age of 68.50 ± 7.68 years (females 68.64 ± 7.38, and males 68.43 ± 7.98). For demographic and clinical data of the PD patients, see Table I and Figure 1. Exclusion criteria for 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 and were longitudinally followed at the First Department of Neurology, Faculty of Medicine and St. Anne's University Hospital, Masaryk University, Brno, Czech Republic. All subjects were clinically examined. Speech

recordings were obtained from all participants and they also underwent an MRI examination using the 3T Siemens Prisma MR scanner (Siemens Corp., Erlangen, Germany) with reading task inside the scanner (for more information see Section 2.3). Each subject signed an informed consent form and the study was approved by the local ethics committee.

TABLE I
CLINICAL CHARACTERISTICS OF THE PARTICIPANTS

	mean	std	min	1Q	median	3Q	max
PD dur. (y)	5.69	5.17	0.50	2.00	4.00	8.75	20.00
UPDRS III	14.03	6.09	6.00	9.50	14.00	16.50	29.00
LED (mg/day)	857.31	496.60	80.00	500.00	775.00	1257.63	1850.00
age (y)	68.50	7.68	53.00	63.00	70.00	73.75	81.00

[1] UPDRS III – Unified Parkinson's disease rating scale, part III (motor examination) [32]; LED – Levodopa equivalent dose [33]

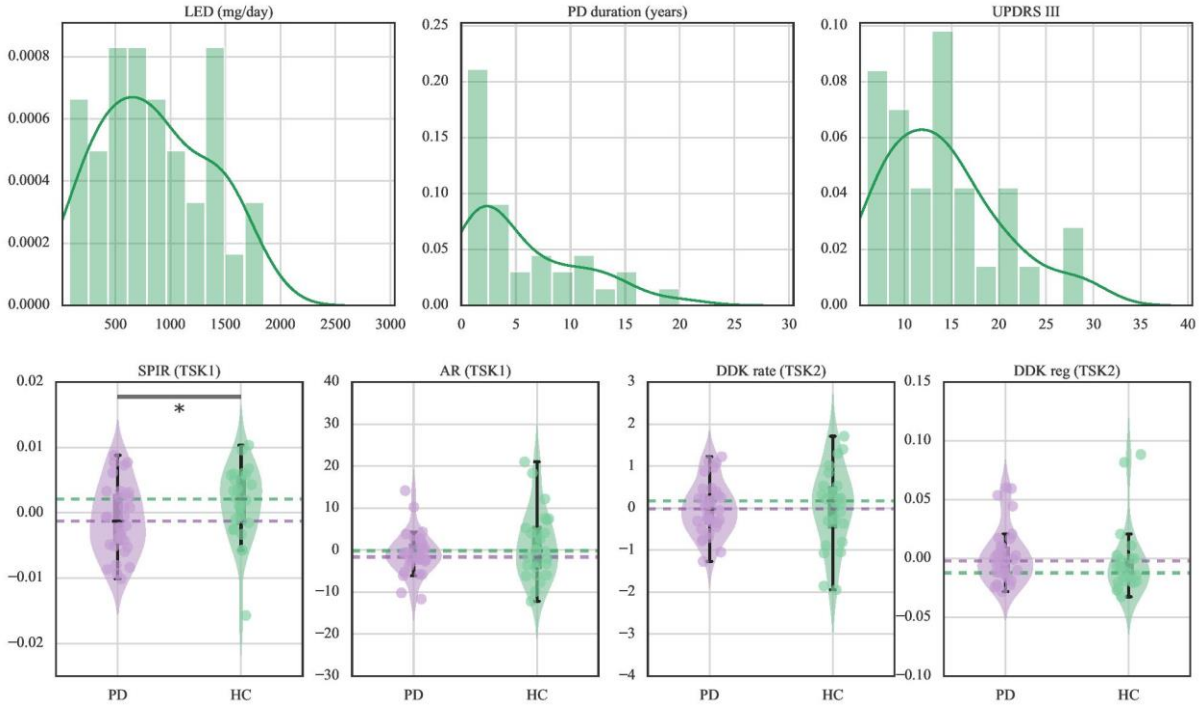

Figure 1: Demographic and clinical data of the PD patients.

Acoustic Analysis of Voice and Speech

Speech/voice acquisition inside the MR scanner brings many limitations, especially due to very strong background noise (coming from gradient system), small space around the head (which introduces spectral distortion in acoustic signal) and necessity to use a MR compatible microphone (that provides much worse characteristics than e.g. a professional condenser microphone). Therefore, we analysed the neural correlates of speech rhythmicity indirectly, i.e. we used two protocols inside and outside the scanner, respectively. The protocol inside the scanner was used to activate brain regions responsible for speech planning, programming and execution. These activations were consequently correlated with acoustic measures extracted from speech/voice outside the scanner. Although this approach is indirect, it allows us to examine the functional neuroanatomy of speech production in HC and measure alterations in the structural and functional integrity of the speech network in PD.

The protocol inside the MR scanner consisted of overt reading of short emotionally neutral sentences and watching a string of "Xs" (a baseline condition). Altogether there were 48 sentence reading trials and 24 baseline trials in random order. The duration of all stimuli was 5 s with black screen in between them for period of 11 s (Rektorova et al., 2007, Brabenec et al, PRD, 2018).

The speech protocol performed outside the MR scanner contains 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/ syllables repetition as constant and long as possible, repeated at least 10 times; performed on one breath), i. e. the speech tasks most commonly used in the field of HD analysis that enable to assess the rhythmicity of speech (Brabenec et al. 2017). During the acquisition, we placed a large capsule cardioid microphone M-AUDIO Nova mounted to a boom arm RODE PSA1 at a distance of approximately 20 cm from the patient's mouth. Acoustic signals were digitized using audio interface M-AUDIO Fast Track Pro with fs = 48 kHz sampling frequency and 16-bit resolution. The respective acoustic measures (see Table II) were extracted using software Praat (Boersma et al. 2019) and Matlab by a trained acoustic engineer who was blind to the patients' clinical data.

TABLE II
OVERVIEW OF ACOUSTIC FEATURES

Specific disorder	Speech tasks	Acoustic feature	Feature definition
Inappropriate silences	Reading (TSK1)	SPIR	Speech index of rhythmicity. Number of pauses relative to total speech time after removing periods of silence lasting less than 50 ms.
Unnatural speech rate	Reading (TSK1)	AR	Number of speech sounds produced per second after pauses longer than 50 ms were removed.
Slow alternating motion rate	Diadochokinetic task (TSK2)	DDK rate	Diadochokinetic rate, representing the number of syllable vocalizations per second. Considering first 30 syllables.
Irregular alternating motion rate	Diadochokinetic task (TSK2)	DDK reg	Diadochokinetic regularity, defined as the standard deviation of distances between following syllables nuclei. Considering first 30 syllables.

MRI sequences and processing

The following MRI sequences were used: magnetisation-prepared rapid gradient-echo (MPRAGE) high-resolution sequence (240 sagittal slices, slice thickness = 1 mm, TR = 2300 ms, TE = 2.36 ms, FA = 8°, FOV = 256 mm, matrix size 256×256) and gradient-echo echo-planar imaging sequence during reading task (73 scans, 44 transversal slices, slice thickness = 3 mm, TR = 12000 ms, scan acquisition time = 2750 ms, TE = 33 ms, FA = 80°, FOV = 192 mm, matrix size 64×64) acquired during reading task.

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. T1-weighted images were segmented and the DARTEL imported versions of grey matter and white matter were obtained for each subject. Normalization into standard MNI space was performed. Grey matter probability maps were Jacobian-modulated in order to preserve the original grey matter amount and smoothed using a spatial filter with the Gaussian kernel (FWHM = 6 mm). Lastly, the values of images were divided by total intracranial volume (TIV) to correct for the effects of overall brain size.

The pre-processing of the functional data consisted of realignment and unwarping, normalisation into standard anatomical space (MNI), and spatial smoothing using gaussian filter kernel with FWHM of 5 mm. The level of motion was evaluated using inner fence criterion (Brabenec et al, PRD 2018, Ross 1983). Individual subject masks were calculated using Mask_explorer (Gajdos 2016) and checked for excessive signal dropouts. Following data quality assessment 6 subjects (2 HC and 4 PD) were excluded from fMRI analysis. Upon having final fMRI dataset, group mask was calculated and data inserted into general linear model. The reading task time courses were convolved with a canonical haemodynamic response function and six movement parameters obtained during realignment and unwarping were used as nuisance regressors. Contrast files with the activation effects were computed and then entered into one-sample t-test with age and gender as covariates of no interest to produce the reading task activation map.

Regions of interest

Ten components of the speech production network were identified based on literature review (Eickhoff 2009, Rektorova MDS 2007). The center coordinates for ROIs were defined as maximum activations in the fMRI reading task activation map within the individual components of the speech production network for both the left and right hemisphere, see Table III. Spheres with 6 mm radius were created around the center coordinates and intersected with fMRI group mask (Gajdos 2016). The final masks then served as speech production network ROIs and were used in the subsequent analyses.

TABLE III
SPEECH PRODUCTION NETWORK ROIS

Area	x	y	z
Left network coordinates			
inferior frontal gyrus	-48	11	23
precentral gyrus	-54	-7	29
insula	-30	17	8
superior temporal gyrus	-57	-25	5
putamen	-18	8	8
thalamus	-12	-19	5
cerebellum	15	-64	-16
supplementary motor area	-3	2	59
anterior cingulate cortex	-6	20	32
premotor cortex	-42	-4	53
Right network coordinates			
inferior frontal gyrus	48	11	26
precentral gyrus	57	-7	26
insula	48	8	-1
superior temporal gyrus	57	-25	5
putamen	21	11	8
thalamus	12	-19	2
cerebellum	-15	-61	-19
supplementary motor area	3	-1	65
anterior cingulate cortex	6	20	29
premotor cortex	36	-4	50

Statistical Analysis

Mann-Whitney U test was used in order to assess differences between HC and PD in acoustic measures, grey matter volumes within ROIs, and reading task activations within ROIs. Age and gender were included as covariates of no interest and were regressed out using general linear model.

Subsequently, Spearman's partial correlations (after regressing out the effects of age, gender, and levodopa equivlent dose [LED] in PD group) of grey matter volume within ROIs with selected acoustic measures were calculated for both HC and PD group separately.

3 Results

Violin plots of acoustic features in PD and HC groups after the removal of age and gender effect can be seen in Fig. 2. Based on the Mann-Whitney U test, we identified significant differences ($p < 0.05$) only in speech index of rhythmicity (SPIR, TSK1). Feature values were lower in PD as compare to HC, indicating that PD patients produced less rhythmical speech than controls.

In terms of grey matter volume within ROIs, PD patients were found to have significantly reduced grey matter volume in both left and right superior temporal gyrus ($p < 0.05$). Correlations with the acoustic features are reported in Table IV. The left and right STG volumes in PD patients correlated most significantly with the diadochokinetic regularity (DDK reg, TSK2, $R = -0.61$ and -0.67 respectively, $p < 0.001$). The direction of the correlation was negative, meaning that lower GM volumes were associated with increased irregularity during the diadochokinesis, in other words with impaired speech rhythmicity in PD. In addition, the left and right STG volumes were positively correlated with the DDK rate (TSK2, $R = 0.39$), i.e. grey matter loss in PD was associated with reduced DDK rate.

Regarding activations in ROIs during the reading task performed in the scanner, no significant differences between PD and HC were observed. We further explored the relationship between acoustic features evaluating speech rhythmicity and speech task-induced BOLD signal increases within our ROIs. In HC, we observed negative correlations between the DDK reg variable acquired outside the scanner and BOLD signal increases in the left insula, left IFG, left putamen, as well as in the right putamen and right thalamus, meaning that increased activation in these regions was related to increased speech regularity, whereas in PD we observed inverse (positive) correlations between DDK reg and activations of the right IFG and right PMC, meaning that increased BOLD signal in these areas was associated with decreased regularity) (see Table IV). As for the DDK rate, a negative correlation with increased BOLD in the left SMA was observed in HC, whereas in PD the DDK rate was negatively correlated with many cortical and subcortical regions including the right IFG, left STG, left thalamus and right cerebellum. In PD, we further observed negative correlation between articulation rate (AR, TSK1, $R = -0.41$) and BOLD signal in the left SMA while no significant correlations were found in HC subjects.

Table IV: Grey matter volumes

HC	AR	SPIR	DDK rate	DDK reg					
'L_IFG'	0,02	0,05	0,22	0,04		p	0,92	0,83	0,31	0,86
'L_Precent	-0,13	0,17	0,35	-0,32			0,52	0,42	0,10	0,13
'L_Insula'	-0,13	0,17	0,18	-0,12			0,52	0,41	0,41	0,58
'L_STG'	0,24	-0,03	-0,23	-0,10			0,25	0,89	0,27	0,64
'L_Putame	-0,27	0,20	0,18	0,00			0,19	0,35	0,39	1,00
'L_Thalam	0,16	0,07	0,46	-0,29			0,43	0,74	0,02	0,17
'R_Cerebe	-0,39	0,25	0,18	-0,18			0,05	0,23	0,39	0,41
'L_SMA'	-0,10	0,27	0,21	-0,15			0,65	0,20	0,33	0,48
'L_ACC'	0,07	0,40	0,12	-0,28			0,75	0,05	0,57	0,18
'L_PMC'	0,00	0,14	0,12	-0,11			0,99	0,49	0,56	0,60
'R_IFG'	0,04	0,14	0,20	-0,10			0,86	0,50	0,34	0,63
'R_Precen	-0,14	0,32	0,44	-0,22			0,49	0,11	0,03	0,30
'R_Insula'	0,01	0,28	0,28	-0,20			0,97	0,17	0,18	0,35
'R_STG'	-0,06	0,05	0,13	-0,17			0,76	0,80	0,55	0,42
'R_Putame	-0,25	0,10	0,28	-0,08			0,22	0,64	0,18	0,70
'R_Thalam	0,07	0,11	0,47	-0,24			0,73	0,60	0,02	0,26
'L_Cerebel	-0,28	0,32	0,09	-0,09			0,18	0,12	0,67	0,69
'R_SMA'	0,09	0,12	-0,14	0,22			0,68	0,56	0,50	0,31
'R_ACC'	0,00	0,08	0,35	-0,31			1,00	0,71	0,09	0,13
'R_PMC'	-0,31	0,20	0,04	-0,10			0,13	0,33	0,85	0,64
R										
PD	AR	SPIR	DDK rate	DDK reg					
'L_IFG'	0,02	0,29	0,36	-0,47		p	0,92	0,13	0,06	0,01
'L_Precent	-0,01	0,06	0,50	-0,52			0,96	0,77	0,01	0,01
'L_Insula'	0,11	0,01	0,39	-0,49			0,56	0,94	0,04	0,01
'L_STG'	0,16	-0,07	0,39	-0,61			0,43	0,71	0,04	0,00
'L_Putame	-0,01	0,28	0,23	-0,20			0,94	0,14	0,25	0,32
'L_Thalam	0,02	-0,04	0,60	-0,39			0,91	0,86	0,00	0,04
'R_Cerebe	-0,02	0,10	0,35	-0,34			0,92	0,62	0,07	0,07
'L_SMA'	-0,10	-0,05	0,10	0,03			0,61	0,78	0,61	0,86
'L_ACC'	0,08	-0,20	0,20	-0,45			0,69	0,30	0,30	0,02
'L_PMC'	0,15	0,16	0,28	-0,41			0,45	0,42	0,15	0,03
'R_IFG'	0,15	0,26	0,28	-0,53			0,44	0,17	0,15	0,00
'R_Precen	0,06	0,13	0,54	-0,52			0,78	0,49	0,00	0,00
'R_Insula'	0,15	0,05	0,26	-0,48			0,44	0,80	0,19	0,01
'R_STG'	0,33	0,29	0,39	-0,67			0,09	0,14	0,04	0,00
'R_Putame	-0,09	0,33	0,29	-0,18			0,66	0,08	0,13	0,36
'R_Thalam	-0,14	0,09	0,54	-0,32			0,49	0,65	0,00	0,10
'L_Cerebel	0,05	0,07	0,39	-0,50			0,81	0,73	0,04	0,01
'R_SMA'	0,05	-0,12	0,09	-0,11			0,79	0,56	0,65	0,57
'R_ACC'	0,02	0,03	0,34	-0,41			0,91	0,87	0,07	0,03
'R_PMC'	0,27	0,23	0,16	-0,29			0,17	0,25	0,43	0,13

Table IV: Reading task activations

Gmcorrected - R									
HC	AR	SPIR	DDK rate	DDK reg					
'L_IFG'	0,37	0,30	0,08	-0,51		p	0,11	0,19	0,73	0,03
'L_Precentral'	-0,08	-0,18	0,02	-0,17			0,74	0,44	0,93	0,49
'L_Insula'	0,02	0,16	0,04	-0,53			0,93	0,51	0,87	0,02
'L_STG'	-0,14	-0,05	0,08	-0,22			0,54	0,85	0,73	0,37
'L_Putamen'	-0,06	0,20	0,12	-0,62			0,79	0,40	0,61	0,00
'L_Thalamus'	-0,02	0,26	-0,03	-0,31			0,93	0,28	0,89	0,20
'R_Cerebellum'	0,25	0,20	0,08	-0,22			0,29	0,39	0,74	0,38
'L_SMA'	-0,20	0,07	-0,47	-0,21			0,40	0,76	0,04	0,40
'L_ACC'	-0,09	-0,20	0,03	-0,27			0,70	0,39	0,89	0,26
'L_PMC'	-0,24	-0,05	0,00	-0,31			0,31	0,85	1,00	0,19
'R_IFG'	0,08	-0,04	0,11	-0,43			0,73	0,86	0,66	0,07
'R_Precentral'	-0,11	-0,26	0,19	-0,20			0,65	0,26	0,43	0,40
'R_Insula'	0,01	0,10	0,14	-0,28			0,97	0,68	0,56	0,25
'R_STG'	-0,42	0,04	-0,11	-0,09			0,07	0,87	0,65	0,70
'R_Putamen'	0,07	0,09	0,01	-0,64			0,78	0,69	0,96	0,00
'R_Thalamus'	0,06	0,22	-0,19	-0,48			0,81	0,36	0,43	0,04
'L_Cerebellum'	0,12	-0,15	0,00	-0,18			0,62	0,52	1,00	0,46
'R_SMA'	-0,41	0,10	-0,09	-0,24			0,07	0,68	0,72	0,32
'R_ACC'	-0,23	-0,04	0,15	-0,39			0,34	0,87	0,54	0,10
'R_PMC'	-0,03	0,13	-0,08	-0,05			0,89	0,59	0,75	0,84
R									
PD	AR	SPIR	DDK rate	DDK reg					
'L_IFG'	-0,02	-0,07	-0,13	-0,16		p	0,92	0,73	0,52	0,45
'L_Precentral'	0,07	0,07	-0,19	0,15			0,72	0,74	0,36	0,47
'L_Insula'	0,01	-0,12	-0,12	0,13			0,97	0,55	0,56	0,53
'L_STG'	0,22	-0,05	-0,51	0,00			0,28	0,79	0,01	1,00
'L_Putamen'	0,14	0,01	-0,18	-0,04			0,50	0,95	0,37	0,85
'L_Thalamus'	0,14	0,03	-0,43	0,09			0,49	0,90	0,03	0,65
'R_Cerebellum'	0,12	0,01	-0,39	0,29			0,54	0,96	0,05	0,15
'L_SMA'	-0,41	-0,05	-0,30	0,19			0,04	0,80	0,13	0,35
'L_ACC'	-0,15	-0,13	-0,11	0,17			0,46	0,54	0,58	0,41
'L_PMC'	-0,23	0,15	-0,32	0,09			0,25	0,47	0,11	0,66
'R_IFG'	-0,12	-0,06	-0,55	0,50			0,54	0,78	0,00	0,01
'R_Precentral'	0,05	0,19	-0,32	0,16			0,80	0,35	0,11	0,42
'R_Insula'	-0,38	-0,01	-0,13	0,27			0,06	0,94	0,54	0,18
'R_STG'	-0,09	0,21	-0,21	0,06			0,67	0,29	0,29	0,77
'R_Putamen'	0,05	-0,02	-0,08	0,01			0,83	0,94	0,68	0,96
'R_Thalamus'	-0,07	-0,18	-0,34	0,17			0,74	0,38	0,09	0,42
'L_Cerebellum'	0,21	-0,10	-0,38	0,24			0,29	0,64	0,05	0,25
'R_SMA'	-0,33	-0,02	-0,19	0,19			0,10	0,92	0,35	0,35
'R_ACC'	-0,39	-0,18	-0,15	0,28			0,05	0,38	0,45	0,17
'R_PMC'	-0,37	0,33	-0,32	0,44			0,06	0,10	0,11	0,03

4 Discussion

In this paper we investigated neural underpinnings of speech rhythmicity alterations in PD patients as compared to age-matched healthy controls. As predicted, we found abnormal (decreased) speech rhythmicity in PD patients even on their regular dopaminergic medication as compared to HC. Regarding MRI results, we observed decreased gray matter volume of bilateral STG in PD patients that correlated with reduced diadochokinetic rate and regularity. The STG plays a critical role in representing phonological information that guides the motor system during speech production via the dorsal language pathway (Hickok and Poppel, 2007; Brabenec 2017, Maruyama 2018, Gao 2016, Ibanez 2013). The STG also makes an important contribution to processing auditory feedback during speech production. Gray matter volume decrease in left STG in PD was reported in meta-analysis of VBM studies (Pan 2012). Cortical thinning in this region has been shown already in mild PD (Guimares 2017) and bilateral gray matter loss in STG seems to be more prominent in severe PD (Guimares 2017) and in PD patients with dementia (Xia 2013, Lee 2013). In our previous study (Rektorova, 2012) we reported altered connection between the periaqueducatal grey matter (i.e. the subcortical region involved in voiced speech production) with the right STG which was associated with altered speech loudness. In that study, speech rhythmicity was not evaluated. Altered functional connections between the STG and motor/premotor areas in PD as compared to controls were also reported by Arnold et al. (2014) and Elfmarkova et al. (2016) regardless of dopaminergic medication condition (ON vs OFF medication). The right STG was found to have reduced resting state functional connections with left thalamus and left Rolandic operculum while the left STG had reduced connection with the right Rolandic operculum (New, 2015). Left STG connectivity with right Rolandic operculum was positively related with the Parkinson's Disease Questionnaire (PDQ-39) Communication scores, however, acoustic analysis was not performed. Taken together, these findings suggest that grey matter loss in STG is associated with altered speech rhythmicity in PD and may reflect defective sensorimotor integration during speech production.

In the current study we were not able to demonstrate differences in speech-task induced BOLD increases between HC and PD on dopaminergic medication. However, we observed major engagement of left cortical structures - left IFG and left insula in HC that was related to diadochokinetic regularity, whereas in PD right cortical structures – right IFG and right PMC were involved in the same task performance, however, showing the inverse correlation between the acoustic measure and brain activation compared to HC. Functional reorganization in PD patients has been described by Harrington et al. (2018), where successful inhibition in PD differed from HC by strengthened connectivity of right hemisphere cortical regions. To explain this phenomenon, authors suggested compensatory mechanisms and reorganization of intrinsic networks. Compensatory mechanisms were proposed also in a study by Isaacs et al. (2019), where PD group demonstrated greater recruitment of right hemisphere regions during verbal suppression. Thereupon, the enhanced involvement of right hemisphere cortical areas in our study implies attempts for compensation due to basal ganglia degeneration in PD. This is in line with results of Baumann et al. (2018), where increased right-sided superior temporal activity correlated with improved intelligibility after effective Lee Silverman Voice Treatment. Increased involvement of the right-sided cortical regions may also be at least partially caused by

dopaminergic medication (Elfmarkova 2016, PRD). Despite the fact that the effect of LED was regressed out in our data analyses, we cannot exclude the impact of dopaminergic medication on our functional imaging results (all PD patients were scanned in the ON state on their dopaminergic medication). On the other hand, it has been demonstrated that brain reorganisation with more engagement of the right hemisphere may not always be efficient and it may even lead to clinical symptoms worsening. For example, compensatory recruitment of right-sided language regions after stroke may add to post-stroke language impairment and low-frequency rTMS over the right posterior inferior frontal gyrus, in combination with speech and language therapy, significantly improves language recovery in subacute ischemic stroke and favors recruitment of left-hemispheric language networks (e.g. Thiel et al., 2013). Inverse correlation between the magnitude of activation of right-sided cortical regions with diadochokinetic regularity in our PD patients as compared to HC points to rather pathological (inefficient) brain reorganization than successful compensation.

Regarding correlations between DDK regularity with subcortical structures, in HC we observed correlations with right thalamus and both left and right putamen. By contrast, no correlations with BG structures were observed in PD, supporting the notion of inefficient involvement of these structures in speech rhythmicity control in PD (Eickhoff et al., 2009; Fujii and Wan, 2014).

Another important finding relates to the result of negative correlations of diadochokinetic rate with activations of speech production network regions in PD. Diadochokinetic rate is a measure of speech rate and articulation calculated as number of syllable vocalizations per second. Interestingly, after listening to the DDK task recordings in our PD cohort we found out that increased diadochokinetic rate in PD patients led to poor intelligibility of their speech production (see supplementary data). Although we did not find differences in DDK rate between PD and HC groups, a negative association between the DDK rate and BOLD signal increases within the dorsal language pathway regions in PD could be attributed to attempts of our patients to downregulate speech tempo to control for poor articulation when asked to perform the diadochokinetic task at faster rates (Caliguri 1989 , Martinez-Sanchez 2016, Thaut 2001). Increased activations connected with downregulation of diadochokinetic rate could mean that PD must recruit more areas in order to compensate for their defective response inhibition (Manza 2017, Harrington 2018, Issacs 2019, Arnold 2013) required to sustain the necessary pauses between syllables.

A limitation of this study was that the speech samples were not recorded inside the scanner, so essentially we were doing indirect correlations between imaging measures associated with a reading task in the scanner and acoustic measures derived from speech battery performed outside the scanner. Nevertheless, this approach allowed us to examine the functional neuroanatomy of speech production in HC and measure alterations in the structural and functional integrity of the speech network in PD. Our work provides insight into the neural correlates of speech rhythmicity control and neural underpinnings of altered speech rhythmicity in PD patients. Acoustic speech rhythmicity parameters and distinct patterns of speech network engagement may serve as a indicator of successful speech therapy in PD. Furthermore, our MRI results may help define new targets for non-invasive brain stimulation as a potential treatment of speech rhythmicity and intelligibility alterations in this patient population.

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