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Non-invasive stimulation of the auditory feedback area for improved articulation in Parkinson's disease

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ABSTRACT

Introduction: Hypokinetic dysarthria (HD) is a common symptom of Parkinson's disease (PD) which does not respond well to PD treatments. We investigated acute effects of repetitive transcranial magnetic stimulation (rTMS) of the motor and auditory feedback area on HD in PD using acoustic analysis of speech.
Methods: We used 10 Hz and 1 Hz stimulation protocols and applied rTMS over the left orofacial primary motor area, the right superior temporal gyrus (STG), and over the vertex (a control stimulation site) in 16 PD patients with HD. A cross-over design was used. Stimulation sites and protocols were randomised across subjects and sessions. Acoustic analysis of a sentence reading task performed inside the MR scanner was used to evaluate rTMS-induced effects on motor speech. Acute fMRI changes due to rTMS were also analysed.
Results: The 1 Hz STG stimulation produced significant increases of the relative standard deviation of the 2nd formant ($p = 0.019$), i.e. an acoustic parameter describing the tongue and jaw movements. The effects were superior to the control site stimulation and were accompanied by increased resting state functional connectivity between the stimulated region and the right parahippocampal gyrus. The rTMS-induced acoustic changes were correlated with the reading task-related BOLD signal increases of the stimulated area ($R = 0.654$, $p = 0.029$).
Conclusion: Our results demonstrate for the first time that low-frequency stimulation of the temporal auditory feedback area may improve articulation in PD and enhance functional connectivity between the STG and the cortical region involved in an overt speech control.

1. Introduction

Hypokinetic dysarthria (HD) in PD is a multidimensional speech disorder characterized by monopitch and monoloudness, reduced stress, imprecise consonants, airflow insufficiency, microperturbations in frequency/amplitude, impaired speech rate and rhythm etc. [1–3]. The pathophysiology of HD is not fully understood, and dopaminergic and surgical treatments have only limited effects on motor-speech dysfunction. Although dopaminergic medication may lead to some improvement of speech prosody via increased connectivity of the sensorimotor and associative basal ganglia circuitries [4], voice treatment based on increasing voice loudness and intonation through auditory feedback control currently seems to be the best treatment option for HD in PD [5,6].

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method that uses rapid changes of a magnetic field to modulate neuronal excitability in the targeted brain region as well as in distant interconnected brain regions. The therapeutic potential of repetitive transcranial magnetic stimulation (rTMS) has been tested for various PD symptoms [7,8]; regarding HD, authors have focused on the primary orofacial area (OFM1) with some promising results [9,10]. Nobody has yet targeted the right posterior superior temporal gyrus (STG), a cortical region involved in the auditory feedback of voiced speech that displays abnormal connections with subcortical and cortical motor speech areas in PD [4,11,12]. We hypothesized that targeted modulation of the STG neuronal excitability by rTMS might induce

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Table 1
Demographic and clinical variables.

	PD patients
Gender Female/Male	5/11
Age (years)	M = 67.21 (SD 6.18)
Duration of PD (years)	M = 6.81 (SD 5.00)
LED [19] (mg)	M = 758.25 (SD 489)
UPDRS III [20]	M = 18.6 (SD 7.33)
ACE-R [21]	M = 91.37 (SD 4.68)
BDI-II [22]	M = 7.68 (SD 3.58)
3F Test [16]	M = 67.05 (SD 8.87)

M - Mean; SD - Standard deviation; PD - Parkinson's disease; LED - Levodopa equivalent dose; UPDRS III - Unified Parkinson's disease rating scale; ACE-R - Addenbrooke's Cognitive Examination Revised; BDI-II - Beck depression inventory.

improvement of speech prosody and articulation in PD by modulating connectivity between the auditory feedback area and brain regions engaged in overt speech production. We performed an fMRI-rTMS-behavioural exploratory study, since fMRI may serve as a valuable readout of rTMS-induced aftereffects [13,14].

2. Methods

2.1. Participants

We enrolled 16 patients with clinically established PD [15]. All had mild to moderate HD based on the assessment of a speech therapist (MK) and the results of a 3F Test total score [16] that consists of three subtests assessing faciokinesis, phonorespiration, and phonetics (see Supplementary Material: Table 1). The maximum total score is 90 (normal speech), and the minimum score is 0. We included PD patients with a 3F Test total score < 80, i.e. below the normative score for aged healthy controls [16].

For demographic and clinical data, see Table 1. None of subjects had a history or presence of hallucinations, psychosis, depression, or dementia. The participants underwent an MRI examination prior to and immediately after each rTMS condition. Their speech was recorded inside the scanner using an fMRI speech protocol described previously [17], and acoustic analysis of recorded data was performed off-line [1,18]. All participants were tested in the ON medication state without dyskinesias; none of them underwent speech therapy during the study. All participants were right-handed and they reported Czech as their first language. All patients signed an informed consent form that was approved by the local ethics committee.

2.2. rTMS

Participants underwent five sessions of rTMS (DuoMAG™ XT-100, Deymed Diagnostic, Czech Republic) applied consecutively over two active stimulation sites (the OFM1; MNI coordinate X = -58, Y = -4, Z = 22, and the right posterior STG; MNI coordinate X = 40, Y = −38, Z = 14), and over a control stimulation site (vertex; V). Frameless stereotaxy (Brainsight Neuronavigation, Rogue Research, Canada) was employed to navigate a figure-8-shaped air-cooled coil over our targets of interest. Both high-frequency stimulation (10 Hz, 90% of the resting motor threshold [RMT], 5 s trains, 25 s inter-train interval, 2250 pulses per session) and low-frequency stimulation (1 Hz, 100% RMT, 1800 pulses per session administered in one train) were utilized over the STG and vertex regions while (based on our previous results) only 10 Hz stimulation was used for the OFM1 stimulation [10]. We used a cross-over study design and stimulation conditions (including 1 Hz rTMS to the right STG, 10 Hz rTMS to the right STG, 10 Hz rTMS to the OFM1, 1 Hz rTMS to the V, and 10 Hz rTMS to the V) were randomised across subjects and sessions. One stimulation session consisted of fMRI – rTMS – fMRI. All subjects underwent five stimulation sessions during two weeks. Each stimulation session was separated by at least one day without any stimulation, see Fig. 1. We rather chose a control stimulation site than a sham coil stimulation because of a cross-over study design where patients may distinguish between the sham and active stimulation.

2.3. MRI data acquisition

Participants were scanned with a 3T Siemens Prisma MR scanner (Siemens, Erlangen, Germany). High-resolution anatomical T1-weighted images were acquired for the Brainsight neuronavigation system (TR = 2300 ms, TE = 2.33 ms, FA = 8°, FOV = 224 mm; slice thickness 1 mm; 240 sagittal slices; matrix size 224 × 224) [4]. EPI BOLD sequences during the speech task (47 transversal slices, slice thickness = 3 mm, TR = 12000 ms, scan acquisition time = 2750 ms, length of pause = 9250 ms, TE = 35 ms, FA = 90°, FOV = 204 mm, matrix size 68 × 68) [17], and EPI BOLD resting state sequences (45 transversal slices, slice thickness = 3 mm, TR = 2510 ms, TE = 35 ms, FA = 70°, FOV = 192 mm, matrix size 64 × 64) [23] were acquired prior to and immediately after each rTMS condition, see Fig. 1. The MRI

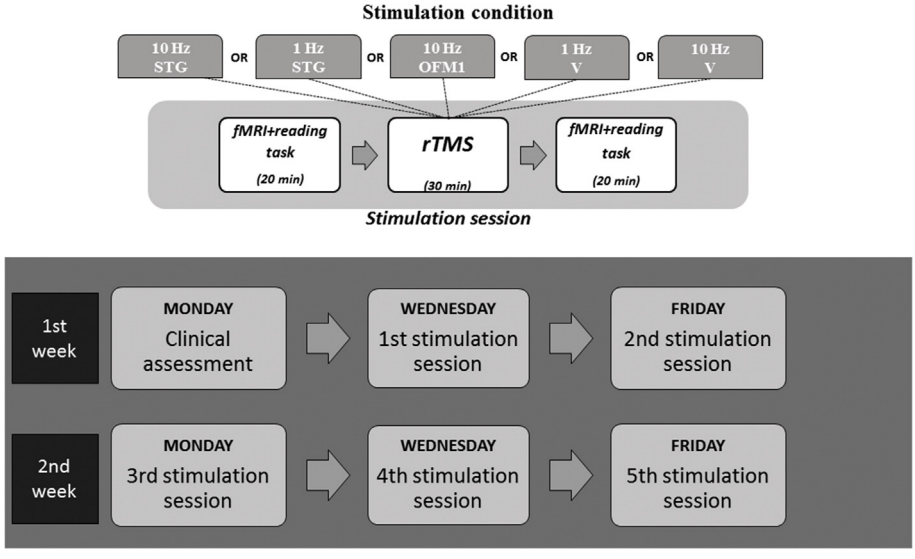

Fig. 1. Design of a cross-over study.

scanning protocol lasted up to 25 min, i.e. we were within the time interval of described behavioural rTMS-induced aftereffects [8,9,18]. The whole fMRI-rTMS-fMRI session lasted 1.5 h.

2.4. fMRI data analysis

Preprocessing and data analyses were performed in SPM12 running under Matlab 2014a. The preprocessing of the functional data consisted of realignment and unwarping, normalization into standard anatomical space (MNI), and spatial smoothing with 5 mm FWHM. The level of motion was thoroughly checked. For the task data, standard deviations (SD) in the scans of individual subjects were calculated. The scans were identified as outliers based on inner fence criterion as shown in equations (1) and (2).

$$SDT+ = SDq75 + 1.5(SDq75 - SDq25) \quad (1)$$

$$SDT- = SDq25–1.5(SDq75 - SDq25) \quad (2)$$

SDq25 is the lower quartile and SDq75 is the upper quartile. Scans with a score lower than SDT- or higher than SDT+ were excluded. This method was applied because of the long TR (12 s) in our event-related fMRI design, which predetermined the greatest movement to happen outside the image acquisition time. All suprathreshold scans belonged to one session of the same subject, therefore that subject was excluded from the task data analysis.

The extent of motion in resting-state data was controlled in terms of frame-wise displacement (FD). All subjects displayed less than 25% of scans with FD > 0.5 mm. The scans that showed FD > 1.5 mm were removed and replaced with interpolated images using two adjacent volumes. No more than 2% of the subject scans were replaced. In addition, the six movement regressors (obtained during realignment and unwarping of functional scans), FD, and the extracted signals from white matter and cerebrospinal fluid were regressed out of the data in subsequent analysis.

For the task-induced fMRI data analysis, we compared task-induced BOLD signal changes prior to and after each stimulation condition. Contrast maps were created to evaluate the reading effect as compared to the baseline condition (string of Xs); one-sample *t*-test was used. We were specifically interested in task-induced BOLD signal changes in the regions of interest (ROIs), i.e. areas centred over the stimulation sites with significant rTMS-induced behaviour aftereffects. The relationship between rTMS-induced changes in activation in our ROIs with changes in speech parameters was assessed using Spearman partial correlations after controlling for the effects of age, gender, and levodopa equivalent dose [19].

Concerning resting-state data analysis, we compared seed-based connectivity changes prior to and after each stimulation condition. The mean seed signals from our ROIs were extracted and used as a regressors of interest in the design matrix. Contrast maps were entered into a paired *t*-test model to estimate the change of connectivity between the seed and the whole brain (in a voxel-wise manner) as a result of rTMS. Age, gender, and LED were included as covariates of no interest.

2.5. Speech task and acoustic data analysis

Each participant performed a distinct reading task inside the MR scanner prior to and immediately after each rTMS condition. The speech data acquisition lasted 15 min and consisted of overt reading of short emotionally neutral sentences or just viewing a string of “Xs” (i.e. a baseline condition). There were 48 sentence reading trials and 24 baseline trials, these trials alternated pseudo-randomly. All stimuli were displayed for 5 s. The screen was black in between successive stimuli for 11 s [11,17].

Due to limited speech recording conditions affected by a noise of the MR scanner, we focused on acoustic parameters that partially describe speech prosody and articulation [18]. More specifically, in terms of prosodic parameters we quantified monopitch (relative standard deviation of fundamental frequency) and inappropriate silences (speech index of rhythmicity, total pause time). The articulation was quantified using formants, which are resonances of the oro-naso-pharyngeal tract that are modulated mainly by simultaneous movements of the tongue and jaw [1]. More specifically, the front-back (horizontal) gesture is changed primarily by the tongue and affects the second formant. The open-close gesture, primarily dominated by the jaw, is manifested in the first formant.

Linear mixed models or nonparametric Friedman tests were used for the evaluation of effects of each stimulation condition on the relative change of acoustic parameters. Paired t-tests or Wilcoxon signed-rank tests were used for comparison of these parameters prior to and after each stimulation condition.

3. Results

3.1. Acoustic analysis results

Linear mixed model showed statistically significant effect of the stimulation condition on the relative change of standard deviation of the second formant ($p = 0.024$). The relative change after the 1 Hz STG stimulation (mean = 15.4) was significantly higher as compared to relative change after the 1 Hz V stimulation (mean = −0.7) and also as compared to the 10 Hz OFM1 stimulation (mean = −0.3), $p = 0.037$ and $p = 0.046$, respectively. One outlier was excluded from data analyses.

Pair *t*-test revealed that the 1 Hz stimulation of the right STG induced significant increase in the relative standard deviation of the second formant (mean before = 0.140; mean after = 0.155; $p = 0.019$) with a medium effect size (Cohen's $d = -0.681$).

The described changes in the acoustic parameter after 1 Hz stimulation of the right STG were perceived as either ‘improved’ (10 patients) or ‘no change’ (6 patients) in articulation and speech intelligibility based on post hoc evaluation of speech recordings by the speech therapist (MK) who was blinded in terms of which stimulation conditions were assessed.

We did not find other significant effects of the stimulation condition on the relative changes of studied acoustic parameters, see Suppl. material, Table 3 for details.

In the secondary analysis, the Wilcoxon test showed that the low-frequency stimulation of the right STG induced a significant increase of the total pause time of pauses longer than 50 ms (median before = 0.472; median after = 0.571; $p = 0.019$) with a medium effect size ($r = -0.411$). There was a trend towards increased values of the speech index of rhythmicity (median before = 0.035; median after = 0.038; $p = 0.07$) with a medium effect size ($r = -0.319$). High-frequency rTMS over the STG induced a significant increase of the range of the first formant (median before = 3057; median after = 3161; $p = 0.044$) with a medium effect size ($r = -0.356$). Other stimulation conditions did not produce any significant changes in our speech parameters as assessed by the Wilcoxon test, see Suppl. material, Table 5 and 6. No side effects of rTMS were observed.

3.2. fMRI results

The fMRI contrast between the reading task and the baseline condition revealed significant activation of the left thalamus, right supplementary motor area, right inferior frontal gyrus, right cerebellum, left middle temporal gyrus, and right superior temporal gyrus (detailed in the Supplementary material, Table 2).

In terms of the reading task-induced BOLD signal increases no effects in whole-brain analysis were detected after 1 Hz STG stimulation (threshold $p = 0.05$ with FWE correction at the cluster level with initial cut $p = 0.0005$ uncorrected). However, a significant correlation was

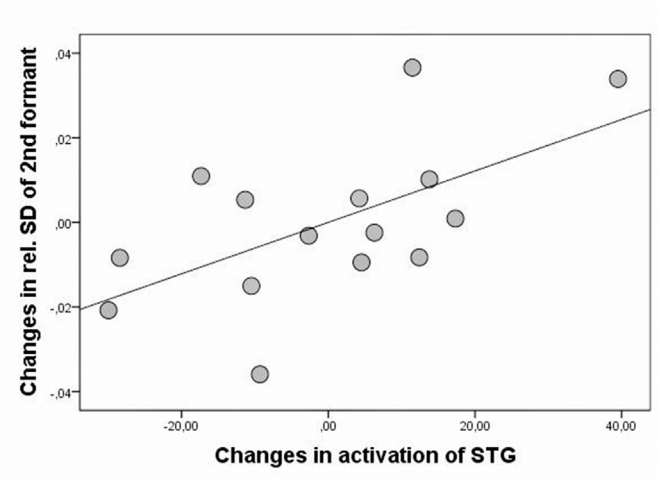

Fig. 2. Correlations between rTMS-induced changes in the speech variable and changes in the right STG activation.

found between low-frequency rTMS-induced changes in activation of the right STG and changes in relative standard deviation of the second formant (R = 0.654, p = 0.029), see Fig. 2.

Voxel-wise whole brain seed-based connectivity of the resting state fMRI data revealed that the 1 Hz STG stimulation significantly increased resting state functional connectivity (rs-FC) between the right STG (our seed region) and the right parahippocampal gyrus (MNI coordinates: 33, −19, −14), see Fig. 3a. Moreover, the 1 Hz STG stimulation–induced functional connectivity changes between the STG and the right parahippocampal gyrus (PHG) were significantly higher as compared to connectivity changes after the 1 Hz V stimulation (paired *t*-test, p = 0.004).

Of note, the 10 Hz STG stimulation significantly increased resting state functional connectivity between the STG (seed) and the right inferior parietal lobule (IPL; MNI coordinates: 42, −46, 40); see Fig. 3b. The 10 Hz STG stimulation–induced connection changes between the STG and the right inferior parietal lobule were significantly higher as compared to connectivity changes after the 10 Hz V stimulation (paired *t*-test, p = 0.027).

4. Discussion

Precise speech production requires mapping phonological representations onto articulatory networks and relies on auditory-motor integration between the superior temporal gyrus that is involved in representation of the sound structure of words and the anterior components of the dorsal language pathway, the basal ganglia, thalamus, and cerebellum [24,25]. Our results demonstrated for the first time that acute increases of the right posterior STG activation and functional connectivity induced by low-frequency rTMS may lead to significant improvement of articulation parameters in PD suffering from HD. Particularly the low-frequency (1 Hz) rTMS positively affected speech articulation by modulating the movements of tongue and jaw which are manifested in formants [1,18], and the effect was significantly higher than the effect produced by the low-frequency stimulation of vertex or of high-frequency stimulation of the orofacial primary motor area.

Based on the literature, 1 Hz stimulation decreases cortical excitability and 10 Hz rTMS increases it when applied over the primary motor cortex [26], but effects may differ when rTMS is applied over other brain areas [27].

Here we showed that low-frequency rTMS led to significant behavioural effects that were superior to rTMS-induced effects over the control stimulation site. These positive effects were accompanied by enhanced functional connection between the stimulated region and the right parahippocampal gyrus (PHC). Moreover, the rTMS-induced changes in articulation were associated with the amount of rTMS-induced changes in activation of the stimulated area during overt sentence reading.

High-frequency rTMS led to enhancement of resting state functional connectivity of the STG with the right IPL. However, the behavioural changes induced by this stimulation condition were not superior to control site stimulation.

According to the DIVA model (Directions Into Velocities of Articulators), the control of speech production consists of a feedforward control system (motor commands) and a feedback control system (auditory and somatosensory maps). The posterior STG is engaged in the complex auditory representations of incoming auditory signal during the overt speech [28]. The inferior parietal lobule is involved in the integration of motor commands and sensory feedback during the speech production [24,29]. According to a dual-pathway model of speech processing, the dorsal pathway maps acoustic speech signals to frontal lobe articulatory networks [24,29], while the ventral pathway processes speech signals for semantics and comprehension [24,30]. The

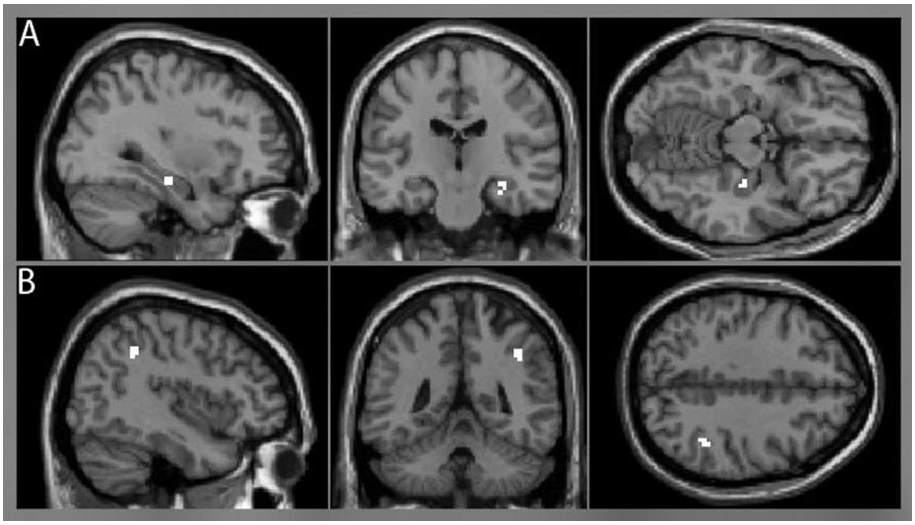

Fig. 3. Changes in STG seed-based resting-state functional connectivity after 1 Hz rTMS (A) and 10 Hz rTMS (B), rs-FC increases are depicted in white, displayed at p < 0.05 with FWE correction at the cluster level with initial cut p = 0.0005 uncorrected.

parahippocampal gyrus (PHG) is mostly engaged in the ventral pathway [30]; its specific role in the speech production control remains to be elucidated. We may speculate that the PHG is involved in articulation planning during the voiced sentence reading task that is dependent both on the auditory and somatosensory feedback and sentence comprehension.

In contrast to the results of previous studies, we found no effect of high-frequency rTMS applied over the OFM1 [9,10]. Those authors observed that particularly voice quality and loudness were modified by the stimulation. However, we were not able to accurately analyse the voice intensity and harmonic-to-noise ratio from the audio recordings because of the high level of acoustic noise produced by the MRI scanner. Therefore, we had to focus solely on assessing intonation, speech fluency and articulation.

In conclusion, we demonstrated for the first time that low-frequency rTMS over the right STG (i.e. the auditory feedback area) may induce significant acute effects on articulation precision in PD that is related to the amount of rTMS-induced activation of the stimulated area. Our results were further supported by fMRI findings that revealed rTMS-induced enhancement of STG connectivity with the cortical structure engaged in the sentence comprehension and overt speech control. Further research needs to be done using repeated sessions of rTMS to assess long-term effects and clinical relevance of distinct non-invasive brain stimulation for treatment of hypokinetic dysarthria in patients with PD.

Disclaimer

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Authors' roles

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique

Brabenec 1C, 2C, 3A; Klobusiakova 1C, 2B, 3B; Barton 2B, 3B; Mekyska 1B, 1C, 2B, 2C, 3B; Galaz 1C, 2A, 2B; Zvoncak 1C, 2B, Kiska 1C, 2B; Mucha 1C, 2B; Smekal, 2C, 3B; Kostalova 1C, 2C, 3B; Rektorova 1A, 1B, 2A, 2C, 3B

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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.2018.10.011.

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