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ORIGINAL ARTICLE

Repetitive transcranial magnetic stimulation for hypokinetic dysarthria in Parkinson's disease enhances white matter integrity of the auditory–motor loop

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Abstract

Background and purpose: In our previous study, repeated sessions of repetitive transcranial magnetic stimulation (rTMS) over the auditory feedback area were shown to improve hypokinetic dysarthria (HD) in Parkinson's disease (PD) and led to changes in functional connectivity within the left-sided articulatory networks. We analyzed data from this previous study and assessed the effects of rTMS for HD in PD on the diffusion parameters of the left anterior arcuate fasciculus (AAF), which connects the auditory feedback area with motor regions involved in articulation.

Methods: Patients were assigned to 10 sessions of real or sham 1-Hz stimulation over the right posterior superior temporal gyrus. Stimulation effects were evaluated using magnetic resonance diffusion tensor imaging and by a speech therapist using a validated tool (Phonetics score of the Dysarthric Profile) at baseline, immediately after 2 weeks of stimulation, and at follow-up visits at Weeks 6 and 10 after the baseline.

Results: Altogether, data from 33 patients were analyzed. A linear mixed model revealed significant time-by-group interaction ($p = 0.006$) for the relative changes of fractional anisotropy of the AAF; the value increases were associated with the temporal evolution of the Phonetics score ($R = 0.367$, $p = 0.028$) in the real stimulation group.

Conclusions: Real rTMS treatment for HD in PD as compared to sham stimulation led to increases of white matter integrity of the auditory–motor loop during the 2-month follow-up period. The changes were related to motor speech improvements.

KEYWORDS
dorsal language pathway, DTI, hypokinetic dysarthria, Parkinson's disease, rTMS

INTRODUCTION

Hypokinetic dysarthria (HD) is common in patients with Parkinson's disease (PD). It is characterized by monoloudness and monopitch, imprecise articulation, voice harshness, and speech timing deficits [1]. Impairment of auditory feedback is an important factor contributing to HD [2], and auditory feedback control is the main strategy employed in the current Lee Silverman Voice Treatment for HD [3]. In PD patients, previous studies also showed abnormal activation and connectivity of the right posterior superior temporal gyrus (STG), which is involved in auditory feedback processing [4, 5].

The effects of dopaminergic medication on HD are limited, and recent research showed that it may improve some but not all aspects of voice alterations [6]. Deep brain stimulation, yet another well-established treatment of motor symptoms of PD, might even lead to deterioration of speech intelligibility [7, 8]. Therefore, other interventions have been tested. In a previous study [9], we described the long-term effects of multiple sessions of low-frequency repetitive transcranial magnetic stimulation (rTMS) over the right STG on HD, along with specific increases in speech-related activations and functional connectivity changes within the (left-sided) regions of the articulatory network. HD symptoms were assessed using a validated tool, the 3F Test–Dysarthric Profile (3FT), which consists of three subtests assessing faciokinesis, phonorespiration, and phonetics (see Appendix S1). The effects were significant for the Phonetics subtest (which evaluates articulation, prosody, and speech intelligibility), gradually built up after the last stimulation session, and lasted for (at least) 8 weeks, which was our last follow-up visit. In the current work, we used magnetic resonance diffusion tensor imaging (DTI) data from that study with the aim of exploring long-term rTMS effects on white matter (WM) integrity changes in the left anterior arcuate fasciculus (AAF). This WM tract is engaged in auditory–motor integration during articulation, as it connects the ventral portion of the left precentral gyrus to the postcentral gyrus and the superior temporal gyrus [10–12]. Previous research also showed that WM integrity of arcuate fasciculus is partially disrupted in PD patients [13].

In current studies, DTI has been used for assessment of long-term changes in WM integrity that are induced by physical or cognitive training in healthy adults [14]. Similar improvements of WM integrity were observed after rTMS treatment in various patient groups [15, 16].

We hypothesized that real rTMS treatment of HD in PD would increase WM integrity as compared to sham stimulation [15–17], and that these changes would be specific to our tract of interest and correlate with HD improvements.

METHODS

Patients and study design

In this randomized, parallel group, single-blinded, sham-stimulation-controlled trial, we enrolled PD patients with mild to moderate HD; based on the assessment of a speech therapist, the most common symptoms were problems with prosody, followed by decreased voice quality and impaired articulation. A validated diagnostic scale, the 3FT, was used (a higher score indicates better speech performance; see Appendix S1) [9]. All participants underwent a baseline assessment (T0), 10 stimulation sessions, a follow-up assessment immediately after multiple rTMS sessions (T1), and follow-up assessments 6 weeks (T2) and 10 weeks (T3) after the baseline assessment. All participants were on a stable dopaminergic treatment at least 4 weeks before baseline assessment and during the entire study. The patients were tested in the ON medication state without dyskinesias; none of them had speech therapy during the study. None of the subjects had a history or presence of hallucinations, psychosis, depression, or dementia. All participants were right-handed, and they reported Czech as their first language. All the investigators, except for the person who applied the rTMS, were blinded to the treatment condition.

All patients signed an informed consent form that was approved by the local ethics committee. This trial was registered in ClinicalTrials.gov (NCT04203615).

rTMS treatment

All subjects underwent 10 rTMS sessions in 2 weeks [9]. For rTMS treatment, the DuoMAG XT-100 stimulator by Deymed Diagnostic was used. Frameless stereotaxy was used for coil navigation. Both real rTMS (1 Hz, 100% resting motor threshold, 1800 pulses per session) and sham rTMS were utilized over the right posterior STG (Montreal Neurological Institute [MNI] coordinates x = 40, y = −38, z = 14) [18]. The stimulation coil in the sham group produced only an acoustic signal but no magnetic field.

Magnetic resonance imaging sequences and processing

Imaging was performed on a 3-T Prisma scanner (Siemens) at baseline assessment (T0) and at follow-up assessments 2 weeks (T1), 6 weeks (T2), and 10 weeks (T3) after the baseline assessment.

A diffusion sequence with the following parameters was used: 30 diffusion directions for b-value = 1000 s/mm^2 and 10 acquisitions without diffusion weighting (b = 0 s/mm^2), repetition time = 8700 ms, echo time = 97 ms, isovoxel = 2 mm, acquisition matrix = 114 × 114 × 64. Ten acquisitions with b = 0 s/mm^2 with opposite phase polarity were acquired.

FSL software [19] was used for preprocessing. Data were first corrected for susceptibility-induced distortions using the topup tool [20] and for movement and eddy current artifacts using the eddy tool [21]. Non-brain tissue voxels were automatically excluded using the Brain Extraction Toolbox [22]. The output brain masks were checked one by one. The function DTIFIT was used to model the diffusion tensor of each voxel in the DTI data, and parametric maps were calculated. The parameters of interest were fractional anisotropy (FA) and mean diffusivity (MD).

Masks of WM regions of interest (ROIs; left AAF) were obtained from a probabilistic atlas described in Rojkova et al. [23]; see Figure 1. Masks were also obtained for the same tract on the right side of the brain. Moreover, we used the left corticospinal tract (CST) as a control tract of interest.

Probabilistic masks of our ROIs, originally in MNI152 space, were inverse transformed to each subject's high-resolution T1 data and

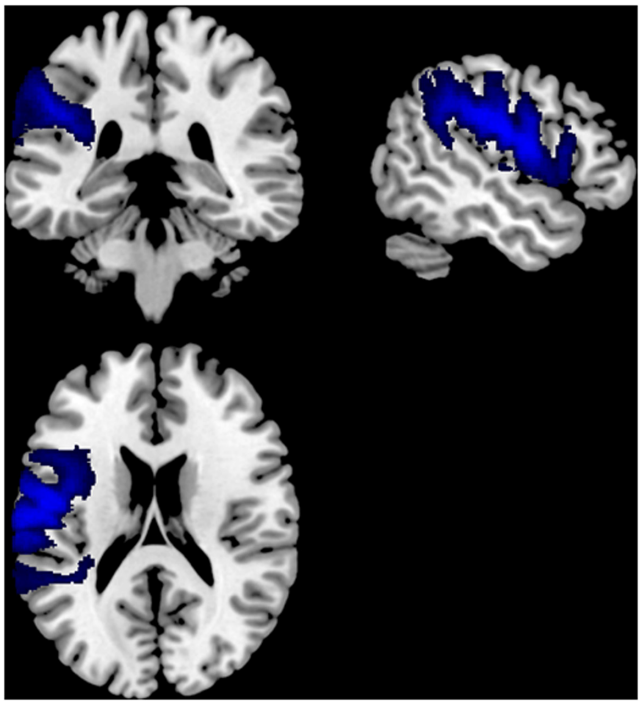

FIGURE 1 Mask of the white matter regions of interest- the left anterior arcuate fasciculus.

then registered to the subject's native diffusion-weighted space, using SPM12 tools (http://www.fil.ion.ucl.ac.uk/spm/software/spm12). The resulting probabilistic masks were applied to the parametrical maps.

Masks were kept probabilistic; therefore, the value of the diffusion parameters in each voxel were weighted by the probability of the voxel being included in the mask. This explains the unusually low values of (especially) FA in our WM tracts of interest.

Statistical analysis

We used the relative changes from baseline of diffusivity measures to obtain approximately normal distribution of residuals at T1, T2, and T3 follow-up visits. Linear mixed models (LMMs) were run to determine the effects of rTMS on relative changes of diffusivity measures within our ROIs. The fixed factors in LMMs were treatment group (real vs. sham), time (T0, T1, T2, T3), and the time-by-treatment group interaction. Age, gender, and levodopa equivalent dose were used as covariates in LMMs. Post hoc pairwise between-groups and within-groups comparisons of estimated marginal means were performed between each time point, adjusting for multiple comparisons using the Bonferroni correction. A Spearman correlation analysis was used to investigate associations between the relative changes of diffusivity parameters and relative changes in Phonetics scores. It was calculated from all time points and separately for the real rTMS group and the sham stimulation group. Statistical procedures were performed with SPSS version 25.0 (IBM).

RESULTS

Patients

As described previously [9], 20 participants were randomly assigned to the real rTMS group and 19 participants were assigned to the sham group. The real and sham stimulations were well tolerated, without any side effects. During the study, six participants did not complete the 10 stimulation sessions, mostly due to withdrawal of consent. Our final sample consisted of 20 subjects in the real rTMS group and 13 subjects in the sham group. The real rTMS group and the sham group did not significantly differ at baseline in clinical and demographic variables (see Table 1). At baseline, there were also no significant differences in DTI metrics.

Speech assessment

For relative changes of Phonetics subtest scores, the LMM showed a significant effect of group ($F_{1, 30.3} = 4.2$, $p = 0.048$). In the real rTMS group, the relative change of Phonetics scores was higher than in the sham group (real vs. sham mean difference = 10.28, $p = 0.048$). The post hoc comparison revealed that the significant difference between the real and sham groups was at the T2 follow-up visit (mean difference = 12.5, $p = 0.026$) and at the T3 follow-up visit (mean difference = 12.5, $p = 0.031$; see Table 2).

DTI results

For the relative changes of FA of the left AAF, the LMM showed a significant effect of time-by-treatment group interaction ($F_{2, 34.1} = 5.8$, $p = 0.006$; see Figure 2). A direct comparison of the two groups showed a significant difference in the FA relative changes at T3 (T3 – T0; $p = 0.037$). The post hoc pairwise within-groups comparisons revealed mild relative FA increases in the real rTMS group and mild relative decreases in the sham stimulation group, although the results were insignificant ($p = 0.160$ and $p = 0.051$, respectively; see Figure 2).

A significant but mild positive correlation was found between the relative FA changes of the left AAF and relative changes of the Phonetics score ($R = 0.367$, $p = 0.028$) for the real stimulation group. In the sham group, this correlation was not significant ($R = -0.043$, $p = 0.8$).

For the relative changes of MD of the left AAF, the LMM showed a nonsignificant effect of time-by-treatment group interaction ($F_{2, 34.5} = 2.6$, $p = 0.086$).

We did not find any significant time-by-treatment interaction for the changes of DTI metrics in the right AAF or the left CST. For all DTI results, see Appendix S1.

DISCUSSION

Our longitudinal, randomized, sham-controlled study revealed that real rTMS treatment for HD in PD as compared to sham stimulation

TABLE 1 Demographic and clinical variables at baseline

Variable	PD real rTMS group	PD sham rTMS group	Mann–Whitney
Gender, female/male	6/14	4/9	$p > 0.05$
Age, years	Mdn = 71.7 (IQR = 62.2–75.5)	Mdn = 71.5 (IQR = 60.9–78.0)	$p > 0.05$
Duration of PD, years	Mdn = 4.0 (IQR = 2.0–10.5)	Mdn = 3.0 (IQR = 1.0–8.2)	$p > 0.05$
LED	Mdn = 990.0 (IQR = 610.0–1416.2)	Mdn = 750.0 (IQR = 500.0–970.0)	$p > 0.05$
UPDRS III	Mdn = 14.0 (IQR = 11.0–20.0)	Mdn = 13.5 (IQR = 8.7–17.0)	$p > 0.05$
3FT	Mdn = 64.0 (IQR = 54.0–71.0)	Mdn = 74.0 (IQR = 62.0–77.5)	$p > 0.05$
Mild/moderate dysarthria	18/2	13/0	
Left AAF FA values	Mdn = 0.107 (IQR = 0.106–108)	Mdn = 0.109 (IQR = 0.108–0.110)	$p > 0.05$
Left AAF MD values	Mdn = 0.0001 (IQR = 0.00008–0.00012)	Mdn = 0.0002 (IQR = 0.00018–0.00022)	$p > 0.05$

Abbreviations: 3FT, 3F Test–Dysarthric Profile; AAF, anterior arcuate fasciculus; FA, fractional anisotropy; IQR, interquartile range; LED, levodopa equivalent dose; MD, mean diffusivity; Mdn, median; PD, Parkinson disease; rTMS, repetitive transcranial magnetic stimulation; UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 2 Estimated marginal means of relative change of Phonetics score

Time	Real, mean (SE)	Sham, mean (SE)	*p*
T1	14.6 (3.8)	7.8 (4.4)	0.256
T2	20.4 (3.5)	7.9 (3.9)	0.026
T3	23.1 (3.7)	10.6 (4.2)	0.031

positively modulated WM integrity of the auditory–motor loop during the 2-month follow-up period. The lower FA values indicate structural damage of tissue and could be influenced by the degree of myelination, axonal diameter, or fiber organization [24, 25]. A recent review showed that physical training or speech therapy could improve WM integrity, and FA can be used to measure these changes [14]. Using a fiber dissection method, a recent neuropathological study [26] showed that the AAF connects the auditory feedback area in the posterior part of the STG to the speech output area at the ventral premotor cortices and may thus serve both precise monitoring of speech articulation and precise speech output [27]. Our finding was further supported by the association between temporal changes in FA values in the left AAF and improvements of HD as assessed by a speech therapist using a validated tool.

Our results are in accord with previous studies indicating that multiple sessions of rTMS could have positive effects on WM integrity. For example, Allendorfer et al. [15] and Li et al. [28] found that 10 sessions of high-frequency rTMS led to increased FA values of WM tracts in stroke patients, and similar changes in WM were observed in patients with treatment-resistant depression after 4 weeks of high-frequency rTMS [16]. According to study by Zhao et al. [17], improvement of WM integrity in stroke patients could be also induced by low-frequency rTMS. The exact mechanism of these structural changes is unknown. According to animal models, rTMS could promote survival and maturation of newborn oligodendrocytes and enhance myelination [29, 30].

Of note, our result was WM tract specific, because we did not find any time-by-treatment interaction effects for WM integrity of either the CST (our control track of interest) or of the right AAF. Others have already demonstrated that WM integrity may change in tracts contralateral to the stimulated site. Studies in stroke patients have shown that low-frequency rTMS has an effect on interhemispheric balance and may change WM integrity of contralateral tracts via corpus callosum connections [31]. A study by Qiu et al. [32] demonstrated that effects of rTMS on interhemispheric balance could be also observed in healthy participants. In that study, continuous theta-burst stimulation (i.e., inhibitory stimulation) over the left motor cortex enhanced cortical excitability of the right-sided motor areas. In accord with the current result, in our previous article [9], we also described contralateral (left-sided) changes of resting-state functional connectivity and task-related activations of the articulatory network regions due to the rTMS treatment applied over the right auditory feedback area in the same patient cohort.

Interestingly, the post hoc analysis revealed that the differences between both groups were significant 8 weeks after the last stimulation session. The delayed long-term effects of the multiple session rTMS may relate to the rTMS-induced long-term potentiation effects and/or elevation of brain-derived neurotrophic factor that may contribute to changes in synaptic plasticity [33, 34] and lead to long-lasting plasticity changes [35, 36]. It has been shown that

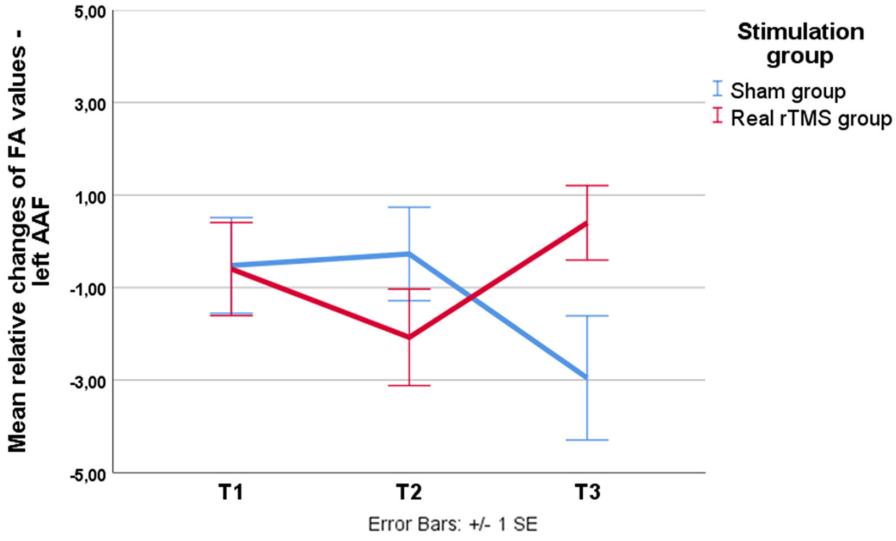

FIGURE 2 Relative fractional anisotropy (FA) values from anterior arcuate fasciculus (AAF) at visits T1, T2, and T3 as compared to baseline. rTMS, repetitive transcranial magnetic stimulation.

the process of plastic reorganization after rTMS may take time to develop and cause more pronounced aftereffects 4–15 weeks later [37, 38]. Similar long-term modulation of WM integrity was also observed in studies focused on dance intervention and musical training in elderly people [39, 40].

A study limitation is that most of the participants had only mild dysarthria and therefore the rTMS effects cannot be generalized to the whole PD population. Another limitation was that the sham and real stimulation groups were unbalanced. However, LMMs are quite robust for analyses of unbalanced groups [41].

This article extended the findings of our previous paper [9] and showed for the first time that multiple rTMS sessions applied over the posterior STG, that is, the region providing auditory feedback for speech production, may have long-lasting positive modulatory effect on WM integrity of the tract engaged in the auditory–motor loop and motor aspects of speech in PD. This finding is further supported by the observed association between the FA changes of the AAF and changes in clinical HD outcomes. The left AAF might underlie the spread of rTMS effects from a stimulation site via the corpus callosum to remote left primary motor and premotor brain areas involved in precise articulation.

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CONFLICT OF INTEREST

Nothing to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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