Clinical Neurophysiology 132 (2021) 851–856

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Opposite effects of one session of 1 Hz rTMS on functional connectivity between pre-supplementary motor area and putamen depending on the dyskinesia state in Parkinson's disease

Anja Flamez [a,1,**], Guo-Rong Wu [b,1,*], Wietse Wiels [a], Peter Van Schuerbeek [c], Johan De Mey [c], Jacques De Keyser [a], Chris Baeken [d,e,f]

[a] Department of Neurology, UZ Brussel, Vrije Universiteit Brussel (VUB), Laarbeeklaan 101, 1090 Brussels, Belgium
[b] Key Laboratory of Cognition and Personality, Faculty of Psychology, Southwest University, Chongqing, China
[c] Department of Radiology, UZ Brussel, Vrije Universiteit Brussel (VUB), Laarbeeklaan 101, 1090 Brussels, Belgium
[d] Department of Psychiatry, UZ Brussel, Vrije Universiteit Brussel (VUB), Laarbeeklaan 101, 1090 Brussels, Belgium
[e] Ghent University, Department of Head and Skin and GHEP Lab, C. Heymanslaan 10, 9000 Ghent, Belgium
[f] Eindhoven University of Technology, Department of Electrical Engineering, Eindhoven, the Netherlands

ARTICLE INFO

Article history:
Accepted 9 December 2020
Available online 3 February 2021

Keywords:
Pre-SMA
Parkinson's disease
LF rTMS

HIGHLIGHTS

- A single session of sham-controlled pre-supplementary motor area 1 Hz rTMS has no effect on levodopa induced dyskinesias.
- It has opposing effects on functional connectivity depending on the dyskinesia state.
- After the ingestion of levodopa, functional patterns were not different from baseline.

ABSTRACT

Objective: To explore the effects of low-frequency repetitive transcranial magnetic stimulation (LF rTMS) on cortico-striatal-cerebellar resting state functional connectivity in Parkinson's disease (PD), with and without dyskinesias.
Methods: Because there is increasing evidence of an involvement of the pre-supplementary motor area (pre-SMA) in the pathophysiology of levodopa induced dyskinesias, we targeted the right pre-SMA with LF rTMS in 17 PD patients. We explored the effects of one sham-controlled LF rTMS session on resting state functional connectivity of interconnected brain regions by using functional MRI, and how it is modified by levodopa. The clinical effect on motor function and dyskinesias was documented.
Results: As expected, one LF rTMS session did not alleviate dyskinesias. However, real, and not sham LF rTMS significantly increased the functional connectivity with the right putamen in patients with dyskinesias. In patients without dyskinesias, the real LF rTMS session significantly decreased functional connectivity in the right putamen and the cerebellum. We found no effects on functional connectivity after levodopa ingestion.
Conclusion: One session of 1 Hz rTMS has opposing effects on pre-SMA functional connectivity depending on the PD patients' dyskinesia state.
Significance: Patients dyskinesias state determines the way LF rTMS affects functional connectivity in late stage PD.

1. Introduction

Levodopa-induced dyskinesias (LID) are a complication of long-term dopamine replacement therapy in patients with Parkinson's disease (PD). The past decade, the effect of motor cortex (MC) low-frequency repetitive transcranial magnetic stimulation (LF

* Corresponding author at: Key Laboratory of Cognition and Personality, Faculty of Psychology, Southwest University, Chongqing, China.
** Corresponding author at: Department of Neurology UZ Brussel, Laarbeeklaan 101, 1090 Jette, Belgium.
E-mail addresses: anja.flamez@uzbrussel.be (A. Flamez), guorongwu@swu.edu.cn (G.-R. Wu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.clinph.2020.12.024
1388-2457/

rTMS) on LID has been investigated in several preliminary studies yielding conflicting results (for an overview see Flamez et al. 2016).

Functional Magnetic Resonance Imaging (fMRI) studies have reported inconsistent changes in functional connectivity in the cerebellar-basal ganglia-cortical pathways in Parkinson disease brain relative to healthy controls, depending on disease duration, the presence of certain motor and non-motor features, and the modulatory effect of dopaminergic therapy (for review see Filippi et al. 2018). According to a meta-analysis (Herz et al. 2014a), the most robust task dependent fMRI finding in PD patients is the reduced activity in the putamen, correlating positively with motor impairment and improving with dopaminergic treatment. Regarding the activation of cortical areas in PD brain, an altered pre-supplementary motor area (pre-SMA) activity in PD patients off medication is invariably present, although that the direction of the activity alterations (increased versus decreased) is not consistent across studies (Herz et al. 2014a). Resting state functional MRI (rs-fMRI) is a task independent technique detecting spontaneous low-frequency fluctuations in the Blood Oxygenation Level Dependent (BOLD) signal and diverse analysis methods are used (seed-based analysis, network-based approach, ...) to investigate how PD influences resting state activity and functional connectivity in the human brain (Prodoehl et al. 2014). Using a network model Wu et al. (Wu et al. 2009) found an altered functional connectivity in 18 interconnected brain areas important in motor processes in PD, including decreases in the supplementary motor area (SMA) and putamen, and increases in the cerebellum, normalized by administration of levodopa. Recently, the involvement of the cerebellum in PD has been highlighted, suggesting not only a pathological but also a compensatory role (Wu and Hallett 2013).

Morphometric and fMRI evidence argue an involvement of the prefrontal cortex in the pathophysiology of LID in PD (Cerasa et al. 2013; Cerasa et al. 2012). Task-related neural activity and its modification after ingestion of levodopa has been studied using functional MRI in PD patients with dyskinesias, highlighting the involvement of putamen and pre-SMA in those patients. In dyskinetic patients, the intake of levodopa induced a putaminal hyperactivation starting before any clinical sign of LID was present, as well as an excessive increase in pre-SMA activity. On top, it seemed that the pre-SMA was the only cortical area showing increased responsiveness to levodopa in dyskinetic patients (Herz et al. 2014b; Herz et al. 2015). A rs-fMRI study discovered that levodopa ingestion differently influences corticostriatal resting state functional connectivity (rsFC) depending on the dyskinesia state of the PD patient, and that this could be helpful in predicting whether the patient would develop dyskinesias or not (Herz et al. 2016). Finally, there is increasing evidence pointing towards a crucial role of the cerebellum in the generation of LID (Kishore et al. 2014; Kishore and Popa 2014).

Since rTMS allows for non-invasive modification of underlying cortical activity, a combined rTMS and fMRI approach has been used to study rTMS induced changes in brain activity of the targeted cortex and interconnected brain regions in human volunteers (Siebner et al. 2009). In late stage PD patients, a recent combined resting state fMRI/rTMS study showed that a single session of continuous theta burst stimulation (cTBS), a patterned rTMS technique used to decrease excitability of the underlying cortex (Huang et al. 2005), significantly reduced LID when applied to the right inferior frontal cortex (IFC) but not to the left MC (Cerasa et al. 2015). All the above suggests that right centered prefrontal areas are involved in the pathophysiological mechanisms of LID and merit to be further explored in the search for an adequate treatment of LID.

Therefore, in our present combined rTMS/fMRI study, we investigated how one sham-controlled session of right pre-SMA LF rTMS affects resting state functional connectivity in late stage PD patients with and without dyskinesias. We hypothesized that depending on the dyskinesia status of the patient, real rTMS (and not sham) would influence the pre-SMA-striatal-cerebellar FC differently. Furthermore, we explored the effects of ingesting a dose of levodopa on the post rTMS resting state neural activity, motor function and dyskinesias. Given the one session LF rTMS setup, we did not expect significant influences on dyskinesias.

2. Methods

2.1. Patient population

The study had been approved by The Ethics Committee of the UZBrussel and all patients provided their written informed consent. Seventeen righthanded patients with the diagnosis of idiopathic Parkinson's disease, according to the United Kingdom Parkinson's Disease Society Brain Bank Criteria (Hughes et al. 1992), were enrolled. Patients' demographics and characteristics are described in Table 1. Because this study was part of a larger research project the in- and exclusion criteria for study participation were reported elsewhere (Flamez et al. 2019).

2.2. Study protocol

We performed each imaging procedure after a 12 hours overnight dopaminergic treatment withdrawal (practically defined OFF). We used several imaging techniques in each subject: a structural MRI, a rs-fMRI scan before (T_0) and after the rTMS session (T_1), and 15 and 45 minutes after subsequent ingestion of levodopa (T_2 and T_3 respectively) (levodopa challenge test, see below). This procedure was performed twice in each patient, one containing a real pre-SMA rTMS session and one sham. Patients were randomized to first receive real or sham rTMS by flipping a coin, prior to the first imaging procedure. To minimize carry-over effects of rTMS (Rossi et al. 2009) we introduced a time window of at least one week between both rTMS sessions. Medical treatment remained unchanged throughout the duration of the trial.

Prior to the imaging procedure and in patients practically defined OFF state, two blinded raters assessed patients' motor disability with the motor part of the Unified Parkinson's Disease Rating Scale (UPDRSIII) (Fahn and Elton 1987) and rated dyskinesias with the modified Abnormal Involuntary Movement Scale (mAIMS) (Guy 1976). Immediately following the LF rTMS session, a levodopa challenge test was performed. Patients received 125% of their morning levodopa equivalent dose as a soluble immediate release levodopa/benzeraside formulation. Resting state fMRI scans were performed at 15 (T_2) and 45 minutes (T_3) after levodopa ingestion. Subsequently, patients were videotaped, and patients' motor disability and dyskinesias were reassessed 60 minutes after levodopa ingestion (see Fig. 1).

2.2.1. Imaging procedure

During the resting state measurements, involving 7.5 minutes of scanning, patients were asked to stay awake with their eyes closed. Scans were performed on a 3 T Philips Achieva MRI system (Philips, Best, the Netherlands) with an eight-channel SENSE head coil. An anatomical image was obtained using a 3D T1-weighted TFE sequence (TR/TE = 12.00/3.71 ms; Flip angle = 10°; FOV = 24 $0 \times 240 \times 200$ mm^3; resolution = $1.00 \times 1.00 \times 2.00$ mm^3; number of slices = 100). The resting state fMRI measurement was conducted using the SE-EPI sequence (TR/TE = 3000/70 ms; Flip angle = 90°; FOV = 230×230 mm^2; resolution = 1.80×1.80 m m^2; Slice thickness/gap = 4.00/1.00 mm; number of slices = 24; number of dynamics = 150). During resting state fMRI, all patients were asked to stay awake with their eyes closed.

Table 1
Patients' baseline characteristics.

	Dyskinesia	No dyskinesia	*p*-values
Gender (female/male)	4/5	2/6	0.40[a]
Age (years)	72.89 (9.85)	68.75 (10.73)	0.42[b]
Disease duration (years)	10.11 (4.37)	11.13 (6.24)	0.70[b]
Hoehn and Yahr OFF†	3 (2)	2 (1)	0.335[c]
UPDRSIII OFF*	25.78 (7.79)	19.87 (4.58)	0.081[b]
LID Yes/No	9	8	
Daily equivalent levodopa dose (mg)	876.67 (410.09)	885.00 (446.19)	0.969[b]
RMT (%)	55.22 (3.77)	58.50 (4.50)	0.12[b]

Data are presented as mean (SD) or median values (range) †.
* UPDRSIII in OFF prior to the real rTMS session. There is no significant difference with the baseline UPDRSIII scores prior to the sham rTMS session (paired *t*-test p = 0.95).
LID: levodopa induced dyskinesias; OFF: practically defined OFF after 12 hours medication withdrawal; RMT: resting motor threshold; UPDRSIII: motor part of the Unified Parkinson's Disease Rating Scale; rTMS: repetitive Transcranial Magnetic Stimulation.
[a] Chi-square test.
[b] Independent *t*-test.
[c] Mann-Whitney test.

The MRI data were analysed with SPM12 software (Wellcome Department of Cognitive Neurology, London, UK) and the GLMFlex toolbox. The anatomical images were segmented into grey matter, white matter, and cerebrospinal fluid. The fMRI images were corrected by slice-timing, realignment, and co-registered to the anatomical image. The fMRI data are excluded if (1) the maximum distance of translational movement > 3 mm; (2) the maximum degree of rotational movement > 3°.

Following, all brain volumes were normalized to a standard MNI template and resampled into 3-mm isotropic voxels.

Several spurious or nonspecific sources of variance were removed through linear regression of 1) the six head motion parameters and their temporal derivatives, 2) the non-neuronal sources of noise estimated using the anatomical component correction method (aCompCor) (Behzadi et al. 2007; Muschelli et al. 2014), and to remove physiological confounders (heart rate and respiratory noise) (Whitfield-Gabrieli and Nieto-Castanon, 2012), 3) the first-order Legendre polynomial. Before the voxel-based correlation analysis the residual time series were band-pass filtered (0.01–0.08 Hz). Here, the right pre-SMA seed region was selected (6 mm sphere with centre MNI coordinates at x = 2, y = -5, z = 68). Correlation maps were obtained by extracting the BOLD time course from pre-SMA, then computing the correlation coefficient between that time course and the time courses from all the other brain voxels. The resulting correlation values were converted into z-scores with Fisher's z-transform to improve the normality and smoothed with a 6-mm full-width half-maximum (FWHM) Gaussian filter.

2.2.2. rTMS stimulation protocol

We delivered 1 Hz rTMS to the right pre-SMA with a Magstim high-speed magnetic stimulator (Magstim Company Limited, Minneapolis, USA) through a 70 mm figure-of eight-shaped coil. We determined the position of the coil, in order to target the pre-SMA, with our 3D-MRI localization method (Peleman et al. 2010). Immediately after the baseline rs-fMRI session (T_0) was completed, a series of 1000 pulses at a rate of 1 Hz (duration of 16 minutes) at 90% of the thumb resting motor threshold was applied. The Magstim 70 mm Double Air Film sham coil, identical to its active variant but without stimulation output, was used for sham stimulation.

2.3. Statistical analysis

We used SPSS 25 (Statistical Package for the Social Sciences; IBM Corp., Armonk, NY) for the analysis of all the behavioral results. To evaluate whether the LF rTMS application affected Parkinson symptoms (UPDRSIII) and/or dyskinesias (mAIMS), ratings were analyzed separately using a repeated measure analysis of variance (ANCOVA). Given our recent findings on the relation between disease duration and LF rTMS effect on pre-SMA neurometabolites (Flamez et al. 2019) also disease duration was introduced as a covariate. The stimulation Condition (sham/real) and Time (OFF/ON) were the within-subjects' factors. The between-subject factor was the presence or absence of dyskinesias (yes/ no).

The pre-SMA seed-based FC maps were submitted to repeated measures ANCOVA using GLMFlex toolbox, with Dyskinesia (yes/ no) as between-subject factor, and Condition (real/sham) and Time (Pre- and post rTMS/levodopa) as within-subject factors. Age, gender, mean framewise displacement, and disease duration were set as covariates. First, to examine the effects of one LF rTMS session applied to the right pre-SMA, Time was set for the baseline (T_0) and immediately after the LF rTMS session (T_1). Second, to explore the influence of levodopa, Time was set for the baseline (T_0) prior to, and 15 (T_2) and 45 minutes (T_3) after levodopa ingestion. The FWE option at cluster level $p < 0.05$ was set for all analyses to control for multiple comparisons.

The xjView MATLAB toolbox was used to obtain the anatomical labels and Montreal Neurological Institute (MNI) coordinates (http://www.alivelearn.net/xjview).

3. Results

3.1. Clinical assessment

As expected, after ingestion of levodopa, UPDRS motor scores improved in all patients and mAIMS scores increased only in the dyskinesia group (Table 2). Indeed, the ANCOVA for the UPDRSIII assessment showed besides a significant main effect of Time ($F(1,14) = 31.89$, $p < 0.01$), no other main or interaction effects for Condition, Dyskinesia, and Disease duration (p's > 0.05). Also, the crucial interaction between Time, Dyskinesia, rTMS Condition was not significant ($F(1,14) = 0.11$, $p = 0.75$). The ANCOVA for the mAIMS scores showed only a significant interaction effect between Time and Dyskinesias ($F(1,14) = 24.92$, $p < 0.01$), all other main and interaction effects were not significant (*p's* > 0.05). Again, the crucial interaction effect between Time, Dyskinesia, rTMS Condition, and disease duration was not significant ($F(1,14) = 1.26$, $p = 0.28$). As expected, only in Parkinson patients with LID, at the

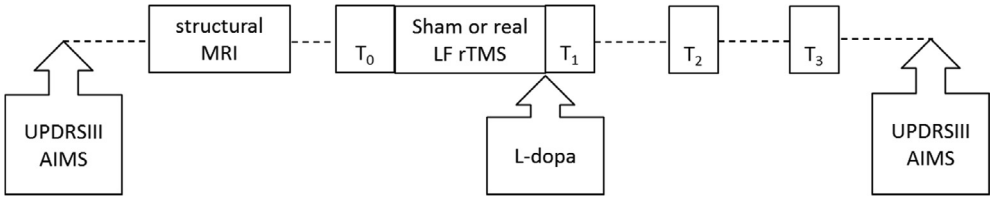

Fig. 1. rTMS/fMRI study protocol.

Table 2
Motor function and dyskinesia scores.

	OFF		ON	
	Sham	Real	Sham	Real
UPDRSIII				
Dyskinesia	25.22 (6.40)	25.78 (7.80)	10.11 (5.44)	10.56 (5.55)
No dyskinesia	20.38 (3.25)	19.88 (4.58)	7.50 (2.00)	7.50 (3.34)
AIMS				
Dyskinesia	0.00 (0.00)	0.00 (0.00)	6.11 (4.14)	6.89 (3.62)
No dyskinesia	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)

Data are presented as mean values (SD).
AIMS: Abnormal Involuntary Movement Scale; OFF: practically defined OFF after 12 hours of medication withdrawal; ON: 1 hour after levodopa ingestion; UPDRSIII: motor part of the Unified Parkinson's Disease Rating Scale.

end of the experiment and after levodopa ingestion follow-up T tests showed a significant increase in AIMS scores after the real ($T(8) = 5.71$, $p < 0.01$) as well as the sham procedure ($T(8) = 4.32$, $p < 0.01$). As expected, no differences after real or sham in this dyskinesia group were detected ($T(8) = 1.08$, $p = 0.31$). AIMS scores did not significantly change for the PD patients without dyskinesia (p's > 0.05). Of note, nonparametric statistical analysis did not result in different clinical outcomes.

3.2. rs-fMRI

The first repeated measures ANCOVA, examining the effects of one sham-controlled LF rTMS in OFF (before the ingestion of levodopa) with Dyskinesia (yes/no) × Condition (real/ sham LF rTMS) × Time (T_0 and T_1), yielded two significant interaction clusters with the (right) pre-SMA: one in the cerebellum (k = 224 voxels: MNI coordinates: x = -9 y = -57 z = -6: peak F-value = 15.93; region: left cerebellar lingual area), and one in the right putamen (k = 174 voxels: MNI coordinates: x = 15 y = 9 z = 6: peak F-value = 40.79, region: right putamen) (see Fig. 2). Post hoc analysis showed that in PD patients without dyskinesias one real LF rTMS session significantly decreased right pre-SMA rsFC within the right cerebellum (k = 41 voxels, MNI coordinates: x = 39 y = −36 z = −9, peak T-value = -3.06) and left cerebellum (k = 20 voxels, MNI coordinates: x = −6 y = −48 z = −6, peak T-value = -4.65), and the right putamen (k = 62 voxels, MNI coordinates: x = 30 y = 12 z = 0, peak T-value = -4.13) and that one real LF-rTMS in PD patients with dyskinesias significantly increased pre-SMA rsFC in the right putamen (k = 40 voxels, MNI coordinates: x = 18 y = 6 z = 6, peak T-value = 5.91). Sham stimulation did not change right pre-SMA rsFC. More information is provided in the Supplemental Material (Figure S1). Of note, the use of non-parametric permutation tests yielded similar results as the repeated measure ANCOVA (Nichols and Holmes 2002). No scan was removed according to the motion criteria.

The second repeated measures ANCOVA, exploring the effect of levodopa ingestion on pre-SMA FC, with Dyskinesia × Condition × Time (T_0, T_1, T_2 and T_3) yielded no significant interaction clusters, indicating that the ingestion of levodopa after the LF rTMS session did not differentially affect the pre-SMA rsFC between the two groups. However, due to motion artifacts we could only include ten patients (five already had motion artifacts at T_2 and another two PD patients were excluded by motion artifacts at T_3: three in the dyskinesia group and four in the no dyskinesia group).

4. Discussion

To our knowledge, this is the first functional connectivity study exploring the effect of one session of LF rTMS applied to the right pre-SMA in late stage PD patients. It was well tolerated but, as expected, did not alleviate dyskinesias.

4.1. Pre-SMA-putaminal functional connectivity

Depending on patients' dyskinesia state, one session of real, and not sham pre-SMA LF rTMS yielded opposite effects on pre-SMA-putaminal functional connectivity. Our results showed that whereas 1 Hz rTMS increased right pre-SMA FC with the right putamen in patients suffering from LID, pre-SMA-putaminal FC decreased in patients without dyskinesias. Because LF rTMS decreases motor cortex excitability in normal control subjects when applied directly over the motor cortex (Chen et al. 1997), and because task-related fMRI studies show that the activity in the posterior putamen is reduced and the pre-SMA activity is altered in PD patients (Herz et al. 2014a), inhibitory pre-SMA rTMS may further reduce putaminal FC in non-dyskinetic patients. On the contrary, since in dyskinetic PD patients hyperactivity of cortical motor areas has been documented (Rascol et al. 1998), it seems plausible that inhibitory LF rTMS applied to the pre-SMA results in FC increases with the ipsilateral putamen. Indeed, in a task related fMRI trial it has been shown that levodopa intake induces a hyperactivity of the pre-SMA in the NoGo condition only in the dyskinetic patients (Herz et al. 2014b), whereas the resting state functional connectivity between MC/SMA (+pre-SMA) and putamen is decreased after levodopa ingestion in LID (Herz et al. 2016). Also, it has been proposed that LID are caused by a maladaptive synaptic plasticity (Wang and Zhang 2016). Using a continuous theta burst stimulation protocol Huang and co-workers demonstrated in PD patients that dopamine is required to induce long term potentiation (LTP), and that depotentiation could subsequently not be induced in the subset of patients suffering from LID (Huang et al. 2011). Therefore, the loss of depotentiation ability seems to play a crucial role in the development of LID in PD. Since there is increasing evidence that rTMS protocols can induce LTP/LTD like plasticity in the human brain (Huang et al. 2017), we can speculate that in our dyskinetic patients one session of LF rTMS on the pre-SMA alters plasticity, hereby improving FC with the ipsilateral putamen.

Importantly, opposite effects of putaminal FC depending on the dyskinesia state has already been reported in relation to dopaminergic modulation of cortico-striatal FC in late stage PD patients (Herz et al. 2016). In this ROI based rsFC study - after the ingestion of levodopa - functional connectivity between putamen and primary sensorimotor cortex of the most affected hemisphere decreased in patients with LID and increased in patients without LID. Although in our study there was an opposite effect of rTMS on putaminal FC depending on the dyskinesia state, after the ingestion of levodopa, FC patterns were not different from baseline. In line with Herz' findings (Herz et al. 2016) one could assume that levodopa may restore the previously rTMS induced FC changes in

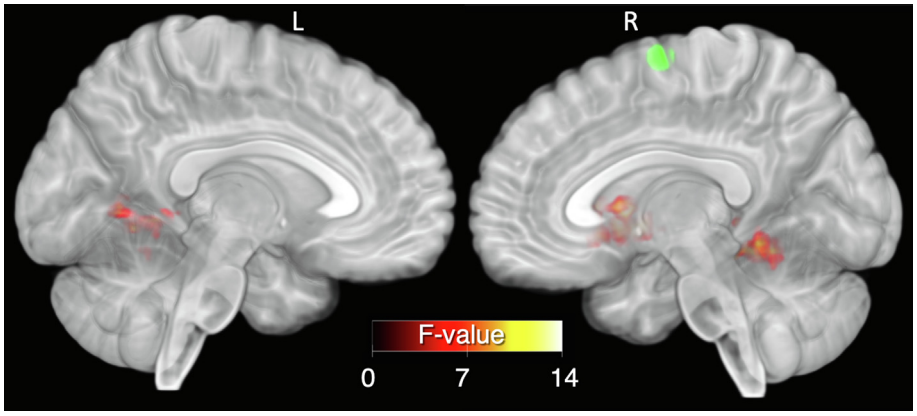

Fig. 2. Sagittal views of the significant interaction effects of full factorial ANOVA, examining the effects of one sham-controlled low frequency repetitive Transcranial Magnetic Stimulation (LF rTMS) session with Dyskinesia (yes/no) × Condition (real/ sham LF rTMS) × Time (T0 and T1), yielding two significant interaction clusters with the (right) pre-supplementary motor area (green), in the cerebellum and right putamen (red).

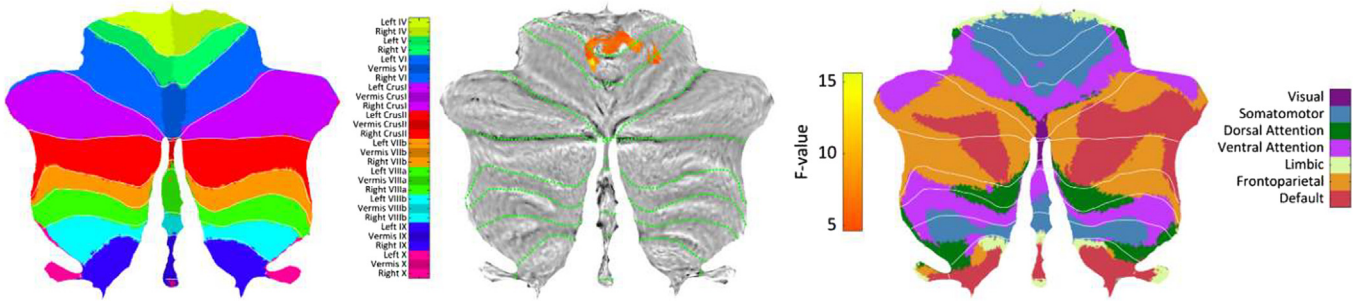

Fig. 3. Coronal views of the significant cerebellar cluster (middle) with the anatomical (left) and functional atlas representation (right) (Buckner et al. 2011).

our patients. However, this assumption should be considered as preliminary because 15 and 45 minutes after levodopa ingestion we had to exclude seven participants due to motion artefacts.

4.2. Pre-SMA-cerebellar functional connectivity

One session of real, and not sham, pre-SMA LF rTMS significantly decreased FC with the somatomotor part of the cerebellum (Fig. 3) only in patients without dyskinesias. Recent evidence highlights the role of the cerebellum in PD (Wu and Hallett 2013). Task and resting state fMRI studies found an increased neuronal activation in the cerebellum which was normalized by the administration of levodopa (Wu et al. 2009; Wu and Hallett 2005). This could indicate a more compensatory role for the cerebellum in PD. Compensating for a hypofunctional striato-thalamo-cortical loop by increasing activity in the cerebello-thalamo-cortical circuit might be necessary to maintain motor function, at least in the early stages of the disease (Wu and Hallett 2013). It could also explain why in our study one session of pre-SMA LF rTMS decreases FC of the pre-SMA with the cerebellum only in the non-dyskinetic patients, modulating compensatory mechanisms. Whereas in PD patients with LID FC with the cerebellum is not altered indicating a loss of the ability to modulate compensatory cerebellar mechanisms, suggesting that these compensatory mechanisms might be less effective in those patients.

The role of the cerebellum in the generation of dyskinesias is supported by other inhibitory cTBS studies (Brusa et al. 2012; Kishore et al. 2014; Koch et al. 2009). Multiple sessions of bilateral cerebellar cTBS in PD patients were able to reduce LID for up to several weeks after the end of the stimulation period. This was accompanied by a reduction of cerebellar metabolism (Brusa et al. 2012), or an alteration of motor cortex excitability (Kishore et al. 2014; Koch et al. 2009). The mechanism however underlying these induced changes is still unclear.

4.3. Limitations of our study

Of course, the relatively small sample size is a clear limitation, in spite that the focus of the study was on brain imaging and that the diagnostic criteria were very stringent. Besides a relatively small sample size, given the low therapeutic potential of single session studies, a multiple LF rTMS session approach could have yielded more robust effects, on the behavioral level as well as on pre-SMA FC. Furthermore, we choose to stimulate the right pre-SMA whereas in the literature other areas are proposed in the management of dyskinesias, such as the right IFC (Cerasa et al. 2015) or the cerebellum (Brusa et al. 2012; Kishore et al. 2014; Koch et al. 2009). Finally, the inclusion of a levodopa challenge test in PD patients seems challenging given that this resulted in the considerable exclusion of rs-fMRI scans due to motion artefacts.

In conclusion, although one session of right pre-SMA LF rTMS did not alleviate dyskinesias in late stage PD patients, it may have opposite effects on functional connectivity with the putamen, depending on their dyskinesia state. Multiple session studies should be performed to confirm our findings and enhance its therapeutic potential.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant No. 61876156), and the Willy Gepts Fund UZBrussel, Belgium.

Declaration of Competing Interest

The authors report no financial interests or potential conflict of interest.

Ethical standards

This study has been reviewed by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients gave their informed consent prior to their inclusion in the study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.12.024.

References

Behzadi Y, Restom K, Liau J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage 2007;37:90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042.

Brusa L, Ceravolo R, Kiferle L, Monteleone F, Iani C, Schillaci O, Stanzone P, Koch G. Metabolic changes induced by theta burst stimulation of the cerebellum in dyskinetic Parkinson's disease patients. Parkinsonism Relat Disord 2012;18:59–62. https://doi.org/10.1016/j.parkreldis.2011.08.019.

Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BT. The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol 2011;106:2322–45. https://doi.org/10.1152/jn.00339.2011.

Cerasa A, Koch G, Donzuso G, Mangone G, Morelli M, Brusa L, Stampanoni Bassi M, Ponzo V, Picazio S, Passamonti L, Salsone M, Augimeri A, Caltagirone C, Quattrone A. A network centred on the inferior frontal cortex is critically involved in levodopa-induced dyskinesias. Brain 2015;138:414–27. https://doi.org/10.1093/brain/awu329.

Cerasa A, Morelli M, Augimeri A, Salsone M, Novellino F, Gioia MC, Arabia G, Quattrone A. Prefrontal thickening in PD with levodopa-induced dyskinesias: new evidence from cortical thickness measurement. Parkinsonism Relat Disord 2013;19:123–5. https://doi.org/10.1016/j.parkreldis.2012.06.003.

Cerasa A, Pugliese P, Messina D, Morelli M, Gioia MC, Salsone M, Novellino F, Nicoletti G, Arabia G, Quattrone A. Prefrontal alterations in Parkinson's disease with levodopa-induced dyskinesia during fMRI motor task. Mov Disord 2012;27:364–71. https://doi.org/10.1002/mds.24017.

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohan LG. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398–403. https://doi.org/10.1212/wnl.48.5.1398.

Fahn S, Elton RL. UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease. Florham Park, NJ: Macmillan; 1987:153–163.

Flamez A, Cordenier A, De Raedt S, Michiels V, Smetcoren S, Van Merhaegen-Wieleman A, Parys E, De Keyser J, Baeken C. Bilateral low frequency rTMS of the primary motor cortex may not a be suitable treatment for levodopa-induced dyskinesias in late stage Parkinson's disease. Parkinsonism Relat Disord 2016;22:54–61. https://doi.org/10.1016/j.parkreldis.2015.11.009.

Flamez A, Wiels W, Van Schuerbeek P, De Mey J, De Keyser J, Baeken C. The influence of one session of low frequency rTMS on pre-supplementary motor area metabolites in late stage Parkinson's disease. Clin Neurophysiol 2019;130:1292–8. https://doi.org/10.1016/j.clinph.2019.04.720.

Filippi M, Elisabetta S, Piramide N, Agosta F. Functional MRI in Idiopathic Parkinson's Disease. Int Rev Neurobiol 2018;141:439–67. https://doi.org/10.1016/bs.irn.2018.08.005.

Guy W. Abnormal Involuntary Movement Scale. ECDEU assessment manual for psychopharmacology. Washington, DC: US Government Printing Office; 1976.

Herz DM, Eickhoff SB, Løkkegaard A, Siebner HR. Functional neuroimaging of motor control in Parkinson's disease: a meta-analysis. Hum Brain Mapp 2014a;35:3227–37. https://doi.org/10.1002/hbm.22397.

Herz DM, Haagensen BN, Christensen MS, Madsen KH, Rowe JB, Løkkegaard A, Siebner HR. The acute brain response to levodopa heralds dyskinesias in Parkinson's disease. Ann Neurol 2014b;75:829–36. https://doi.org/10.1002/ana.24138.

Herz DM, Haagensen BN, Christensen MS, Madsen KH, Rowe JB, Løkkegaard A, Siebner HR. Abnormal dopaminergic modulation of striato-cortical networks underlies levodopa-induced dyskinesias in humans. Brain 2015;138:1658–66. https://doi.org/10.1093/brain/awv096.

Herz DM, Haagensen BN, Nielsen SH, Madsen KH, Løkkegaard A, Siebner HR. Resting-state connectivity predicts levodopa-induced dyskinesias in Parkinson's disease. Mov Disord 2016;31:521–9. https://doi.org/10.1002/mds.26540.

Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967;17:427–42. https://doi.org/10.1212/wnl.17.5.427.

Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6. https://doi.org/10.1016/j.neuron.2004.12.033.

Huang YZ, Lu MK, Antal A, Classen J, Nitsche M, Ziemann U, Ridding M, Hamada M, Ugawa Y, Jaberzadeh S, Suppa A, Paulus W, Rothwell J. Plasticity induced by non-invasive transcranial brain stimulation: a position paper. Clin Neurophysiol 2017;128:2318–29. https://doi.org/10.1016/j.clinph.2017.09.007.

Huang YZ, Rothwell JC, Lu CS, Chuang WL, Chen RS. Abnormal bidirectional plasticity-like effects in Parkinson's disease. Brain 2011;134:2312–20. https://doi.org/10.1093/brain/awr158.

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinical pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–4. https://doi.org/10.1136/jnnp.55.3.181.

Kishore A, Popa T, Balachandran A, Chandran S, Pradeep S, Backer F, Krishnan S, Meunier S. Cerebellar processing alterations impact motor cortical plasticity in Parkinson's disease: clues from dyskinetic patients. Cereb Cortex 2014;24:2055–67. https://doi.org/10.1093/cercor/bht058.

Kishore A, Popa T. Cerebellum in levodopa-induced dyskinesias: the unusual suspect in the motor network. Front Neurol 2014;5:1–11. https://doi.org/10.3389/fneur.2014.00157.

Koch G, Brusa L, Carillo F, Lo Gerfo E, Torriero S, Oliveri M, Mir P, Caltagirone C, Stanzione P. Cerebellar magnetic stimulation decreases levodopa-induced dyskinesias in Parkinson's disease. Neurology 2009;73:113–9. https://doi.org/10.1212/WNL.0b013e3181ad5387.

Muschelli J, Nebel MB, Caffo BS, Barber AD, Pekar JJ, Mostofsky SH. Reduction of motion-related artifacts in resting state fMRI using aCompCor NeuroImage 2014; 96:22-35. doi: 10.1016/j.neuroimage.2014.03.028.

Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2002;15:1–25. https://doi.org/10.1002/hbm.1058.

Peleman K, Van Schuerbeek P, Luypaert R, Stadnik T, De Raedt R, De Mey J, Bossuyt A, Baeken C. Using 3D-MRI to localize the dorsolateral prefrontal cortex in TMS research. World J Biol Psychiatry 2010;11:425–30. https://doi.org/10.1080/15622970802669564.

Prodoehl J, Burciu RG, Vaillancourt DE. Resting state functional magnetic resonance imaging in Parkinson's disease. Curr Neurol Neurosci Rep 2014;14:448. https://doi.org/10.1007/s11910-014-0448-6.

Rascol O, Sabatini U, Brefel C, Fabre N, Rai S, Senard JM, Celsis P, Viallard G, Montastruc JJ, Chollet F. Cortical motor overactivation in parkinsonian patients with L-dopa-induced peak-dose dyskinesia. Brain 1998;121:527–33. https://doi.org/10.1093/brain/121.3.527.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety of TMS Consensus Group, Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;12:2008–39. https://doi.org/10.1016/j.clinph.2009.08.016.

Siebner HR, Bergmann TO, Bestmann S, Massimini M, Johansen-Berg H, Mochizuki H, Bohning DE, Boorman ED, Groppa S, Miniussi C, Pascual-Leone A, Huber R, Taylor PC, Ilmoniemi RJ, De Gennaro L, Strafella AP, Kähkönen S, Klöppel S, Frisoni GB, George MS, Hallett H, Brandt SA, Rushworth MF, Ziemann U, Rothwell JC, Ward N, Cohen LG, Baudewig J, Paus T, Ugawa Y, Rossini PM. Consensus paper: combining transcranial stimulation with neuroimaging. Brain Stimul 2009;2:58–80. https://doi.org/10.1016/j.brs.2008.11.002.

Wang Q, Zhang W. Maladaptive synaptic plasticity in L-dopa-induced dyskinesia. Front Neural Circuits 2016;10:105. https://doi.org/10.3389/fncir.2016.00105.

Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2012;2:125–41. https://doi.org/10.1089/brain.2012.0073.

Wu T, Hallett M. A functional MRI study of automatic movements in patients with Parkinson's disease. Brain 2005;128:2250–9. https://doi.org/10.1093/brain/awh569.

Wu T, Hallett M. The cerebellum in Parkinson's disease. Brain 2013;136:696–709. https://doi.org/10.1093/brain/aws360.

Wu T, Wang L, Chen Y, Zhao C, Li K, Chan P. Changes of functional connectivity of the motor network in the resting state in Parkinson's disease. Neurosci Lett 2009;460:6–10. https://doi.org/10.1016/j.neulet.2009.05.046.