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Sent: 14 March 2020 02:42
To: Giorgio Fuggetta <Giorgio.Fuggetta@roehampton.ac.uk>; submit@humanbab.net <submit@humanbab.net>
Subject: Re: Re: Research article for consideration for publication in Human Behaviour and Brain

Dear Dr Fuggetta,

We have received your carefully-revised manuscript and I am pleased to let you know that the paper has been accepted for publication in Human Behaviour and Brain in its inaugural issue to come out in April. Our production editor will contact you in due course. Once again, great thanks for your support!

Warm regards,
Li-Hai

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----- Original -----
From: "Giorgio Fuggetta" <Giorgio.Fuggetta@roehampton.ac.uk>;
Date: Sat, Mar 14, 2020 05:39 AM
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Subject: Re: Re: Research article for consideration for publication in Human Behaviour and Brain

Dear Professor Tan,

Please find attached the Figures, Tables, Revision Cover Letter and revision of the manuscript entitled: 'A neurophysiological insight into use of repetitive transcranial magnetic stimulation as potential therapeutic tool in Parkinson's disease', by Giorgio Fuggetta (PhD), Marco Sandrini (PhD) Chiara Arcaro (BSc), Michele Tinazzi (MD., PhD.), and Paolo Manganotti (MD., PhD.) for consideration for publication as research article in Human Behaviour and Brain.

I am looking forward to hearing from you soon.

Best wishes,

Giorgio

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Title:

A neurophysiological insight into use of repetitive transcranial magnetic stimulation as potential therapeutic tool in Parkinson's disease

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Keywords: resting-state neural oscillations; brain stimulation; pathophysiology; Parkinson disease; entrainment of oscillations; neuromodulation

Abstract

Parkinson's disease (PD) patients show pronounced slowing of resting-state oscillatory brain activity compared to healthy controls. In addition, repetitive transcranial magnetic stimulation (rTMS) has shown to have possible therapeutic effects on motor symptoms of PD. However, the precise electrophysiological mechanisms behind these effects are unknown. In this cross-over, sham-controlled study, 15 off-drugs PD patients underwent two sessions where active or sham high-frequency rTMS at 10 Hz was performed on the primary motor cortex (M1). Active rTMS, improved overall motor performance and induced an increase of oscillatory activity with a shift of EEG low α peak towards higher frequencies 30 minutes after active brain stimulation. The pattern of brain rhythm modulations suggests that 10 Hz rTMS over M1 seems to be able to act on the thalamo-cortical resonance interplay entraining neural oscillations at the same frequency, in association with a clinical improvement of motor performance in PD.

Introduction

The abnormal synchronization and alteration in neural network oscillations between cortical and deep brain structures underlies the pathophysiology of various brain disorders including Parkinson's disease (PD) [1-6]. In particular, it has been demonstrated that moderately advanced, non-demented PD patients show pronounced slowing of resting-state oscillatory brain activity compared to healthy controls, consisting of a widespread increase in θ and low α relative power values with a slight change in the cortical distribution of high α power [7].

Transcranial magnetic stimulation (TMS), with rapidly oscillating magnetic fields administered by a coil positioned on the scalp, allows non-invasive stimulation of the human brain [8]. It is well documented that repetitive TMS (rTMS) protocols do not pose significant risks in the general population or PD patients [9, 10]. Moreover, rTMS has proved to have a therapeutic role improving symptoms of various neurological and psychiatric disorders [11-14]. Of all the movement disorders, PD has received the most attention with regard to rTMS therapeutic studies [11]. Several studies have indicated that patients with PD have cortical dysfunction [15]. An extensive evidence based synthesis of established and potential therapeutic applications of rTMS in the neurological and psychiatric domains [12] gave a recommendation of possible efficacy for the effect of high-frequency rTMS (5–25 Hz) of bilateral (multiple) M1 areas on motor symptoms of PD but no recommendation for low-frequency or high-frequency rTMS of unilateral M1 representation of the hand. However, where no recommendation has been proposed, the absence of evidence should not be taken as evidence for the absence of effect. This is especially true for treatments with very variable individual responses, such as rTMS [12].

rTMS can be used in basic research to study how perturbations in activity in a focal brain area affect the neural network oscillations [16, 17], demonstrating that it can interact

with spontaneous oscillatory rhythms existing in the cortical circuits activated by the stimulation [18-22]. This may induce an activity-dependent modulation according to phase-locking synchrony between cortical oscillations and the pattern of the stimulation [20]. Interestingly, the modification of cortical oscillatory activity through the use of rhythmic repetitive stimulation [23, 24] may readjust pathological patterns of brain activity. This would allow an opportunity to induce new oscillatory patterns, which could adequately modulate the neural response of a network (i.e., entrainment) [25]. Modulating these rhythms may be a valuable therapeutic approach, optimally designed in closed-loop stimulation techniques [26]. It is also tempting to consider that the frequency- and pattern dependent therapeutic effects of rTMS could come, at least in part, from an interaction with some altered oscillations involving cortical networks [20].

The general purpose of this electrophysiological study was to enhance the understanding of the probable electrophysiological mechanism underlying the therapeutic effects of rTMS in PD patients. To achieve this, the effect of rTMS induced modulation of oscillatory activity was compared with the alteration of oscillations in PD. The hypothesis that, in PD patients at rest, a transient effect of modulation of alpha band oscillations (8-12 Hz) can be externally entrained by the 10 Hz frequency of rTMS used was tested. The resolution of this matter is of considerable interest because it may suggest new ways to use combined EEG/TMS techniques as both a diagnostic test and therapeutic tool to restore proper neural oscillations in PD. To address this issue, we used surface EEG to quantify the cortical oscillatory activity pre- and post-rTMS over M1.

Several lines of evidence support the use of the aforementioned frequency of rTMS in the current study. Firstly, reviews of clinical trials which have assessed the therapeutic effects of rTMS in PD, have demonstrated stronger beneficial effects of high-frequency as compared with low-frequency rTMS over M1 on motor symptoms in PD patients [11, 12, 27].

Furthermore, a series of studies using positron emission tomography (PET) provide evidence that short trains of 10 Hz rTMS can stimulate subcortical dopamine release in the striatum (specifically, the caudate nucleus and putamen) in healthy subjects and PD patients [28-31]. Additionally, the release of dopamine in the putamen was greater in the more affected hemisphere in mild hemiparkinsonian patients [29]. Thus it has been demonstrated that 10 Hz rTMS can act indirectly on the subcortical level via stimulation at connected cortical areas [29]. Lastly, it has been proposed that high-frequency stimulation has sufficiently short time intervals between pulses to build up a large “summation” of neural activity, which consequently results in greater recruitment and activation of cortico-thalamic descending pathways [20, 22]. Overall high-frequency rTMS at 10 Hz seems to have the potential to act on the abnormal processing in the cortico–basal ganglial loops which underlies PD causes [11].

Results

No adverse side effects of rTMS were reported by any of the participants during all experimental conditions. The results of the two interventions (10 Hz rTMS or sham rTMS) are shown by Figure 1 for clinical scores and by Figure 2 for relative power which reflected the regional oscillatory activity of neural assemblies.

Clinical motor performance

There was a significant main effect of ‘Time of evaluation’ with $F_{(1,14)} = 22.9, p < 0.001 \eta p^2 = .62$, which seems to suggest an overall decrease of motor subscale of UPRS score after each of rTMS interventions as compared with the motor evaluation before each the rTMS session (14.0 vs. 10.5). Interestingly, there was a significant two-way interaction ‘rTMS condition’ by ‘Time of evaluation’ with $F_{(1,14)} = 37.7, p < 0.001 \eta p^2 = .73$. Post-hoc

comparisons for the significant interaction showed that both rTMS conditions improved overall motor performance. In particular active rTMS was associated with an improvement of motor response of 35.4% (13.93 vs. 9.00, $p < .001$) and sham rTMS orived motor performance by 14.6% (14.13 vs. 12.07, $p < .01$). However active rTMS improved overall motor performance significantly more than sham rTMS 35 minutes post-stimulation (9.00 vs. 12.07, $p < .01$, Bonferroni corrected). Figure 1 shows total UPDRS III score pre- and post-rTMS interventions.

< Figure 1 about here >

Relative power α (8.00-12.75 Hz) frequency band

Table 2 summarise ANOVA statistical results of relative EEG power for frontal, central, parietal and occipital electrodes at α (8.00-12.75 Hz) frequency band.

< Table 2 about here >

A significant variation among the rTMS conditions was found in fronto-central electrode sites but reached statistical significance at central electrodes site only. First, it was checked if there was a significant difference in the pre-stimulation period comparing active vs. sham conditions for the entire α frequency band of interest. There were no significant differences in pre-stimulation period between the two interventions for central electrodes site. Post-hoc comparisons for the significant interaction 'rTMS condition' x 'Time of evaluation' x 'frequency bin' revealed that for active rTMS condition and frequency bin 9.00-9.75 Hz, there was a significant difference with an increase of regional oscillatory activity comparing the relative power values pre-stimulation and post-stimulation with whose obtained 30 minutes after the end of active rTMS intervention (7.0 and 7.2 vs. 10.5 %, $p < .05$, Bonferroni corrected). No other significant modulation of

cortical oscillations was observed, particularly following sham rTMS. Thus, as shown in Figure 2, active rTMS, but not ‘sham’ stimulation, induced a modulation of oscillatory activity with a shift of dominant frequency α peak towards higher frequencies at central electrodes site. No other frequency bands were significantly affected by the experimental manipulations.

< Figure 2 about here >

Discussion

The general purpose of this study was to gain new insight into a probable electrophysiological mechanism underlying the possible therapeutic effects of rTMS in PD patients. In particular, we aimed to evaluate if brain stimulation with TMS may readjust pathological patterns of brain oscillatory activity which is altered in PD patients [7, 32]. The main finding of the current study was that excitatory rTMS at 10 Hz induced a specific increase of amplitude in low- α relative power with a shift of the dominant α frequency towards higher frequencies in PD patients 30 minutes post stimulation. This direct electrophysiological modulation of cortical oscillatory activity was concomitant with the improvement in clinical motor symptoms observed in the same group of patients.

Data published to date suggest possible antiparkinsonian effects of non-invasive rTMS on motor symptoms, especially when applied at high-frequency on large M1 regions of both hemispheres. The majority of studies show global improvement of motor part of UPDRS, especially of movement speed or gait velocity, following the focal stimulation of hand representation [12]. In particular, a small number of single session, proof-of-principle studies have shown a 10–30% improvement of clinical motor symptoms of active rTMS, with no effects after sham stimulation [11]. The improvement of motor performance of the current

study was 20.8% greater in the case of active rTMS as compared to sham rTMS of the motor cortex in PD. This is consistent with the findings of previous clinical trials.

A number of investigations have demonstrated that the rhythmic aspects of non-invasive transcranial magnetic stimulation over M1 can induce a modification of cortical oscillatory activity [18-22]. In particular, high-frequency stimulation (>5Hz) leads to an immediate synchronization of EEG activity with an increase of power particularly in the α band, consistent with entrainment of oscillatory activity [21, 22]. Additionally, this work shows direct evidence for causal entrainment of brain oscillations by rTMS using concurrent EEG in PD. In the current study, the rTMS aftereffects significantly emerged after 30 minutes from the end of the trains of stimulation. Recently, it has been postulated [33] that some molecular mechanisms can explain the slow building up of rTMS-induced after-effects (generally 5–10 min) in humans [34, 35]. Research investigating the pathophysiology of PD mostly focuses on basal ganglia dysfunction. However, the main output from the basal ganglia is via the thalamus, and corticothalamic feedback constitutes the primary source of synapses in the thalamus [4]. We therefore focused on the thalamocortical interplay to explain the results of the current proof-of-principle study.

A pathophysiological framework of alternation of brain oscillations in common for PD, neurogenic pain, epilepsy, tinnitus and major depression has been proposed by Rodolfo Llinas [3] and called Thalamocortical dysrhythmia (TCD). In TCD phenomenon, bursting thalamic relay neurons exert a rhythmic influence on thalamocortical modules in the θ frequency band [36]. This will disrupt the normal, state-dependent, flow of information between thalamus and cortex [37], leading to disturbances of sensation, motor performance and cognition. The existence of TCD has been demonstrated by a series of Magnetoencephalography (MEG), EEG and single cell physiology studies in patients at rest [2-6]. The pathophysiological framework of TCD has been adopted to explain the genesis of

parkinsonian symptoms [4]. In a ground breaking study by Sarnthein and Jeanmonod [4], during the surgical intervention in PD patients, local field potentials (LFPs) were recorded from pallidal-recipient thalamic nuclei VL_a and VA. Simultaneously, EEG was recorded from several sites on the scalp. The highest thalamocortical coherence was found in the θ frequency band (4 –9 Hz) with a mean peak frequency of 7.5 Hz. The functional coupling between the thalamus and cortex was confirmed by the high θ coherence between the two which reached 70% and was maximal with frontal scalp sites on both hemispheres. The high thalamocortical coherence underlines the importance of thalamic function for the genesis of scalp EEG [4].

Overall, the current electrophysiological results suggest that targeting the specific cortical areas in the most affected hemisphere by brain stimulation could affect the cortical dysfunction in PD directly, or could modify activity in the basal ganglia networks that are corticostriatal and cortico subthalamic projections [38]. Indeed, the rTMS 10 Hz in the present study appears to be able to modulate the rhythmic thalamocortical interplay by entraining the resonance between the thalamus and cortex at ~ 10 Hz thus generating a state that seems to restore proper neural oscillations in association with a clinical improvement of motor performance in PD. Such improvement could be related to an increase in dopamine release, although the slight improvement of motor symptoms after sham rTMS also suggest the possibility of a partial intervention of placebo effects in PD as in previous studies [29, 39]. Nevertheless, after controlling for the placebo or auditory effects with sham rTMS condition, we were able to demonstrated that active rTMS was able to act on internally generated and persistent thalamic frequency range activity and served as a trigger to temporally re-establish proper thalamo-cortical resonance oscillatory network function, with a consequent increased α rhythmicity in PD patients at rest 30 minutes post stimulation. These results support the hypothesis that electrical brain stimulation like TMS can trigger an

oscillation and reset the ongoing rhythmic activity of a local thalamic pacemaker [20, 28, 40]. Once oscillators are reset, regionally-specific endogenous rhythms of the brain may reemerge, and through this mechanism restores normal brain function [41]). Thus, the cortical targets of non-invasive brain stimulation might be conceptualised as ‘entry ports’ for modulation of activity in specific bihemispheric, cortico subcortical neural networks [38].

Some limitations of the current study should be mentioned. First, given that our sample size was relatively small, findings reported here should be reproduced in larger cohorts before firm conclusions can be drawn. Second, the study employed a within-subject design so did not have a real sham/control group. Third, because of the lack of a control stimulation condition (i.e. different stimulation frequency) nonspecific effects of the stimulation cannot be ruled out.

In conclusion, the results of present investigation pointed to the potential of rTMS as therapeutic tool to reverse the pathological slowing of oscillatory brain activity observed of Parkinson’s disease. This investigation provides an insight into the mechanisms underlining the possible therapeutic effects of rTMS and can lead to sensitive treatment efficacy measures based on indexes of EEG oscillations; examining the effects of rTMS within the framework of dysrhythmic thalamocortical interplay [20]. Future work should look at changes of multi-band EEG power across various brain regions and advanced data analysis methods could be employed to provide comprehensive evidences. Future studies, recoding the EEG signal from an increased number of electrodes as compared to the current investigation, would allow accurate source location analysis in order to link the brain oscillation effect to thalamo-cortical loop. Future applied clinical research can attempt to further develop therapeutic strategies to restore of normal oscillatory patterns which is associated with effective treatment of PD. Specifically, to conduct multiple stimulation sessions (e.g., one session per day for a week) and then examine the clinical improvements and neural changes.

Materials and methods

Subjects

In this cross-over, sham-controlled study a total of 16 patients were initially recruited. However, one patient was excluded in the absence to obtain a reliable determination of the rest motor threshold. Thus, fifteen patients (age 45-80 years) with idiopathic Parkinson's disease (disease duration 2–13 years) were included in this study. Level of cognitive impairment was determined using the mini-mental state examination (MMSE) [42]. Disease duration was based on the patients' subjective estimate of the time of occurrence of the first motor symptoms. Side of onset was based on the body-half in which these symptoms first occurred. Unified Parkinson's disease Rating Scale motor scores (UPDRS-III) [43] and modified Hoehn and Yahr stages [44] were obtained 12 hours after an overnight withdrawal of anti-parkinsonian medication, i.e. in 'off-drug' state by a trained physician prior to and after rTMS sessions. Subject characteristics are listed in Table 1. Written informed consent was obtained from all participants and Ethics approval was provided by the regional Medical School Ethics Committee of Verona University, Italy. Ethics review criteria conformed to the Helsinki declaration.

< Table 1 about here >

Experimental paradigm

Subjects were tested in a quiet and dimly light room. First, motor performance was assessed clinically, and then they were seated in a comfortable armchair at rest and awake state. Second, the EEG cap was mounted and the impedance check completed. Third, TMS parameter of the motor threshold at rest was measured (See below). Fourth, patients were instructed to close their eyes and remain awake for two minutes immediately before,

immediately after and until 30 minutes after the end of rTMS delivery. PD patients were asked to keep their eyes closed during the EEG recordings to maximize occipital alpha oscillations and its influence on thalamo-cortical circuit as in previous studies [3, 45]. One of the two interventions, i.e. active rTMS or sham rTMS at 10 Hz (see below) was performed on the hand motor area of the primary motor cortex (M1) contralateral to the most affected body side while the EEG activity was recorded continuously. The EEG cap from the PD patients was removed after 30 minutes post rTMS intervention. Thirty-five minutes after the end of the rTMS intervention, a clinician performed the motor evaluation with UPDRS-III again. The order of the two rTMS sessions was randomised across patients, and each session was separated by 48 hours in order to minimise carry-over effects. The duration of rTMS effects on motor symptoms is considered to outlast less than one hour after a single rTMS intervention (Edwards et al., 2008). Patients were naive to rTMS prior to the study and were unfamiliar with the differences between sham and active rTMS regarding its acoustic and tactile artifacts. Twenty intermittent trains of 40 pulses (800 stimuli), were delivered for each of the two rTMS conditions at 10 Hz and intensities of 90% of individual resting motor threshold (RMT). The duration of each train was of 4 seconds and the intertrain interval (ITI) was 30 seconds. The total duration rTMS was 10 minutes.

Transcranial magnetic stimulation

TMS was performed using a high-power Magstim-Rapid stimulator (Magstim, Whitland, UK). The rTMS was applied over the left or right primary motor cortex (M1) (in the proximity of the C3 or C4 electrode) simultaneously with EEG data collection. TMS was delivered through a figure-of-eight coil (70 mm standard coil; Magstim), oriented so that the induced electric current flowed in a posterior–anterior direction over the underlying motor cortex. The coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle away from the midline perpendicular to the line of the central sulcus

to achieve the lowest motor threshold. A sham rTMS condition was carried out to control for the air and bone-conducted auditory stimuli that could contaminate EEG oscillations in the target motor system. The sham rTMS condition was performed with the coil tilted at 90° to the skull in order to avoid real stimulation of the motor cortex.

Motor Evoked Potentials (MEPs) were recorded from the left or right thenar eminence (TE) muscle using Ag/AgCl surface electrodes in a bellytendon montage. The amplified and bandpass-filtered (50 Hz–5 kHz) EMG signal was fed into a Micromed Machine (Micromed, Treviso, Italy). The optimal position for right TE activation was determined by moving the coil in 0.5-cm steps around the motor hand area of the left or right motor cortex of the most affected hemisphere. The optimal position was defined as the site where stimuli of slightly suprathreshold intensity consistently produced the largest MEPs with the steepest negative slope in the target muscle (referred to as "motor hot spot"). The intensity of rTMS in all two conditions was set to 90% of individual RMT. The motor threshold, which reflects the global excitability of the corticospinal motor pathway, has been defined as the intensity of TMS that produces an identifiable MEP of ~50 μ V in at least five out of ten TMS pulses [46].

Electroencephalographic acquisition and analysis

Continuous EEG was recorded with a MR compatible EEG amplifier (SD MRI 32, Micromed, Treviso, Italy). The EEG signal was recorded from 19 Ag/AgCl electrodes sites. Electrode montage and placement was according to the International 10–20 system. According to the 10-20 system, the reference electrode was at AFz site, whereas the ground electrode was at FCz site as in previous studies using the same system [21, 28]. The impedance was kept below 10 k Ω . The activities in the right TE muscle and in the right eye vertical electroculogram (vEOG) were bipolarly registered from two surface electrodes in two EMG channels. To ensure the subjects' safety, the wires were carefully arranged to avoid loops and physical contact with the subject. To avoid electrical saturation of EEG channels

induced by TMS, the EEG amplifier had a resolution of 22 bits with a range of ± 25.6 mV. An anti-aliasing hardware band-pass filter was applied with a bandwidth between 0.15 and 269.5 Hz. EEG data were sampled at a frequency of 1024 Hz using the software package SystemPlus (Micromed, Treviso, Italy).

A re-reference off-line was obtained by the application of reference electrode standardisation technique (REST) in the study of EEG default mode network [47]. The EEG data were processed off-line using commercial software (Vision Analyser, Brain Vision, Munich, Germany). To demonstrate the rTMS effect on modulation of EEG oscillations, the following four pairs of homologous electrodes across hemispheres were selected for analyses: F3/F4, C3/C4, P3/P4 and O1/O2. The 120 seconds immediately before, immediately after, and 30 minutes after each 10 minutes brain stimulation of 20 intermittent trains of rTMS were considered for analysis. Two minutes of continuous data were divided into thirty consecutive, non-overlapping epochs of 4,096 data points. Subsequently, the data were digitally filtered with a band-pass of 1–46 Hz. Epochs with eye movements and muscle or movement artefacts (as indicated by HEOG activity exceeding ± 40 μ V and activity at other electrodes exceeding ± 70 μ V) were excluded. This resulted in the exclusion of ~ 7 epochs per rTMS condition (23% rejection rate). A discrete Fast Fourier Transform (FFT) of the remaining epochs with a resolution of 0.25 Hz was computed for all electrodes and then averaged. Non-overlapping hamming-windows controlled spectral leakage. The FFT power value measurements within each frequency between 2.0 and 45.75 Hz were averaged to create 44 non-overlapping < 1 Hz frequency bins. The relative power (which reduces the effect of inter-subject variation in absolute power) at each frequency bin was measured, by taking the absolute power at each bin divided by the sum of absolute power of all frequency bins over the entire frequency range (2.0-45.75 Hz) as in a previous study [32]. Using relative power rather than absolute power results in a lower variance of power values within subject

groups [7]. The α frequency band (8.00-12.75 Hz) of interest was chosen for statistical analyses and contained 5 frequency bins.

Statistical analyses

Data were analysed using SPSS for Windows version 20. First, we examined the effects of rTMS protocol on the overall motor performance in PD patients. Thus, a total score of the motor subscale of UPDRS was submitted to a repeated measures ANOVA with the factors: “rTMS condition” (Active rTMS and sham rTMS); and “Time of evaluation” (pre-stimulation, post-stimulation and 35 minutes post-stimulation). Second, to assess whether the rTMS artificially induced modulation of neural oscillations in the α frequency range in eyes-closed resting state, mean relative power values were submitted to four separate repeated measures ANOVA for frontal (F3/F4), central (C3/C4), parietal (P3/P4) and occipital (O1/O2) pairs of electrodes. Each ANOVA had the factors: “rTMS condition” (Active rTMS and sham rTMS); “Time of evaluation” (pre-stimulation, post-stimulation, and 30 minutes post-stimulation); and frequency bin (8.00-8.75, 9.00-9.75, 10-10.75, 11.00-11.75 and 12.00-12.75 Hz). For each ANOVA, the sphericity assumption was assessed with Mauchly’s test. Greenhouse-Geisser epsilon adjustments for non-sphericity were applied where appropriate. Post-hoc paired t-test adjusted for multiple comparisons with Bonferroni method was used. For all statistical tests, $p < .05$ was considered significant.

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Figures and tables legends

Table 1: Subject characteristics

Table 2: ANOVA statistical results of relative EEG power for frontal, central, parietal and occipital electrodes at α (8.00-12.75 Hz) frequency band

Figure 1: Total UPDRS III score before and after each type of rTMS intervention. Values are presented as mean (\pm SEM). Active rTMS improved overall motor performance 35 minutes post stimulation relative to Sham rTMS. ** $p < .01$; Bonferroni corrected.

Figure 2: Superimposition of mean (\pm SEM) relative power transformation from 2 to 29.75 Hz averaged over central electrodes. Active rTMS at 10 Hz, but not 'sham' stimulation, induced a power increase 30 minutes post brain stimulation within the α (8.00-12.75 Hz) frequency with a shift of dominant frequency α peak towards higher frequencies. * $p < .05$; Bonferroni corrected.

Table 1. Subject characteristics

	Parkinson 's disease patients (N=15)
Age (years, mean \pm SD)	64.1 \pm 12.6
Gender (σ / ρ)	13/2
MMSE (mean \pm SD)	27.7 \pm 2.8
Side of onset (left/right)	9/6
Disease duration (years, mean \pm SD)	4.9 \pm 3.4
H and Y modified "OFF" (1/1.5/2/2.5/3)	2/5/4/1/3
UPRS-III "OFF"(mean \pm SD)	14.0 \pm 6.5
Stimulation side (left/right)	8/7

MMSE= The Mini Mental State Examination, H and Y modified=modified version of the Hoehn and Yahr rating scale, UPDRS-III=motor part of the Unified Parkinson's Disease Rating Scale.

Table 2. ANOVA statistical results of relative EEG power for frontal, central, parietal and occipital electrodes at α (8.00-12.75 Hz) frequency band.

Effect	Frontal	Central	Parietal	Occipital
Time	F(2,28)=4.3, *, $\eta^2p = .24$	F(2,28)=1.4, p = ns, $\eta^2p = .09$	F(2,28)=5.3, *, $\eta^2p = .27$	F(2,28)=2.3, *, $\eta^2p = .14$
rTMS condition	F(1,14)=0.0, p = ns, $\eta^2p = .00$	F(1,14)=0.2, p = ns, $\eta^2p = .02$	F(1,14)=0.2, p = ns, $\eta^2p = .01$	F(1,14)=0.0, p = ns, $\eta^2p = .00$
Frequency bin	F(1.7,24.5)=6.9, **, $\eta^2p = .33$	F(1.7,23.6)=5.8, *, $\eta^2p = .29$	F(2.0,28.2)=4.3, *, $\eta^2p = .23$	F(1.8,25.9)=6.0, **, $\eta^2p = .30$
Time * rTMS condition	F(1.2,16.5)=0.1, p = ns, $\eta^2p = .01$	F(1.2,17.2)=0.1, p = ns, $\eta^2p = .01$	F(2,28)=0.1, p = ns, $\eta^2p = .01$	F(1.2,16.6)=0.0, p = ns, $\eta^2p = .00$
Time * frequency bin	F(3.4,48.4)=2.8, *, $\eta^2p = .16$	F(3.5,48.8)=1.4, p = ns, $\eta^2p = .09$	F(3.6,51.0)=1.4, p = ns, $\eta^2p = .09$	F(4.1,57.9)=3.1, *, $\eta^2p = .18$
Condition * Frequency bin	F(2.3,32.3)=0.5, p = ns, $\eta^2p = .04$	F(2.0,28.5)=0.5, p = ns, $\eta^2p = .03$	F(4,56)=0.1, p = ns, $\eta^2p = .00$	F(2.5,35.6)=0.2, p = ns, $\eta^2p = .02$
Time * rTMS condition * frequency bin	F(3.1,42.8)=0.5, p = ns, $\eta^2p = .07$	F(2.7,38.1)=3.4, *, $\eta^2p = .20$	F(4.3,60.8)=2.1, p = ns, $\eta^2p = .13$	F(3.1,43.9)=0.8, p = ns, $\eta^2p = .05$

ns — non-significant. Significant main effect of TMS condition is indicated in bold.

* $p < .05$, ** $p < .01$.

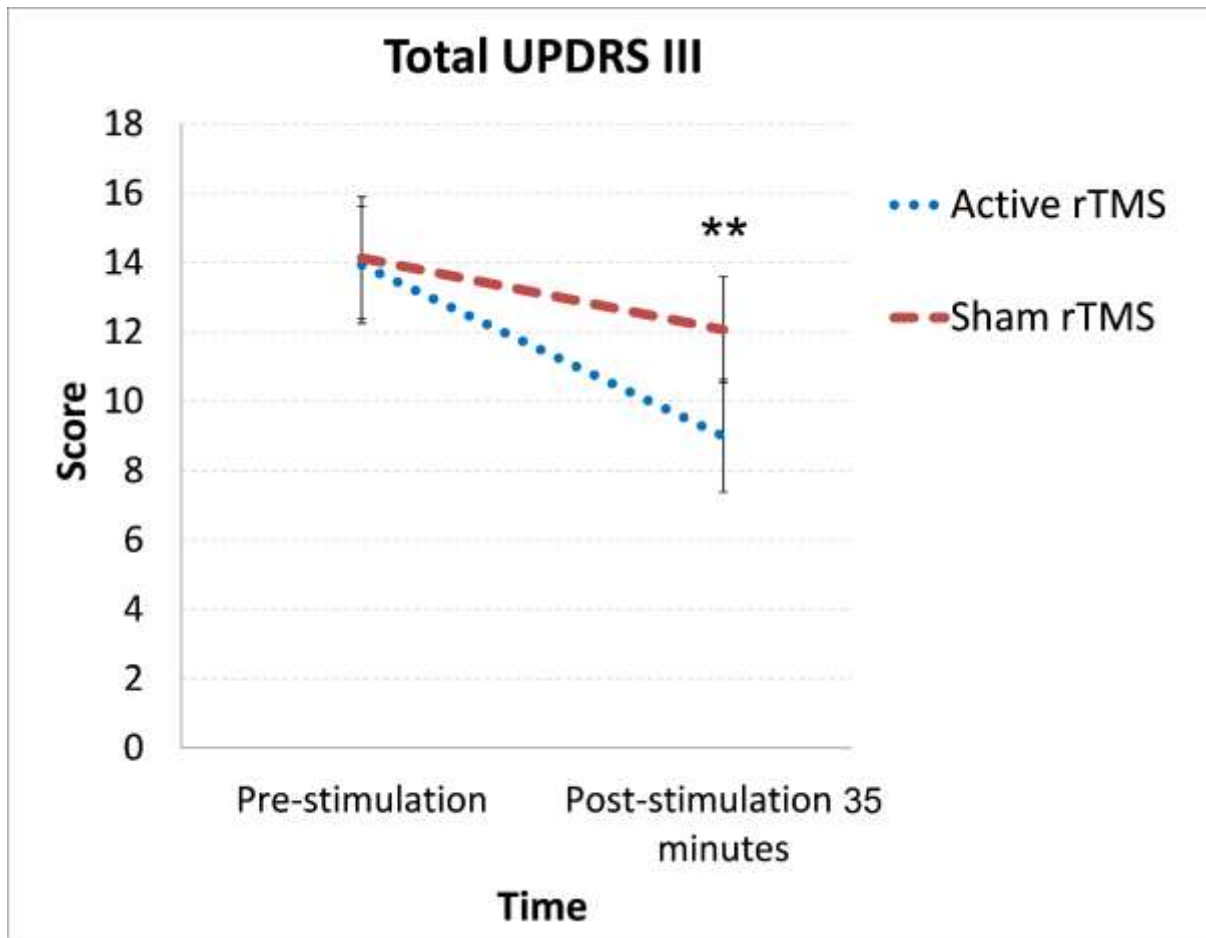


Figure 1.

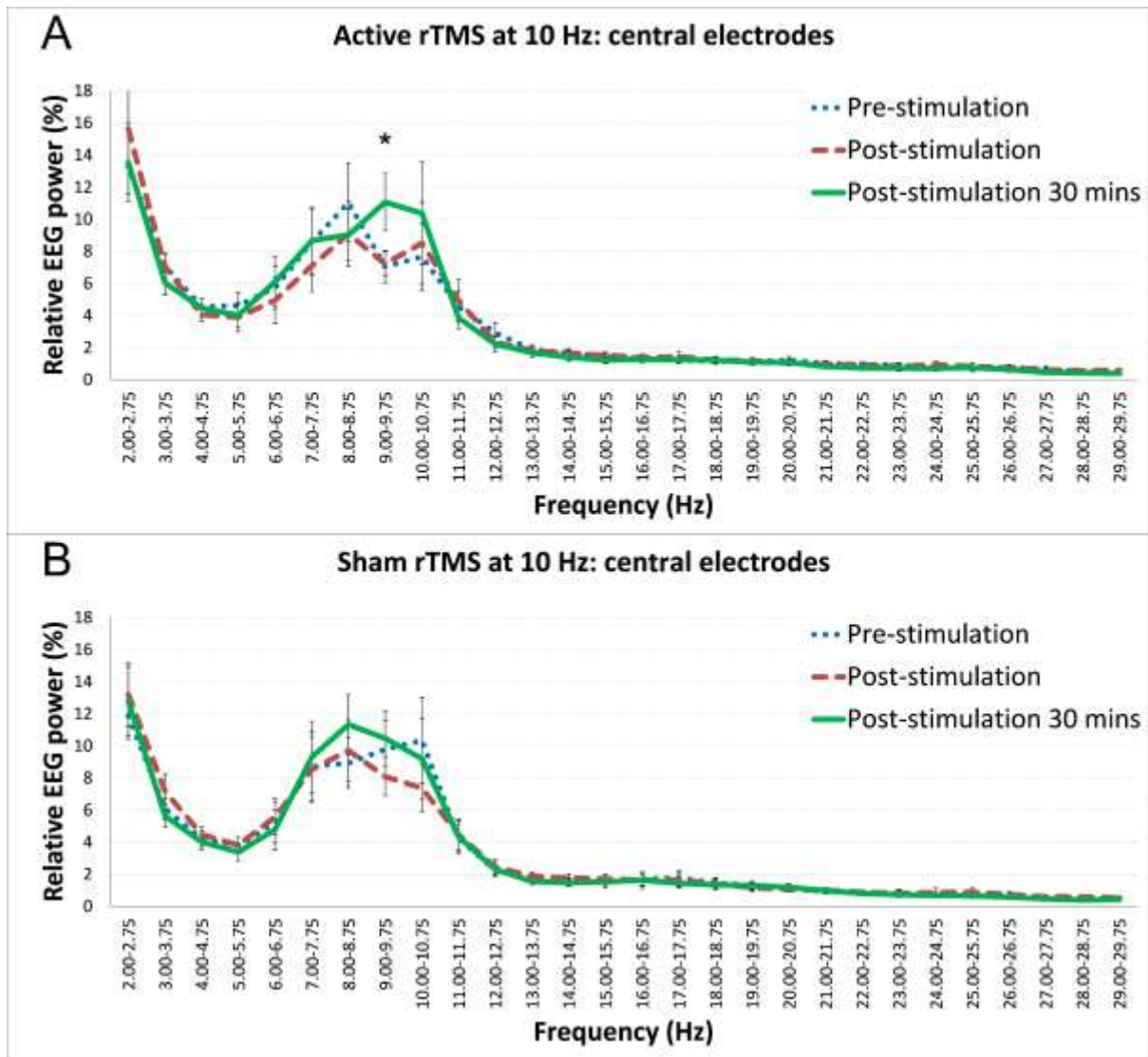


Figure 2.