

Research paper

Low-frequency rTMS over the Parieto–frontal network during a sensorimotor task: The role of absolute beta power in the sensorimotor integration



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HIGHLIGHTS

- Electrophysiological rTMS-induced changes of beta power at rest and during a visuomotor task.
- Changes of absolute beta power patterns in the parietal–frontal circuit.
- To better understand the reorganization and neural plasticity mechanisms in the parieto–frontal network during the sensorimotor integration process.

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ABSTRACT

Several studies have demonstrated that Repetitive Transcranial Magnetic Stimulation (rTMS) promotes alterations in the Central Nervous System circuits and networks. The focus of the present study is to examine the absolute beta power patterns in the Parieto–frontal network. We hypothesize that rTMS alters the mechanisms of the sensorimotor integration process during a visuomotor task. Twelve young healthy volunteers performed a visuomotor task involving decision making recorded (Catch a ball in a free fall) by Electroencephalography. rTMS was applied on the Superior Parietal Cortex (SPC; Brodmann area [BA] 7) with low-frequency (1 Hz – 15 min – 80% Resting Motor Threshold). For each Frontal and Parietal region, a two-way ANOVA was used to compare the absolute beta power before and after TMS for each condition of the study (Rest 1, Task and Rest 2). The results demonstrated interactions (TMS vs. Condition) for the Frontal electrodes: Fp1, Fp2 and F7 and an effect of TMS (before and after) for F4. The results for the Parietal region showed a main effect of Condition for the P3, P2 and P4 electrodes. Thus, our paradigm was useful to better understand the reorganization and neural plasticity mechanisms in the parieto–frontal network during the sensorimotor integration process.

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1. Introduction

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive method consisting in inducing repeated pulses which can

be used to promote a temporary functional interference at the site of its application [1,2]. Besides the focal effects, studies applying low-frequency rTMS reported modulation of neural activity [3] and task performance subtended by the stimulated region and other regions connected to the target one [4,5]. It is generally accepted that Parietal and Frontal regions are strongly interconnected comprising a neural network involved in the decision making process during visuomotor tasks [6–8]. In order to visualize the possible interferences of rTMS and their propagation resulting from the

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stimulation in areas anatomically connected to the target region, researchers have been using TMS combined with quantitative electroencephalography (qEEG) [9,10]. These integrated tools are useful to understand the reorganization and neural plasticity mechanisms during the decision making process of the sensorimotor tasks [11,12].

In the current study, we seek to investigate the alterations provoked by low-frequency rTMS on the sensorimotor integration process. We utilized a task in which individuals had to identify visual stimuli and make a decision, catch a ball in free fall or maintain the hand closed; such task was already used in other studies from our laboratory, and it allowed observing the sensorimotor integration process from a visual-motor perspective [13–15]. In this context, we investigate the changes in the absolute beta power in the stimulated region and in the Frontal areas. We hypothesize that rTMS alters the mechanisms of the sensorimotor integration process. In an attempt to test this hypothesis, we created a temporary and transient modulation, in a region classically known as a cortical area responsible for integrating different sensory information. Specifically, we tested the beta band absolute power alterations in distinct cortical regions after applying 1 Hz rTMS. We decided to choose beta, since this oscillatory activity has been investigated in studies which associate it with sensory and motor process in the Parietal and Frontal regions during decision making tasks [16] and due to few studies discuss the effects of TMS on motor tasks through beta observation, especially in decision-making situations [17,18]. With regards to the initial question, our task had required the participants to make a decision, expressed in the GO/NOGO paradigm.

2. Materials and methods

Twelve healthy, right-handed volunteers of both sexes (4 males, 8 females; mean age 24 ± 2 years), with normal or corrected-to-normal vision and no history of psychiatric or neurological disorders participated in the experiment. The Edinburgh inventory was applied to identify the hand laterality [19] and the Screening questionnaire for Transcranial Magnetic Stimulation was employed to verify if subjects had contraindications to receive TMS [20]. The study was approved by the Ethics Committee of the Federal University of Rio de Janeiro. Written informed consent was obtained before the start of the experiment, according to the Declaration of Helsinki.

The experimental procedure was performed in a sound-protected and light-attenuated room, to minimize sensory interference. Subjects were seated on a comfortable chair and, during the execution of the task; the right arm was resting on a pedestal, to minimize muscular artifacts. The study consisted of seven stages. In the first, third, fifth and seventh stages, qEEG signal were acquired at rest for 3 min. In these stages the subjects were instructed to keep still and keep their eyes open. In the second and sixth stages, the visuomotor task was executed with simultaneous qEEG collection in 4 blocks of 20 trials each (10 'GO' and 10 'NOGO'). In the fourth stage, TMS was applied for 15 min without qEEG recording. Timeline of Experimental design: Rest 1 before rTMS (3 min); time lag between Rest 1 and task (2 min); task ($4 \times 4.67 - 18.68$ min); time lag between task and Rest 2 (~ 2 min); Rest 2 before rTMS (3 min); TMS procedures (~ 10 min); rTMS application (15 min); time lag between rTMS application and Rest 1 after rTMS (~ 2 min); Rest 1 after rTMS (3 min); time lag between Rest 1 and task (~ 2 min); task ($4 \times 4.67 - 18.68$ min); time lag between task and Rest 2 (~ 2 min); Rest 2 after rTMS (3 min).

Catching a ball in a free fall is a visuomotor task designed by our laboratory, consisting of an electromagnetic system composed by two tennis-ball releasing solenoids placed in front of the subjects,

so that the balls were released at 80 cm above the floor, straight onto the subject's right hand. Light-emitting diodes (LED) coupled to the system issued three kinds of visual stimuli at eye level. The first LED (blue color) blinked for 400 ms as a cue (S1), an attention signal. After an inter-stimuli break of 2-sec, the next LED was lit up 3 sec in one of two colors, representing the stimuli 'GO' or 'NOGO' (S2–green and red, respectively). If 'GO' appeared on the screen, a ball was instantaneously released, and subjects were instructed to open their right hand and catch the falling ball. If 'NOGO' appeared, the ball was not released and the subjects were instructed to maintain the hand closed. The exhibition of 'GO' and 'NOGO' stimuli was randomized; each of them accounted for 50% of all trials within each block of the study.

TMS pulses were delivered through a figure-eight air cooled coil with a 70-mm diameter connected to a Neuro-MS Stimulator (made by Neurosoft medical equipment, Brazil). Prior to the rTMS session, we determined the Resting Motor Threshold (RMT) for each subject. TMS single-pulses around 40% of the stimulator intensity were initially applied on the motor cortex [21]. We moved the coil around this reference point, corresponding to approximately 5 cm on the left of the vertex, in order to find the stimulation that would elicit Motor Evoked Potentials (MEPs) in the right Abductor Pollicis Brevis muscle (APB) recorded by electromyography (EMG). The TMS stimulator intensity was gradually increased by 5% steps until we recorded at least 5 of 10 consecutive MEPs with a peak-to-peak amplitude of at least $50 \mu\text{V}$ [21]. We chose to apply 80% of each subject's RMT ($\bar{X} = 47.4$; $\text{SD} = 9.41$), since this intensity has been used in several studies as a safety measure to avoid seizures [21].

The Superior Parietal Cortex (SPC) was the brain area selected to receive the rTMS. The SPC has been associated with the initial stage of the sensorimotor integration process, which encodes exteroceptive information and sends them to Frontal regions that will create the motor plans [22,23]. The SPC was localized using the correspondence of the Pz electrode (10–20 EEG system). The coil was stabilized and immobilized by a mechanical support, a 3D articulated arm. The orientation of the coil was along the rostro-caudal axis, with the handle pointing caudally [23]. During 15 min, wearing earplugs for their hearing protection, subjects received TMS stimulation with low-frequency (1 Hz).

Data was acquired at rest and during the visuomotor task through the International 10/20 system for electrodes [24], using a 20-channel Braintech-3000 EEG system (EMSA-Medical Instruments, Brazil). The 20 electrodes were arranged on a nylon cap (ElectroCap Inc., Fairfax, VA, USA), yielding mono-pole derivations to linked earlobes, set as reference points. In addition, two 9-mm diameter electrodes were attached above and on the external corner of the right eye, in a bipolar electrode montage, in order to monitor artifacts on eye-movements (EOG). Impedance of EEG and EOG electrodes was kept below $5 \text{K}\Omega$. The data acquired had total amplitude of less than $100 \mu\text{V}$. The EEG signal was amplified, with a gain of 22,000, analogically filtered between 0.01 Hz (high-pass) and 100 Hz (low-pass), and sampled at 240 Hz. The software Data Acquisition (Delphi 5.0), developed at the Brain Mapping and Sensorimotor Integration Laboratory, was employed to filter the raw data: notch (60 Hz), high-pass of 0.3 Hz and low-pass of 100 Hz.

In order to quantify artifact-free data, a visual inspection and Independent Component Analysis (ICA) were applied to identify and remove possible sources of artifacts produced by the task, i.e., eye blinks and ocular movements [25]. Using this technique, the signal was decomposed into statistically independent components, and the most artifact-resembling components were removed. Data from individual electrodes exhibiting loss of contact with the scalp or high impedances ($> 10 \text{k}\Omega$) were not considered. The ICA-filtered data were re-inspected for residual artifacts. The mean and SD of the eliminated components were: mean: 3.2813; SD: 0.829. A classic estimator was applied to the Power Spectral Density (PSD),

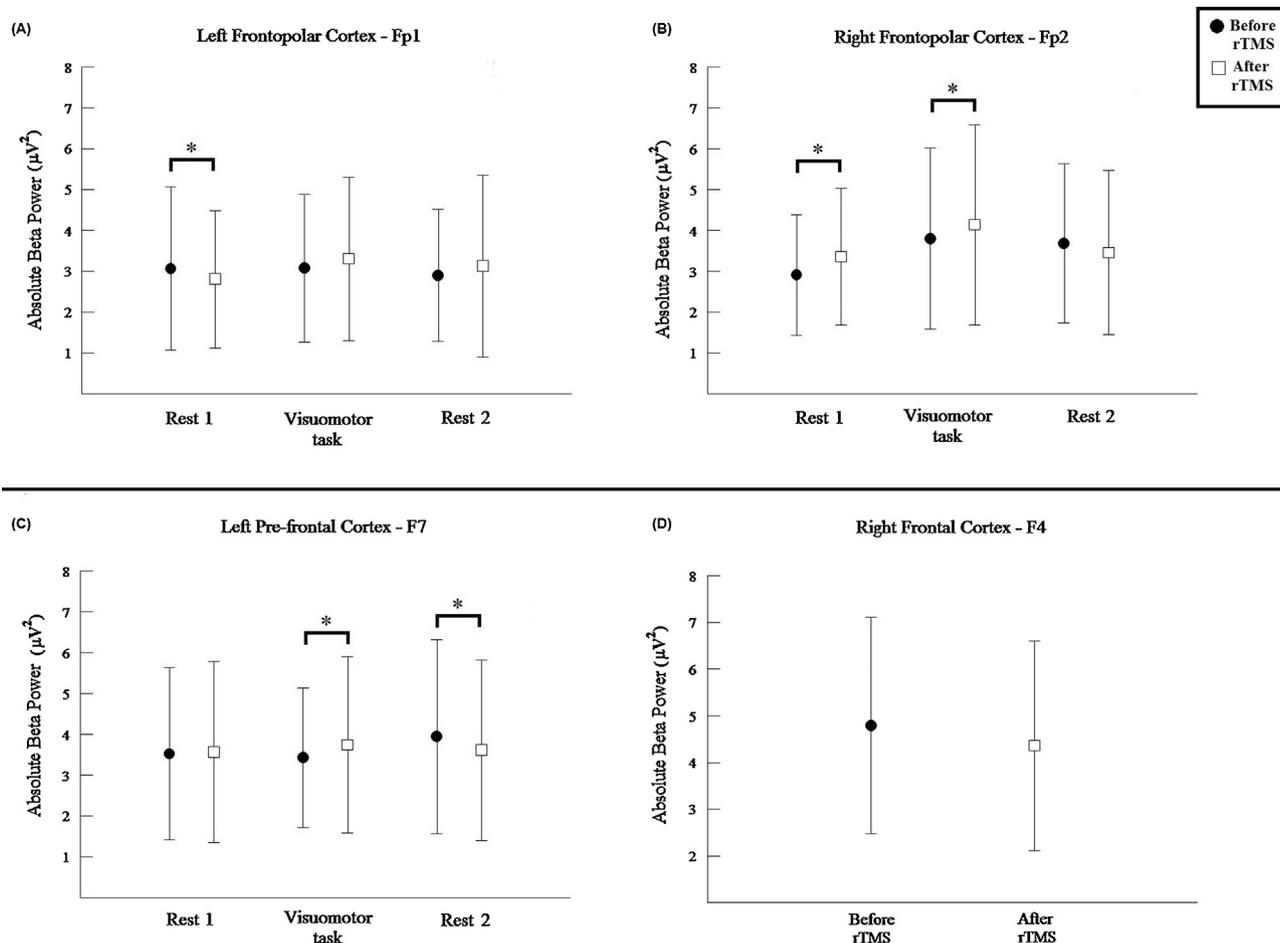


Fig. 1. Electrodes of the Frontal region: (A–C) Mean and Standard Deviation of absolute beta power for interaction between TMS (Before and After) and Condition (Rest 1, task and Rest 2); (A) Electrode Fp1 ($p \leq 0.0166$); (B) Electrode Fp2 ($p \leq 0.0166$); (C) Electrode F7 ($p \leq 0.0166$). (D) Mean and Standard Deviation of absolute beta power for main effect of TMS for electrode F4.

estimated directly from the square modulus of the FT (Fourier Transform), which was performed by MATLAB (Matworks, Inc.). Quantitative EEG parameters were reduced to 4 sec periods for the visuomotor task stages, and the selected epoch started 2 sec before and ended 2 sec after the trigger (markings of the S2 stimulus trigger). The time before was related to the task preparation, and the time after was associated with the action of catching a falling ball.

The statistical analysis of absolute beta power was performed using a two-way repeated measure ANOVA with two factors: TMS (Before and After) and Condition (Rest 1, Task and Rest 2) for each electrode of the Frontal (Fp1, Fp2, F7, F8, F3, Fz and F4), and Parietal (P3, Pz and P4) cortex. Correction for multiple comparisons was performed using the Bonferroni method ($p \leq 0.05/3 = 0.0166$). All conditions were experimented during each TMS modalities. When an interaction between factors was found, a paired *t*-test was performed aiming to compare the TMS (before and after) within each condition. Furthermore, a Post hoc *Scheffé* test was applied when it was necessary ($p \leq 0.05$). The PASW Statistics 18 system was used to analyze the data, the spreadsheet was composed by 3186 cells.

3. Results

In the Frontal cortex, we found an interaction (i.e., TMS vs. Condition) for the electrodes: Fp1 ($F_{(2)} = 5.227$; $p = 0.005$); Fp2 ($F_{(2)} = 7.514$; $p = 0.001$) and F7 ($F_{(2)} = 5.673$; $p = 0.003$) and a main effect for TMS (before and after) for the electrode F4 ($F_{(1)} = 26.075$; $p = 0.000$). The F8, F3, and Fz electrodes did not show any signifi-

cant interaction among the factors or other main effect for TMS or Condition.

The Fp1 and Fp2 electrodes (i.e., the frontopolar cortex) showed difference between TMS modalities at different conditions (see Fig. 1A, B). The inspection of the interaction for the Fp1 electrode showed a significant difference only at Rest 1 ($p = 0.032$). The absolute beta power decreased after TMS when compared to before TMS modality. Differences were found for the Fp2 electrode at Rest 1 ($p = 0.000$) and Task ($p = 0.015$) conditions; we identified an absolute beta power increase for both conditions after TMS when compared to before TMS. The electrode F7 (i.e., left lateral Frontal cortex) (see Fig. 1C) showed differences between before and after TMS for Task ($p = 0.007$) and for Rest 2 ($p = 0.034$) conditions. Absolute beta power increased during the task execution, however, at Rest 2, absolute beta power decreased after TMS. In the Frontal cortex (F3 and F4), only the Right Frontal cortex (F4) demonstrated significant results (see Fig. 1D), with a main effect of TMS. This result demonstrates an absolute beta power decrease after rTMS application.

In the analysis of the SPC, we found a main effect of condition for the P3 ($F_{(2)} = 6.718$; $p = 0.001$); the Pz ($F_{(2)} = 8.614$; $p = 0.000$) and P4 ($F_{(2)} = 5.037$; $p = 0.007$) electrodes. The Post hoc *Scheffé* results demonstrated that, for the P3 electrode, Rest 1 was different from task ($p = 0.024$) and task was different from Rest 2 ($p = 0.003$); for the Pz electrode, Rest 1 was different from task ($p = 0.029$) and task was different from Rest 2 ($p = 0.000$) and for the P4 electrode, task was different from Rest 2 ($p = 0.007$) (see Fig. 2A–C). These results

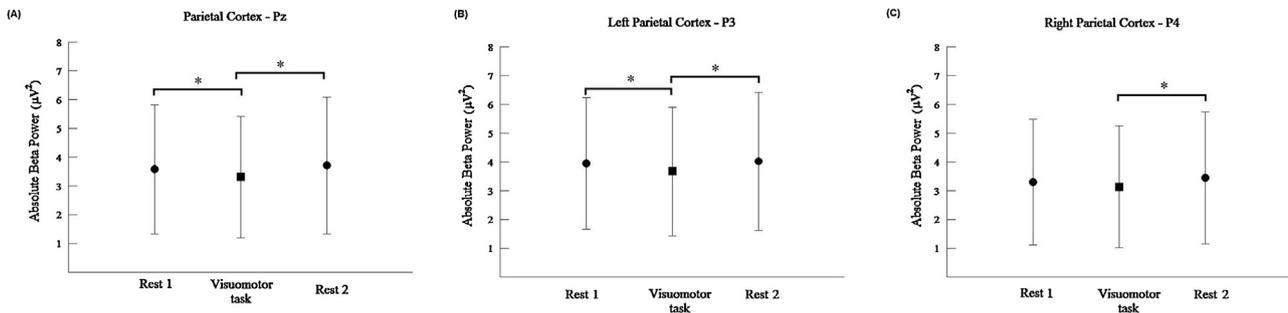


Fig. 2. Electrodes of the Parietal region: Mean and Standard Deviation of absolute beta power for main effect of Condition (rest 1 vs. task vs. rest 2): (A) Electrode Pz ($p \leq 0.0166$); Post hoc Scheffé: Rest 1 vs. task ($p = 0.029$); task vs. Rest 2 ($p = 0.000$); (B) Electrode P3 ($p \leq 0.0166$); Post hoc Scheffé: Rest 1 vs. task ($p = 0.024$); task vs. Rest 2 ($p = 0.003$); (C) Electrode P4 ($p \leq 0.0166$); Post hoc Scheffé: task vs. Rest 2 ($p = 0.007$).

of all Parietal electrodes, evidenced a decrease of the absolute beta power, for the condition related to the task execution, when compared with other conditions.

4. Discussion

The aim of the current study is to investigate the rTMS induced modulations of Parietal and Frontal beta activity at rest and during a task involving catching a free falling ball. We hypothesized that rTMS alters the mechanisms of the sensorimotor integration process during a catching task. The electrophysiological changes of each significant Frontal and Parietal electrodes were highlighted, shedding light on how these areas work when they are under rTMS influence.

The Frontopolar region is related to the use of superior executive functions, such as planning, problem solving, logic reasoning and fact retrieval by the episodic memory, when executing several cognitive paradigms [26]. We found a beta power decrease after TMS for the left region and a beta power increase for the right region at Rest 1. There are two possible explanations for differences in the frontopolar regions. First, association with rTMS, this can be related to the inhibitory effects produced by lower TMS frequency, showing that application provoked changes in regions behind the target region; Second, specificity of right hemisphere's features due to the Fp2 electrode still had presented differences during the task execution. The beta power increase suggests an engagement of the right region during the task after rTMS. This finding indicates that the right hemisphere participates more effectively in visuo-spatial information. The study of Corballis [27] highlights that the right hemisphere process related to perception and spatial patterns is higher than the left hemisphere. According to Hamidi et al. [16], this can be explained because of the right hemisphere dominance for spatial information storage and for perceptual functions associated with this hemisphere and with Parietal region.

However, the main effect of TMS for the F4 electrode, demonstrated a decrease in beta power after rTMS. Such decrease in the right hemisphere could be associated with the specificity of task execution, in other words, during the ball catch, the lateral prefrontal cortex responds according to the demands of visual spatial features of the sensorimotor task. Due to this region is related to executive and motor functions [33,34], beta decrease could be related to the fact that after rTMS, the subjects performed the task again.

Furthermore, during the visuomotor task, catching a ball in a free fall, the right and left lateral prefrontal regions exert different functions. We only observe absolute beta power modifications in the left lateral prefrontal region. Niedermeyer and Silva [28] highlight that the lateral prefrontal region receives temporal influences, arising from anterior regions, related to the supply of multimodal sensory information to the voluntary movement execution. Badre and

Wagner [29] and the O'Reilly [30] studies point out that the lateral prefrontal cortex and other lateral regions compose a neural network that is associated with information coming from the posterior regions related to action plans [14,17]. Moreover, for F7 electrode, we observed an absolute beta power differentiation between before and after TMS modalities during the task and at Rest 2. This means that, when subjects were under the TMS effects, the left prefrontal cortex increased its activity in order to execute the task. According to the Woźniak-Kwaśniewska et al. [31] study, TMS applied on the Dorsolateral Prefrontal Cortex (DLPFC) with four different active rTMS protocols (1 Hz, 10 Hz, continuous and intermittent theta bursts—cTBS and iTBS) and a sham protocol showed a decrease in beta and gamma power in the prefrontal cortex. This reduction of beta power was associated with the type of protocol applied and, as a consequence, could be observed in the left or right side, or even bilaterally. Source location revealed a DLPFC deactivation bilaterally, i.e., low beta with 1 Hz and iTBS; high beta with 1 Hz, iTBS and cTBS. Such beta power findings were interpreted as a reduction of inhibitory mechanisms associated with DLPFC. These data are in agreement with our results with relation to power reduction of higher frequencies. These frequencies (20–80 Hz) are correlated to local transmission inhibitory processes, especially through rapid cells activity that affect excitatory pyramidal neurons [32]. Therefore, a higher activated reduction localized in the F7 region may suggest a decrease in cortical inhibition. The beta power increase after TMS showed that the left region is involved during task execution. Thus, when subjects were under the TMS effects, the left prefrontal cortex activity increased.

In the Parietal regions, we found a main effect for condition in all electrodes (P3, Pz and P4). These patterns of results show changes among conditions, indicating that each electrode presented a different beta activity pattern. The absolute beta power was different between rests (i.e., Rest 1 and 2) and the visuomotor task condition for P3 and Pz. We found a beta power decreased when subjects executed the motor task, and returned to the same pattern of the first rest condition after the task execution. P4 electrode differently, only presented differences between task and rest 2. Oliveira [23] highlights left and right Parietal differences, such as the left side involved in action planning for both hands and the right side related only to the contralateral hand. However, our results demonstrated that both regions participated equally in the visuomotor execution, and that they are capable to return to the same rest pattern.

In this study, we sought to elucidate the electrophysiological changes in the Parietal and Frontal regions during a sensorimotor integration task before and after applying low-frequency rTMS. These regions work together as a neural network for sensorimotor transformation, which is essential for action planning and motor behavior. Our paradigm was useful to better understand the reorganization and neural plasticity mechanisms in the parieto-frontal network during the sensorimotor integration process. This was

confirmed by our results through the absolute beta power, which showed interferences in both regions. Another important factor of the study was related to the frequency of beta and its key role in a task sensorimotor integration. The low-frequency rTMS of the parietal region was capable to promote changes during the task execution. Thus, the paradigm developed by our laboratory is an interesting tool that integrates visuo-motor components with a possibility to manipulate different areas during a functional task, proving to be an exploratory tool capable of understanding the brain function in the sensorimotor integration process.

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