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ORIGINAL ARTICLE

The role of low-frequency rTMS in the superior parietal cortex during time estimation

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Abstract
The low-frequency repetitive transcranial magnetic stimulation (rTMS) application has been associated with changes in cognitive processes embedded during time perception tasks. Although several studies have investigated the influence of neuromodulation on time perception, the effect of the 1-Hz rTMS application on the superior parietal cortex is not clearly understood. This study analyzes the effect of the low-frequency rTMS on time estimation when applied in the parietal medial longitudinal fissure. For the proposed study, 20 subjects were randomly selected for a crossover study with two conditions (sham and 1 Hz). Our findings reveal that participant underestimate 1-s time interval and overestimate 4-s and 9-s time intervals after 1-Hz rTMS ($p \leq 0.05$). We conclude that the 1-Hz rTMS in the parietal medial longitudinal fissure delays short interval and speed up long time intervals. This could be due to the effect of parietal inhibition on the attentional level and working memory functions during time estimation.

Keywords Time perception · Time estimation · Superior parietal cortex · Transcranial magnetic stimulation

Introduction

For humans to estimate the time interval, dynamic interactions of the central nervous system to process and interpret temporal events in the environment are necessary [1–3]. In this case, encoding temporal information about environment involves both cognitive and sensory integration process [4, 5], which requires a complex mechanism of neural oscillations, which synchronized the cortical inputs during the time-interval interpretation [6–8]. Although few studies have analyzed the superior parietal cortex (SPC) association parameters in time estimation by cortical inhibition using repetitive transcranial magnetic stimulation (rTMS), the rTMS neuromodulation effect has been observed when applied in the SPC with association between them [9–12].

Although there are no specific regions to estimate time intervals, there is a cortical and subcortical region synchronism at time scales from milliseconds to hours [13, 14]. In particular, the SPC associated with the frontal cortex (frontoparietal circuit) acts in the supra-temporal timing [15], due to its role in attentional modulation, decision making, stimulus perception, and sensorimotor integration [16]. For instance, studies by Coull, Cheng, and Meck [14] and Barzman, Geise, and Lin [17] have shown that the SPC function is essential in the time interval interpretation in visual tasks with explicit durations. They suggest a functional role based on the synchronization of planning processes and the perceptive capacity of stimuli through cognitive tasks, which

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have been evidenced by neuroimaging, neuropsychological tests, and psychopharmacological investigations in humans [13, 18, 19]. In addition, Vicario, Martino, and Koch [10] have investigated the SPC activity in both brain hemispheres of healthy individuals, during time perception task execution by employing rTMS. The results evidenced that the cortical inhibition in the right SPC produces overestimation, due to neuromodulation in the cognitive demand during the task execution [20]. Interestingly, Gongora et al. [21] observed that rTMS applied on the SPC may modify the interpretation and judgment during the visuomotor cognitive tasks. The present study has the aims to analyze the effect on time interval interpretations after low-frequency rTMS applied in the parietal medial longitudinal fissure, corresponding to the Pz electrode reference according to the 10–20 system of the electroencephalography.

Materials and methods

Subjects

For this study, 20 healthy participants (24 ± 1.2 years, age group = 20–30 years), all right-handed (Edinburgh Handedness Inventory) [22] were selected. This study had a randomized, double-blind, crossover design with a 1-day treatment period (1 Hz or sham). Subjects were randomly selected for each condition: in one group, we first applied active stimulation (1-Hz condition) followed by sham stimulation and in the other group, we applied sham stimulation (control condition) followed by active stimulation. We provided a detailed questionnaire to exclude those subjects with self-reported mental or physical illness, low visual acuity, orthopedic problems, tremors, and those who used any psychoactive or psychotropic substance during the study period.

The subjects also completed the rTMS screening questionnaire to identify conditions that could represent a risk factor for adverse effects [23]. We excluded the subjects with one or more positive responses in the screening. Subjects signed the free and informed consent term. The ethics committee of the Federal University of Rio de Janeiro approved the protocol for the study (no. 520.189).

Experimental procedure

(1) Randomization: Subjects were randomly selected for one of two conditions with wash-out phase of 4 days: the first received active stimulation of 1 Hz and the other one received simulated stimulation in SPC; (2) Participants stayed in a sound and electrical insulation room; (3) Experimental procedure: 1-Hz rTMS or sham stimulation was applied for 15 min. Execution of the time estimation task in both conditions. A 20-in. monitor was positioned on a table in front of the individuals, and it was turned on only during task execution, with four time intervals presented randomly, with 2 blocks of 40 repetitions each, and 3-min intervals between blocks (Fig. 1).

Time estimation task

A 20-in. monitor was placed in front of the subjects at a distance of 70 cm and was turned on only during the task. We analyzed the time estimation using a program that records the displayed time interval (i.e., 1 s, 4 s, 7 s, or 9 s) [24, 25]. We performed the task in two phases: in the first, the display shows the command “enter” to start, then, the program produces a yellow circle in the monitor center that is displayed randomly for 1 s, 4 s, 7 s, or 9 s. In the second, the software displays an empty field on the monitor to enter the estimated time interval, and then the subject presses the “enter” key to complete the task (Fig. 2). Each subject performed 2 task blocks with 40 trials per block.

Behavioral analysis

We analyzed the time estimation in both conditions (sham and 1 Hz). A software registered the time intervals (i.e., 1 s, 4 s, 7 s, or 9 s), and marked time estimation by the subject (the difference between the exhibited time and the time estimation).

We transformed the behavioral variable into measures representing the estimated proportion of target duration [26]. The ratio of target duration estimation was calculated by dividing the estimated time by the presented target duration for each task. This analysis is similar to the relative error (RE), and a coefficient below 1.0 indicates that estimated time is less than the real time, while the opposite represents the estimated time longer than the real duration, an underestimation or overestimation of time, respectively [26, 27].

rTMS protocol

The rTMS pulses were emitted through an eight-shaped coil having a diameter of 70 mm connected to a Neuro-Ms Stimulator (Medical Equipment manufactured by Neurosoft, Russia). First, before the rTMS session, the resting motor threshold (rMT) was defined for each individual as the lowest stimulus intensity that promoted motor evoked potentials (MEPs) with a peak-to-peak amplitude of more than 50 μV [21]. To determine the amplitude required for the rTMS use, the coil was directed with the cable back to 45°. rTMS single-pulse around 40% of the stimulator intensity was initially applied on the motor cortex [28]. The coil was moved around this reference point, corresponding to approximately 5 cm on the left of the vertex (i.e., electrode C3 of the 10-20 EEG system), to locate what would stimulate MEP in the right

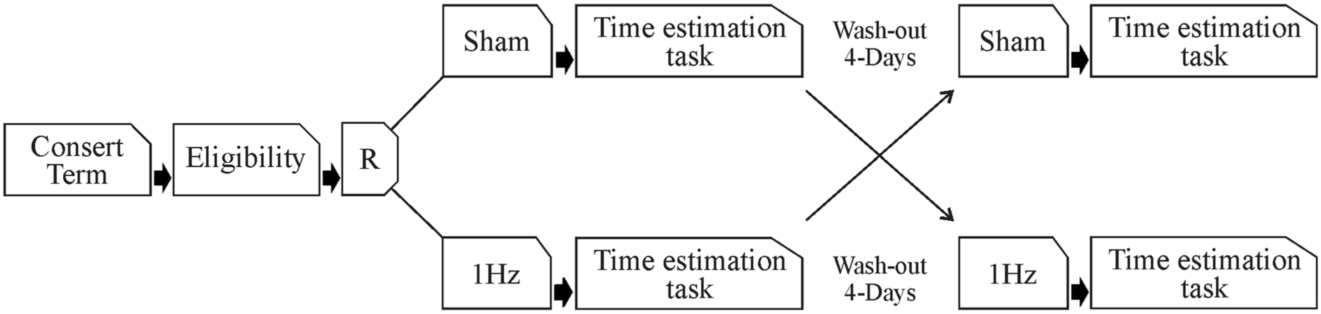


Fig. 1 Participants signed consent form and were selected based on the eligibility criteria. They were randomized to sham or 1-Hz condition in which they performed the experimental procedure, and with wash-out phase of 4 days between conditions

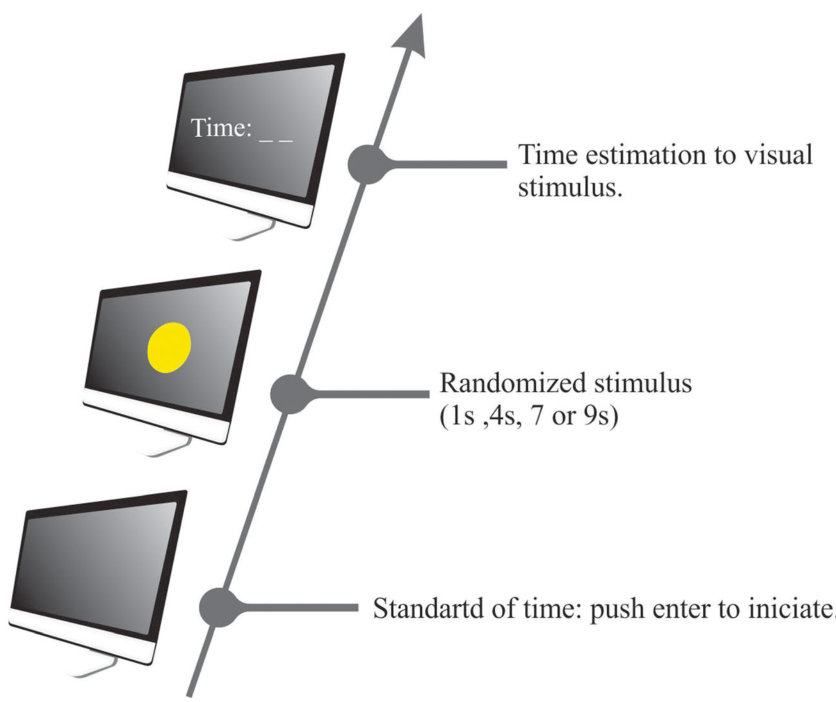
abductor pollicis brevis muscle recorded by electromyography. The stimulator intensity was gradually increased to register at least 5 of 10 consecutive MEPs. After finding the rMT for each subject, this measure was used as a reference to calculate the stimulation intensity with rTMS. Eighty percent of the rMT was applied (mean = 46.2, SD = 9.12) since this intensity has been used as a safety measure to avoid seizures [29, 30] and but it has neuromodulatory effects [21, 31].

The rTMS application in SPC was localized using the Pz electrode correspondence (EEG system 10–20) [32, 33]. The SPC was chosen due to its association with spatial attention since it correlates spatial changes between an original target and new location points proposed by this target [34]. The coil was stabilized and immobilized by a mechanical support, an articulated 3D arm. The coil orientation was along the rostrocaudal axis, with an angulation of 45 degrees. All subjects used ear protectors. We applied a series of 900 stimuli at the rate of 1 Hz lasting 15 min on the experimental condition [35]. For the control condition (sham rTMS), sham coil replaced the coil used to apply rTMS 1 Hz. Sham coil produced sounds and vibrations, mimicking the physical effects of rTMS without a magnetic field [36].

Statistical analysis

We conducted two-way repeated measures ANOVA with experimental conditions (sham and 1 Hz) and time (1 s, 4 s, 7 s, and 9 s) in order to understand the low-frequency rTMS during a time estimation task effect. We estimated the size effect as partial squared eta ($\eta^2 p$), and we calculated the statistical power and the 95% confidence interval for dependent variables. We interpreted the magnitude of the effect by using the recommendations suggested by Hopkins et al. [37]: 0.0 = trivial; 0.2 = small; 0.6 = moderate; 1.2 = large; 2.0 = very large; 4.0 = almost perfect. The probability of 5% for type I error was adopted in all analyses ($p \leq 0.05$). To detect the real

Fig. 2 Experimental procedure of the time estimation task



difference in the population, we interpreted the statistical power from 0.8 to 0.9 = high power [38]. All analyses were conducted using SPSS for Windows version 20.0 (SPSS Inc., Chicago, Il, USA).

Results

No statistically significant difference was observed for the 7-s interval ($p > 0.05$). However, for the 1-s interval [$F(1.158) = 4.929$; $p = 0.028$; $\eta^2 p = 0.30$, power = 98%], there was a statistically significant difference between the 1 Hz and sham conditions, with subjects after 1-Hz rTMS underestimating time intervals compared to sham condition (95% CI = 0.002 to 0.016) (Fig. 3a).

The 4-s interval result was statistically significant for the sham and 1-Hz conditions [$F(1.158) = 11.631$; $p = 0.001$; $\eta^2 p = 0.7$; power = 99%]; subjects after the 1-Hz rTMS overestimated the task regarding to the sham condition (95% CI = 0.01 to 0.03) (Fig. 3b), as well as for the 9-s interval [$F(1.79) = 4.180$; $p = 0.044$; $\eta^2 p = 0.50$, power = 99%], with subjects overestimating the time intervals after rTMS of 1 Hz (95% CI = 0.02 to 0.04) (Fig. 3c).

Discussion

In the present study, we analyzed the effect of rTMS application in the parietal medial longitudinal fissure on the time estimation task judgment. Our findings for the 1-s interval after rTMS application at 1 Hz demonstrated an underestimation compared to the sham condition. This result indicates that the inhibitory rTMS shortens the subjective timing. This is consistent with an effect on sustained attention to the visual stimulus. In this case, due to the effect on attention in the 1-s interval task, there is fewer pulse accumulation of the temporal information due to the speed reduction of the internal clock, based on the scalar expectancy theory. Thus, for the 1-s interval, it is observed that the attention level modulates the cortical area activity associated with the parietal medial longitudinal fissure (Pz electrode) that allows the accumulation of information and judgment in motor or cognitive activities [39–41]. In addition, subjects synchronize time slots close to 1 s automatically through neural integration with subcortical structures. This fact indicates that the time interpretation becomes close to the task actual duration [13, 42]. Moreover, our findings for the 1-s interval indicate that the time limit between automatic and cognitive synchronism may be shorter than the target task time [43]. In this context, the 1-s interval interpretation may be considered automatic, justifying the differences between the conditions during the time estimation task execution [44–46].

In the 4-s and 9-s interval judgment analysis after the inhibitory neuromodulation, an overestimation effect of the target intervals occurred. We argue that the cortical circuits processing time intervals in this range trigger a compensatory behavior in the neural activity synchronization in attentional levels due to the effects of rTMS application [13, 47, 48]. This adjustment related to the timing process of the 4-s and 9-s intervals has implications for neurobiological aspects of cognitive and executive actions. Recordings of dopamine neurons in the substantia nigra and ventral tegmental area during a Pavlovian task in monkeys, by Fiorillo, Newsome, and Schultz [49], reveal differences in dopamine neuron activity when interval between reward and conditioned stimulus and was 1 or 2 s versus longer intervals, above 2 s, which substantiate findings in 4 s and 9 s, versus 1 s. Moreover, the most environmentally advantageous behavior (i.e., cognitive judgment, motor fit in decision making) depends on the temporal patterns recognition through external oscillators (i.e., sensory receptors) [4]. Possibly, they depend on the dopaminergic neurotransmission by reinforcing the feedback loops of interaction between the base nuclei and the cortical areas during time-interval processing between the frontal cortex and SPC [4].

A further examination of overestimation findings after 1-Hz rTMS in the 4-s and 9-s intervals also indicates that as time intervals increase, a reduction in inhibitory influence on PC may occur and could disrupt neural inputs related to the time perceptual ability [45, 50, 51]. Therefore, overestimation could occur through temporary inhibitions in the brain circuit communication between the prefrontal cortex and PC, which

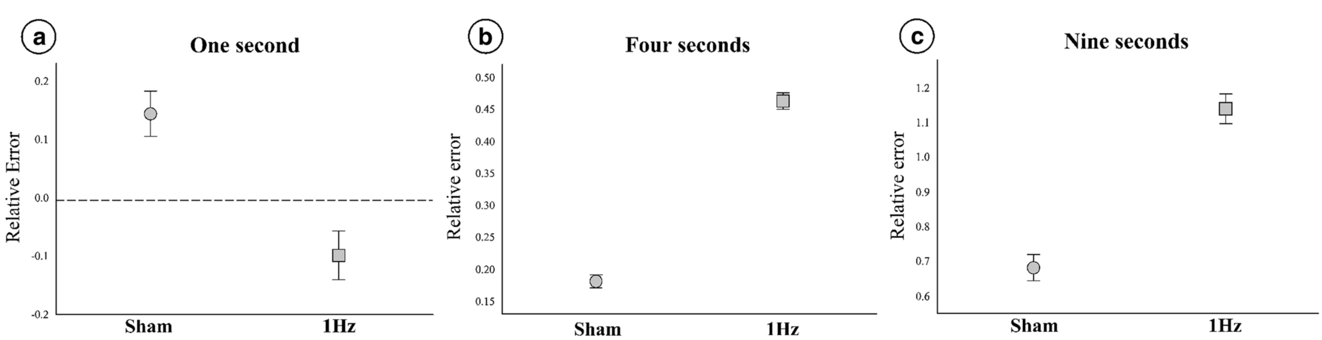


Fig. 3 The relative error of the time estimation in the sham and 1-Hz conditions for 1 s, 4 s, and 9 s, shown as an average ± standard deviation

is necessary to process the perception and interpretation of the time intervals during the trial in the task. Moreover, subjects under the effect of inhibitory rTMS overestimate time at long intervals, due to greater variability in cortical synchronization during the perceptual process consistent with Weber's law. This reinforces the argument that there is an increase in the recruitment of cognitive resources to the demand of the time estimation task, exerting a cumulative effect on information processing pertinent to the task execution. Accordingly, the short and long interval processing could respond differently to 1-Hz rTMS, due to the difference in cognitive demand [50, 52]. Moreover, it is noteworthy that current findings do not support central tendency effects, involving tasks with a mixture of long and short intervals [53, 54], which supports the premise discussed above that timing mechanisms for 1 s and 4 s or 9 s are likely to be different.

The present study demonstrated changes in the estimated proportion of target duration, and several studies show that RE based according to the scalar expectancy theory [2, 46, 55]. These studies have based on the scalar property of timing, where the standard deviation of time judgments increases as a constant fraction of the mean time judgments for time interval target [56]. However, we observed an intriguing result for the 7-s target duration, the participants have no difference in the target duration interpretation in both conditions. Initially, we did a data review and we did not find any error. We did this verification to discard any bias that could influence the common literature discussion that the short time interval target is associated with a sub-estimation, whereas a long interval target results in a super estimation [57, 58]. Although our results may indicate these are not variability parameters, we understand that timing for 7 s was influenced of the rTMS by a brief time modulation when the accumulator sent a signal to long-term memory in order to compare the current time interval with previous store values [59, 60].

The second possibility of our results may be related with the sham rTMS inducing an increase in dopamine neurotransmission, which may reshape the pacemaker activity in order to compare the accumulator pulses with the long-term memory [3, 61]. Moreover, Albrecht et al. [62] suggest that dopamine may be deactivating the precuneus in the "default mode network" and this could influence several connections of the precuneus. On that reasoning line, these dopaminergic effects can slow and speed an internal clock respectively. Following the data above, the no difference in the 7-s time interval may be the key moment in which the dopamine may influence the comparison between the pulses in the accumulator with the long-term memory to modulate the time estimation [63].

The present study has some limitations, among them the size of the sample, but the moderate effects in the analyses decrease the possibility of a type II error. Another limitation is non-association with tasks at the sub-second level because the software does not provide the possibility of stimuli with intervals below 1 s, which would provide a broader view of neurophysiology in timing. In addition, another limitation refers to 1-Hz rTMS at 80% RMT on Pz reference. The effects derived from the rTMS stimulus in the adjacent areas may have promoted a bias in our results. It could be controlled with 1-Hz rTMS applied over right and left SPC or reducing by RMT percentage. Furthermore, 1-Hz rTMS at 80% RMT may cause residual effects. We minimized its effects with 4 days of wash-out [64]. Another limitation is possible learning effect due to time estimation task repetitions which was minimized with random task stimulus.

Conclusion

The low-frequency rTMS, when applied in the SPC, promoted a change in the subjects' judgment, which could be due to the effects of inhibitory stimulus to produce cortical changes in active areas like modular clocks that influence cognitive processes (attention and memory, which are essential in the temporal information processing). Future studies will be needed to shed light on the brain neuromodulation role in the mediation of behavioral phenotypes associated with healthy or pathological conditions, since they comprise the elucidation of the brain mechanisms that support the time interval perception in humans.

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Conflict of interest The authors declare that they have no conflict of interest.

Compliance with ethical standards

The ethics committee of the Federal University of Rio de Janeiro approved the protocol for the study (no. 520.189).

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