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ORIGINAL ARTICLE

Low-frequency rTMS in the superior parietal cortex affects the working memory in horizontal axis during the spatial task performance

Jéssica Alves Ribeiro[1] · Francisco Victor Costa Marinho[1,2] · Kaline Rocha[1,2] · Francisco Magalhães[1,2] · Abrahão Fontes Baptista[3] · Bruna Velasques[4] · Pedro Ribeiro[4] · Mauricio Cagy[4] · Victor Hugo Bastos[5] · Daya Gupta[6] · Silmar Teixeira[1,2]

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Abstract
Spatial working memory has been extensively investigated with different tasks, treatments, and analysis tools. Several studies suggest that low frequency of the repetitive transcranial magnetic stimulation (rTMS) applied to the parietal cortex may influence spatial working memory (SWM). However, it is not yet known if after low-frequency rTMS applied to the superior parietal cortex, according to Pz electroencephalography (EEG) electrode, would change the orientation interpretation about the vertical and horizontal axes coordinates in an SWM task. The current study aims at filling this gap and obtains a better understanding of the low-frequency rTMS effect in SWM. In this crossover study, we select 20 healthy subjects in two conditions (control and 1-Hz rTMS). The subjects performed an SWM task with two random coordinates. Our results presented that low-frequency rTMS applied over the superior parietal cortex may influence the SWM to lead to a larger distance of axes interception point ($p < 0.05$). We conclude that low-frequency rTMS over the superior parietal cortex (SPC) changes the SWM performance, and it has more predominance in horizontal axis.

Keywords Spatial working memory · Transcranial magnetic stimulation · Spatial plane

Introduction

Working memory (WM) is the process of temporarily maintaining and manipulating of information for a brief time period [1]. The WM capacity can be understand as the ability to maintain information about the locations of objects that are no longer present [2, 3]. In this case, changes in the ability to maintain information active for processing in working memory are observed more pronounced when subjects are requested to manipulate this information, rather than only to maintain it [4]. This WM process was interpreted as spatial working memory (SWM), i.e., the temporary maintenance of object location and the ability to manipulate this information [5]. This feature is required for future goal-directed behavior and allows us to act beyond the confines of the here and now [1, 6].

Some studies suggested that the left frontal area is related to WM verbal representations, while the right, with visuospatial tasks [7]. WM on the object identity principle was detected in the brain rostral areas [8]. On the other hand, WM based on visuospatial stimuli was located more in brain dorsal areas, such as the superior frontal lobes and superior parietal lobes [9]. WM requires top-down (cognitive control and goal-directed) and bottom-up attention (captured by external sensory stimuli) related with the superior parietal cortex (SPC) [10, 11]. It is also well-known that the brain areas

✉ Francisco Victor Costa Marinho
victormarinhophb@hotmail.com

1 Brain Mapping and Plasticity Laboratory, Federal University of Piauí, Av. São Sebastião no. 2819, Nossa Sra. de Fátima, Parnaíba, PI 64202-020, Brazil

2 The Northeast Biotechnology Network (RENORBIO), Federal University of Piauí, Teresina, Brazil

3 Center for Mathematics, Computation and Cognition, Federal University of ABC, São Bernardo do Campo, São Paulo, Brazil

4 Brain Mapping and Sensorimotor Integration Laboratory, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

5 Brain Mapping and Functionality Laboratory, Federal University of Piauí, Parnaíba, Brazil

6 Department of Biology, Camden County College, Blackwood, NJ, USA

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manipulating the WM require the integration of visual, conceptual, and motor information that is process partly by the SPC [12].

WM has been investigated using repetitive transcranial magnetic stimulation (rTMS), modulating neuronal excitability. In particular, low-frequency rTMS (≤ 1 Hz) applied over cortical areas can modulate the response precision during cognitive tasks [13]. For instance, Postle et al. [14], when applying the rTMS over the SPC, observed that participants worsened performance in a WM task and presented alterations in the frontoparietal networks, especially when the task requires spatial attention [10, 14]. This fact leads us to develop a study paradigm to SWM with aim to investigate if the effect of low-frequency rTMS over the SPC could change the spatial plan performance. We have formulated the hypothesis that the low-frequency rTMS over the SPC can be associated with axes of the spatial plan producing an opposite deviation in the spatial plan predominant axis.

Materials and methods

Sample

The study was composed of 20 healthy participants (24 ± 1.2 years, age group = 20–30 years), all right-handed (Edinburgh Handedness Inventory) [15, 16]. The subject selection was based on a randomized, double-blind, crossover design with 1-day treatment period (1 Hz or sham), separated by a 4-day interval period between conditions. Subjects were randomly selected to one of two conditions: one condition applied active stimulation (1-Hz condition) followed by sham stimulation and the other applied sham stimulation (control condition) followed by active stimulation. We applied a detailed questionnaire in order to exclude those subjects with self-reported mental or physical illness, low visual acuity, orthopedic problems, tremors, and used any psychoactive or psychotropic substance during the study period.

Subsequently, the participants completed the rTMS screening questionnaire to identify conditions that could represent a risk factor for adverse effects [17]. We excluded the participants with one or more positive responses in screening. Participants signed the free and informed consent term. The protocol was approved by the ethics committee of Federal University of Rio de Janeiro (no. 520.189).

Experimental procedure

Participants stayed in a room with sound and electrical insulation in order to perform the task with 2 blocks and 20 trials per block with 3-min interval between blocks. We recorded the data about SWM performance in both conditions (control and 1 Hz).

rTMS application localization

The SPC was the brain area selected to receive the rTMS due to a consistent association with several higher cognitive functions, among them, the WM [18]. The SPC involves the ordering, updating, and manipulation of items in WM [19]. When TMS disruption occurs, it causes distinct types of WM errors, which may cause deficits in the manipulation, and rearrangement of information SWM [20].

rTMS application

The rTMS pulses were emitted by means of an eight-shaped coil having a diameter of 70 mm connected to a neuro-Ms stimulator (medical equipment manufactured by Neurosoft, Russia). Firstly, 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]. In order to determine the amplitude required for the rTMS use, the coil was directed with the cable back to 45°. TMS single-pulses around 40% of the stimulator intensity were initially applied on the motor cortex [22]. 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), in order to locate what would stimulate MEP in the right abductor pollicis brevis (APB) muscle recorded by electromyography (EMG). Five percent steps gradually increased the stimulator intensity until we record steps 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 of each subject was applied (mean = 46.2, SD = 9.12) since this intensity has been used as a safety measure to avoid seizures [23].

The rTMS application in the SPC was localized using the Pz electrode correspondence (EEG system 10–20) [13, 16]. The SPC was chosen due to its relation with spatial attention since it correlates spatial changes between an original target and new location points proposed by this target [24]. 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° caudally. 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 [25]. For the control condition (sham rTMS), sham coil replaced the coil used to apply 1-Hz rTMS. Sham coil produced sounds and vibrations, mimicking the physical effects of rTMS with absence of a magnetic field [20].

Working memory task

The SWM task consisted in random stimuli presented on a 20-in. monitor (1600 × 900 pixels resolution) a black background. The spatial locations (preparatory stimulus) were showed randomly in the cross-format (+) with a radius of 0.29 cm (16 pixels) from different coordinates (vertical: corresponding to the Y-axis, and horizontal: corresponding to the X-axis). The cross stimulus remained on-screen during 2 s in order for the spatial location to be memorized by the participant. After the cross disappears, a circle in a target format (red and white circles) with a radius of 2.45 cm (154.72 pixels) appeared randomly on the monitor's left side in upper, middle, or lower spatial plane. Subsequently, the target "traveled" on spatial plane in order for the reference point of the first stimulus to be interpreted. When the subject interpreted that the target center was located at correspondent point of preparatory stimulus location (cross), he touched the "enter" key on the keyboard finishing the task and a new trial started (Fig. 1).

The working memory task parameters analysis

An SWM task designed by our laboratory presented the stimuli and recorded performed responses. A program registered the performance in the vertical and horizontal position of the preparatory stimulus and the target judgment by the participant. The program "marked" the moment that the participant produced the hit on the target. When the participant touched the "enter" key on the keyboard, the software recorded the task performance between the preparatory stimulus (cross) and the target position.

Statistical analysis

We conducted a two-way ANOVA with condition factor (control and 1 Hz) and axis factor (X and Y) in order to understand the influence of low-frequency rTMS in an SWM task. Furthermore, in order to establish a statistical association between the subjects selectivity for the horizontal or vertical axes, we conducted a binomial logistic regression model considering dependent (X and Y-axes) and independent (performance task) variables.

The effect size was estimated as partial squared eta ($\eta^2 p$). The statistical power and 95% confidence interval were calculated for dependent variables. The magnitude of the effect was interpreted using the recommendations suggested by Hopkins et al. [26]: 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 analyzes ($p \leq 0.05$). In order to detect the real difference in the population, the statistical power was interpreted with 0.8 to 0.9 = high power [27]. All analyzes were conducted using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

The two-way ANOVA presented no interaction between condition and axis ($p > 0.05$). On the other hand, the main effect was found for condition [$F(2378.1) = 5.83$, $p = 0.002$, $\eta^2 p = 0.28$, power = 97%] with the subject in control condition performed better than that in 1 Hz condition (95% CI = 0.002 to 0.016), (Fig. 2). We also found the main effect for axis factor [$F(2379.1) = 21.18$, $p = 0.001$, $\eta^2 p =$

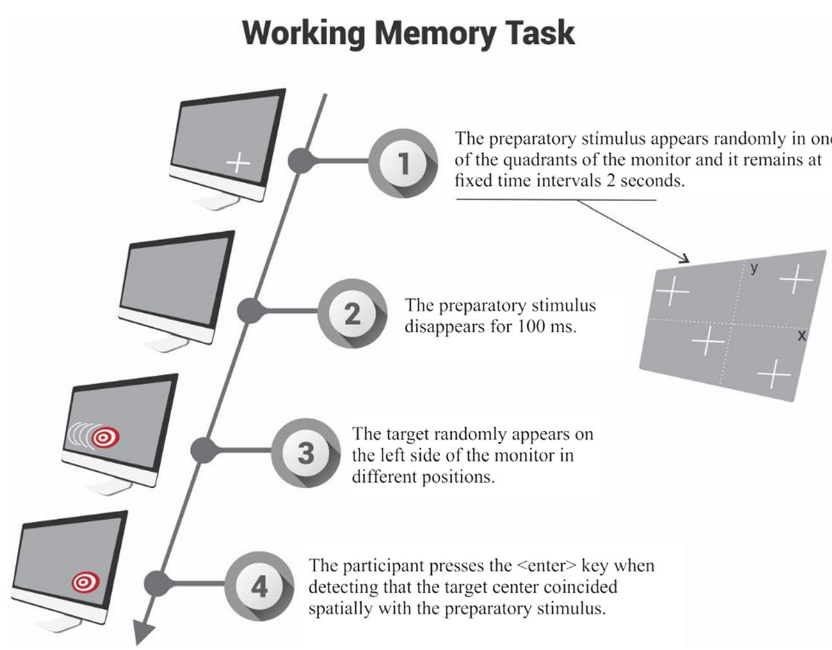

Fig. 1 Spatial working memory task representation

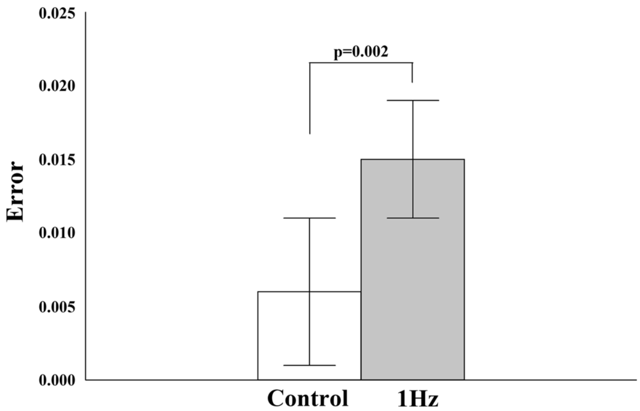

Fig. 2 Error task during both conditions, shown as an average ± standard deviation. Significantly different results are highlighted indicated by a *p* value

0.49, power = 99%] with the X-axis more selective than Y-axis (95% CI = 0.01 to 0.03), (Fig. 3).

We performed a binomial logistic regression to determine the SWM subject's performance in the horizontal and vertical positions (X and Y-axes) in function of the control and 1-Hz conditions (Fig. 4). The results demonstrate that the rTMS use has an association with task performance on the X-axis (Table 1). The binomial logistic regression model was statistically significant (χ^2 (8) = 50.38, $p < 0.005$). The model explained 59% (Nagelkerke R^2) of the variation in the SWM behavior and correctly classified the performance arrangement in the horizontal position in relation to the vertical position in 66.3% of the cases. The test sensitivity was 73.3%, with a specificity of 59.3%, positive predictive value of 86.05%, and negative predictive value of 65.56% for the spatial WM behavior of the horizontal position in relation to the vertical position.

Discussion

Our results indicate that the rTMS applied in the SPC alters the participants' performance when carrying out the spatial

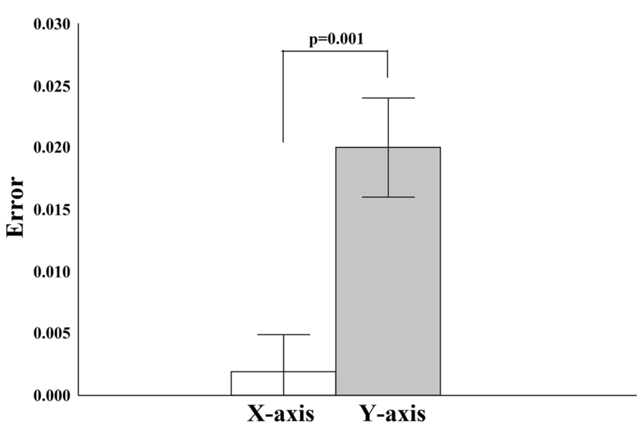

Fig. 3 Error task for both axes, shown as an average ± standard deviation. Significantly different results are highlighted indicated by a *p* value

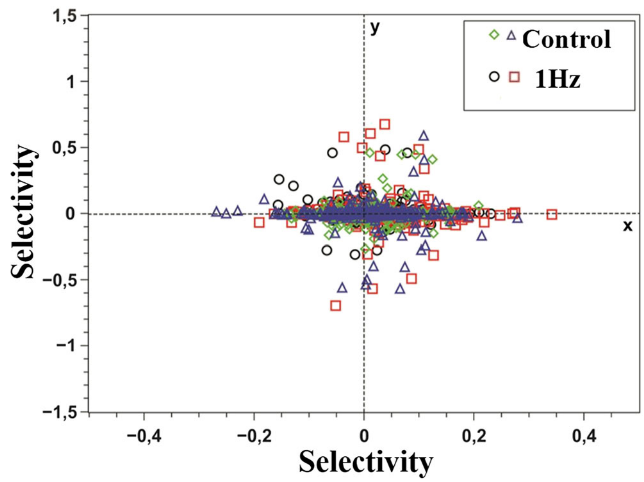

Fig. 4 Model for the selectivity of horizontal and vertical coordinates in SWM task in control and 1-Hz conditions

WM task. The two-way ANOVA analysis and binomial logistic regression made it possible to observe the greater spatial selectivity in relation to X-axis. It was easier for the participants to memorize the information location of the preparatory stimulus position and to integrate it into the object. In addition, the data significance for the inhibitory rTMS suggests the modulation of frontoparietal activity in the SWM recruitment, equaling the preference for task spatial planes.

The low-frequency rTMS on working memory

Our preparatory stimulus was a single trial between two positions, that is, a bisection of two vertical and horizontal straight lines (Y and X-axes) that are associated forming the location. Initially, we thought that both coordinates were selected simultaneously to hit the target, but we saw that during the WM task, the horizontal axis is more selected. We understand that the spatial dimension of the vertical coordinate is represented as more centralized by being more easily discriminated because the ability of spatial WM depends on the interaction between visuospatial attention, CNS accommodation, and task-processing-specific sites [16, 28]. In this context, the preparation stimulus was able to access the WM and promote the

Table 1 Spatial working memory behavior in the horizontal and vertical positions (X-axis in comparison with Y-axis) in function of the control and after the rTMS application in 1-Hz conditions

Condition	*B*	SE	Wald	df	*p*	Odds ratio	95% CI for odds ratio	
							Lower	Upper
Control	− 2.152	1.050	4.19	1	0.04*	0.116	0.015	0.911
rTMS 1 Hz	− 4.146	1.108	13.99	1	0.001*	0.016	0.002	0.139
Constant	0.097	0.087	1.25	1	0.264	1.112		

stimulus sufficient to capture the attention to the task. These facts are in agreement with a study that found that simple and repeated stimuli, like arrows, are more relevant to access memory. In addition, the WM best performance is related to the attention to better capture the marked cognitive stimuli (i.e., size, color, and brightness) provided by our task [29].

On the other hand, our finding was different from the study by Proctor and Cho [30], who also analyzed coded stimuli and responses along the horizontal and vertical dimension. The authors observed that participants encoded better information for the horizontal dimension than for the vertical dimension, but emphasize that this may have occurred due to the task structure rather than the horizontal dimension [30]. We propose the occurrence of a greater residual effect for the horizontal error (X-axis) in our study because the participants had the perspective of the object exit in this axis, that is, the aim always exits horizontally. Thus, the object direction may have increased the sensitivity for X-axis. In this context, the task we presented may have promoted a learning response, and this may reinforce the WM behavior, and promote and increase the sensitivity to the horizontal coordinate [31]. Our results indicate that after an inhibitory rTMS in the SPC, there is modulation in WM performance. The WM main function is to actively maintain information relevant to the task in an easily accessible state, a function that is thought to be performed over a range of supra second. According to our results, there was active maintenance deficit as a low-frequency rTMS effect, as we did observe performance disparity between the participants of the sham condition and 1 Hz [23, 32].

One of the study limitations refers to 1-Hz rTMS at 80% RMT on Pz reference. This fact may lead to effects derived from the rTMS stimulus spreading to the adjacent areas and it may have advanced promoted a bias in our results. It could be controlled with 1-Hz rTMS applied over the right and left SPC or reducing RMT percentage. Furthermore, 1-Hz rTMS at 80% RMT may cause residual effects. We minimized its effects with interval between the application (sham or 1 Hz) of 4 days [33]. Another limitation is possible learning effect due to SWM task repetitions. We believe that effect was minimized with the task random stimulus.

Conclusion

We conclude that the low-frequency rTMS applied in the SPC may change the SWM performance with the subject selectivity more distant the intersection point between axes. Independent of the conditions of the subjects, there was more predominance on the horizontal axis. Future studies using SWM tasks and rTMS over the SPC could analyze the parietal-dorsolateral network in order to establish a larger understanding about sensory-visuospatial integrations tasks. This may permit to be used in the behavioral neuroscience as a parameter directing to neurological disease.

Compliance with ethical standards Participants signed the free and informed consent term. The protocol was approved by the ethics committee of Federal University of Rio de Janeiro (no. 520.189).

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

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