

Left prefrontal repetitive transcranial magnetic stimulation impairs performance in affective go/no-go task

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Functional neuroimaging studies have associated affective go/no-go function with lateral prefrontal activation, but they have not established a causal role and have not determined whether one hemisphere is predominantly engaged. In the present study, 11 normal volunteers underwent slow repetitive transcranial magnetic stimulation of the left and right dorsolateral prefrontal cortex, and the occipital cortex prior to performance of a picture-based affective go/no-go task. We found an interfering

effect of left prefrontal repetitive transcranial magnetic stimulation compared with both right prefrontal and occipital repetitive transcranial magnetic stimulation. This impairment concerned positive and negative task stimuli to a similar extent, and tended to be greater in shift compared with nonshift blocks. Our findings demonstrate a functionally relevant lateralization of the prefrontal contribution to affective go/no-go tasks. *NeuroReport* 16:615–619 © 2005 Lippincott Williams & Wilkins.

Key words: Affective go/no-go task; Categorization; Dorsolateral prefrontal cortex; Emotion; Transcranial magnetic stimulation

INTRODUCTION

Patients with affective disorders show neuropsychological deficits, which include poor response selection and inhibition, difficulties labeling affect, and mood-congruent attentional bias [1]. The severity of some of these deficits may be assessed using an affective go/no-go task [2]. This task requires the affective categorization of rapidly presented stimuli. The investigational advantage of this task is that it explicitly links emotional and cognitive functions, in that response selection and inhibition must be guided by emotional content.

Functional magnetic resonance imaging (fMRI) has been used to identify brain regions activated during affective go/no-go tasks. Contrasting an affective with a font-based go/no-go task, Elliott *et al.* [3] found left prefrontal and anterior cingulate activation in healthy study participants. In patients with mania and major depression, this affective go/no-go task (and, in particular, its emotionally salient trials) produced a different pattern of activation in the prefrontal cortex and other brain regions [4,5]. These findings suggest an association of prefrontal cortical function with affective go/no-go processing. The present investigation sought to further explore the relationship between prefrontal cortex and affective go/no-go function. Specifically, the aims of the study were to determine whether: (1) the dorsolateral prefrontal cortex (DLPFC) has functional significance (as opposed to an epiphenome-

nal role), (2) one hemisphere is predominantly engaged, and (3) responses to positive and negative task stimuli differentially involve the left and right DLPFC in the affective go/no-go task.

We employed low-frequency transcranial magnetic stimulation (TMS) in healthy participants to transiently and selectively impair normal functioning of the left and right DLPFC, and the occipital cortex (active control) [6,7]. Repetitive TMS (rTMS) over each of these brain regions was immediately followed by testing affective go/no-go function. We expected that rTMS-induced transient disturbance of the DLPFC, but not of the occipital cortex, would result in impaired affective go/no-go task performance.

MATERIALS AND METHODS

Study participants: Eleven right-handed volunteers participated in the study (six women), aged 38.3 ± 4.2 (mean \pm SE). Exclusion criteria included history of neurological and psychiatric disorders and contraindications to rTMS [8]. The study was approved by the local research ethics committee (Hospital das Clinicas, University of Sao Paulo) and written informed consent was obtained from all participants.

Procedure: We employed a picture-based affective go/no-go task. Participants were familiarized with the task

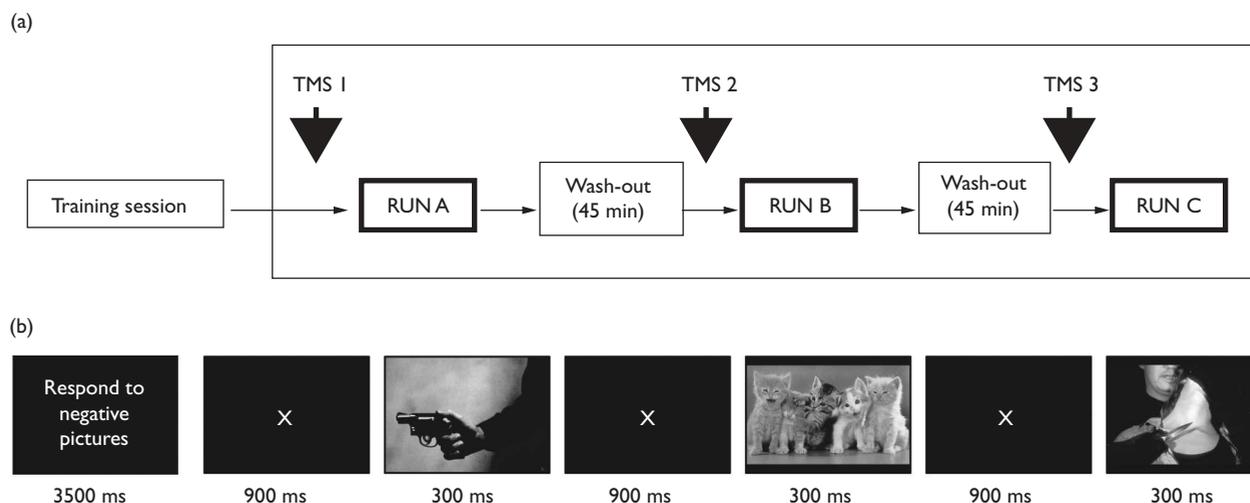


Fig. 1. (a) Design of the experiment. The labels TMS1, TMS2, and TMS3 (TMS: transcranial magnetic stimulation) correspond to the application sites of right and left dorsolateral prefrontal cortex, and occipital cortex (control), which were stimulated in randomized order across participants. (b) Example trials of the affective go/no-go task. Participants had to respond to target stimuli by button press, but withhold the response to distractors.

in a training session, which included a test run (Fig. 1a). Over the course of the TMS experiment, participants completed the task three times (runs a, b, and c). In each run, different sets of pictures were presented. Prior to each run, rTMS was applied to one of three brain regions (right DLPFC, left DLPFC, or occipital cortex) to transiently disturb brain activity. By including occipital rTMS, we chose an 'active' control condition, because this allowed one to control for nonspecific effects of rTMS. Sham TMS, the potential alternative control, does not reliably mimic the peripheral sensations associated with TMS, which may interfere in repeated measures designs with the need to keep the participants blind to the control condition [9,10]. We separated rTMS sessions by wash-out periods (45 min) to avoid carry-over effects. TMS sites and versions of the task were pseudorandomized and counterbalanced across participants according to the Latin square method.

Affective go/no-go task: The task was adapted from the one used by Murphy *et al.* [2]. Instead of words, photographs were presented to the participants (Fig. 1b). Each rTMS session was followed by one run of the task. Each run consisted of 10 blocks with nine positive and nine negative pictures each. Prior to each block, an instruction was given specifying either positive or negative pictures as targets ('respond to positive pictures' [P] or 'respond to negative pictures' [N]). Participants were requested to respond to targets by immediate button press, but to withhold responses to distractors. Instructions were presented in a PPNNPPNPP order in all runs. Following Murphy *et al.* [2], we discarded the first two blocks of each run, considering them 'warming-up' for the task. Accordingly, each run consisted of four blocks requiring set-shifting (instruction opposite to the previous block) and four nonshift blocks. The dependent measure of interest was the number of errors, which was composed of false alarms plus omissions. The photographs presented in our task were taken from a standardized picture set (*International Affective Picture System*) that has produced reliable valence ratings in

different populations [11]. Only positive and negative photographs were selected. The mean valence value was 7.1 (± 0.5) for positive and 2.8 (± 0.7) for negative pictures (9-point scale). Participants were informed that no neutral pictures would be presented throughout the experiment.

Transcranial magnetic stimulation: rTMS (1 Hz, 10 min) was administered using a Dantec stimulator (Medtronic, Minneapolis, Minnesota, USA) with a figure-of-eight coil (outside diameter of each wing 7 cm). The DLPFC stimulation site was determined by measuring 5 cm anterior and in a parasagittal line from the optimal site of stimulation to elicit motor-evoked potentials in the first digital interosseus muscle. The coil was held tangentially to the skull with the handle pointing back and away from the midline at 45° [12]. Using this coil position, the TMS-induced current flow was in the anterolateral direction. For occipital stimulation, the coil center was placed on the midline and 2 cm above the inion; the coil was held tangentially to the skull such that the TMS-induced current direction was perpendicular to the parasagittal plane. We chose to set the magnetic stimulus intensity to a fixed level of 60% of maximum stimulator output, instead of tuning to individual motor thresholds, as there is no evidence that motor thresholds correlate with the effects of rTMS outside the motor cortex [9,13]. In our study participants, 60% TMS intensity corresponded to an average of 151% of resting motor threshold (range 104–187%).

Data analysis: Data were analyzed using SPSS for Windows. Differences between conditions were assessed using a mixed ANOVA with the within-participants factors 'rTMS site' (left DLPFC, right DLPFC, occipital=control), 'shift' (shift blocks, nonshift blocks), 'valence' (positive, negative task stimuli), and 'section' (first half, second half of task blocks) and the between-participants factor 'gender'. The factor 'section' allowed one to determine a potential difference between early (first half) and late (second half) responses within the blocks (series of 18 pictures following an instruction). Statistically significant main effects or

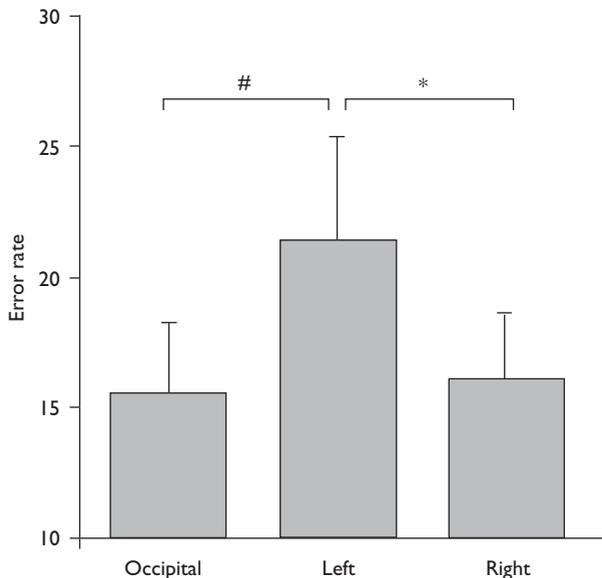


Fig. 2. Effects of repetitive transcranial magnetic stimulation on the affective go/no-go task ($F[2,18]=4.9$, $p=0.02$). The error rate represents the total number of errors per condition. Error bars show the SEM. #, $F[1,9]=6.1$, $p=0.04$. *, $F[1,9]=5.8$, $p=0.04$.

interactions were further explored by conducting simple effects.

RESULTS

The average number of errors in the control condition (occipital rTMS) was 15.5 (± 2.7 ; mean \pm SE). This number was composed of 7.6 (± 1.4) false alarms and 7.9 (± 1.5) omissions.

The mixed ANOVA revealed significant effects for the factors 'shift' ($F[1,9]=5.5$, $p=0.04$) and 'rTMS site' ($F[2,18]=4.9$, $p=0.02$), but not for the factors 'valence' ($F < 1$, n.s.), 'section' ($F < 1$, n.s.), and 'gender' ($F < 1$, n.s.). The significant main effect of the factor 'shift' was due to a higher error rate during shift relative to nonshift blocks, indicating higher task demands in the shift blocks.

The significant main effect of the factor 'rTMS' was due to an interfering effect of left rTMS compared with both right rTMS ($F[1,9]=5.8$, $p=0.04$) and occipital rTMS (control stimulation; $F[1,9]=6.1$, $p=0.04$; Fig. 2). Following left rTMS, the error rate was 21.5 (± 3.9). This corresponded to a 35–38% increase in error rate relative to right (16.1 \pm 2.5) and occipital rTMS (15.5 \pm 2.7). All rTMS conditions showed lower error rates than the pre-TMS training session (24.8 \pm 3.5).

The interfering effect of left rTMS concerned false alarms and omissions in similar proportions (Fig. 3). Right rTMS, in contrast, did not produce significant changes in error rates relative to control stimulation ($F < 1$, n.s.; Figs 2 and 3).

The interaction effect between 'rTMS' and 'shift' showed a trend ($F[2,18]=2.8$, $p=0.09$), with larger impairment in the shift than in the nonshift blocks. No significant effect was found for the rTMS \times valence interaction ($F < 1$, n.s.), for the rTMS \times section interaction ($F[2,18]=1.0$, n.s.), and for the rTMS \times gender interaction ($F[2,18]=1.8$, n.s.).

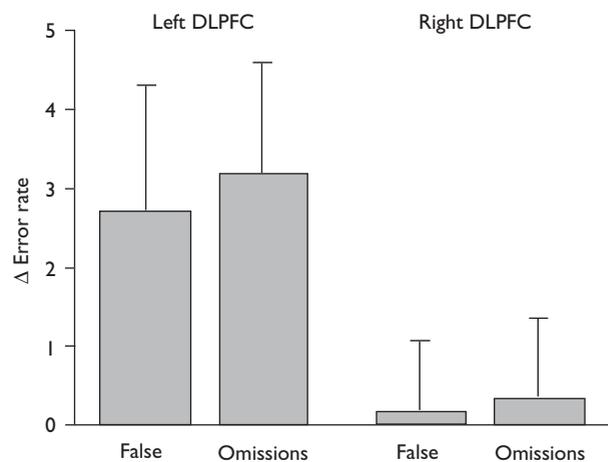


Fig. 3. Effects of left and right repetitive transcranial magnetic stimulation (rTMS) on false alarms and omissions. The Δ error rate represents the difference to occipital rTMS (control). Error bars show the SEM.

DISCUSSION

Our main finding is that slow rTMS of the left DLPFC had an interfering effect on affective go/no-go task performance in healthy adults. No interfering effect was observed with right rTMS relative to control stimulation, and there was a significant difference between left and right rTMS, suggesting a functional difference between left and right DLPFC in relation to this task.

Our finding is in line with a recent fMRI study by Elliott *et al.* [3], who observed activation in the left prefrontal cortex during an affective go/no-go task. Our study adds to this result in two ways: First, rTMS allowed the study of the functional significance of specific brain regions in this task [6,7]. By creating a transient 'virtual lesion' in the left DLPFC, we established a causal role for this region in affective go/no-go task performance. Second, our analysis involved the direct comparison between left and right DLPFC, which revealed a significant lateralization effect to the left. Although such lateralization was also suggested by the above fMRI study, this study did not test for actual differences between hemispheres, which would have required testing the condition \times hemisphere interaction [14].

Like Elliott *et al.* [3], we used the emotional valence of the presented stimuli as a response criterion in our go/no-go task. Previous fMRI studies have employed other response criteria, for example, on the basis of color or alphabet. Interestingly, several of these studies suggest a preponderance of the right prefrontal cortex [15–17]. Although these studies did not test the condition \times hemisphere interaction, one could speculate that there is a hemispheric specialization during go/no-go tasks depending on the response criterion. The affective variant of the task might predominantly involve the left prefrontal cortex, whereas other nonaffective forms of the task might implicate right prefrontal regions more strongly. This suggestion is consistent with the findings by Elliott *et al.* [3], who in fact observed left prefrontal activation when comparing an affective with a font-based variant of the task.

On the basis of the present findings, we cannot exclude the possibility that nonaffective aspects of the task may also be impaired by left rTMS. Attentional set-shifting could be one of these aspects, because the interfering effect tended to be greater in shift than in nonshift blocks. It should, however, be noted that the set-shifting required in our task cannot be considered an entirely nonaffective process, because participants had to shift their attention from *positive* to *negative* targets and vice versa. Another nonaffective aspect of our task is working memory. Although this function is closely associated with (bilateral) DLPFC activity, our data suggest that impaired working memory is not the predominant factor that accounts for our finding. If left rTMS particularly affected the working memory aspect of our task, one would expect that participants lose the instruction over the course of a picture series, resulting in higher error rates during the second half than during the first half of the task blocks. However, we found no TMS \times section interaction.

Altogether, we acknowledge that our data do not allow one to completely disentangle all subfunctions that might have been affected by left rTMS. For this purpose, modifications of the present paradigm need to be studied, using the same rTMS protocol as in the present study. Such modifications include set-shifting tasks without go/no-go component, working memory tasks, and nonaffective go/no-go tasks. Although desirable, it seems problematic to include several tasks in one rTMS experiment using an offline procedure, because the interfering effect of rTMS tends to subside rapidly [6,7].

With regard to hemispheric specialization, different models have been proposed. One of them distinguishes between the processing of 'categorical' and 'coordinate' relations, associated with the left and right hemispheres, respectively [18–20]. While this model has resulted from studies of the visual system, one might consider applying this distinction to other cognitive domains also. With respect to our experiment, it could be suggested that the left-lateralized rTMS effect is due to the categorical nature of the task employed, requiring the 'affective classification' of presented stimuli. A different brain lateralization model posits that the left hemisphere is dominant for positive emotions and the right hemisphere for negative emotions [14,21,22]. On the basis of this theory, one would have expected that left rTMS had a stronger impact on responses to positive stimuli and right rTMS on responses to negative stimuli. However, we did not find a significant rTMS \times valence interaction in our experiment.

The present study included occipital rTMS. A drawback of this control condition is that we cannot definitely exclude an effect of occipital rTMS on task performance. Because slow rTMS is known to produce transient 'virtual lesions' in the stimulated brain region [6,7], one may expect that occipital rTMS might also have some *interfering* effect on task performance. In this case, the impairment related to left rTMS would be even larger than assumed in this study. Alternatively, occipital rTMS could theoretically have an *enhancing* effect on task performance. This alternative seems unlikely, because right rTMS produced results similar to occipital rTMS. One way to test for an effect of occipital rTMS is to compare the occipital condition with the pre-TMS training session. This comparison showed a lower error rate in the occipital condition. However, this difference is very likely related to a training effect and does not allow one to

claim an enhancing or exclude an interfering effect of occipital rTMS, both of which could be buried under the training effect.

CONCLUSION

Using slow rTMS in healthy participants, we studied the functional role of the DLPFC in a picture-based affective go/no-go task. Left prefrontal rTMS impaired task performance relative to right and occipital rTMS. This impairment similarly concerned omissions and false alarms, and tended to be larger in shift than in nonshift blocks. No significant difference was observed between responses to positive and negative stimuli. In conclusion, our findings suggest a causal role for the left DLPFC in the performance of affective go/no-go tasks.

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