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## Effect of low-frequency transcranial magnetic stimulation on an affective go/no-go task in patients with major depression: Role of stimulation site and depression severity<sup>☆</sup>

Felix Bermpohl<sup>a,\*</sup>, Felipe Fregni<sup>a,b</sup>, Paulo S. Boggio<sup>b</sup>, Gregor Thut<sup>a,1</sup>,  
Georg Northoff<sup>a,2</sup>, Patricia T.M. Otachi<sup>b</sup>, Sergio P. Rigonatti<sup>b</sup>,  
Marco A. Marcolin<sup>b</sup>, Alvaro Pascual-Leone<sup>a</sup>

<sup>a</sup> *Harvard Center for Non-invasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Kirstein Building KS 454, 330 Brookline Avenue, Boston, MA 02215, USA*

<sup>b</sup> *Psychiatry and Psychology Institute, University of Sao Paulo, Rua Ovidio Pires de Campos 785-3 andar, CEP 01060-970, São Paulo, Brazil*

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### Abstract

Repetitive transcranial magnetic stimulation (rTMS) holds promise as a therapeutic tool in major depression. However, a means to assess the effects of a single rTMS session on mood to guide subsequent sessions would be desirable. The present study examined the effects of a single rTMS session on an affective go/no-go task known to measure emotional–cognitive deficits associated with major depression. Ten patients with an acute episode of unipolar major depression and eight partially or completely remitted (improved) patients underwent 1 Hz rTMS over the left and right dorsolateral prefrontal cortex prior to task performance. TMS over the mesial occipital cortex was used as a control. We observed significantly improved performance in depressed patients following right prefrontal rTMS. This beneficial effect declined with decreasing depression severity and tended to reverse in the improved group. Left prefrontal rTMS had no significant effect in the depressed group, but it resulted in impaired task performance in the improved group. Our findings indicate that the acute response of depressed patients to rTMS varies with the stimulation site and depression severity. Further studies are needed to determine whether the

<sup>☆</sup> The study was carried out at the Psychiatry and Psychology Institute, University of Sao Paulo, Brazil.

\* Corresponding author. Present address: Department of Psychiatry and Psychotherapy, Charité Campus Mitte, Universitätsmedizin Berlin, Schumannstr. 20/21, D-10117 Berlin, Germany. Tel.: +49 30 450517176; fax: +49 30 450517962.

*E-mail address:* [felix.bermpohl@charite.de](mailto:felix.bermpohl@charite.de) (F. Bermpohl).

<sup>1</sup> Present address: Functional Brain Mapping Laboratory, Department of Neurology, University Hospital Geneva, 24, Rue Micheli du Crest, CH-1211 Geneva 14, Switzerland.

<sup>2</sup> Present address: Department of Psychiatry and Psychotherapy, University of Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany.

present paradigm could be used to predict antidepressant treatment success or to individualize stimulation parameters according to specific pathology.

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## 1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive and well-tolerated means to stimulate the human brain (Pascual-Leone et al., 1999, 2000). In psychiatry, repetitive TMS (rTMS) has been studied primarily as a potential antidepressant treatment. The mechanisms of action remain unclear, but many studies support an antidepressant effect of rTMS when applied over the dorsolateral prefrontal cortex (DLPFC; for review, see Holtzheimer et al., 2001; Burt et al., 2002; Gershon et al., 2003). However, effect sizes vary considerably between studies, and some have found no antidepressant properties of rTMS (e.g., Kimbrell et al., 1999; Loo et al., 2003a; Hausmann et al., 2004a). The heterogeneity of findings might largely be due to a high variability across depressed patients in their response to rTMS. Potentially relevant factors include the site of magnetic stimulation (left versus right DLPFC; Pascual-Leone et al., 1996b), pulse frequency (Pascual-Leone et al., 1994; Sachdev et al., 2002), stimulation intensity (Loo et al., 2001), clinical state (e.g., depressed or euthymic; George et al., 1996; Pascual-Leone et al., 1996a), depression subtype (e.g., psychotic features; Grunhaus et al., 2000), duration of depressive episode (Holtzheimer et al., 2004), age (Kozel et al., 2000; Janicak et al., 2002), previous response to rTMS (Dannon et al., 2000), metabolic brain state prior to TMS (Kimbrell et al., 1999; Teneback et al., 2001), and potential interactions between some of these factors. It seems important to study the factors influencing the response of depressed patients to rTMS, because their knowledge shows promise for optimizing treatment parameters and improving our understanding of the pathophysiology of major depression.

Previous studies have used different output measures to assess the response of depressed patients to rTMS. The most frequently used parameters are depression rating scales, such as the *Hamilton Rating Scale for Depression* (HRSD) (Hamilton, 1967) and

the *Beck Depression Inventory* (Beck et al., 1996; for overview, see Burt et al., 2002; Gershon et al., 2003). Other response measures previously used in the study of depression include motor cortex excitability (Maeda and Pascual-Leone, 2003), metabolic changes (Catafau et al., 2001; Mottaghy et al., 2002; Loo et al., 2003b), and cognitive task performance (Hausmann et al., 2004b). In the present study, we adopted an affective go/no-go task (AGN task) to examine the response of depressed patients to rTMS. This task requires subjects to respond to stimuli of one valence (e.g., positive) while inhibiting responses to stimuli of the opposite valence (e.g., negative). Since response selection and inhibition are guided by emotional content, the task provides a means of studying the interface between cognition and emotion. We employed the AGN task, because it can be used to quantify neuropsychological deficits typically observed in depressed patients which, for instance, concern response selection and inhibition, the recognition of affect, and mood-congruent attentional bias (Rubinow and Post, 1992; Elliott, 1998; Murphy et al., 1999). In addition, the AGN task has been shown to involve the lateral prefrontal cortex (Elliott et al., 2000, 2002), which is the common target region of therapeutic rTMS in mood disorders and is assumed to play a role in the pathophysiology of major depression (Mayberg, 2003; Phillips et al., 2003).

Using the AGN task, the present study aimed to further explore two of the above-mentioned factors potentially modulating rTMS outcome, namely the site of stimulation and the clinical state of the patient. With respect to the site of stimulation, the predominant hypothesis in the field is that depressed patients benefit from high-frequency (fast) rTMS over the left DLPFC and low-frequency (slow) rTMS over the right DLPFC (Burt et al., 2002; Gershon et al., 2003). This hypothesis is closely linked to the ‘imbalance’ hypothesis of depression, which postulates that a relative hypoactivity in the left relative to the right prefrontal cortex plays a critical role in the pathophysiology of

depression (Sackeim et al., 1982). Fast left prefrontal rTMS might enhance and slow right prefrontal rTMS might reduce the activity in the targeted brain areas, thus restoring normal balance between the hemispheres. This view is consistent with various lesion (Morris et al., 1996; Paradiso et al., 1999), rTMS (Pascual-Leone et al., 1996a; George et al., 1999; Klein et al., 1999), and functional neuroimaging studies (Ebert et al., 1991; Sackeim et al., 1993; Kocmur et al., 1998; Mottaghy et al., 2002) associating depression with prefrontal asymmetry in favor of the right hemisphere. However, there are also a considerable number of studies that do not support the above hypothesis. For instance, a recent meta-analysis of functional neuroimaging studies did not find a significant difference between left and right prefrontal activity in depressed patients (Nikolaus et al., 2000; see also Iidaka et al., 1997; Tutus et al., 1998). Moreover, some rTMS studies observed unexpected effects, with better treatment response to slow than to fast rTMS over the left DLPFC (Kimbrell et al., 1999; Padberg et al., 1999). Because of these divergent findings, the asymmetry hypothesis of depression remains a matter of debate, and it seems desirable to further assess the assumption of beneficial effects of fast rTMS over the left DLPFC and slow rTMS over the right DLPFC (Burt et al., 2002). Since most work has focused on these two, potentially beneficial combinations of site and frequency of prefrontal rTMS, there is a lack of investigations that compare different stimulation sites for a given TMS frequency. In the present study, we administered slow (1 Hz) rTMS to the left and right DLPFC as well as the mesial occipital cortex (active control) prior to AGN task performance in order to examine the influence of stimulation site and depression severity on the response to TMS. We applied rTMS in one short (10-min) session per stimulation site to focus on the acute effects of rTMS and to avoid sustained adverse effects potentially induced in patients with major depression by left prefrontal rTMS at 1 Hz, as would be predicted by the above hypothesis. To determine the influence of the clinical state of patients with major depression on rTMS outcome, we compared acutely depressed with improved (i.e., partially or completely remitted) patients. The inclusion of partially remitted patients allowed the study of the gradual changes of rTMS effects with improving HRSD scores. Based on the

imbalance theory of depression, we anticipated improved AGN task performance following right prefrontal rTMS at 1 Hz in acutely depressed patients and we hypothesized that this beneficial effect would disappear with improving HRSD scores.

## 2. Methods

### 2.1. Participants

All patients participating in this study were recruited from the psychiatric outpatient clinic of the University of Sao Paulo, Brazil. In all cases, the diagnosis of unipolar major depressive disorder was established using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995) and case note review. All patients had a history of at least three previous major depressive episodes, were right-handed and had not had a change of psychotropic medication within 2 weeks of the experiment. At baseline, patients were assigned to one of two study groups according to their scores in the 21-item

Table 1  
Demographic and clinical characteristics of the study participants

Characteristic	Depressed ( <i>n</i> = 10)	Improved ( <i>n</i> = 8)
Sex, F/M, no.	6/4	5/3
Age, mean $\pm$ S.D., years	56.8 $\pm$ 9.3	50.6 $\pm$ 9.4
Education, mean $\pm$ S.D., years	11.2 $\pm$ 4.1	13.0 $\pm$ 3.0
Duration of illness, mean $\pm$ S.D., years	15.8 $\pm$ 11.6	20.7 $\pm$ 9.6
Previous episodes, mean $\pm$ S.D., no.	5.9 $\pm$ 2.6	5.8 $\pm$ 1.1
Psychotropic medication naïve, no.	4	2
Psychotropic medication, no.		
SSRI	1	3
Tricyclic antidepressants	4	2
Atypical neuroleptics	0	1
Benzodiazepines	3	2
Current psychotherapy	4	2
Positive family history, no.	5	5
HRSD score, mean $\pm$ S.D.	20.3 $\pm$ 2.5	9.9 $\pm$ 2.9
Motor threshold, % output	44.9 $\pm$ 6.9	41.1 $\pm$ 9.7

Abbreviations: F, female; M, male; SSRI, selective serotonin reuptake inhibitors; HRSD, Hamilton Rating Scale for Depression. Family history refers to first degree relatives.

*Hamilton Rating Scale for Depression* (HRSD; Hamilton, 1967). The cut-off between groups was a priori set to an HRSD score of 18. Ten patients with an acute depressive episode (HRSD score of 18 or higher) were compared with eight partially or completely remitted patients (HRSD score <18, range 6–13). For convenience, these two study groups will be referred to as ‘depressed’ and ‘improved’. Study groups did not considerably differ with regard to treatment (Table 1). Each group had five patients with current antidepressant medication. The acutely depressed group had two more unmedicated patients, which may be outweighed by the slightly larger number of acutely depressed patients currently under psychotherapy. Besides treatment, further clinical variables, including the time since first diagnosis, number of previous episodes, and family history, were comparable between study groups (Table 1), indicating that the groups did not differ with regard to the form of depression in general but rather with regard to the current state of the illness. Exclusion criteria included any comorbid axis I disorder, current neurological disorder, substance abuse within 2

months of study participation, history of closed head injury resulting in loss of consciousness, or contraindications to TMS (Wassermann, 1998). None of the patients had a history of electroconvulsive therapy (ECT). 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 patients.

## 2.2. Procedure

The experimental design was adapted from a previous study in healthy volunteers (Berman et al., 2005). We used an AGN task with photographs from the *International Affective Picture System* (Lang et al., 1999). Patients were familiarized with the task in a training session followed by a baseline run (Fig. 1A). This baseline test served as a further practice opportunity and, in addition, allowed the overall assessment of task performance, independent of rTMS. Since this run was not included in the pseudo-randomization of conditions, we did not use it as a (no-TMS) control

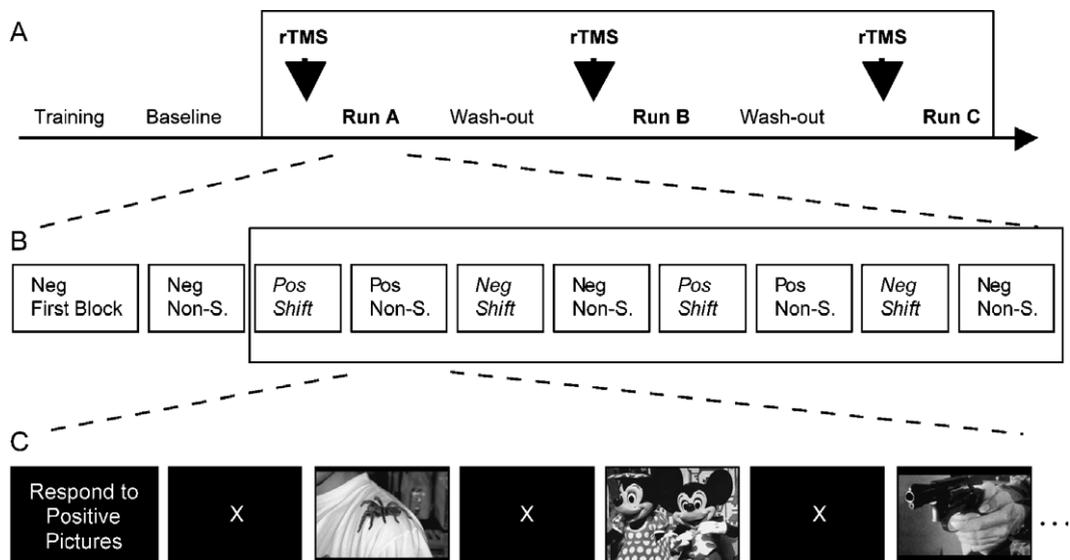


Fig. 1. Study design. (A) Design of the experiment. rTMS conditions (right DLPFC, left DLPFC, mesial occipital) were arranged in Latin Square order. The Latin Square did not include the baseline run. Different sets of photographs were presented for each task performance (baseline, runs a, b, c). The wash-out period was 45 min. (B) Example of a single run of the affective go/no-go task. The first two blocks within each run were discarded from the analysis. In half of the blocks, positive test stimuli were designated as targets (Pos); in the other half, patients had to respond to negative test stimuli (Neg). In shift blocks, the target valence changed relative to the preceding block. The target valence remained the same in non-shift blocks (Non-S). Each run consisted of 4 shift and 4 non-shift blocks. (C) Beginning of a single block. Altogether, 9 positive and 9 negative test stimuli were presented during each block. The instruction was presented for 3500 ms, the pictorial stimulus for 300 ms, and the fixation cross for 900 ms. The button response to a picture was given during the subsequent fixation cross period.

condition for the analysis of rTMS effects. Over the course of the rTMS experiment, patients completed the task three times (runs a, b and c). In each run, different sets of pictures were presented. Before each run, rTMS was applied to one of three brain regions (right DLPFC, left DLPFC, or mesial occipital cortex). By including mesial occipital rTMS, we chose an ‘active’ control condition that also controlled for non-specific effects of rTMS, such as discomfort due to muscle contractions, head-tapping, and clicking sounds. Sham rTMS, the potential alternative control, does not reliably mimic the peripheral sensations associated with the magnetic field change, which may interfere in repeated measures designs with the need to keep the subjects blind to the control condition (Loo *et al.*, 2000; Robertson *et al.*, 2003). We separated rTMS sessions by wash-out periods of 45 min to avoid carry-over effects. Stimulation sites and picture sets per run were pseudo-randomized and counterbalanced across patients according to the Latin Square method.

### 2.3. Affective go/no-go task

The task was adapted from the one used by Murphy *et al.* (1999) (Fig. 1B,C). Instead of words, photographs were presented to patients (Fig. 1C). Each run of the task comprised 10 blocks with 9 positive and 9 negative pictures each. In each block, either positive or negative pictures were specified as targets (‘respond to positive pictures’ or ‘respond to negative pictures’). Subjects were requested to respond to targets by immediate button press, but to withhold responses to distractors. Blocks requiring set-shifting (target valence opposite to the previous block) were distinguished from non-shift conditions (target valence identical to the previous block; Fig. 1B). The dependent measure of interest was the number of errors, composed of false alarms and missing responses (omissions). To ensure unequivocal assignment of responses to the respective trials, implausibly early (<300 ms after picture onset) and delayed (>1200 ms) responses were considered omissions. Given that reaction times were not obtained during ‘no-go’ trials (representing 50% of the total number of trials) as well as during omissions (on average representing 24% of the ‘go’ trials in the depressed group), we did not use reaction times as an outcome variable in our analysis. Following Murphy

*et al.* (1999), we discarded the first two blocks of each run, considering them practice and familiarization with the task (Fig. 1B). This resulted in a total of 144 analyzed trials (18 trials \* 8 blocks) per run.

### 2.4. Transcranial magnetic stimulation

TMS was administered using a Dantec stimulator (Medtronic, Minneapolis, MN, 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 to and in a parasagittal line from the optimal site of stimulation to elicit motor evoked potentials in the first digital interosseus muscle (Pascual-Leone *et al.*, 1996b). For mesial occipital stimulation, the coil center was placed on the midline and 2 cm above theinion. rTMS (1 Hz) was administered over each of the three target regions for 10 min. The magnetic stimulus intensity was set to a fixed level of 60% of maximum stimulator output, which corresponded on average to 137% (range 104–171%) of resting motor threshold in the depressed patients and to 152% (range 105–187%) in the improved patients. The difference between study groups was not statistically significant (Table 1).

### 2.5. Data analysis

Data were analyzed using SPSS for Windows. Differences related to groups and conditions were assessed using a mixed analysis of variance (ANOVA) with the between-subjects factor group (depressed, improved) and the within-subjects factors rTMS site (right DLPFC, left DLPFC, mesial occipital=control), shift (shift blocks, non-shift blocks), and valence (positive, negative task stimuli). Statistically significant main effects or interactions were further explored by conducting simple effects analyses. The significance level was always kept at  $P < 0.05$ .

## 3. Results

### 3.1. Task performance at baseline prior to rTMS

The total number of errors was 36.0 ( $\pm 13.2$ ; mean  $\pm$  S.D.) in the acutely depressed group and 24.4

( $\pm 9.2$ ) in the improved group (Fig. 2A). The comparison between groups revealed a significantly better performance in improved patients (*t*-test for independent groups;  $t=2.2$ ,  $P=0.04$ ). The average difference between the two groups was 11.6 errors. In addition to this group difference, we observed a significant correlation between task performance and HRSD scores independent of group (Fig. 2B; Pearson  $r=0.57$ ,  $P=0.014$ ). Larger HRSD scores were associated with larger error numbers in the AGN task.

### 3.2. TMS\*group interaction

Across groups, there was no significant effect of rTMS ( $F<1$ , n.s.). However, the TMS\*group interaction was significant ( $F_{[2,32]}=4.1$ ,  $P=0.03$ ), indicating differential rTMS effects between groups (Fig. 3). In acutely depressed patients, right prefrontal rTMS significantly reduced the error number relative to control stimulation ( $F_{[1,9]}=7.7$ ,  $P=0.02$ ), while left prefrontal rTMS had no significant effect ( $F<1$ , n.s.). Furthermore, depressed patients showed no significant difference between right and left prefrontal rTMS ( $F_{[1,9]}=1.1$ ,  $P=0.32$ ). In the improved group, left prefrontal rTMS significantly increased the error number relative to control stimulation ( $F_{[1,7]}=5.4$ ,  $P=0.05$ ). In addition, this group showed a trend towards a disruptive effect of right prefrontal rTMS ( $F_{[1,7]}=4.86$ ,  $P=0.063$ ). Also in this group, no significant difference was observed between right and left prefrontal rTMS ( $F<1$ , n.s.).

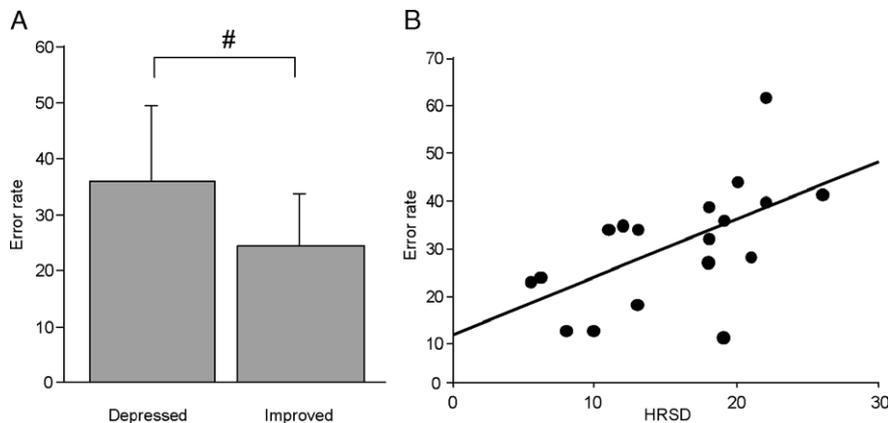


Fig. 2. Task performance at baseline. (A) Error numbers for acutely depressed and improved patients. Error bars show the S.D. #,  $P=0.04$ . (B) Positive correlation between task performance and depression severity (HRSD scores). Pearson  $r=0.57$ ,  $P=0.014$ . Note that acutely depressed patients had HRSD scores  $\geq 18$ .

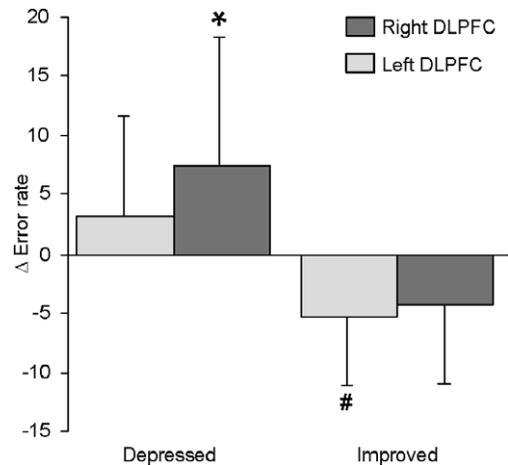


Fig. 3. TMS\*group interaction ( $P=0.03$ ). The *y*-axis represents difference values in error numbers relative to mesial occipital rTMS (active control). The average number of errors associated with mesial occipital rTMS was  $31.7 (\pm 7.8)$  in the acutely depressed group and  $16.4 (\pm 4.7)$  in the improved group. Positive  $\Delta$  error numbers represent improvement and negative  $\Delta$  error numbers represent impairment of task performance. Error bars show the S.D. \*,  $P=0.02$ ; #,  $P=0.05$ .

Fig. 4 shows the individual effects of right and left prefrontal rTMS for the acutely depressed group. Compared with mesial occipital rTMS (active control stimulation), right prefrontal rTMS led to improved task performance in 9 out of 10 depressed patients. In contrast, left prefrontal rTMS produced heterogeneous changes in error number, with improvement in some patients and impairment in others.

### 3.3. Correlation between right prefrontal rTMS effect and depression severity

To further assess the effect of right prefrontal rTMS in relation to the severity of depression symptoms, we correlated its impact on AGN task performance (as indexed by the error number relative to control stimulation) with the severity of depression (as indexed by HRSD scores) (Fig. 5). This analysis revealed a significant positive correlation (Pearson  $r=0.57$ ,  $P=0.013$ ). The larger the HRSD score of a patient, the more this patient improved following right prefrontal rTMS. This correlation remained significant even if the patient with the greatest  $\Delta$  error number ( $=26$ ), a relative outlier, was excluded from the analysis (Pearson  $r=0.54$ ,  $P=0.03$ ). For left prefrontal rTMS, we found no significant correlation (Pearson  $r=0.27$ , n.s.).

### 3.4. Effects of set-shifting and valence

Across groups, there was a significant effect of the factor shift ( $F_{[1,16]}=12.57$ ,  $P=0.003$ ), with larger error numbers during shift than during non-shift blocks, indicating greater difficulty in the shift blocks. The average error number was  $13.5 (\pm 4.5)$  for the shift blocks compared with  $10.9 (\pm 4.6)$  for the non-shift blocks. In contrast, there was no significant main effect of valence ( $F=1.1$ , n.s.).

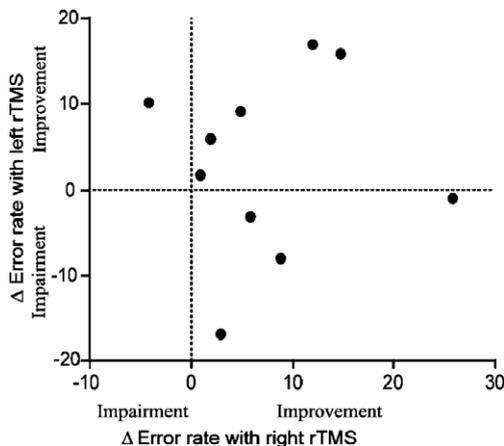


Fig. 4. Individual effects of right and left prefrontal rTMS in the depression group. Both axes represent difference values in error numbers relative to mesial occipital rTMS (active control). Positive  $\Delta$  error numbers represent improvement and negative  $\Delta$  error numbers represent impairment of task performance.

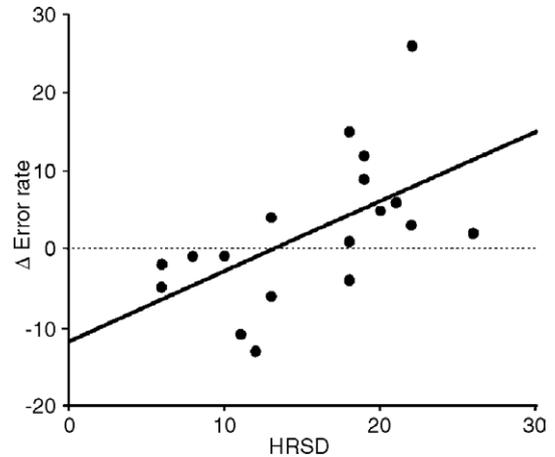


Fig. 5. Positive correlation between the effect of right prefrontal rTMS and depression severity (HRSD scores). The  $y$ -axis represents difference values in error numbers (right DLPFC versus control). Positive  $\Delta$  error numbers represent improvement and negative  $\Delta$  error numbers represent impairment relative to control. Note that acutely depressed patients had HRSD scores  $\geq 18$ . Pearson  $r=0.57$ ,  $P=0.013$ .

The factor shift tended to affect the TMS\*group interaction, as reflected in a trend for the three-way interaction TMS\*group\*shift ( $F_{[2,32]}=2.7$ ,  $P=0.08$ ). This trend was due to a more pronounced TMS\*group interaction in the shift blocks compared with the non-shift blocks. However, the kind of TMS\*group interaction did not change between shift and non-shift blocks.

The factor valence neither significantly influenced the effect of TMS ( $F_{[2,32]}=1.4$ , n.s.) nor the TMS\*group interaction ( $F<1$ , n.s.), indicating that TMS affected responses to positive and negative task stimuli in a similar way in our experiment.

## 4. Discussion

We found that the AGN task performance correlated with depression severity (HRSD score) in acutely depressed and improved (i.e., partially or completely remitted) patients. One session of slow rTMS over the right DLPFC enhanced the AGN task performance in acutely depressed patients. This beneficial effect declined with decreasing depression severity (HRSD score) and tended to reverse in the improved group. Slow rTMS over the left DLPFC had no significant

effect on performance in the depressed group, but it resulted in impaired task performance in the improved group. Taken together, our findings indicate that the acute response of depressed patients to slow rTMS depends on the stimulation site and the clinical state prior to rTMS.

The significant correlation between AGN task performance and HRSD scores confirms previous studies suggesting that the AGN task is an adequate method to assess neuropsychological deficits associated with major depression (Murphy et al., 1999; Elliott et al., 2002). This finding also suggests that in its linkage of emotional and cognitive functions, the AGN task may be used as a rough indicator for the general clinical state of depressed patients. This could make the AGN task a valuable tool for studying acute rTMS effects in depressed patients, given that it allows the objectivation of small changes produced by only one session of rTMS, which is difficult to achieve using the HRSD or other rating scales. Such acute effects may have predictive value for the response of patients to multiple sessions of rTMS applied as a therapeutic means.

In acutely depressed patients, we observed improved AGN task performance following slow rTMS over the right DLPFC. The enhancing effect was specific to this stimulation site and patient group, and it appeared in 9 out of 10 patients. Our finding is in line with therapeutic rTMS studies associating improvement of mood (Feinsod et al., 1998; Klein et al., 1999; Menkes et al., 1999; Fitzgerald et al., 2003) and motor symptoms (Hoppner et al., 2003) with slow rTMS over the right DLPFC. The finding is also consistent with the imbalance hypothesis of depression, which implicates a relative hyperactivity of the right relative to the left prefrontal cortex in the pathophysiology of depression (Sackeim et al., 1982). Based on this hypothesis, one might assume that, in our study, 1-Hz rTMS over the right DLPFC transiently suppressed activity in this region. This might have reduced the detrimental prefrontal asymmetry during the subsequent task period. The imbalance hypothesis would also explain the significant impairment associated with left prefrontal rTMS in the partially or completely remitted patients. It has been suggested that prefrontal asymmetry disappears with remission (George et al., 1995; Kocmur et al., 1998; Mottaghy et al., 2002); one may therefore

speculate that, in our study, left prefrontal rTMS transiently re-established 'depression-like' left prefrontal hypoactivity in the partially or completely remitted patients, resulting in temporary 'depression-like' impairment in AGN task performance. One might further speculate that right prefrontal rTMS caused a reverse imbalance (right prefrontal hypoactivity) in the partially or completely remitted group. Such a reverse imbalance might explain the trend towards impaired task performance associated with right prefrontal rTMS in this group.

In the acutely depressed group, slow rTMS over the left DLPFC induced not even a trend ( $F < 1$ ) towards an effect on AGN task performance. Based on the imbalance hypothesis of depression, one could have expected a disruptive effect, since slow left prefrontal rTMS might aggravate the prefrontal asymmetry. The absence of such disruption might reflect a floor effect. Given the baseline hypoactivity observed in the left DLPFC of many acutely depressed patients (Ebert et al., 1991; Sackeim et al., 1993; Kocmur et al., 1998; Mottaghy et al., 2002), it seems possible that left prefrontal rTMS might not be able to further suppress the activity in this region. However, it should be noted that the response to left prefrontal rTMS varied considerably between the individual acutely depressed subjects, with some patients showing improvement and others impairment (Fig. 4). Such large variability between individual responses to 1-Hz rTMS has been observed in other studies and might potentially be related to variable baseline metabolism in the left DLPFC (Kimbrell et al., 1999; Loo et al., 2003b).

The present experiment also showed no significant difference between left and right prefrontal rTMS in the acutely depressed group. The absence of such a difference might be due to the relatively low number of study participants combined with the above-mentioned high variability in the left prefrontal rTMS condition. Potentially, it could also be due to an improvement associated with left prefrontal rTMS. However, our data did not show such a trend ( $F < 1$ ).

The HRSD score correlated with the improvement in AGN task performance induced by right prefrontal rTMS (1 Hz). The more severely depressed a patient was, the greater the beneficial effect of slow rTMS over the right DLPFC. With decreasing HRSD scores, this enhancing effect disappeared and turned into the trend towards a disruptive effect in the improved group. Our

findings therefore demonstrate a differential response to right prefrontal rTMS (1 Hz) within depressed patients as a function of the individual clinical state at treatment. This finding is in accordance with previous studies of rTMS effects on mood in healthy normals (George et al., 1996; Pascual-Leone et al., 1996a; see, however, Mosimann et al., 2000) and manic patients (Grisaru et al., 1998; Erfurth et al., 2000; Michael and Erfurth, 2004; see, however, Kaptan et al., 2003). Similar to the improved patients in our experiment, these studies found that the effects of rTMS on mood were opposite between normal (or manic) subjects and acutely depressed patients. Our finding is also in line with previous functional neuroimaging studies reporting that DLPFC abnormalities appear during acute episodes and normalize during remission (Drevets, 2000; Mayberg, 2003), indicating state dependency of prefrontal changes in major depression.

It could be argued that the improved task performance associated with right prefrontal rTMS in the depressed group is simply the result of a non-specific alerting effect, occurring in the more unpleasant prefrontal rTMS conditions and the more 'distracted' acutely depressed patient group. However, the following considerations speak for a more specific effect of rTMS in our experiment. First, one would expect some alerting effect also in the partially or completely remitted patients. However, these patients showed impairment rather than improvement in the prefrontal rTMS conditions compared with mesial occipital rTMS (Figs. 3 and 5). Similarly, healthy subjects with no history of major depression have previously shown impaired AGN task performance associated with left prefrontal compared with mesial occipital rTMS (Berpohl et al., 2005). Second, a non-specific alerting effect should affect not only the right but also the left prefrontal rTMS condition. However, the depressed group did not show a trend towards improvement in the left prefrontal rTMS condition ( $F < 1$ ), and we found no correlation between left prefrontal rTMS effect and depression severity across study groups. Third, rTMS was administered before rather than during task performance in the present experiment (off-line rTMS procedure). It seems relatively unlikely that the pain-related alerting effect would considerably outlast the period of painful stimulation.

The differential effect of rTMS between groups tended to be more pronounced in the shift than in the

non-shift blocks. This trend might be due to higher task demands in the shift blocks, as reflected in the main effect of the factor shift. It seems plausible that more demanding blocks of the task are more likely to be disrupted or to benefit from rTMS (Pascual-Leone et al., 1999, 2000).

The lateralization theory of valence postulates that the left hemisphere is dominant for positive emotions and the right hemisphere for negative emotions (Davidson and Irwin, 1999; Murphy et al., 2003; Wager et al., 2003). Based on this theory, one would have expected that left prefrontal rTMS might have had a stronger impact on responses to positive stimuli and right prefrontal rTMS on responses to negative stimuli. In our experiment, however, the rTMS effect did not differ between responses to positive and negative task stimuli. One plausible explanation for this is that our experiment was not sufficiently powered to reveal the valence lateralization effect.

Our study design using off-line rTMS was based on the study by Romero et al. (2002), who observed a decrease in excitability over the primary motor cortex outlasting a 10-min block of 1-Hz rTMS. In this study, the effect lasted for about 10 min after the train completion. Similar to other cognitive off-line rTMS studies (cf. Robertson et al., 2003), we assumed that rTMS-induced modulation of cortical excitability would comparably apply to non-motor cortical areas such as the DLPFC and the mesial occipital cortex. To account for potential differences between these non-motor regions and motor cortex as well as for inter- and intra-individual variability, we used an inter-run interval (45 min) that was more than four times longer than the effect observed by Romero et al. (2002). Nonetheless, it is acknowledged that we cannot exclude a remaining carry-over effect. Such an effect has to be considered, given that cumulative plastic changes of motor cortex excitability were found when rTMS was repeated after 24 h (Baumer et al., 2003). However, carry-over effects should not have influenced our results, because we have counterbalanced conditions according to the Latin Square method in the present experiment. Therefore, rTMS effects lasting longer than 45 min would have equally affected the three conditions studied.

To ensure high TMS intensities in all study participants, the present experiment set the intensity to a fixed level of 60% of maximum stimulator output

(which was above motor threshold in all subjects). This is a pragmatic and adaptable approach that might in the future allow reducing the experiment duration and limiting the number of TMS pulses. Although this method is uncommon in therapeutic rTMS studies, several virtual lesion studies in normal humans have previously selected a fixed intensity defined by the stimulator output (e.g., Beckers and Zeki, 1995; Corthout et al., 1999; Lewald et al., 2002). The present study did not determine the magnetic stimulus intensity based on individual motor thresholds, as there is no evidence that motor thresholds correlate with the effects of rTMS outside the motor cortex (Stewart et al., 2001; Robertson et al., 2003). Also in our study, the effects of rTMS did not vary with motor thresholds. When motor thresholds were used as a covariate in the overall ANOVA, our finding of a TMS\*group interaction remained significant ( $P=0.02$ ). Neither the enhancing effects of right prefrontal rTMS observed in the acutely depressed group nor the impairing effects of left prefrontal rTMS observed in the improved group correlated with motor thresholds (Pearson  $r=0.52$ ,  $P=0.13$  and Pearson  $r=0.30$ ,  $P=0.46$ , respectively).

Another methodological consideration concerns the antidepressant medication of the patients studied. Although the naturalistic medication of acutely depressed and improved patients involved comparable substances and dosages, we cannot exclude that slight differences in medication account for part of the group differences reported here. A final methodological consideration refers to our mesial occipital control condition. Such an active control TMS controls for non-specific rTMS effects better than a sham control. However, one could argue that the difference observed in the depressed group between right prefrontal and mesial occipital rTMS might have been due to a disruptive effect of occipital rTMS rather than to an enhancing effect of right prefrontal rTMS. Since sham TMS was not used in the experiment, we cannot exclude this possibility. However, it seems unlikely for two reasons. First, when we compared the occipital rTMS condition with the pre-TMS baseline run in the depressed group, we did not find any significant difference ( $P=0.13$ ). Second, mesial occipital rTMS was associated with better rather than worse AGN task performance in improved patients.

In summary, our results reveal beneficial effects of rTMS in acutely depressed patients that are apparent

after a single 10-min session of stimulation when rTMS effects are assessed using an AGN task. It is conceivable that the paradigm used here could have clinical implications as a convenient tool for probing the responsiveness of a patient to rTMS before therapeutic long-term rTMS treatment is considered. The paradigm could provide an early index for rTMS outcome and establish a more individualized treatment approach. Such a behavioral index appears desirable, given the high variability across depressed patients in their responsiveness to rTMS, presumably related to the existence of different sub-types of depression (Holtzheimer et al., 2001; Burt et al., 2002; Gershon et al., 2003). In the present study, for example, one patient showed a beneficial effect of left prefrontal rTMS and a detrimental effect of right prefrontal rTMS (Fig. 4, left upper quadrant). Unlike other acutely depressed patients, this patient might profit from left rather than right prefrontal rTMS at 1 Hz. A recent study has suggested that previous response to therapeutic rTMS might be a predictor of the success of future sessions (Dannon et al., 2000). At this point, however, we do not yet know whether a subject's response to one rTMS session corresponds to the response of the same subject to multiple sessions. Further studies are needed to elucidate whether the individual response pattern observed in the present paradigm is predictive of the long-term benefit associated with certain stimulation parameters.

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