

# Acute effects of repetitive transcranial magnetic stimulation on attentional control are related to antidepressant outcomes

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**Background:** Repetitive transcranial magnetic stimulation (rTMS) applied over the dorsolateral prefrontal cortex (DLPFC) is a new treatment procedure that holds promise of more insight into the pathophysiology of depression because the DLPFC may play an important role in the interplay between emotional and attentional information processing. We sought to investigate whether acute neurocognitive effects of rTMS are related to antidepressant outcomes. **Methods:** Between January 2005 and May 2007, we examined the effects of a single session compared with 2 weeks of rTMS over the left DLPFC on cognition and mood in therapy-resistant patients with depression. We used a crossover placebo-controlled double-blind design and differentiated rTMS treatment responders and nonresponders. We used a task-switching paradigm to measure cognitive function. **Results:** After 2 weeks of high-frequency rTMS over the left DLPFC, depressive symptoms improved in more than half (53%) of our therapy-resistant population. After a single session, mood did not improve but attentional control was increased solely within our group of treatment responders. **Limitations:** Our results should be interpreted as preliminary because our sample was small and because the cognitive task we used has not been tested for validity and reliability. In addition, despite minimal stimulation of the DLPFC during sham stimulation, it is possible that the stimulation was partially active. Finally, benzodiazepines may have had impairing effects on the attentional task. **Conclusion:** Cognitive reactivity after a single session of rTMS may hold promise as a predictor of beneficial treatment outcomes. Moreover, within the group of responders, attentional control appears to play an important role in the progress of mood disorders.

**Contexte :** La stimulation magnétique transcrânienne répétitive (SMTr) appliquée au niveau du cortex préfrontal dorsolatéral (CPFDL) est une nouvelle modalité thérapeutique qui recèle la promesse d'une meilleure compréhension de la physiopathologie de la dépression, parce que le CPFDL pourrait jouer un rôle important dans l'interaction entre le traitement de l'information émotionnelle et attentionnelle. Nous avons voulu vérifier si les effets neurocognitifs de la SMTr sont liés à des résultats antidépresseurs. **Méthodes :** Entre janvier 2005 et mai 2007, nous avons comparé les effets d'une seule séance à ceux de 2 semaines de traitement par SMTr appliqué au niveau du CPFDL gauche sur la cognition et l'humeur chez des patients dépressifs réfractaires au traitement. Nous avons utilisé un protocole à double insu contrôlé par placebo avec permutation des groupes pour distinguer les participants répondant à la SMTr de ceux n'y répondant pas. Nous avons utilisé un paradigme de changement de tâches pour mesurer le fonctionnement cognitif. **Résultats :** Après 2 semaines de traitement par SMTr à haute fréquence, appliqué au niveau du CPFDL gauche, les symptômes dépressifs se sont améliorés chez plus de la moitié (53 %) de notre population réfractaire au traitement. Après une seule séance, l'humeur ne s'est pas améliorée, mais le contrôle de l'attention avait augmenté, et ce, uniquement dans notre groupe répondant au traitement. **Limites :** Nos résultats doivent être considérés comme préliminaires puisque notre échantillon était petit et que la tâche cognitive utilisée n'a pas fait l'objet de tests de validité et de fiabilité. En outre, malgré le faible degré de stimulation du CPFDL pendant la stimulation factice, il est possible que cette dernière ait été partiellement active. En terminant, les benzodiazépines peuvent avoir eu des effets négatifs sur l'exécution de la tâche attentionnelle. **Conclusion :** La réactivité cognitive après une simple séance de SMTr pourrait se révéler prometteuse à titre de prédicteur des effets bénéfiques du traitement. De plus, dans le groupe ayant répondu au traitement, le contrôle de l'attention semble jouer un rôle important dans la progression des troubles de l'humeur.

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## Introduction

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive method of neuronal depolarization of specific areas of the human brain, is a relatively new technology that holds promise for therapeutic advances and insight into the pathophysiology of depression.<sup>1</sup> To date, numerous open and controlled clinical trials have demonstrated that high-frequency (> 1 Hz) rTMS applied over the left dorsolateral prefrontal cortex (DLPFC) and low-frequency (< 1 Hz) rTMS applied over the right DLPFC have antidepressant effects (for a review see Gershon and colleagues<sup>2</sup>). On the other hand, a detailed review of the literature reveals that the data to date are inconsistent.<sup>1,3</sup> Because of these contradictory results, the efficacy of rTMS remains a topic of debate.

Recent positive, sham-controlled studies with more aggressive treatment parameters and large numbers of sessions demonstrated the efficacy of rTMS in the treatment of depression.<sup>4,5</sup> Therefore it appears desirable to further assess the antidepressant effects of high-frequency rTMS over the left DLPFC,<sup>6</sup> and one promising avenue might be to investigate characteristics of treatment responders versus non-responders. This makes it possible to search for markers of rTMS effects and to investigate possible mechanisms underlying its therapeutic efficacy. It has recently been argued that the heterogeneity of research findings might be due to a high variability in response to rTMS among depressed patients.<sup>7</sup> Whereas previous research focused mainly on exogenous stimulation parameters, we sought to investigate endogenous features predicting outcomes of treatment.

Positron emission tomography and functional magnetic resonance imaging (fMRI) studies have established a regulative role for a specific cortico-subcortical circuit in mood disorders<sup>8</sup> and, accordingly, have postulated that a dorsal circuit plays an important role in the interplay between emotional and attentional information processing.<sup>9</sup> We sought to explore underlying attentional mechanisms related to the outcome of antidepressant therapy with rTMS, starting with nonemotional stimuli. Although rTMS is currently used as a new tool for neuropsychological research in healthy individuals,<sup>10</sup> cognitive function in studies investigating clinical populations is frequently viewed as epiphenomena.<sup>3</sup> The most common observation of previous studies is that rTMS has no major detrimental cognitive effects after several weeks of daily rTMS in depressed patients.<sup>11</sup> Some of these studies reported improvement among depressed patients on a number of cognitive tests, including verbal memory,<sup>12</sup> verbal fluency<sup>13</sup> and list recall,<sup>14</sup> after 2 weeks of high-frequency (1–20 Hz) rTMS over the left DLPFC.

Research performed in our laboratory suggests that one session of placebo-controlled high-frequency rTMS over the left DLPFC in medication-free patients with depression has a beneficial effect on task-switching performance but not on mood (unpublished data). We administered stimulation within the parameters used in recent clinical studies that reported an antidepressant outcome. As a result, one could suggest that cognitive changes emerge before an antidepressant effect of rTMS is observed and that later changes in depressive symptoms might be a secondary effect of this

treatment. Previous studies have demonstrated no correlation between improvement in mood and improvements in executive function after a single session of high-frequency rTMS,<sup>15</sup> after 5 sessions (in healthy volunteers),<sup>16</sup> or after anodal transcranial direct current stimulation<sup>17</sup> and rTMS<sup>18</sup> (in depressed patients), all administered over the left DLPFC. However, when exploring the interplay between attentional and emotional function, it may be that very specific components of cognitive function should be investigated because selective attention and working memory are heterogeneous constructs. Therefore, it may be that immediate effects of rTMS on attentional control and mood should be investigated using a placebo-controlled design differentiating responders and non-responders.<sup>19</sup> In the present study, we included a homogeneous group of medication-free, therapy-resistant patients with depression to investigate the influence of a single session of rTMS over the left DLPFC compared with 2 weeks of daily sessions.

Cognitive flexibility, which is required during task-switching, is an operationalization of attentional control, a core function of the DLPFC that is impaired among depressed patients.<sup>20</sup> We extended our previous single-session rTMS study using a task-switching paradigm (unpublished data) to measure cognitive function before and after rTMS. We tested cognitive performance before treatment, after a single session and after 2 weeks of rTMS. In light of our previous results and those in the existing literature, we hypothesized that rTMS would have a significant beneficial effect on depressive symptoms only after 2 weeks of treatment and that positive effects on task-switching performance after 1 session of high-frequency rTMS would differentiate treatment responders and nonresponders. We defined responders as those showing a 50% or more reduction in their Hamilton Depression Rating Scale (HAM-D) scores after treatment. Furthermore, we predicted that after 2 weeks of rTMS cognitive improvements would be observed only in treatment responders, whereas the cognitive performance of nonresponders would not change.

## Methods

The present study was part of a larger project investigating the influence of rTMS on different neurocognitive markers. Data on 5 of our participants were also included in a previous study on the effects of 1 session of rTMS (unpublished data).

### Participants

We recruited a homogeneous group of right-handed patients with refractory depression from in- and outpatient facilities of the University Hospital of Brussels (UZ Brussel) between January 2005 and May 2007. The local Medical Ethics Committee of UZ Brussel approved our study protocol. After a full description of the experiment, we obtained written informed consent from all participants.

A detailed psychiatric examination along with the structured Mini International Neuropsychiatric Interview<sup>21</sup> confirmed the diagnosis of a major depressive episode with melancholic features for all participants. We assessed treatment resistance using the Thase and Rush criteria.<sup>22</sup>

We weaned patients from their antidepressants or augmentation medications, including mood stabilizers or antipsychotics, for at least 2 weeks before administering rTMS. If the patients were using fluoxetine, we required them to be free of antidepressant pharmacotherapy for at least 3 weeks. A trained psychiatrist (C.B.) closely monitored the patients during the weaning process. Once the patients had withdrawn, they remained on a steady dose of their somatic medication and, if necessary, on a steady dose of benzodiazepines. We used the following types and doses of benzodiazepines: tranxene (10 mg twice daily), alprazolam (1 mg twice daily), rivotril (0.5 mg 3 times daily) and zolpidem (10 mg once daily). We included only patients who did not need rescue medication or concomitant therapies during this period in our study, and we included patients only if this condition had been maintained for about 2 weeks. We allowed no change in any of their medications during the stimulation sessions. If patients required any changes in medication, we considered them to be dropouts.

All participants underwent a physical and neurologic examination (electroencephalography) and structural 3-dimensional magnetic resonance imaging (MRI) of the brain for nonstereotactic identification of the stimulation site (Brodmann area 9/46, left DLPFC). None of the patients had received rTMS before, and all met the safety criteria for rTMS.<sup>23</sup> We included only patients whose scores on the 17-item HAM-D<sup>24</sup> were 21 or higher. We excluded patients if they had any history of physical illness likely to affect brain physiology; head injury; comorbid psychiatric conditions, including alcohol or substance abuse; bipolar disorder; or contraindications to rTMS.

### Stimulation protocol

The rTMS stimulation parameters were well within the established safety guidelines.<sup>23</sup> We performed magnetic stimulation using a MAGSTIM high-speed magnetic stimulator (Magstim Company Ltd.) combined with a figure-8-shaped coil.

On the first treatment trial, we established a stimulation intensity of 110% of the motor threshold of the right abductor pollicis brevis muscle using electromyography. We determined the precise DLPFC site using MRI, marked the skull and administered stimulation with the coil at a fixed position for all sessions of rTMS.

We delivered 10 sessions of high-frequency (10 Hz) rTMS daily from Monday to Friday over a period of 2 weeks. We used the following parameters for each session: 40 trains of 3.9 seconds' duration separated by an intertrain interval of 26.1 seconds, resulting in 1560 pulses per session. The total stimulation time was about 20 minutes. At the start of their rTMS treatment, each patient also received 1 sham placebo-stimulated session. We used a crossover design to determine what type of stimulation would be administered during the first session (rTMS or sham). Sham stimulation was administered at the same location on the skull as rTMS, but the figure-8-shaped coil was held at a 90° angle, resting on the scalp with only 1 edge, in compliance with recent sham guidelines.<sup>25</sup> During stimulation, all participants wore earplugs and blindfolds to guarantee "optimal" blinding.

### Clinical mood assessments

To evaluate antidepressant outcome, we assessed the efficacy of rTMS using the HAM-D scores at baseline and after 2 weeks. We considered patients to be responders to treatment if the HAM-D score after treatment had decreased by 50% or more from baseline.<sup>19</sup> To evaluate immediate subjective mood changes, we asked patients to indicate their current mood states on visual analogue scales that included subscales for depression, anger, fatigue, vigour and tension. We asked participants to describe how they felt "at that moment" by indicating on horizontal 10-cm lines whether they experienced these 5 mood states on a scale from "totally not" to "very much." We used the scales to record mood at various stages of the experiment: at baseline ( $T_{pre}$ ), immediately after rTMS ( $T_{post}$ ), about 30 minutes after the first session ( $T_{post30}$ ) and at the end of the rTMS treatment period ( $T_{posttreatment}$ ).

### Task-switching paradigm

Participants performed a computerized self-paced switching task. The device consisted of a board (connected to a personal computer) with 1 push button in the middle and 8 push buttons positioned in a semicircle around the central button. In addition, a speaker and a pedal were connected to the device.

The paradigm included 3 continuous task blocks in which the first 2 blocks consisted of repetitive tasks (1 with 28 visual stimuli and 1 with 28 auditory stimuli), whereas the last block consisted of switch trials. The 2 motor responses involved different stimulus modalities and, therefore, non-overlapping neural systems.

During the first block, we instructed patients to remove their fingers from the central push button and put out the illuminated push buttons. At each visual trial, 4 of the 8 push buttons could illuminate randomly, 1 at a time. For visual trials, we recorded 2 components of the reaction time: namely, initiation time and movement time. Initiation time, a central cognitive component, referred to the time required to initiate a response and corresponded to the time that lapsed between stimulus onset and the release of the middle push button. Movement time, a peripheral executive component, referred to the motor activity or the time required to complete the response.<sup>26</sup>

In the second block, we instructed participants to press a foot pedal when they heard a buzzer. In this task, only total reaction time could be recorded. We instructed participants to place their feet above the pedal and to respond to the signal as quickly and as accurately as possible.

The third block, the double task condition, was an alternating switch block with 29 auditory and 28 visual stimuli that were randomly mixed. During the switch block, 24 of the 29 auditory signals and 25 of the 28 visual signals were switch trials (we analyzed only the switch trials). Because of a technical problem, the first trials were lost and only 22 auditory and 22 visual switch trials could be recorded. We instructed patients to focus their attention on the visual stimuli and to switch attention when the auditory stimuli appeared. After each response to a visual trial, patients had

to return their fingers to the central push button as quickly as possible, triggering stimulus onset asynchrony for the next trial. After every auditory signal, they had to take their feet off the pedal to trigger stimulus onset asynchrony for the next trial. In each of the 3 tasks, stimulus onset asynchrony differed randomly between 3000 ms and 6000 ms. We used the same trial sequence for all participants. If errors occurred, we replaced stimuli to obtain the same amount of correctly performed reactions for every participant. We removed movement times greater than 3000 ms (considered to be a delayed reaction time) and less than 200 ms (considered to be an anticipatory reaction time) from our analyses. We considered delayed or anticipatory reaction times for initiation time and auditory reaction times to be errors, and these were replaced by a new stimulus.

### Statistical analysis

We conducted a multivariate analysis of variance (MANOVA) to analyze short-term mood changes after a single session of high-frequency rTMS for mood scores, evaluated with 5 visual analogue subscales as dependent variables. We conducted a  $2 \times 3 \times 2$  mixed MANOVA with stimulation (rTMS, sham) and time ( $T_{pre}$ ,  $T_{post}$ ,  $T_{post30}$ ) as within-subject factors and treatment response (responder/nonresponder) as a between-subject factor.

For task-switching analyses, we used 3 dependent variables for each analysis of variance (ANOVA): namely, the mean reaction time in milliseconds on visual (initiation time and movement time) and auditory (total reaction time) switch trials, corrected for individual processing speed. More specifically, we used the reaction time on visual and auditory switch trials from block 3 minus the reaction time on repetitive trials from block 2 and block 1, respectively.

For the expected acute effects of rTMS on task-switching results, we performed 3 sets of repeated-measures ANOVA to analyze the immediate effects of rTMS on cognition for all participants. The basic design was a  $2 \times 2 \times 2 \times 2$  design with stimulation condition (rTMS, sham) and time ( $T_{pre}$ ,  $T_{post30}$ ) as within-subject factors and treatment response (responders/nonresponders) and order (first sham/first rTMS) as between-subject factors.

Moreover, we performed 3 sets of mixed ANOVA to analyze the expected treatment effects of 2 weeks of rTMS on measures of cognitive processing. We used a  $2 \times 2$  factorial design, including time (pre- to posttreatment) as a within-subject factor and treatment response (responders/nonresponders) as a between-subject factor. For each participant, we based premeasures of cognitive processing on the first task-switching performance, which occurred before either rTMS or sham stimulation.

To further explore changes in cognitive function within groups of responders and nonresponders separately, we used Wilcoxon signed-rank nonparametric tests as conservatively as possible within the context of our small group sizes. Statistical significance was set at  $p < 0.05$  for all analyses. We conducted statistical analyses using SPSS software, version 12.0 (SPSS Inc.).

## Results

### Participants

We included 15 patients with refractory depression in our study. The mean age of patients was 45.6 (range 22–61, standard deviation [SD] 5.9) years. All patients were right-handed, according to the van Strien Hand Preference scale.<sup>27</sup> An overview of the demographic and clinical characteristics of all participants at baseline is presented in Table 1.

In 10 patients, the depressive episode had been diagnosed for the first time more than 3 years before our study and was considered to be at least stage III treatment resistant: these patients had a minimum of 2 unsuccessful trials with selective serotonin or serotonin–norepinephrine reuptake inhibitor therapy and 1 failed trial with tricyclic antidepressants, as described by Thase and Rush.<sup>22</sup> Five patients were considered to be stage V treatment resistant: they had unsuccessful trials with a monoamine oxidase inhibitor and a failed course of bilateral electroconvulsive therapy.

All patients tolerated the experimental procedure well; 2 participants reported a mild headache just after stimulation. We observed no difference in the Thase and Rush<sup>22</sup> treatment-resistance score ( $t < 1$ ) or in the types of antidepressants used ( $\chi^2_3 = 1.473$ ,  $p = 0.69$ ) among rTMS responders and nonresponders.

### Effects of rTMS on depressive symptoms (treatment response)

Eight out of 15 patients (53%) reported a 50% reduction in their scores on the HAM-D after 2 weeks of rTMS (treatment

**Table 1: Demographic and clinical patient characteristics at baseline**

Characteristic	Mean (SD)*
Age, yr	45.6 (5.87)
Sex, male:female	6:9
HAM-D score	23.3 (3.4)
BDI score	32.23 (7.28)
Age at onset of first depressive episode, yr	38.1 (16.4)
Failed antidepressant trials, no. (range)	3 (2–5)
Hospital admission during the study, %	54
Suicide risk at the start of the study, %	46

BDI = Beck Depression Inventory;<sup>28</sup> HAM-D = Hamilton Depression Rating Scale;<sup>24</sup> SD = standard deviation.  
\*Unless otherwise indicated.

**Table 2: HAM-D and BDI scores before and after rTMS treatment among responders and nonresponders**

Group	Test; time; mean (SD)			
	HAM-D		BDI	
	Pre rTMS	Post rTMS	Pre rTMS	Post rTMS
Responders (n = 8)	21.5 (8.26)	7.25 (2.76)	30.37 (7.99)	15.5 (5.47)
Nonresponders (n = 7)	24.14 (2.73)	20.42 (7.13)	32.42 (9.39)	29.71 (7.29)

BDI = Beck Depression Inventory;<sup>28</sup> HAM-D = Hamilton Depression Rating Scale;<sup>24</sup> rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation.

responders). At baseline, the HAM-D scores of responders and nonresponders did not differ significantly ( $z = 0.005, p = 0.98$ ). An overview of the group data is presented in Table 2.

*Short-term effects of rTMS on mood and depressive symptoms*

An overview of the visual analogue scale measures before ( $T_{pre}$ ), immediately after ( $T_{post}$ ) and 30 minutes after ( $T_{post30}$ ) rTMS or sham stimulation are presented in Table 3. Because of some missing values on the mood scales, we removed 2 participants from the analysis.

The main effect for treatment response did not reach significance ( $F_{5,7} = 1.986, p = 0.18$ ; stimulation  $F_{5,7} = 0.748, p = 0.61$  and time  $F_{5,7} = 3.463, p = 0.17$ ). We observed no 2-way interaction effects ( $F < 1.61$ ), and the interaction effect between stimulation, time and treatment response yielded no significant effect:  $F_{5,7} = 0.304, p = 0.93$ . Thus there were no short-term mood changes from baseline caused by high-frequency rTMS applied over the left DLPFC when comparing ratings immediately after or 30 minutes after stimulation for responders and nonresponders.

*Effects of rTMS on task-switching: treatment response*

Data on the effects of rTMS on task-switching are outlined in

Table 4 and Table 5. As predicted, the 2-way interaction between time and treatment response was significant  $F_{1,13} = 6.191, p = 0.027$  for initiation time in visual trials. The main effect of time was not significant ( $F < 1, p = 0.38$ ), whereas the main effect of treatment response was significant ( $F_{1,13} = 9.134, p = 0.010$ ). For movement time in visual trials, neither the main nor the interaction effect reached statistical significance ( $F < 1, p > 0.47$ ).

As expected, the 2-way interaction between time and treatment response in auditory reaction trials was significant ( $F_{1,13} = 14.088, p = 0.002$ ). The 2 main effects were not significant ( $F < 2.61, p > 0.51$ ).

Among our group of responders, 2 weeks of rTMS significantly decreased initiation time ( $z = 2.240, p = 0.025$ ) in visual trials and reaction time ( $z = 2.521, p = 0.012$ ) in auditory trials. In contrast, among nonresponders cognitive function did not change for either component of visual and auditory reaction times ( $z < 1.014, p > 0.26$ ). Most importantly within the context of this design, reaction times of responders and nonresponders did not significantly differ during their first task-switching performance (initiation time  $z = 1.154, p = 0.25$ ; movement time  $z = 0.694, p = 0.49$ ; auditory reaction time  $z = 0.581, p = 0.33$ ). Moreover, after rTMS there was a significant difference between responders and nonresponders in reaction times on initiation time ( $z = 2.199, p = 0.029$ ) and

**Table 3: Visual analogue scale measures before, immediately after and 30 minutes after rTMS or sham stimulation**

Visual analogue scale	Stimulation; time; mean (SD)					
	rTMS			Sham		
	Before	Immediately after	30 min after	Before	Immediately after	30 min after
Depression	5.65 (3.62)	5.56 (2.57)	5.76 (3.14)	6.54 (3.12)	5.63 (3.36)	5.53 (3.62)
Anger	1.56 (2.24)	0.86 (1.24)	0.65 (0.84)	1.22 (1.37)	0.43 (0.42)	0.74 (0.52)
Tension	4.99 (2.57)	4.34 (2.37)	4.56 (4.05)	4.65 (2.15)	4.85 (3.33)	4.63 (3.97)
Fatigue	6.12 (3.42)	6.98 (2.01)	7.98 (2.36)	7.54 (1.62)	6.83 (1.17)	7.69 (2.96)
Vigour	1.45 (2.01)	1.67 (2.07)	1.53 (1.45)	1.45 (1.53)	1.73 (0.69)	1.65 (2.01)

rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation.

**Table 4: Reaction time latencies in switch trials during task-switching with rTMS or sham stimulation in responders and nonresponders**

Group; trial	Stimulation; time; mean (SD), ms					
	rTMS			Sham		
	Before	Immediately after	2 wk after	Before	After	
<b>Responders (n = 8)</b>						
Auditory reaction time	447.98 (29.40)	414.46 (53.25)	385.14 (38.87)	441.76 (32.85)	420.96 (43.70)	
Initiation time, visual trials	467.30 (47.10)	409.81 (58.46)	375.51 (74.39)	447.05 (49.04)	430.67 (20.42)	
Movement time, visual trials	313.82 (36.86)	312.66 (32.47)	326.67 (29.22)	310.88 (35.23)	320.18 (46.30)	
<b>Nonresponders (n = 7)</b>						
Auditory reaction time	440.63 (56.68)	436.59 (52.10)	437.25 (83.54)	465.14 (68.54)	439.78 (34.99)	
Initiation time, visual trials	442.07 (38.88)	431.29 (37.20)	432.41 (100.18)	438.84 (51.67)	429.77 (46.23)	
Movement time, visual trials	306.12 (23.31)	310.71 (25.65)	309.23 (30.50)	305.07 (36.15)	326.44 (52.53)	

rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation.

auditory reaction times ( $z = 2.315, p = 0.021$ ), but not on movement time ( $z = 0.347, p = 0.78$ ).

We tested the same factorial design for repetitive trials. However, no main or interaction effects reached statistical significance ( $F < 1.2, p > 0.29$ ).

### Short-term effects of rTMS on task-switching

Because the factor order was not implicated in any main or interaction effect ( $F < 1.4$ ), we left this factor out of all subsequent analyses.

As predicted, the key 3-way interaction among treatment response, stimulation condition and time was significant for short-term effects of rTMS on initiation time in visual reaction times ( $F_{1,13} = 5.369, p = 0.039$ ). The main effect of time ( $F_{1,13} = 6.105, p = 0.029$ ) and the 2-way interaction between stimulation condition and time ( $F_{1,13} = 4.976, p = 0.046$ ) also reached statistical significance. The other main or 2-way interactions yielded no significant effects ( $F < 2.98, p > 0.11$ ).

Our ANOVA of movement time in visual trials yielded no main or interaction effects ( $F < 1.18$ ). The 3-way interaction ( $F_{1,13} = 0.003, p = 0.96$ ), indicating no effects of rTMS or sham stimulation on this component of visual reaction time among responders and nonresponders alike.

For auditory reaction times, the key 3-way interaction ( $F_{1,13} = 3.308, p = 0.09$ ) yielded no significant effects. Moreover, the main or interaction effects were not significant ( $F < 1, p > 0.48$ ), indicating no effects of rTMS or sham stimulation on this component.

We used Wilcoxon signed-rank nonparametric tests to further explore the interaction effects among responders. We found that, in contrast to sham stimulation ( $z = 0.420, p = 0.67$ ), reaction times for initiation time significantly decreased after rTMS ( $z = 2.308, p = 0.017$ ). We observed no changes among nonresponders ( $z < 0.943, p > 0.34$ ). Moreover, we found a significant difference in initiation time between changes after rTMS compared with sham stimulation among responders,

with the change after rTMS being greater ( $z = 2.100, p = 0.036$ ). Among nonresponders, the differences in changes before and after rTMS compared with sham stimulation did not reach significance ( $z = 1.840, p = 0.06$ ). To sort out a nonspecific influence of rTMS on cognitive function, we tested the same factorial design for repetitive trials. However, no main or interaction effects reached statistical significance ( $F < 1.3, p > 0.58$ ).

## Discussion

Evidence suggesting that rTMS might be a promising treatment procedure with rapid onset of action has aroused growing interest. However, inconsistent research findings on rTMS treatment outcomes indicate that further investigation of the possible underlying mechanisms and the characteristics of treatment responders is warranted.<sup>29</sup>

We therefore performed rTMS in a homogeneous research group of therapy-resistant medication-free patients with depression. We administered rTMS over the left DLPFC, which is a typical stimulation target in mood disorders, and measured depressed mood symptoms and attentional control before rTMS, after 1 session and after 10 sessions.

Subjective mood reports did not change after a single session of high-frequency rTMS. We measured positive treatment outcomes using the HAM-D. Although our sample was small, more than half (53%) of our therapy-resistant population experienced a decrease of at least 50% in their HAM-D scores after 2 weeks of daily high-frequency rTMS over the left DLPFC.

Among responders, we observed a significant improvement in attentional control after 1 double-blind placebo-controlled rTMS session. We demonstrated that a specific component of visual switch trials (i.e., initiation time) had improved after high-frequency rTMS. Movement time in visual switch trials and auditory switch trials (i.e., the motor component of switching) was not influenced by rTMS. Although it is known that both reaction and movement times are prolonged among patients with severe depression, it appears

**Table 5: Reaction time latencies in repetitive trials during task-switching with rTMS or sham stimulation in responders and nonresponders**

Group; trial	Stimulation; time; mean (SD), ms				
	rTMS			Sham	
	Before	Immediately after	2 wk after	Before	After
<b>Responders (n = 8)</b>					
Auditory reaction time	384.32 (34.73)	369.16 (27.74)	375.05 (23.91)	384.60 (35.36)	354.72 (53.30)
Initiation time, visual trials	371.43 (38.44)	365.90 (43.18)	359.71 (44.24)	365.70 (40.57)	362.03 (37.63)
Movement time, visual trials	2302.02 (30.80)	308.56 (42.69)	319.27 (33.46)	304.89 (34.26)	308.28 (39.60)
<b>Nonresponders (n = 7)</b>					
Auditory reaction time	375.50 (53.32)	385.43 (51.53)	383.90 (31.63)	387.78 (67.92)	364.40 (63.92)
Initiation time, visual trials	348.90 (24.63)	352.54 (23.09)	348.82 (23.16)	357.62 (27.51)	352.23 (13.19)
Movement time, visual trials	310.44 (35.90)	312.32 (44.44)	298.33 (48.47)	307.60 (58.10)	324.05 (63.61)

rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation.

that 2 weeks of rTMS does not influence motor aspects (movement time) of attentional control. These current findings are in accordance with the previous research conducted in our laboratory, indicating that a single session of rTMS does not affect movement time in healthy volunteers<sup>30,31</sup> or in depressed patients (unpublished data).

The enhancement of attentional control after a single session of placebo-controlled high-frequency rTMS over the left DLPFC is in line with the involvement of the DLPFC in the representation of goal-directed behaviour. The DLPFC has been shown to play a key role in sustaining task-relevant representations of nonemotional and emotional stimuli to accomplish the task goals.<sup>9</sup>

The acute effect of rTMS on cognition in depressed patients that we observed is in line with the results of 1 previous study,<sup>7</sup> but contrasts those of another study.<sup>32</sup> Compared with the latter experimental study, we used a relatively intensive treatment protocol (10 Hz, 110% of motor threshold, 1560 pulses per session), which may account for the rapid attentional control improvements. On the other hand, because the attentional control changes emerged in the group of treatment responders only when no mood effects had as yet occurred, cognitive effects are specific and interpretable, holding intriguing implications for clinical practice. Although recent sham-controlled studies used more aggressive treatment parameters (e.g.,  $\geq 110\%$  motor threshold;  $> 10$  sessions<sup>4,5</sup>) than we did, we also observed effects in a comparable depressed population after 2 weeks of treatment. Nevertheless, because in the present study we did not include a control group that received 2 weeks of sham stimulation, it might be that patients who showed cognitive changes after 1 session of rTMS are participants with the highest placebo response after 2 weeks of treatment. Although such a placebo response is not likely to occur among treatment-resistant patients, the only way to rule out the possibility that cognitive changes might be related to a placebo effect is to have a control group receiving 10 days of sham stimulation. Moreover, it has been shown recently that 1–4 additional weeks of rTMS seems to increase the response rate,<sup>33</sup> which might decrease the predictive value of cognitive tasks.

Most importantly, the current results highlight a link between higher attentional and emotional information processing, these 2 processing pathways being part of the same dorsolateral cortico-subcortical network. Neuroimaging studies are gradually beginning to unravel the underlying dynamics of these affective processing pathways. Reduced left DLPFC function within a fronto-subcortical network is thought to play a pivotal role in the pathophysiology of depression and to connect emotional and cognitive information processing.<sup>34</sup> Importantly, neuroimaging research faces the critical problem of understanding cause and effect, whereas rTMS can demonstrate causal relations in information processes. However, in psychiatry, rTMS has been studied mainly as a potential antidepressant treatment. Only limited research has been reported on cognitive effects of rTMS immediately after termination of stimulation, probably because cognitive effects have been investigated mainly to evaluate aspects of treatment safety.<sup>15</sup> To our knowledge, no other controlled studies

have demonstrated the role of specific attentional control processes on treatment outcome (unpublished data). However, prior studies have investigated acute changes after rTMS that may trigger an antidepressant outcome.

Wagner and coworkers<sup>15</sup> investigated the effects of 1 session of rTMS on healthy volunteers using a divided attention task. They proposed that the acute effects of rTMS on cognition may be produced by identical neurochemical changes that underlie successful antidepressant treatments. However, the fact that the study was based on a group of healthy volunteers made it difficult to link attentional changes during the hours after an rTMS session with the neurochemical changes underlying the antidepressant treatment.

Shajahan and colleagues<sup>35</sup> demonstrated an increased perfusion in the anterior cingulate cortex after the first rTMS session in depressed patients, but reported no improvements in verbal fluency. However, verbal fluency might not be the best choice to represent processes associated with the DLPFC and the left dorsolateral circuit. In line with our results, a study by Möller and colleagues<sup>36</sup> found that the P300, a major endogenous brain event-related potential component that has been found to be reduced in patients with depression, significantly increased in amplitude after rTMS over the left prefrontal cortex compared with sham stimulation. An increase in P300 amplitude is indicative of improved attentiveness.<sup>36,37</sup> Most importantly, no significant antidepressant effects were observed in this study after 5 days of stimulation. Finally, Bermpohl and colleagues<sup>7</sup> suggested that the affective go/no-go task, may be employed for its ability to predict an rTMS treatment response. Given the linkage between emotional and cognitive functions, the latter affective/cognitive task might serve as a rough indicator for clinical treatment response. In the present study, we used a nonemotional task focusing on attentional goal representations, and our results suggest that task-switching performance might be a promising predictor for the response of patients to multiple sessions of rTMS therapy. Moreover, higher attentional control appears to play an important role in the progress of mood disorders.

### Limitations

A number of important shortcomings deserve to be highlighted. Our results should be interpreted as preliminary because our sample was rather small. In addition, the absence of a control condition must be taken into account when interpreting the effects of rTMS that we observed. Another limitation of our study was the sham stimulation condition: despite the sham stimulation being performed at a 90° angle for minimal stimulation of the DLPFC, it is possible that the stimulation was partially active.<sup>25</sup> In addition, the cognitive task that we used has not been tested for reliability and validity. Finally, benzodiazepines may impair an attentional task, but they may improve scores on some subscales of the HAM-D. Therefore, we do not believe that this interfered with our results. Moreover, if necessary, patients received a steady dose of their benzodiazepines for a reasonable time before entering the study, and we permitted no temporary changes during the stimulation protocol.

In sum, our results suggest that rTMS primarily influences

higher attentional function. However, future research combining rTMS with functional brain imaging is necessary to provide further evidence of these cognitive changes as a marker of antidepressant effects.

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