The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/119615

Please be advised that this information was generated on 2019-03-21 and may be subject to change.
Objective: Several studies have demonstrated increased left orbitofrontal cortex (OFC) activity during negative and depressed mood. These mood states have also been associated with reduced memory for positive emotional stimuli. The aim of the present study was to investigate whether slow, inhibitory repetitive transcranial magnetic stimulation (rTMS) over the left OFC would improve memory for positive material. Methods: We carried out a study with a double-blind, within-subjects design, in which 12 healthy volunteers received 20 minutes of slow rTMS over the left OFC, placebo treatment over the left OFC and rTMS over the left dorsolateral portion of the prefrontal cortex. Effects on memory for fearful and happy faces were investigated. Results: Memory for happy faces was significantly improved after rTMS over the left OFC compared with placebo ($t_{10} = 2.4, p = 0.037$). Conclusions: These findings suggest a role of the OFC in positive emotional memory, which is in accordance with neuroimaging and neuropsychological data. It may be argued that dense projections from the OFC to the limbic emotional circuit are involved in emotional memory and, therefore, play a role in the effects of rTMS that we observed.

Introduction
Both fundamental and clinical repetitive transcranial magnetic stimulation (rTMS) studies of patients with depression have often targeted the left dorsolateral portion of the prefrontal cortex (DLPFC). Reduced left DLPFC functioning is thought to play a pivotal role in the pathophysiology of depression; hence, high-frequency rTMS is applied to boost neuronal activity locally. However, the DLPFC is not the only cortical brain region involved in depression. Several functional neuroimaging studies have demonstrated that both depressed mood and clinical depression are associated with increased activity in the more rostral part of the PFC, the orbitofrontal cortex (OFC), although findings of depression being linked to reduced OFC activity have also been reported. According to Drevets et al, the left OFC, in particular,
is involved in mood regulation and depressive symptomatology. In sum, slow, inhibitory rTMS over the left OFC might have positive effects on mood.

A robust cognitive emotional phenomenon in both mild and clinical depression is reduced memory for positive material. Heightened levels of the stress hormone cortisol and elevated depressed mood are associated with reduced memory for happy facial expressions. Further support for this notion was recently provided by Harmer et al., who demonstrated antidepressant actions in terms of increased positive emotional memory after a single administration of the antidepressant reboxetine to healthy volunteers. These findings show that acute manipulation procedures by way of pharmacological agents or rTMS in healthy volunteers can function as a human model for depression. In addition, reductions on autonomic indices of anxiety have been shown after applying slow rTMS over the left OFC in healthy volunteers, pointing at the possibility for improvements in emotion processing.

In the present study, the effects of a single session of slow, inhibitory rTMS over the left OFC on emotional memory and mood were investigated. It was hypothesized that subjects would show enhanced positive emotional memory after rTMS over the left OFC compared with placebo rTMS. Slow rTMS over the left DLPFC, which has shown counterintuitive antidepressant effects, was added to the design for explorative purposes.

Methods

Twelve young, healthy volunteers (6 men, 6 women) were enrolled in the study. All participants were right-handed, with a mean score of 45.4 (standard deviation [SD] 2.4) on the Edinburgh Handedness Inventory (the Handedness Inventory ranges from 0 [extreme left handedness] to 48 [extreme right handedness]), and were aged between 18 and 25 years. None of the subjects had a history of psychiatric or neurological conditions, and all had normal or corrected-to-normal vision. Written informed consent was obtained, and volunteers were paid for participation. The study was approved by the medical ethics committee of Utrecht University, in accordance with the Declaration of Helsinki. All participants were unaware of the aim of study.

We used a double-blind, placebo-controlled, within-subjects study design, in which participants received 20 minutes of real 1-Hz left-sided subthreshold rTMS over the frontopolar cortex, targeting the OFC or the DLPFC, or placebo rTMS over the OFC, on 3 consecutive occasions at similar times of day. Condition order was randomized across the group. Stimulation intensity was set at 80% of the motor threshold, mean 59.8 (SD 11.9). Stimulation parameters were in accordance with the safety guidelines formulated by the International Federation of Clinical Neurophysiology (www.ifcn.info/about_fs.htm).

Before the experimental sessions, which took place on a separate day, participants were invited to the laboratory and informed about safety issues and experimental procedures. A safety screening questionnaire was administered to check for contraindications, and right-handedness was established. Next, individual motor thresholds were estimated from the left primary motor cortex, using the thumb movement visualization method. Stimulation sites were defined on the basis of the International 10–20 EEG System. The left frontopolar region targeting OFC and the DLPFC corresponded to the Fp1 and F3 electrode sites, respectively. Structural magnetic resonance imaging studies have confirmed that the Fp1 electrode position corresponds to the frontopolar cortex. However, a degree of variability (< 20 mm) is apparent with respect to targeting the left DLPFC and the F3 electrode position.

TMS was performed using a Neotonus (Marietta, Ga.) magnetic brain stimulator (maximum output 2300 A peak/1750 VAC peak) and an iron-core coil with a current magnetic induction field of about 2 T. Placebo TMS was performed using an identical coil, but with a metal plate built in the housing directly under the iron core (Neotonus). Consequently, the brain is effectively shielded from actual stimulation, but the coil mimics the sounds, clicks and sensation of real TMS.

After rTMS and mood assessment, attention-modulated memory for neutral, fearful and happy facial expressions in a spatial display was tested.

Participants were seated in front of the computer screen (distance to screen 20”) and performed 4 trials in random order (neutral–happy trials and neutral–fearful trials). The faces used were adapted pictures of actors posing with neutral, fearful and happy emotional expressions taken from the Pictures of Facial Affect and the Karolinska Directed Emotional Faces set. Two trials consisted of a display with 4 neutral and 4 happy faces, whereas the other 2 trials consisted of 4 different neutral and 4 fearful faces. The order of the trials was continuously randomized both within and between rTMS conditions. Each face was presented for 2 seconds at a different location in a serial manner within a 13” frame on a 16” computer monitor (Fig. 1A). After presentation of the eighth and final face (acquisition phase), all the faces reappeared in the top corner of the blank screen, and participants were instructed to relocate the faces to their proper position (relocation phase) (Fig. 1B). It should furthermore be noted that during the relocation phase of the test, the participants did not receive any metric position information. The deviation in millimetres between the relocation and the original
positive emotional memory bias. To attain the average emotional memory bias, difference scores were calculated: the mean happy minus neutral face deviation and mean fearful minus neutral face deviation. (The current definition of memory is closely related to the concept of working or short-term memory, which is inextricably bound up with attentional processes.)

Mood was assessed using the Profile of Mood States (POMS) subscales for depression, anxiety and anger.20 Because minor but systematic changes in mood in healthy volunteers are unlikely to be revealed by the POMS conventional scale,21 visual analogue scales allowing responses ranging from 0 (not at all) to 100 (extremely) were used to enhance sensitivity.22

To test the hypothetical increase in memory bias for happy facial expressions and decrease in memory bias for fearful facial expressions after rTMS over the left OFC compared with placebo and left DLPFC rTMS, 2 separate multivariate analyses of variance (MANOVAs) were performed, with stimulation as the within-subjects factor and order as the between-subjects factor for the happy and fearful memory bias, respectively. The α level of significance was set at 0.05 (2-tailed throughout).

## Results

rTMS was well tolerated by all participants. Debriefing after the experiment revealed that all subjects believed that they had received real rTMS on all occasions. Due to technical problems, data for one subject were lost. A separate MANOVA for the memory bias of fearful faces, with stimulation as the within-subjects factor and order of stimulation as the between-subjects factor, yielded no significant effects (all F values ≤ 1, p > 0.41). The MANOVA for the memory bias of happy faces showed a statistically significant main effect of stimulation (F\(_{5,27} = 6.3, p = 0.04\)), without a stimulation × order effect (F\(_{5,26} = 1.7, p = 0.21\)). Paired samples t tests revealed a significantly increased positive emotional memory bias after “real” compared with placebo rTMS over the left OFC (t\(_{10} = 2.4, p = 0.037\)). There was a nonsignificant increase in positive emotional memory bias between left OFC and DLPFC stimulation (t\(_{10} = 1.7, p = 0.12\)). An increase in positive emotional memory bias after DLPFC rTMS compared with the placebo left OFC condition reached a nonsignificant trend (t\(_{10} = 2.0, p = 0.07\)). Figure 2 shows the positive emotional memory biases across the stimulation conditions. Post hoc comparisons between the error deviation scores revealed significantly better performance on happy compared with neutral facial expressions, the so-called “happy superiority” effect, after “real” rTMS over the left OFC (t\(_{10} = 2.6, p = 0.028\)) but not after placebo treatment over the left OFC (t\(_{10} = -1.6, p = 0.15\)), nor after left DLPFC rTMS (t\(_{10} = 0.3, p = 0.76\)). No effects on self-reported mood were observed (p > 0.14 in all cases).

## Discussion

In the present study, we demonstrated that a single session of slow, inhibitory rTMS over the left OFC as compared with placebo rTMS results in improved memory performance for happy faces.

Functional neuroimaging studies have demonstrated elevated OFC activity in depressed mood,23 a mood state that has also been associated with reduced memory for positive stimuli.67 Furthermore, the data are also in agreement with the acute antidepressant action of a selective serotonin reuptake inhibitor in healthy volunteers; increased positive emotional memory was observed independent of mood changes.24 The present data again show that the onset of beneficial changes in emotional information processing can occur relatively fast, given the time course of most clinically assessed improvements.6 Although seemingly counterintuitive, given the evidence for antidepressant properties of fast DLPFC,25 the minor increase in positive memory after slow left DLPFC rTMS (compared with placebo) corroborates the findings of antidepressant effects of the one study where slow rTMS was applied over the left DLPFC.26 Changes in emotion processing, however, were not found in the current study as changes in subjectively experienced

---

**Fig. 2:** Means and standard errors of the mean for positive memory bias after placebo rTMS over the left OFC, real rTMS over the left DLPFC and real rTMS over the left OFC. xSignificant increases in positive emotional memory bias were observed after left OFC rTMS as compared with left OFC placebo rTMS. xSignificantly better performance for happy compared with neutral faces (“happy superiority effect”) was observed after left OFC rTMS. DLPFC = dorsolateral prefrontal cortex, OFC = orbitofrontal cortex, rTMS = repetitive transcranial magnetic stimulation.
mood, but the differences were observed on the more objective behavioural level of the memory task, suggesting once again that subtle shifts can arise even before phenomenological changes occur.\textsuperscript{57}

The minor increase in positive emotional memory bias after “real” DLPFC rTMS was an unexpected effect, because positive effects on motivation and emotion are commonly observed after fast rTMS over the left DLPFC. Nevertheless, the opposite findings for slow rTMS over the left DLPFC have been reported as well.\textsuperscript{23} Given that the direction of the memory effects in the left DLPFC and the OFC condition was similar, it might be argued that the DLPFC rTMS effect was established transsynaptically by way of the OFC.\textsuperscript{23} It should, however, be noted that the DLPFC rTMS effect was not significant, and post hoc tests also revealed that the happy superiority effect was only present in the left OFC rTMS condition. In sum, the neurophysiological explanation for the priority effect was only present in the left OFC rTMS condition and analysis of the data, and the drafting and reviewing of the article, and they gave final approval of the version to be published.

Acknowledgements: The authors were supported by an Innova-
tional Research Grant (#016-115-060) from the Netherlands Organization for Scientific Research (NWO).

Competing interests: None declared.

Contributors: Both authors contributed to the study design, the acquisition and analysis of the data, and the drafting and reviewing of the article, and they gave final approval of the version to be published.

References

16. Kessels RPC, Postma A, De Haan EHF. Object relocation: a program for setting up, running and analyzing experiments on memory for object locations. Behav Res Methods Instrum Comput 1999;31:423-8.