Repetitive transcranial magnetic stimulation modulates the impact of a negative mood induction

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Abstract

High frequency repetitive Transcranial Magnetic Stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) has been found to alleviate depressive symptoms. However, the mechanisms driving these effects are still poorly understood. In the current study, we tested the idea that this intervention protects against negative mood shifts following emotional provocation. We furthermore explored changes in EEG activity (frontal alpha asymmetry) and effects on attentional processing (emotional Stroop). To this end, 23 healthy individuals participated in two sessions separated by one week, whereby they once received 15 min of 10Hz rTMS stimulation (1500 pulses) at 110% of the individual motor threshold, and once sham stimulation. Then, negative mood was induced using sad movie clips. The results revealed a significantly stronger mood decline following rTMS compared to sham stimulation. No changes were observed in frontal alpha asymmetry and attentional processing. Our findings are at odds with the view that high frequency rTMS over the left DLPFC directly protects against the induction of negative mood, but rather suggest that it enhances the effects of emotional provocation. Possibly, in healthy young individuals, this stimulation protocol heightens susceptibility to mood induction procedures in general.

Key words: repetitive Transcranial Magnetic Stimulation; DLPFC; negative mood induction; depression; alpha asymmetry

Introduction

Depression is expected to become the leading cause of disabilities worldwide with about 20% of the population suffering from a mood disorder at least once in a lifetime (Kessler et al., 2005; de Graaf et al., 2012). Even more alarmingly, depression is characterized by high relapse rates, which increase steeply with every subsequent depressive episode, even following psychotherapy (Steinert et al., 2014). These findings underline the importance of improving existing treatments and emphasize the necessity of effective prevention instruments to interrupt this vicious circle.

One technique that has gained attention as a potential treatment adjunct for depression and as a tool for relapse prevention is repetitive transcranial magnetic stimulation (rTMS). rTMS is a non-invasive brain stimulation technique, whereby trains of brief magnetic fields are generated in a coil to induce electric fields in the nerve tissue underneath the coil, leading to

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neuronal depolarization (Hallett, 2007). When applied at high frequencies of >10 Hz (HF), rTMS has been shown to increase neuronal excitability of the stimulated site, which outlasts the stimulation itself (Fitzgerald et al., 2006). Results from meta-analyses have demonstrated that HF rTMS to the left frontal cortex ameliorates depressive symptoms with comparable effect sizes as observed in psychotherapy and pharmacological treatments (for reviews see Fitzgerald et al., 2003; Schutter, 2009; Chen et al., 2013).

In healthy samples, early studies found an increase in negative mood after stimulation of the left prefrontal cortex (George et al., 1996; Pasqual-Leone et al., 1996; Dearing Martin et al., 1997), while more recent studies did not detect any changes in mood as a result of the stimulation itself (Mosimann et al., 2000; Grisaru et al., 2001; Padberg et al., 2001; Baeken et al., 2006, 2008; Baeken et al., 2014; Moulier et al., 2016). Schaller et al. (2011) demonstrated that several sessions of HF rTMS attenuated only depression ratings of healthy individuals as assessed with the Beck Depression Inventory, while subjective mood ratings remained stable. A recent review concluded that a single session stimulation is not sufficient to alter mood states directly in healthy individuals (Remue et al., 2016).

Summarizing, despite the mood enhancing effects of HF rTMS in patient samples, the underlying working mechanisms are not yet fully understood. Studies investigating the effects of DLPCF stimulation on cognitive and emotional processing found that HF rTMS over the left DLPCF can improve task-switching abilities of depressed individuals (Vanderhasselt et al., 2009), and that the same protocol can alter attentional processing of emotional stimuli in healthy women (De Raedt et al., 2010). In the latter study, the authors used an exogenous cueing task that assessed facilitated attentional engagement with angry faces, and difficulties disengaging attention from them. Whereas HF stimulation of the right DLPCF resulted in impaired disengagement from negative faces, stimulation of the left DLPCF resulted in reduced engagement towards these stimuli. Moreover, on the neuronal level, these effects were accompanied by changes in PFC activity.

This suggests that rTMS modulates a neuronal network involved in emotion regulation, thereby attenuating the negative impact of adverse events. Indeed, the PFC has been linked to the regulation of negative emotions in numerous studies (Ochsner et al., 2002, 2004; Phan et al., 2005; Johnstone et al., 2007). Summarizing, different lines of research suggest that HF rTMS over the left DLPCF ameliorates cognitive functions that have been found to be impaired in depressed individuals and have been linked to the emergence and recurrence of depression (Hammar and Ardal, 2009; Snyder, 2013). In light of these findings, it is conceivable that HF rTMS over the left DLPCF has protective effects against a subsequent negative event. Indeed, recent studies have found that HF rTMS over the left DLPCF prior to a stress-inducing task attenuates subsequent decreases in heart rate variability (Remue et al., 2015) and stress hormonal responses (Baeken et al., 2014), as compared to stimulation over the right DLPCF and/or sham stimulation. Based on these considerations, the present study aims at investigating the effects of rTMS stimulation over the left DLPCF on affective responses to a negative mood induction and on attentional processing, which are both of direct relevance to emotion regulation in depression.

In order to get a better understanding of the neurophysiological effects of rTMS on attentional processing and emotion regulation, the electroencephalogram (EEG) is a non-invasive way to study electrocortical field potentials recorded over the left and right frontal cortex. In particular, examining hemispheric differences in alpha power (8–12 Hz) is a commonly used correlate of underlying cortical activity (Coan and Allen, 2004). Stronger right-sided alpha power (conventionally interpreted as reflecting more left-sided brain activity;Henriques and Davidson, 1990; Gotlib et al., 1998) is thought to reflect stronger approach and weaker withdrawal motivation, as well as stronger positive affect (Nusslock et al., 2015). This marker has been linked to current and lifetime depression, as well as to the prospective risk to develop depression (for review, see Allen and Reznik, 2015). Moreover, stronger left lateralized alpha at rest and in response to emotional provocation has been found to predict stronger mood decline and hormonal stress responses (Papousek et al., 2014; Quaedflieg et al., 2015). Furthermore, increased left-lateralized alpha following neurofeedback attenuates subjective habituation to laboratory stress induction (Quaedflieg et al., 2016). Together, these findings show striking parallels with the above-mentioned effects of rTMS over the left DLPCF. Therefore, the current study explored whether the potential effects of rTMS on affective responding are accompanied by changes in frontal alpha asymmetry. In addition, we also assessed asymmetries in the beta band (i.e. 13–30 Hz) as these might be similarly related to the attentional avoidance of angry faces (Schutter et al., 2001, 2008).

This exploratory study investigated whether mood responses to a negative event can be modulated by HF rTMS over the left DLPCF, using a counterbalanced within-subject cross-over design. In particular, healthy individuals received a single session of 10 Hz rTMS, before inducing a negative mood by means of a short movie sequence. Compared to a session of sham rTMS, we expected HF rTMS to attenuate mood decline in response to the movie. Furthermore, we explored whether these potential effects are accompanied by changes in frontal alpha asymmetry, that is, a reduction in relative left lateralized alpha. Finally, as stimulation of the DLPCF affects attentional processing of emotional faces, an emotional Stroop task (van Honk et al., 2002) was used to assess biased processing of angry and sad faces. In particular, we anticipated attenuated interference of emotional (i.e. sad and angry) faces compared to neutral faces after HF rTMS than after sham stimulation.

Materials and methods

Participants

In this exploratory study, 23 right-handed students participated (Age: M = 21.5, SD = 3.0) in return for 50€. Participants were screened for contra-indications to rTMS according to the recommendations by the TMS Consensus Group (Rossi et al., 2009, 2011). Prior to inclusion, we screened participants, using the following exclusion criteria: (1) metal in cranium, (2) use of psychotropic drugs (e.g. cannabis, XTC), (3) a history of severe neurological problems (e.g. epilepsy, head injury or head surgery and brain infarction), (4) history of psychiatric disorders, (5) medication use (i.e. benzodiazepines, antidepressants and neuroléptica), (6) severe physical illness (e.g. heart disease) and (7) pregnancy. Moreover, participants were excluded if they had heightened scores (i.e. above 13) on the Beck’s Depression Inventory (BDI-II; Beck et al., 1996), which was administered during the screening prior to the study. This study was conducted in accordance to the Declaration of Helsinki and approved by the local medical ethical committee (CMO Region Arnhem-Nijmegen, the Netherlands). Participants gave written informed consent.
Material and instruments

**Questionnaires.** In order to assess the time-course of affective responding, two 10-point Likert scales were administered at seven different time points throughout each session (see Figure 1 for an overview). In analogy to previous studies with a similar mood induction procedure (Vrijsen *et al.*, 2013), we asked participants to indicate how happy and how sad they currently felt (anchors: 1 = not at all; 10 = extremely). The scales were combined to a sum score, such that higher values represent a more positive mood state.

In addition, the German and the Dutch translation of the Positive Affect Negative Affect Schedule (Watson *et al.*, 1988; Krohne *et al.*, 1996) were used to assess changes in positive (PA) and negative affect (NA) in response to the mood induction procedure. These scales were administered twice during each session, first at baseline and second after the EEG measure that followed the first mood induction movie (Figure 1).

**rTMS procedure.** Repetitive transcranial magnetic stimulation was administered using a MagStim Rapid2 (Magstim, UK) with a figure-of-eight coil. During the active treatment, participants received 60 trains of 5-s 10 Hz stimulation with an inter-train interval of 25 s. The intensity was set to 110% of the resting motor threshold of the right abductor pollicis brevis. The site of stimulation was F3 according to the international 10–20 system (American Electroencephalographic Society, 1994). We chose for this procedure, as it is the most accurate way to identify the DLPFC without using a neuro-navigation system (Fitzgerald and Daskalakis, 2012). For the sham-stimulation, these parameters were held constant, while only the orientation of the coil was tilted for 45° away from the cortex.

**Mood induction.** The mood induction procedure was adapted from Fitzgerald *et al.* (2011), selecting three clips from the movie ‘Sophie’s Choice’ with different durations (i.e. 12, 6 and 5 min). The first clip was used to induce negative mood, while the two shorter clips were presented to boost the negative mood. Participants were instructed to place themselves into the position of the main actor in order to allow them to fully perceive the negative emotion.

**Resting state EEG.** At three time points throughout each session, resting state EEG was recorded. Each recording consisted of four blocks of 1 min, with alternating instructions to keep the eyes closed or open. EEG was measured using a standard 32-channel setup (BrainVision QuickAmp, Brain Products) according to the international 10–20 system, using 32 electrodes. The signal ground was placed on the nose, the online reference

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**Fig. 1.** Procedural overview.

Note. T1–T7: 7 assessment points of Likert scales.
was located at the left mastoid (A1) while the right mastoid (A2) was serving as additional recording channel. Four electrodes were placed at the eyes to control for horizontal and vertical eye-movement. All electrode impedances were kept below 5 kΩ. Data was recorded at a frequency of 500 Hz applying a band pass filter of 0.3–70 Hz.

For data reduction, all electrodes were re-referenced to the overall mean. Due to presence of excessive muscle activity over T7 and T8 in a large proportion of subjects, these electrodes were excluded from the average reference. An offline filter with 1–30 Hz was applied, before dividing the signal into 75% overlapping epochs of each 2 s, and removing epochs carrying artifacts (i.e. amplitude ≥ 75 μV; maximal voltage step exceeding 50 μV/ms; maximal change in amplitude exceeding 100 μV/500 ms). A Fast-Fourier Transformation (Hanning window: 100% length) was conducted on the remaining epochs, and mean values of the FFT were calculated, separately for α (8–12 Hz) and β (13–30 Hz) frequency bands. A lateralization score for the different frequencies was calculated by subtracting the summed signal from the left frontal electrodes (i.e. F3, F7 and FC5) from the summed signal of the right frontal electrodes (i.e. F4, F8 and FC6) and dividing this by the sum of these six electrodes. More positive values represent relatively stronger right-lateralized power. As previous studies (Boytssova and Danko, 2010; Ben-Simon et al., 2013) suggest that the EEG signal assessed with eyes closed represents a different attentional state from eyes open (i.e. invert directed attention versus onwards direct attention), eyes-open/eyes closed condition was used as an additional within-subjects factor in all subsequent analyses.

Emotional Stroop Task. An emotional Stroop task (van Honk et al., 2002) was used to assess individual differences in attentional bias for emotional faces. Pictures of oval-cut faces from 10 different characters (5 female, 5 male), each displaying three different emotional expressions (i.e. anger, sadness and neutral), were taken from Ekman and Friesen (1976). Two versions of each face, one colored in blue and one in yellow, were presented on a black background. All combinations were presented twice, resulting in 120 trials. Every trial started with a white fixation-cross, replaced by a single face after a random interval of 1500–2500 ms. Participants had to indicate the color as fast as possible by pressing in 120 trials. Every trial started with a white fixation-cross, black background. All combinations were presented twice, resulting in 240 trials. After each trial, a white fixation-cross appeared on the computer screen. Participants were invited to two laboratory sessions separated by one week. The procedure of both sessions was nearly identical, except that they once underwent real rtTMS and once sham TMS (order was counterbalanced across participants). After providing informed consent, they were given the set of questionnaires including the PANAS. This set of questionnaires also provided statistics. Where assumptions of sphericity were violated, we reported Greenhouse–Geisser corrected statistics.

Results

Effects of stimulation on mood

A 2 (intervention: rtTMS, Sham) × 2 (time: T1, T2) RM ANOVA on mood scales revealed no significant interaction, F(1,22) = 0.51, P = 0.484, indicating that the stimulation itself did not alter the mood state. There was a marginal significant overall drop in mood, F(1,22) = 3.95, P = 0.059, η² = 0.15. See Table 1 for an overview of the mood ratings. In order to test whether the stimulation modified mood changes in response to the mood induction, a 2 (intervention: TMS, Sham) × 4 (time: T3, T4, T5, T6) RM ANOVA was conducted. This analysis revealed a significant effect of time [F (1.42, 29.84) = 44.83, P < 0.001, η² = 0.68], which was moderated by intervention [F (2.36, 49.47) = 3.32, P = 0.037, η² = 0.14]. Post-hoc tests indicated that the mood state was comparable between interventions before the mood induction, t(22) = 0.49, P = 0.630, and at the subsequent two assessment points, T4: t(22) = 1.53, P = 0.142, T5: t(22) = 0.38, P = 0.710. After the second mood boost at T6, mood was significantly lower after the rtTMS stimulation as compared to the sham stimulation, t(22) = 2.5, P = 0.030, d = 0.51 (Table 1).

Next, changes in positive affect and negative affect as a result of the mood induction were investigated. A 2 (intervention: TMS, Sham) × 2 (time: T1, T5) RM ANOVA on PANAS-PA scores did only reveal a significant main effect of time, F(1,22) = 26.49, P < 0.001, η² = 0.55, indicating an overall drop in positive affect
Out of the 23 participants, 15 reported that this study was a movie to fully perceive the negative emotion. Hence, this enhanced mood decline after rTMS compared to sham rTMS may be interpreted as improved emotion regulation. That is, participants may have been better able to follow the instructions after receiving the real stimulation. The role of dorsal regions of the PFC in emotional regulation has been demonstrated in previous studies (for review, see Mitchell, 2011), showing the involvement of the left PFC during mood regulation in general, and during the up regulation of mood in particular (Ochsner et al., 2004). Hence, HF rTMS over the DLPFC may have modulated the susceptibility to emotional processing, while the instructions to up-regulate the negative emotion determined the directionality of mood change. Support for this explanation comes from a study by Feeser et al. (2014) who found a strengthening in reappraisal of negative emotions after transcranial direct current stimulation (tDCS) over the right
A particularly promising avenue would be to focus on effects on frontal asymmetry. The DLPFC on frontal asymmetry remains to be investigated. Schutter and van Honk, 2005, demonstrated between left prefrontal and right parietal cortex (for review, see Schutter et al., 2015). It is possible that rTMS resulted in perturbations of the neural system of healthy individuals, which tried to go back into its baseline homeostatic default-state after the stimulation, and thereby amplified the mood decline. According to this line of thought, low frequency (e.g. 1 Hz) stimulation protocol, which initially reduces excitability prior to a negative mood induction, might attenuate the impact of the negative mood induction. However, one may also argue that the perturbations due to rTMS may interfere with mood regulation in general, resulting in an amplified mood decline.

It is important to mention that the differential effects on mood decline occurred only after the negative emotion-booster towards the end of the session, whereas they were not yet evident directly after the first mood induction clips. This pattern was also reflected in changes on the PANAS scale, which showed a significant mood deterioration that remained unaffected by the rTMS intervention. Crucially, the time point of administering the PANAS might not have been suited to identify such changes, since the post-assessment took place before the booster of negative mood. At that moment, recovery from the negative mood might have minimized the mood differences between the stimulation conditions.

In contrast to our expectations, EEG analyses did not reveal any reliable changes in frontal alpha (or beta) asymmetry in response to the emotional provocation. This suggests that the effects of left PFC stimulation on mood were not mediated by a change in frontal alpha asymmetry. However, this does not rule out the possibility of rTMS to affect frontal asymmetry at other time points during the session. Indeed, our subjective mood data suggests that the critical rTMS effects may have taken place after the second mood induction (i.e. the mood booster) rather than directly after the first mood induction. Moreover, it is possible that there were more short-lived rTMS effects on frontal asymmetry that went undetected. For instance, Papousek et al., 2014, found that emotional films acutely induced more right-sided alpha activity that corresponded with deteriorated mood, but these effects had vanished after the movie. This pattern aligns with the capability model of frontal alpha asymmetry (Coan et al., 2006), according to which this EEG marker is most sensitive to affective responding and to individual differences in emotional vulnerability when measured during an emotional challenge (for review, see Allen and Reznik, 2015).

It is also conceivable that the effects of the stimulation are detectable at other cortical regions. The right parietal cortex is one potential region of interest for the effects of neurostimulation in depression. Based on the functional connectivity between left prefrontal and right parietal cortex (for review, see Schutter and van Honk, 2005), Schutter et al. demonstrated beneficial effects of 2 Hz rTMS over this region on depression ratings and cognitive markers of depression (Schutter et al., 2009, 2010). Taken together, the potential effects of rTMS on the DLPFC on frontal asymmetry remains to be investigated. A particularly promising avenue would be to focus on effects that take place during the mood induction or in response to the negative mood booster, next to exploring rTMS effects beyond the frontal cortex.

There are two reasons why we expected attenuations of the interference of negative pictures during the Stroop task, as a function of rTMS. First, we thought that a dampening of the mood decline would lead to weaker interference effects due to the mood congruent processing style (Gilboa-Schechtman et al., 2000). In other words, the less sad participants are, the weaker the impact of negative faces during the task, and hence, the weaker the interference effect. Second, stimulation of the DLPFC is expected to affect cognitive control processes (Vanderhasselt et al., 2006, 2009) that modulate performance during the Stroop task. The high frequency stimulation may have resulted in a reduction of the interference due to an increase in cognitive control. The combination of both aspects might explain why no effects were found on the Stroop task, as they might have canceled out each other. Thus, the current stimulation protocol might have improved cognitive control and reduced positive mood at the same time, both leading to opposite Stroop effects.

The results of this exploratory study should be carefully interpreted, taking several limitations into account. First of all, the crossover design allowed participants to experience both stimulation conditions and thereby to detect slight differences in scalp sensations. However, despite this factor limiting the blinding, our analyses did not indicate any order effects. Still, improved control procedures or study designs might be preferable. Second, MRI based localization might be considered as an alternative to determine the target location (Sparing et al., 2008; Ahdab et al., 2010). Third, this study was conducted with healthy individuals, which have been shown to differ in functional connectivity from depressed patients (for review, see Pizzagalli, 2010). Hence, the neural effects of stimulation may differ between these populations. Fourth, replication with larger samples is essential before drawing solid conclusions. We recommend that these replication studies include a positive mood induction procedure and a contrasting rTMS stimulation protocol (i.e. low frequency stimulation) for which opposite effects would be expected, to disentangle the working mechanism of the current effects. Furthermore, the up- and down-regulation of emotional information by means of neurostimulation is a promising method with potential therapeutic value, worthy of investigation. Finally, more narrowly tracking the time course of changes in alpha asymmetry and other neural correlates may help to better understand the working mechanisms relevant for the current study. For instance, future studies should consider assessing frontal asymmetry during an emotional task, rather than during rest.

In conclusion, this study indicates that rTMS can modulate the impact of a negative mood induction. Contrary to our expectations, HF rTMS over the left DLPFC seems to increase the susceptibility to mood responses in general, while the context determines the directionality of this change. Hence, due to the negative mood induction procedure in the current study, HF rTMS might have been related to a stronger mood decline. These findings provide a new perspective on the effects of rTMS that require subsequent research on possibilities to prevent depressive episodes. As pointed out, potential approaches could focus on low frequency stimulation to prevent a mood decline or on using a positive mood induction after a high frequency rTMS treatment, in order to target the absence of positive affect in depression.
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