Effects of rTMS on an Auditory Oddball Task: a Pilot Study of Cortical Plasticity and the EEG

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Key Words
Depression
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Transcranial Magnetic Stimulation

ABSTRACT
The objective of this study was to explore the effects of 1Hz repetitive transcranial magnetic stimulation (rTMS) applied to dorsal lateral prefrontal cortex (DLPFC) on both an EEG index of cortical excitation and inhibition, event-related desynchronization/synchronization (ERD/S) and on the P300 component of an auditory oddball-induced ERP. Eight normal participants received 15 minutes of 1Hz rTMS at 110% of the resting motor threshold to right DLPFC. ERD/S of alpha and beta bands was measured during an auditory oddball task immediately before and after stimulation. There was significantly less alpha desynchronization post-TMS, and this effect was widespread excepting posterior midline sites. No changes were found to oddball-P300 amplitudes or latencies. In conclusion, the effect of stimulating right frontal areas on error detection related ERPs resulted in decreased latency of the P300 and that there was no effect with right-sided stimulation. With regard to EEG power, changes were found by Okamura and colleagues, with an increase in alpha band power and a shift in peak frequency post left-sided 10 Hz rTMS. Only two studies have focussed on the effects of low frequency stimulation applied to right DLPFC. One study reported an increase in left (contralateral) frontal theta power, and a second study also found no effect of stimulating right frontal areas on error detection related ERPs but found an attenuation of error-related negativity and subsequent increase of error-positivity following medial stimulation.

INTRODUCTION
The investigation of repetitive transcranial magnetic stimulation (rTMS) as a potential clinical treatment is becoming increasingly widespread. It has been proposed to be of use in the management of various psychiatric disorders including schizophrenia (e.g.,) and major depression (e.g.,). However, significant uncertainty remains as to the neurobiological mechanisms underlying the effects of rTMS. The purpose of the present pilot study was to further address this issue, in particular the use of rTMS and its electroencephalographic effects with regards to the treatment of major drug-resistant depression with prefrontal cortical stimulation.

The main approach to investigating rTMS and depression has focused on the stimulation of frontal areas, in particular, dorsolateral prefrontal cortex (DLPFC). This is based upon a frontal activation asymmetry model, which postulates that the left DLPFC is under-active in depressed patients and/or the right DLPFC is over-active. It is argued that high frequency TMS increases activity levels in underlying cortical neurones and that low frequency TMS decreases activity levels and hence specific targeting of appropriate stimulation frequencies can alter this imbalance. Consistent with this theory, clinical studies to date have indicated the antidepressant properties of high frequency stimulation applied to left DLPFC (e.g.,), low frequency stimulation applied to the right DLPFC and the combination of these two approaches.

To date, only a handful of studies have used human electroencephalogram (EEG) to examine the effect of rTMS to dorsolateral prefrontal cortex (DLPFC). Most of these studies have focussed on the effects of high frequency left DLPFC stimulation and have produced heterogeneous findings. For instance, Jing et al., using 10Hz stimulation to left frontal areas, found an increase in latency to the P300 component of the event-related potential (ERP), as did Hansenne and colleagues; despite using 1Hz stimulation. However, Evers et al., found that left-sided stimulation at 20Hz resulted in decreased latency of the P300 and that there was no effect with right-sided stimulation. With regard to ERP power, changes were found by Okamura and colleagues, with an increase in alpha band power and a shift in peak frequency post left-sided 10 Hz rTMS. Only two studies have focussed on the effects of low frequency stimulation applied to right DLPFC. One study reported an increase in left (contralateral) frontal theta power, and a second study also found no effect of stimulating right frontal areas on error detection related ERPs but found an attenuation of error-related negativity and subsequent increase of error-positivity following medial stimulation.

It is noticeable, that despite the array of findings, several results have highlighted the P300 component (as elicited using standard "oddball" protocols) as being reactive to rTMS in some way. The oddball-P300 has been proposed to index a plethora of cognitive functions (including deviance recognition and memory updating) but at its most basic, it appears to be an indicator of mental activity, in terms of its amplitude and latency being affected by unpredictable, unlikely or significant stimuli. The oddball task requires subjects to respond to rare "target" stimuli and to disregard common "standard" stimuli, and is a robust method of eliciting the P300. Consequently, an oddball task was employed in the present study, in order to measure the effects of rTMS on the P300 and to explore the relationship between these effects and cortical excitability. As we were specifically interested in the effects of rTMS on cortical excitability, we chose to analyse the oddball-P300 data using both standard ERP parameters and an EEG measure thought to directly reflect cortical excitability. Event-related desynchronization/synchronization (ERD/S) is just such a method.

In terms of this study, ERD/S is a measure of the average magnitude squared activity in the frequency band of interest, relative to a baseline interval. It allows the measurement of event-related EEG activity as a function of time. Increases in alpha (8-12Hz) and beta (12-30Hz)
synchronization are believed to reflect cortical inhibition or idling: conversely, increased desynchronization of these bands reflects activation. We hypothesized that 1 Hz rTMS would reduce cortical excitability as indexed by increased task-related alpha ERD/decreased alpha ERD and would result in a change to the parameters of the oddball-P300 ERP.

METHODS

Subjects

Eight normal subjects consented and took part in the experiment, aged 19-50 (mean = 31.2), three were male. All reported no known neurological or psychiatric disorders. Approval for the study was granted by the Human Research Ethics Committee of the Alfred Hospital, Melbourne, Australia.

Experimental procedure

Participants completed an auditory oddball task immediately before and after fifteen minutes of 1Hz rTMS to the right DLPFC. The oddball task required the participants to attend to all stimuli and to silently count the number of “target” or rare stimuli and to report this number to the experimenter post-test. This removed the possible motor confounds often found in oddball paradigms requiring button-press responses to targets. Stimuli were binaural 80dB tones of 50ms duration at 1200Hz for targets and 1000Hz for standard stimuli. Two hundred trials were presented with an ISI of 1000ms (+/- 250ms). Targets were pseudo-randomly presented 20% of the time.

Electromyographic (EMG) recordings

EMG was recorded from the left abductor pollicis brevis using self-adhesive electrodes (Medtronic). One electrode was attached to the muscle belly and another on the dorsal aspect of the interphalangeal joint of the thumb. An earth electrode was placed on the mid-forearm. EMG signals were amplified, filtered (with a bandpass of 10Hz - 2.4kHz) and sampled at a rate of 10kHz using a Digidata 1320A Data Acquisition board and pCLAMP 8.0 software (Axon Technologies).

Transcranial magnetic stimulation

Subjects were seated in a reclining chair with a head-rest for head stabilization. Pulses were delivered by a figure-of-8 coil (70mm diameter, peak magnetic field 2.2 T) using a Magstim Super Rapid stimulator (Magstim, UK). The resting motor threshold (RMT) was established by first locating the optimal stimulation site for the left abductor pollicis brevis muscle. The coil was placed on the scalp at the estimated position of the right motor cortex (5cm lateral and 2cm anterior to the vertex). The position of the coil was adjusted until the site that produced the largest MEP response at supra-threshold intensity was found; this position was then marked. The RMT was calculated as the minimum stimulator intensity necessary for eliciting a peak-to-peak MEP >50 uV in at least 5 out of 10 consecutive trials. The site and intensity of the RMT were then used to guide the rTMS. rTMS was applied at 110% of the RMT 5cm anterior to the RMT site in a single 15 minute train, targeting right dorsal lateral prefrontal cortex (rDLPFC).

EEG recordings

EEG data were recorded using Neuroscan SynAmps II amplifiers and SCAN 4.3.1 software using electrodes from 64 scalp sites referenced to an electrode midway between Cz and CPz; using a Quick-Cap with electrodes arranged according to the International 10/20 System (CompuMedics Neuroscan, El Paso, Texas). Electro-oculographic data were recorded using four electrodes above and below the left eye (E1 and E3, respectively), and on the outer canthus of each eye (E5 and E6). Impedances for the above sites were reduced to below 5 kOhm before the start of each session. All data were continuously sampled at 250 Hz with a bandpass of 0.05-100 Hz.

EEG data analysis

Following visual inspection of the data, noisy data blocks were rejected. Ocular artifact rejection was carried out using methods described earlier by Croft and Barry. All data were re-referenced to a common average reference. Data for P300 analysis were filtered with a low pass filter at 30Hz (12dB), epoched from -100ms-659ms around the target stimulus, baseline corrected using the prestimulus interval and averaged in the time domain. Peak activity was measured in the 280-450 ms range at Cz. In order to calculate ERD/S, the data were epoched from -700-1200ms around the target stimulus and the following steps were performed: the data underwent complex demodulation and concurrent filtering (zero phase-shift, 24dB roll-off, envelope computed) into alpha (8-12Hz) and beta bands (13-30Hz); it was trimmed (500ms from each end, to remove filter warm-up artifacts) and averaged. A reference interval of -200-0 ms was used to calculate the percentage change between the active period and the reference using the classic method adapted from Pfurtscheller and colleagues: ERD% = (R-A)/R*100, where R is the reference interval and A is the active or task phase. Thus, desynchronization and synchronization are expressed as a percentage of activity relative to the reference interval (NB, using this formula ERD produces positive scores and ERS negative). ERD/S data contain both phase-locked and nonphase-locked activity. For statistical purposes, the area under the curve for the period 150-650 ms was calculated and contrasted pre- and post-rTMS. This time period was coincident with the main task-related synchronization.

Table 1: Mean values for amplitude (µV), latency (ms) and behavior (number of targets counted) pre- and post-rTMS and the pre- versus post-rTMS t-test values (df=7 for all)

<table>
<thead>
<tr>
<th></th>
<th>Pre-rTMS</th>
<th>Post-rTMS</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude</td>
<td>2.58 (1.92)</td>
<td>3.03 (1.91)</td>
<td>t = -0.54, p = 0.61</td>
</tr>
<tr>
<td>Latency</td>
<td>328.5 (37.64)</td>
<td>322.0 (50.82)</td>
<td>t = 0.463, p = 0.66</td>
</tr>
<tr>
<td>Behavioral</td>
<td>40.12</td>
<td>39.12</td>
<td>t = 1.67, p = 0.14</td>
</tr>
</tbody>
</table>

Data from the peak activity in the 280-450 ms range at Cz, pre- and post-rTMS were contrasted using paired t-tests for both mean amplitudes and latencies.

ERD/S

The ERD/S data were normalized using the following algorithm, t ERD = sqrt(x+1-ERD), where t ERD is the normalized data, sqrt is a square root transform and X is the largest ERD value. The following electrode groupings were devised in order to explore robust effects and to reduce the number of possible multiple comparisons: left frontal (F5, F3, F1, FT7, FC5, FC1), frontal midline (Fz, FCz), right frontal (F2, F4, F6, FC2, FC6, FT8), left central (T7, C5, C3, C1, TP7, CP5, CP3, CP1), central midline (Cz, CPz), right central (C2, C4, C6, T8, CP2, CP4, CP6, TP8), left posterior (P5, P3, P1, PO5, PO7, O1), posterior midline (POz, Oz) and right posterior (P2, P4, P6, PO4, PO6, O2). FC4 and its complement (FC3) were not included for analysis due to technical problems. The six electrode groups were entered into a 2 x 3 ANOVA: TMS (pre and post) x sagittality (frontal, central, posterior) x laterality (left, midline, right).
RESULTS

Behavioral Results

Behavioral data pre- and post-rTMS were contrasted using paired t-tests. There were no significant effects of rTMS on behavioural performance (Table 1).

P300 Component

There were no significant differences in the amplitude or latency of the P300 before and after rTMS (Table 1).

ERD/DS

Analysis of the area under the curve for the data segment 150-650 ms, starting from the peak of post-stimulus alpha synchronization and incorporating the range of the P300 activity, revealed the following: In the alpha band, there was a main effect of rTMS (F1,7 = 6.667; P < 0.05) such that there was significantly less alpha desynchronization post-rTMS during this period (Figure 1). As can be seen in Figure 1, this effect was less at midline posterior sites than laterally (F1,7 = 8.21; p < 0.05). In the beta band, there was an effect at trend level, of less beta desynchronization post-rTMS (F1,7 = 3.73; p = 0.094).

DISCUSSION

Low frequency rTMS applied to the right DLPFC produced no significant alterations in oddball-P300 ERP components. Although previous studies have shown effects of left high frequency stimulation on the P300, no previous studies have investigated the effects of low frequency right-sided stimulation on these parameters. Despite the lack of changes in P300 latency and amplitude, we found clear effects of stimulation on ERD/DS. Specifically, following stimulation alpha desynchronized less in response to the target tones than prior...
to rTMS. This effect was topographically widespread and observed in 6/8 participants.

Typically, alpha desynchronization is thought to index cortical activation/excitation.19,20 and so our findings of less desynchronization post-rTMS would suggest that 1Hz stimulation led to a decrease in cortical excitability. This is consistent with previous studies that have reported that low frequency rTMS stimulation results in a reduction in cortical excitability. For example, 1 Hz rTMS applied to motor or premotor cortex has been shown to reduce excitability of primary motor cortex (e.g.,21-27) and similar effects have been demonstrated in occipital regions.26

However, it should be noted that this understanding of alpha activity, although widely accepted, has been questioned of late (e.g.,25,27), and caveats must be expressed when interpreting one’s findings. In the absence of a sham control, an alternative explanation for these findings is that they are not specific to rTMS effects but due to changes in arousal levels over time or practice effects. However, if this were to be the case then one would expect to see differences in alpha ERD/S between early and late trials. However, three ANOVAs for pre-rTMS, post-rTMS and pre- and post- combined revealed no significant changes or interactions between early and late trials. In addition, the arousal/practice argument is mitigated by the fact that no changes were found to the amplitude or latency of the P300 component; it has previously been found that changes in arousal levels after both P300 amplitudes and latencies (e.g., for review28).

The lack of effects seen on the oddball-P300 ERP, despite the ERD/S changes, may have occurred for several reasons. For instance, the stimulation (over right DLPFC) may not have been in a suitable site to affect the oddball-P300 generators. However, it may have been sufficient to affect background levels of cortical excitability as indexed and assessed by the ERD/S measure. Alternatively, the low experimental power of the study may have led to a type II error and a failure to detect a real ERP-related effect. In either case, the fact that significant changes in alpha ERD/S were observed suggests that ERD/S is a more sensitive measure than ERPs when examining changes in cortical activity induced by frontal rTMS. Further research requiring stimulation at multiple sites and greater subject numbers will be required to resolve this.

To conclude, our study provides supporting evidence that low frequency right prefrontal cortex (PFC) rTMS results in a reduction in cortical excitability. This is consistent with a model of action of rTMS that postulates that its efficacy relates to a reduction of right PFC or increase in left PFC excitability. In addition, this study has established the practicality of the use of ERD/S measures as an index of cortical excitability that is relevant to the study of the effects of rTMS in prefrontal and other brain regions.

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DISCLOSURE AND CONFLICT OF INTEREST

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REFERENCES


