Motor-evoked potential amplitudes elicited by transcranial magnetic stimulation do not differentiate between patients and normal controls

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Abstract

Transcranial magnetic stimulation (TMS) applied over the motor cortex depolarizes neurons and leads to motor-evoked potentials (MEP). To assess cortico-spinal excitability we compared the motor threshold (MT) and the averaged MEP amplitude generated by TMS in patients with major depression (MD) and matched controls. Nineteen patients, who where participants in a protocol comparing the antidepressant effects of rTMS with those of ECT, and thirteen age- and gender-matched normal controls were studied. MT was similar between patients and normal controls. The MEP amplitude response was significantly increased by rTMS, however, the magnitude of the response was similar in patients and normal controls. Correlations between the averaged MEP amplitude and age revealed that older subjects demonstrated significantly lower responses at all time-points. We conclude that cortico-spinal excitability is increased following rTMS, however, differences between patients and normal controls were not apparent with the paradigm used.

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Introduction

The antidepressant effects of transcranial magnetic stimulation (TMS) are currently a matter of active investigation in the psychiatric literature. Recently published studies have reported significant antidepressant effects, particularly for its repetitive form (rTMS) (George et al., 2000; Grunhaus et al., 2000, 2003; Fridmore et al., 2000), however, others (Padberg et al., 1999; Loo et al., 2000) have found mild effects at best. It is unclear why these differences occur between studies. In a recent review Gershon et al. (2003) suggest that patient and illness characteristics, together with methodological variations of TMS and rTMS administration are at the heart of these differences. In this review, Gershon et al. (2003) demonstrated that rTMS studies using higher power, more treatment days, and more pulses per day of treatment, produced more powerful antidepressant effects.

In areas such as neurophysiology, neuropsychology, and brain imaging TMS is being used with increasing frequency as a probe to explore neural function. The ability to directly stimulate localized areas of brain tissue in conscious subjects permits the correlation of complex patterns of brain function to local and distant changes in cortical excitability. A magnetic pulse administered over the motor cortex will induce action potentials that lead to motor-evoked potentials (MEP) in peripheral muscles. Stimulation with low-frequency rTMS leads to inhibition of cortico-spinal excitability and hence to a decrease in MEP amplitude (Chen et al., 1997), whereas high-frequency rTMS leads to increases in cortical excitability, and hence to increases in MEP amplitude (Jennum et al., 1995). This differential cortico-spinal response to either low- or high-frequency rTMS most probably reflects the effects of TMS on inhibitory or excitatory neurotransmission (Ziemann et al., 2000). A variety of methods for testing motor cortex excitability and exploring its significance in neuropsychiatric disorders have been described (Curra et al., 2002; Ziemann et al., 2000).
In major depression (MD) several studies have explored cortico-spinal excitability as a potential biological correlate of illness and recovery. Samii et al. (1966) and Shajahan et al. (1999a,b) described a decrease in the post-exercise facilitation of MEPs following isometric exercise in spite of no change in power of TMS stimulation. This lack of facilitation normalizes with successful antidepressant treatment. Maeda et al. (2000) showed significantly lower excitability on the left hemisphere in motor threshold (MT) and paired-pulse curves in patients with MD. Steele et al. (2000) described prolongations of the EMG silent period in patients with MD. These studies suggest that in the acute phase of MD there is an increase in the motor cortex inhibitory mechanisms and that these findings normalize with successful treatment.

The studies cited above explored changes in cortical excitability resulting from stimulation of the motor cortex. However, when TMS is used as a treatment for MD it is administered over the left dorsolateral prefrontal cortex (LDLPFC) (Pascual-Leone et al., 1996) or the right dorsolateral prefrontal cortex (Klein et al., 1999). It is therefore logical to hypothesize that if TMS effects are mediated by changes in cortical excitability these need to become evident when the target area for TMS in MD is stimulated. Prefrontal cortex excitability can only be studied indirectly through its effects on motor cortex excitability, presumably mediated by cortico-cortical or cortico-subcortical-motor cortex connections. Rollnick et al. (2000) reported that 5 Hz stimulations to the LDLPFC exert an inhibitory effect on motor cortex function (decreased MEP amplitude). Gerschlager et al. (2001) reported decreased MEP amplitude following 1 Hz rTMS to the premotor cortex but no change when they stimulated the prefrontal cortex. With these studies as background we hypothesized that rTMS to the LDLPFC in depressed patients would lead to modification of motor cortex excitability, and that increased excitability (i.e. increased MEP amplitude) would differentiate between patients and normal controls and correlate with improvement in depression ratings. We chose to assay these changes by measuring magnetic MT and the MEP averaged amplitude because these are measures that can be readily performed during rTMS treatments and could therefore have direct clinical applications.

Methods

Subjects

Study protocols were approved by the local Committee for Research on Human Subjects and by the Israel Ministry of Health. All participants signed an informed consent. Inclusion criteria for the study were: (1) a diagnosis of a MD episode according to DSM-IV criteria; (2) a score of 18 or more in the 17-item Hamilton Rating Scale for Depression (HRSD); (3) not meeting any of the exclusion criteria stipulated in the safety guidelines for TMS and rTMS (Wasserman, 1998); (4) being 18 yr old or more; (5) the MD was not secondary to a general medical condition or substance abuse; (6) being right-handed. Ratings were performed by trained research assistants, blind for treatment modality. Because of the clinical severity of the MD patients could not remain totally free from psychotropic medications, therefore lorazepam up to 3 mg/d and occasional brotizolam were the only psychotropic medications allowed during the study. The interval between the last dose of lorazepam or brotizolam and the rTMS study was at least 10 h.

Right-handed, normal controls were recruited for the study and received monetary compensation. Normal volunteers had no personal or family history of neurological or psychiatric disorders, were not using medications known to affect the central nervous system or illicit drugs, and had not ingested alcohol during the 3 d preceding the testing.

The study sample consisted of 19 patients and 13 normal controls. The age distribution (patients 57.16 ± 14.7 and controls 56 ± 17.3, t = −0.2, ns), and gender distribution (12 female and 7 male patients, and 7 female and 6 male control subjects, χ² = 0.27, ns) was comparable between the groups. Patients were significantly depressed (mean 21-item HRSD of 57.16, t = −4.3, p < 0.0001, t = −0.27, ns), and dysfunctional [global assessment of function scale (GAF) 44.3 ± 11.9].

TMS methods

A trained psychiatrist (L.G., P.N.D.) performed the studies using a Magstim Rapid instrument (Magstim Corporation, Sheffield, UK) with a 70 mm wing-span figure-of-eight coil cooled in ice. Subjects were seated in a comfortable chair with support for both hands and wore a tight bathing cap and ear plugs. Patients were encouraged to maintain a relaxed and motionless position as much as possible. Ink markings on the bathing cap where used to reproduce coil position between the sessions. Surface electrodes where attached over the abductor pollicis brevis (APB) and first dorsal interossi areas of the right hand. Electromyographic responses were measured with the MacLab and bioamplifier system equipment. MEPs were recorded and stored for later analysis in a Macintosh computer using the SCOPE.
MacLab software. Recordings were amplified with a bandwidth of 3–5 Hz and sampled at 10 kHz. This equipment allows for digital recording of the EMG. Later analysis of conduction time and area under the curve (AUC) was performed.

**Determination of magnetic MT**

MT over the left motor cortex was determined in all subjects according to the method described by Rossini and Rossi (1998). Coil orientation, to obtain maximal APB response, was determined individually. Machine output was decreased by 2% with each stimulation in order to determine the minimum amount of machine power capable of inducing a 50 µV deflection or a visible twitch in 5 out of 10 trials over the cortical area controlling the contralateral APB.

**Determination of MEP amplitude**

We administered 20 single-pulse magnetic stimuli at 120% MT over the scalp area giving the most intense MEP response. These MEPs were averaged and stored in a McIntosh computer for later analysis. This same procedure was repeated 15 and 30 min after the rTMS treatment (described below). The AUC (mV/ms) of the averaged MEP responses were compared using the baseline, 15-min and 30-min responses. We refer to this measure as the averaged MEP amplitude. The MEP amplitude was performed at baseline during the first rTMS treatment.

**rTMS procedure**

The rTMS stimuli were administered at 90% MT. The rTMS session consisted of twenty 6-s trains, with a 30-s interval between the trains at 10 Hz for a total of 1200 pulses per day. Patients in this study were participating in an ongoing protocol comparing the effects of rTMS and ECT in MD (Grunhaus et al., 2003). The rTMS stimulation was performed at the LDLPFC. The site for stimulation was placed 5 cm anterior to, and in a parasagittal plane with the site of maximal APB stimulation. The figure-of-eight coil, was hand-held flat over the scalp and kept at a 45° angle with the handle oriented towards the back of the head.

**Statistical methods**

The main outcome measures in this study were MT and AUC of the averaged MEP responses. The main hypotheses of the study were tested with paired *t* tests and with a one-way repeated-measures analysis of variance (ANOVA) using the AUC of the averaged MEP responses as the independent variable. Temporal changes in MT and AUC were explored by comparing baseline values with those obtained 15 and 30 min after the rTMS. These time-points were chosen to parallel the reported effects of ECT on EEG which last between 20 and 30 min after the seizure (Abrams, 1998). Demographic comparisons between normal controls and patients were performed using *t* tests and *χ*² tests. Pearson’s correlations (r) between age and AUC, and between baseline MEP amplitude and post-rTMS MEP amplitude (15 and 30 min) were also performed.

**Results**

Measures of MT did not differ between patients and controls (patients 59.3 ± 7.8; controls 60.9 ± 10.5; *t* = 0.5; CI = −4.9–8.3, ns). Baseline, 15- and 30-min responses of the AUC are presented in Table 1. Averaged MEP amplitudes were significantly increased by the rTMS treatment but equally so in patients and normal controls. This effect was most evident at 30 min post-rTMS (post-hoc comparisons with *t* tests for dependent samples, baseline 2.8 ± 2.0; post-30 min, 4.1 ± 4.5, *t* = 2.0, *p* = 0.04).

No significant correlation between severity of the depression, as represented by the HRSD score, and the averaged MEP amplitude either at baseline or following the rTMS stimulation was identified (baseline correlation, *r* = −0.17, ns; 15-min correlation, *r* = −0.25, ns; 30-min correlation, *r* = −0.32, ns).

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**Table 1. ANOVA of area under the curve (AUC) of the MEP amplitude measurements**

<table>
<thead>
<tr>
<th></th>
<th>MDD patients group (n = 19)</th>
<th>Normal controls group (n = 13)</th>
<th>AUC (mV/ms)</th>
<th>t</th>
<th>CI</th>
<th>p</th>
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<tbody>
<tr>
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<td>x ± S.D.</td>
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<tr>
<td>Baseline</td>
<td>3.1 ± 2.3</td>
<td>2.3 ± 1.4</td>
<td>−1.1</td>
<td>−2.3–0.6</td>
<td>ns</td>
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<tr>
<td>15 min post-stimulation</td>
<td>3.0 ± 2.6</td>
<td>3.7 ± 3.3</td>
<td>0.6</td>
<td>−1.4–2.8</td>
<td>ns</td>
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<tr>
<td>30 min post-stimulation</td>
<td>3.6 ± 3.6</td>
<td>4.7 ± 5.6</td>
<td>0.6</td>
<td>−2.3–4.3</td>
<td>ns</td>
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<td></td>
<td>F</td>
<td>d.f.</td>
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<tr>
<td>Group effect</td>
<td>0.07</td>
<td>1.30</td>
<td>ns</td>
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<tr>
<td>Time effect</td>
<td>4.8</td>
<td>2.60</td>
<td>0.01</td>
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<tr>
<td>Interaction effect</td>
<td>2.2</td>
<td>2.60</td>
<td>ns</td>
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*a See Methods section for explanations.*
To investigate a possible effect of rTMS on MEP amplitudes we compared pretreatment MEP amplitude and those obtained 15 and 30 min after the rTMS. Correlations (pooled sample of patients and normal controls, \( n = 32 \)) for both baseline to 15 min (\( r = 0.82, p < 0.0001 \)) and baseline to 30 min (\( r = 0.73, p < 0.0001 \)) of MEP amplitudes were highly significant. These results are presented in Figure 1. Similar significant correlations were obtained when patients or normal controls were compared separately (results not shown).

Age has been identified as influencing responses to magnetic stimulation (Kozel et al., 2000; McConnell et al., 2001). Correlation between the AUC and age (pooled results of patients and controls) revealed that older subjects demonstrated significantly lower responses to the magnetic stimulation at all time-points (baseline, \( r = -0.42, p = 0.05 \); 15 min, \( r = -0.58, p = 0.001 \); 30 min, \( r = -0.55, p = 0.001 \)). These results are presented in Figure 2.

The only adverse effect reported was a very mild local pain during the stimulations, reported by 3 patients and 2 normal controls.

**Discussion**

The two measures of cortical excitability explored in this study responded differently. At baseline neither MT nor averaged MEP amplitude differed between patients and normal controls. The averaged MEP amplitude following rTMS increased significantly at 30 min post-rTMS in both patients and controls. Thus,
Figure 2. Correlation between age and MEP amplitude at (a) baseline ($r = -0.42, p < 0.05$); (b) post-15 min rTMS treatment ($r = -0.58, p < 0.001$) and (c) post-30 min rTMS treatment ($r = -0.55, p < 0.001$).
our working hypothesis that motor cortex excitability, as represented by either the MT or the averaged MEP amplitude, would differentiate between MD patients and normal controls or correlate with changes in depression ratings, following an rTMS treatment was not confirmed.

Triggs et al. (1999) reported decreases in MT in depressed patients being treated with rTMS, and a positive correlation between depression rating changes and MT changes. In a previous study by our group (Dolberg et al., 2002) we were unable to replicate their findings. In our relatively large study \( (n = 60) \) MT was not associated to diagnosis, severity of the depression, response to rTMS, age, or to the presence of psychosis. The differences between our study and that of Triggs et al. (1999) are probably methodological. Triggs et al. defined MT as 100 \( \mu V \) MEP deflections in the EMG, whereas we used the more widely accepted cut-off of 50 \( \mu V \). In the current study we did not measure MT following the administration of rTMS, therefore we have no information on whether dynamic changes in the MT occur following rTMS.

Recent studies suggest that age, and the scalp-to-cortex distance can both reduce the effects of TMS. Kozel et al. (2000) reported that MT was positively correlated with the distance between the scalp and the motor cortex. In a follow-up study from the same group, McConnell et al. (2001), concluded that the absolute intensity of rTMS stimulations must take into account the distance from the prefrontal cortex to scalp, especially in elderly subjects where cortical atrophy may increase this distance. It is likely that the results from our study were influenced by the age of the subjects. Age and averaged MEP amplitude responses were inversely correlated. Thus younger subjects, both patients and normal controls, had significantly more intense averaged MEP amplitudes at all time-points studied.

One objective of this study was to test whether a measure of motor cortex excitability that can be readily obtained during treatment might provide additional clues regarding the clinical effects of rTMS. We are aware that as a measure of motor cortex excitability the averaged MEP amplitude has some limitations. It may suffer from considerable trial-to-trial variability, and it may also underestimate the portion of the cortico-spinal system activated by TMS (Kujirai et al., 1993; Ziemann et al., 2000). By increasing the number of stimulations \( (n = 20) \) in each trial we tried to overcome this limitation of the method. The very significant correlation between the MEPs obtained at baseline and those obtained 15 and 30 min after the rTMS, suggest this methodological improvement was successful in decreasing the variability of the responses. Additional limitations of this study are the use of benzodiazepines in the patient group and not in the control group and the use of the 5 cm rule to target the LDLPFC. While benzodiazepines do not affect MT (Ziemann et al., 1998) these medications may affect the amplitude of the MEP response to suprathreshold stimulation (Borojerdic et al., 2001). Identifying the area for stimulating the LDLPFC with the 5 cm rule, while standard in clinical trials, does result in some variability in coil placement across individuals and may have stimulated neighbouring structures in some subjects. Therefore, any conclusions regarding the neuroanatomical circuitry underlying our results should take this potential confound into account.

The studies on cortical excitability cited previously limited themselves to testing patients during or immediately following rTMS. We recorded MEP responses 15 and 30 min after the rTMS. These time-points were chosen to capture the prolonged effects of rTMS, those that would likely correlate with its antidepressant actions. The delayed response observed on the averaged MEP amplitude supported this assumption, however, it is unclear whether the finding is relevant for the clinical efficacy of rTMS.

It is unclear which LDLPFC efferent neuronal connections are activated by rTMS. Efferent projections of the LDLPFC reach the premotor cortex, the cingular cortex, and the basal ganglia (Fuster, 1997). Paus et al. (2001) recently published a study demonstrating that rTMS stimulation to the left mid-dorsolateral frontal cortex significantly increases blood flow to the anterior cingular cortex, an area implicated in mood disorders (Mayberg, 1997) suggesting that the LDLPFC–anterior cingular circuit is most important to the effects of rTMS. Using an electrophysiological approach, Ger Schlager et al. (2001) performed slow TMS stimulation to several frontal areas finding that only stimulations of the premotor cortex affected the MEP responses of the motor cortex. The effect so demonstrated was inhibitory. Rollnick et al. (2000) also using an electrophysiological strategy reported that 5 Hz rTMS applied to the LDLPFC reduces MEP amplitude responses to stimulation of the motor cortex. They speculated that this effect was related to the tonic inhibitory effects the prefrontal cortex has on motor responses. It is of interest that these two studies found decreased MEP amplitude while giving TMS at low frequency (1 and 5 Hz) to frontal regions. Our finding of increased MEP amplitude may be related to our use of high-frequency stimulation (10 Hz). It has been demonstrated that the effects on excitability of TMS are frequency dependent. This may be also true...
for frontal regions. Experiments combining brain imaging with electrophysiological probing during TMS could help to define the neural circuitry underlying these effects which may involve the prefronto-cingular motor circuits.

It has been repeatedly reported that hypofunction of the LDLPC (Starkstein et al., 1987) is found in patients with MD. Measurements of cortical excitability reported previously, suggest a pattern of increased inhibitory functions in MD, both in frontal and motor cortices. Thus, an excitatory stimulation (the 10 Hz paradigm), if therapeutic, should lead to a reversal of this hypofunction both at the frontal and motor cortices. The results of this study suggest that increased motor cortex excitability does not exist at baseline in patients with MD. We did find that increased motor cortex excitability is achieved with 10 Hz stimulations of the prefrontal cortex. However both patients and normal controls demonstrated comparable responses. We have assumed that the increased motor excitability is related to cortical processes, however during TMS, spinal and peripheral effects can also modify the averaged MEP response (Ziemann et al., 2000). Further studies are needed to define the local, regional, and distant effects of TMS.

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