Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression

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Abstract
The aim of this open study was to evaluate the safety and tolerability of theta-burst transcranial magnetic stimulation (TBS) and to assess preliminarily its therapeutic efficacy in patients with major depression. A total of 33 patients were assigned to receive one of four TBS protocols for 10 consecutive work days. TBS consisted of triple-pulse 50-Hz bursts given at a rate of 5 Hz to the left or right dorsolateral prefrontal cortex at different stimulation parameters. Severity of depression was assessed by the Hamilton Depression Rating Scale. Our results indicate that TBS as applied in this study is safe and well tolerated in depressed patients and seems to have antidepressant properties. Increase of stimulation parameters is not associated with more side-effects and adds to its therapeutic effect.

Introduction
In the last two decades, repetitive transcranial magnetic stimulation (rTMS) has been studied as a therapeutic tool in several neuropsychiatric disorders, primarily for the treatment of major depression (MD) where it has shown a consistent and reproducible therapeutic effect (Feinsod et al. 1998; George et al. 1997, 1999; Pascual-Leone et al. 1996). Previous studies have demonstrated that left high-frequency (> 5 Hz) (George et al. 2000) and right low-frequency (≤ 1 Hz) (Klein et al. 1999) rTMS to the prefrontal cortex (PFC) is effective in the treatment of MD. The antidepressant effects of rTMS might be related to its capacity to modulate neuronal plasticity which has been suggested to be altered in depression (Castren, 2005; Normann et al. 2007). Results of our previous work (Chistyakov et al. 2005a) demonstrated that a positive rTMS treatment response is associated with enhancement of left hemisphere excitability. Furthermore, similar changes in cortical excitability following electroconvulsive therapy (ECT) and pharmacological treatment are correlated with clinical improvement in MD (Chistyakov et al. 2005b). The mechanisms of such excitability shifts are unclear, but might be related to long-term potentiation (LTP) and long-term depression (LTD), as shown in animal studies (Hess & Donoghue, 1996). Human studies with rTMS have demonstrated changes in plasticity and cortical function extending beyond the immediate stimulation period. In general, high-frequency rTMS transiently facilitates cortical responses (Pascual-Leone et al. 1994) while low-frequency rTMS inhibits cortical excitability (Chen et al. 1997). However, these effects have typically been short lasting (10–20 min), of moderate size and variable. Furthermore, the magnitude of the
therapeutic effect of rTMS is modest with a small to moderate effect size. This calls for the design of more effective rTMS paradigms that will achieve a more robust antidepressant effect.

Theta-burst electrical stimulation (TBS) has long been known as a highly effective method to induce LTP and LTD in animals. Recently, Huang & Rothwell (2004) and Huang et al. (2005) reported safe application of TBS without noticeable adverse effects in humans, using rTMS techniques. Three magnetic pulses with an inter-stimulus interval of 20 ms (50 Hz) were applied repeatedly every 200 ms representing the theta rhythm of 5 Hz. This stimulation method produced more robust and enduring changes in cortical excitability (Huang et al. 2007, 2008, 2009; Ishikawa et al. 2005). These changes were shown to be consistent and robust across subjects. Thus theta-burst TMS seems to offer an advantage to some of the shortcomings of conventional rTMS and might be more effective than currently used rTMS treatments.

The aim of the present study was 2-fold: (1) to evaluate the safety and tolerability of TBS of different type, intensity and duration; (2) to assess preliminarily therapeutic efficacy of TBS in patients with MD.

Materials and methods

Subjects

A total of 33 patients were recruited from the population of MD patients hospitalized for treatment of their depression. All provided written informed consent to participate in the study, which was approved by Rambam Medical Center Ethics Committee. Patients aged 20–75 yr were included in the trial if they met DSM-IV criteria for MD and were capable of providing informed consent and cooperate sufficiently in the clinical and neurophysiological assessment. Exclusion criteria were: (1) suicidal risk, (2) evidence of a disease that might affect central and peripheral nerve conduction, (3) seizure disorder, (4) history of head trauma in the last year, (5) systemic uncontrolled disease, (6) implanted electronic devices (e.g. pacemaker, cochlear implant, deep brain stimulator) or metallic implants and (7) drug or alcohol abuse in the last 6 months.

All patients received at least one medication trial as outpatients and were hospitalized due to lack of response or deterioration of their clinical condition. Patients were invited to participate in the study soon after their admission and were maintained on their previous medications throughout the course of TBS treatment. Out of 33 patients, 12 were receiving antidepressants, mostly SSRIs or SNRIs, and 20 were on a combination of antidepressants and mood stabilizers. One patient received only mood stabilizers.

Table 1 summarizes key demographic and clinical characteristics of the 33 study participants and the subgroups. Patients were on average in their sixth decade, with a predominance of females and a chronic course of illness with recurrent depressive episodes. Nineteen patients had unipolar depression and 14 had bipolar depression. Baseline Hamilton Depression Rating Scale (HAMD) scores were in the range of moderate to severe depression.

Initially, 13 patients were randomized to receive one of the two treatment conditions: (1) iTBS (hereafter iTBS1200) to the left dorsolateral prefrontal cortex (DLPFC) \( n = 7 \); (2) continuous TBS (hereafter cTBS1200) to the right DLPFC \( n = 6 \). The intensity of stimulation was 90% of the active motor threshold (aMT). Each treatment session consisted of 600 stimuli repeated twice daily (1200 stimuli per day) for 10 consecutive work days. This protocol was termed ‘short TBS’. As evident from these 13 patients, right-sided cTBS appeared to have a more prominent antidepressant action. Thus, right-sided stimulation was further amended in six patients who received 900 stimuli per session at 100% aMT intensity applied twice daily (a total of 1800 stimuli per day, hereafter cTBS1800), and in 14 additional patients who received 1800 stimuli per session delivered in two consecutive trains of 900 stimuli each separated by a 30-min interval and repeated twice daily (a total of 3600 stimuli per day, hereafter cTBS3600). These protocols were termed ‘amended TBS’.

TBS treatment

TBS was applied through a 70-mm figure-of-eight coil (peak magnetic field 2.2 T) connected to a Magstim Super Rapid2 (Magstim Company Ltd, UK) magnetic stimulator with four booster modules as well as an integrated two-channel EMG amplifier and system acquisition software. The system enables recording of
motor-evoked potentials for threshold determination as well as programming of different modes of stimulation including TBS protocols. The coil was placed tangentially to the scalp with the handle pointed backwards, 5 cm anterior to the site optimal for producing the motor response in the contralateral abductor pollicis brevis (APB) muscle. As originally described by Huang et al. (2005), TBS consisted of triple-pulse 50-Hz bursts given at a rate of 5 Hz (i.e. 200 ms between each burst). For iTBS, a 2-s TBS train was repeated every 10 s. cTBS was applied as a single uninterrupted TBS train. As previously mentioned, the stimulus intensity was 90% aMT in patients who received 1200 stimuli per day (short TBS protocol) and 100% aMT in patients who received 1800 and 3600 stimuli per day (amended TBS protocol). However, due to limitations of the stimulator the maximal TBS intensity which could be applied in the amended TBS protocol was 51% of the maximal stimulator output. For this reason, in seven patients (two who received iTBS1800 and five who received cTBS3600) whose aMT was higher than 51% of the maximal stimulator output, the actual stimulus intensity was 92.3 ± 2.5% aMT.

Patients were seated in an armchair and earplugs were used during the treatment session.

**Assessment of motor thresholds**

The resting motor threshold (rMT) was defined as the lowest stimulus intensity capable of eliciting in the relaxed APB muscle at least five motor responses with amplitude of at least 50 μV in a series of 10 consecutive trials of single-pulse TMS. aMT was measured during a voluntary isometric contraction of the contralateral APB with the force level of about 20% of maximal EMG. It was defined as the minimum stimulus intensity required to produce motor responses >100 μV in five consecutive single-pulse TMS trials.

**Clinical assessment**

Severity of depression was assessed by the HAMD and the Clinical Global Impression (CGI) scale. Ratings were performed by a trained psychiatrist at baseline and weekly thereafter. Marked clinical improvement was defined as a reduction of ≥50% in HAMD.

**Statistical procedures**

The effects of TBS on depression scores were analyzed using repeated-measures ANOVA with group (iTBS1200, cTBS1200, cTBS1800, cTBS3600) as the between-subject factor, and time (baseline, after 1 wk, after 2 wk) as the inter-subject term. Between-group comparisons of the frequencies of categorical variables were carried out by the χ² test. The results were considered significant if *p* < 0.05.

**Results**

**Patient demographics**

A set of one-way ANOVAs revealed no significant group effect on HAMD and other demographic data (Table 1). Baseline HAMD and CGI scores of unipolar and bipolar depression patients did not differ.

**Safety and tolerability**

All but two patients completed the 2-wk treatment protocol without any adverse effects. One patient...
dropped out after four treatment sessions due to local scalp discomfort and painful sensations during cTBS delivered at an intensity of 100% aMT. These sensations persisted even after reducing stimulus intensity to 80% aMT. Another patient who received cTBS3600 dropped out after nine treatment days due to lack of clinical improvement. Given that this patient missed only one day of treatment (two treatment sessions) his ratings were included in the statistical analysis and he was considered as a non-responder.

Stimulus intensity was decreased and the coil was moved 1 cm posteriorly in three other patients who completed the 2-wk treatment protocol but complained about slight pain in the frontal scalp which irradiated to the nose and eye. In two patients who received left iTBS1200, stimulus intensity was reduced from 90% to 80.8 ± 2.1% aMT, and in the third patient who received right cTBS3600, stimulus intensity was reduced from 100% to 91.3% aMT.

The mean aMT for the four groups was 50.5 ± 7.3%, the mean rMT was 66.2 ± 8.3% and the mean TBS intensity was 46.8 ± 5.6%. There were no significant differences in these stimulation parameters among the four groups.

**Antidepressant effect**

Following 2 wk of treatment marked clinical improvement was seen across all patient groups. Repeated-measures ANOVA revealed a significant main effect of time for both HAMD [baseline 28.9 ± 5.4, week 1 16.8 ± 6.4, week 2 13.3 ± 9.0; F(2, 29) = 63.4, p < 0.00001] and CGI [baseline 5.0 ± 0.9, week 1 3.6 ± 0.9, week 2 3.2 ± 1.5; F(2, 29) = 27.4, p < 0.00001]. In the short TBS protocol (1200 stimuli per day, 90% aMT), greater clinical improvement was observed in patients who received right cTBS compared to left iTBS; however, this difference did not reach statistical significance (Fig. 1a, b). Amendment of the right cTBS treatment protocol resulted in additional improvement. A comparison between short and amended TBS protocols, using repeated-measures ANOVA showed a significant time x group interaction for both HAMD [F(2, 28) = 4.1, p < 0.05] and CGI [F(2, 28) = 13.3

![Fig. 1. Hamilton Depression Rating Scale (HAMD) and Clinical Global Impression (CGI) scores after left iTBS1200 (–––) vs. right cTBS1200 (– –) (repeated-measures ANOVA for time x group interaction; (a) p > 0.05, (b) p > 0.05) and short TBS (– ––) vs. amended TBS (– ––) (repeated-measures ANOVA for time x group interaction; (c) p < 0.05, (d) p < 0.0001).](https://academic.oup.com/ijnp/article-abstract/13/3/387/658170/15/January/2019)
indicating a significant dose effect (number and intensity of stimuli) on the magnitude of clinical improvement (Fig. 1c,d).

Table 2 depicts percentages of patients with at least 50% reduction in the HAMD in the different treatment groups. The overall improvement rate was 56.3% with more patients showing marked clinical improvement in the amended TBS groups. However, this difference was not statistically significant due to the small sample size.

There was no difference in the improvement rates between unipolar and bipolar depression patients.

Discussion

Our results show that TBS as applied in the present study is safe and well tolerated in depressed patients. Furthermore, increase of stimulus intensity and number of stimuli was not associated with more side-effects.

The main concern about potential adverse effects of rTMS is its ability to induce seizures. The risk of seizures has been related primarily to stimulation frequency and intensity. For this reason, safety recommendations, which define upper limits of rTMS parameters, were introduced (Wassermann, 1998). However, no such recommendations are available for TBS protocols. Huang et al. (2005) were the first to describe the safe application of magnetic TBS of the motor cortex in humans. Their stimulation protocol consisted of 600 stimuli given continuously or intermittently at an intensity of 80% aMT. Studies that followed used similar stimulation parameters. Grossheinrich et al. (2009) recently reported the safe application of intermittent and continuous TBS at 80% rMT intensity over the DLPFC and medial PFC in healthy subjects, with minor effects on neuropsychological measures and no impact on mood.

We initially used the same protocol as applied by Huang et al. (2005) with a minor modification, i.e. stimulation intensity was increased to 90% aMT. Since no adverse effects were evident in the first 13 patients, treatment parameters were further augmented in subsequent patients. This was done by increasing stimulation intensity from 90% to 100% aMT and number of stimuli from 1200 to 3600 per day, without evidence of seizures or any other significant adverse effects. Only one patient requested to withdraw due to local painful sensation in the stimulated area which persisted even after treatment intensity was reduced to 80% aMT. These findings suggest that TBS treatment can be applied safely in a wide range of stimulation parameters. However, further work needs to be done to determine the safe boundaries for this type of TMS.

The results of this study also indicate that TBS might have antidepressant properties. Similar to other rTMS protocols, treatment response to TBS depends on stimulus intensity, number of stimuli and possibly also on its laterality. Based on our initial treatment parameters (90% aMT stimulus intensity and 600 stimuli per session), right-sided cTBS seems to produce a more prominent antidepressant effect compared to left-sided iTBS. However, no firm conclusions concerning the relationship between laterality and treatment outcome can be drawn on the basis of these findings, since we did not assess therapeutic efficacy of left iTBS at higher intensities and longer durations as we did for right cTBS. Further study is required to find out whether augmented left iTBS protocols can produce a better antidepressant effect.

The fact that right cTBS, which is believed to exert an inhibitory effect on cortical excitability (Huang et al. 2009), produces antidepressant action is in agreement with our previous findings which demonstrated therapeutic efficacy of low-frequency (1 Hz) right-sided rTMS (Klein et al. 1999), which is also known to suppress cortical excitability (Chen et al. 1997). It is possible that when applied to the right DLPFC both cTBS and 1 Hz rTMS can restore disturbed inter-hemispheric balance in depressed patients which results from decreased left hemisphere excitability (Chistyakov et al. 2005a, b).

Our results further indicate that there is significant dose effect since the increase in intensity and number of stimuli can enhance the effect, providing a safe and tolerable treatment option for patients with depression.
of stimuli of right cTBS adds to its therapeutic effect. Yet, it is difficult to determine which of these factors is responsible for this dose effect. It is, however, noteworthy that despite the increase of stimulus intensity from 90% to 100% aMT there were no differences in the actual stimulus intensity between the groups due to technical limitations of the stimulator and patients’ complaints which necessitated reduction of stimulus intensity. Therefore, it is more likely that the number of stimuli is responsible for the observed dose effect.

Concerning the putative antidepressant action of TBS some of the limitations of this study should be noted. First, the trial was open and uncontrolled; therefore a placebo effect cannot be excluded. Furthermore, HAMD and especially CGI are sensitive to observer bias in open trials. Second, the sample size was small particularly with regard to the size of the different subgroups. Third, patients remained on their ongoing pharmacological treatment, thus a medication effect cannot be ruled out. The short duration of our treatment protocol could be viewed as another limitation, since it was shown in other studies that the treatment response accumulates to a clinically meaningful level over 4–6 wk of active treatment (Fitzgerald et al. 2006). However, the fact that TBS treatment produced an antidepressant effect already after 2 wk could suggest that it might be associated with a faster onset of antidepressant action compared to conventional rTMS protocols.

In conclusion, the results of our study provide evidence that TBS is safe and well tolerated. The suggestion that TBS has clinically relevant antidepressant properties should be viewed as preliminary and warrants larger sham-controlled studies.

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Statement of Interest
None.

References


