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Research report

Preliminary assessment of the therapeutic efficacy of continuous theta-burst magnetic stimulation (cTBS) in major depression: A double-blind sham-controlled study

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ABSTRACT

Background: Theta-burst transcranial magnetic stimulation (TBS) has been shown to induce potent and long lasting effects on cortical excitability. In a previous open study, we demonstrated safety, tolerability and antidepressant properties of continuous TBS (cTBS) in major depression (MD). The present study was aimed to evaluate the therapeutic efficacy of cTBS in depressed patients using a double-blind, sham-controlled design.

Methods: Twenty nine patients with MD were randomized to receive either active cTBS to the right dorsolateral prefrontal cortex ($n=15$) or sham cTBS ($n=14$) for 10 consecutive work days. After the 10th session, patients who received sham TBS were crossed over to active cTBS which consisted of 10 daily sessions. Patients who received active cTBS continued with the same treatment protocol for additional 10 treatments. Each treatment session consisted of 3600 stimuli at an intensity of 100% of the active motor threshold. Severity of depression was assessed weekly.

Results: Overall, there was no significant difference in the degree of clinical improvement between active and sham cTBS groups. However, in patients whose medication status remained unchanged before the trial ($n=8$) and in those who were medication-free ($n=3$), active cTBS resulted in a significantly greater reduction of Hamilton depression scores as compared to sham cTBS.

Limitations: A small sample size, confounding effect of medication and short treatment period.

Conclusions: Our results suggest that the antidepressant effect of cTBS is modest, yet it might be beneficial to patients nonresponsive to ongoing pharmacological treatment. A direct comparison between cTBS and conventional rTMS protocols is warranted.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) has been shown to produce antidepressant effects in patients with major depression (MD). This is true for both high frequency rTMS administered to the left dorsolateral prefrontal cortex (DLPFC) (George et al., 2000) and low frequency rTMS administered to the right DLPFC (Fitzgerald et al., 2003; Klein et al., 1999). However, the therapeutic effect of currently available rTMS protocols is relatively moderate and short-lasting.

It has been suggested that the antidepressant action of rTMS is related to its ability to modulate cortical excitability (Chistyakov et al., 2005). When applied at high frequencies (>1 Hz) rTMS can facilitate cortical activity (Pascual-Leone et al., 1998) while at low frequencies (≤ 1 Hz) it suppresses cortical excitability (Chen et al., 1997). Theta-burst stimulation (TBS), a novel form of rTMS, can induce larger and longer-lasting modulation of cortical excitability than standard rTMS (Huang et al., 2005) thus suggesting its potentially greater clinical efficacy. In a previous open study (Chistyakov et al., 2010), we have demonstrated safety, tolerability and antidepressant properties of continuous TBS (cTBS) applied to the right DLPFC in patients with MD using different stimulation protocols (600–900 stimuli per train, with a total of 1200 to 3600 per session). Yet, given the open design of the trial these results were viewed as preliminary and a further double-blind, sham-controlled study was designed to assess the clinical utility of cTBS in MD. The present study was aimed to evaluate the therapeutic efficacy of cTBS in depressed patients using double-blind comparison with sham cTBS.

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2. Materials and methods

2.1. Subjects

A total of 29 in patients with major depression (19 with unipolar and 10 with bipolar depression) were recruited for the study. Patients were hospitalized due to lack of response to previous medication or deterioration of their clinical condition. All patients met DSM IV criteria for MD, as determined by consensus of two senior staff psychiatrists, and were capable to provide written informed consent and to cooperate in the study. Demographic and clinical characteristics of the participants are depicted in Table 1. Overall, the average severity of depression at baseline was moderate to severe.

Exclusion criteria were: (1) suicidal risk, (2) seizure disorder, (3) history of head trauma with documented brain damage in the last year, (4) uncontrolled medical conditions, (5) pacemaker, metallic implants, or any other contraindication to TMS as specified in the safety guidelines for that procedure (Rossi et al., 2009), and (6) drug or alcohol abuse in the last six months.

Twenty six (90%) patients received concomitant pharmacotherapy and three were medication-free throughout the study. Among the patients who were receiving medication, eight (28%) remained on their existing pharmacological treatment (mean duration of previous treatment was 3.3 ± 1.9 months) while in 18 patients (62%) medication status was changed before the trial (within the week prior to cTBS). Table 2 provides details on the type of medications that the patients were receiving.

Initially, patients were randomized to receive either active cTBS ($n=15$) or sham cTBS ($n=14$) to the right DLPFC for 10 consecutive work days (phase 1). After the 10th session, patients who received sham cTBS were crossed over to the active cTBS treatment which consisted of 10 daily sessions (phase 2). Patients who received active cTBS in phase 1 continued with the same treatment protocol in phase 2. In phase 1 (double-blind phase), the rater and patients were blinded to the treatment, whereas phase 2 was single-blinded. The technician who delivered cTBS was not blind and was not involved in the participant's care and assessment.

The study was approved by the local Ethical Committee and all patients gave written informed consent before participation.

2.2. cTBS treatment

Treatment with cTBS was delivered by a Magstim Super Rapid^2 magnetic stimulator with a 70 mm figure-of-eight coil (peak magnetic field: 2.2 T) which was placed tangentially to the scalp over the right DLPC. The stimulation site was defined as a location 5 cm anterior to the optimal coil position ("hot-spot") for producing the motor response in the contralateral abductor pollicis brevis (APB) muscle. The choice of this stimulation site and treatment parameters was based on our previous TBS study which demonstrated positive treatment response with a low attrition rate due to painful sensation and facial muscle twitches (Chistyakov et al., 2010).

Similar to the Huang et al. (2005) original protocol, cTBS consisted of triple-pulse 50 Hz bursts given at a rate of 5 Hz (i.e. 200 ms between each burst) in uninterrupted trains. However, as shown to be superior in our previous study the number of stimuli per train was increased from 600 to 900, Thus, each treatment session included 3600 stimuli delivered in four consecutive trains of 900 stimuli each separated by at least a 15-min interval. The stimulation intensity was 100% of the active motor threshold (aMT). The aMT was defined as the minimum stimulus intensity required to evoke a reproducible motor response ($>100\ \mu V$) to single-pulse TMS over the motor "hot-spot" during a voluntary isometric contraction of the contralateral APB. Evoked and spontaneous muscle activity was recorded using integrated Magstim two-channel EMG amplifier and system acquisition software. In addition, the resting motor threshold (rMT) was measured as the lowest stimulus intensity capable of eliciting at least 5 motor responses with amplitude of at least 50 μV in a series of 10 consecutive trials of single-pulse TMS in the relaxed APB muscle. In the active cTBS group, motor thresholds (aMT, rMT) were assessed twice, at baseline and after 10-treatment sessions. No difference was observed between the two measurements. In the

Table 1
Socio-demographic and clinical characteristics of the total sample and groups (Mean ± SD).

	Total sample ($n=29$)	*Groups*		$F(1,27)/\chi^2$
		Active cTBS ($n=15$)	*Sham cTBS* ($n=14$)	
Gender (M/F)	11/18	5/10	6/8	0.28, *N.S*
Age (years)	51.8 ± 14.2	52.7 ± 11.1	50.9 ± 17.3	0.12, *N.S*
Age at onset (years)	36.9 ± 13.2	39.8 ± 12.4	33.9 ± 13.7	1.48, *N.S*
Length of illness (years)	14.9 ± 11.9	12.9 ± 9.9	16.9 ± 13.9	0.82, *N.S*
Length of current episode (months)	12.6 ± 14.8	10.9 ± 13.4	14.4 ± 16.4	0.4, *N.S*
Number of episodes	2.9 ± 2.3	3.7 ± 2.6	2.1 ± 1.7	3.3, *N.S*
Number of previous hospitalizations	0.9 ± 1.6	1.1 ± 1.8	0.8 ± 1.4	0.23, *N.S*
HDRS at baseline	25.8 ± 3.7	26.7 ± 3.9	24.8 ± 3.2	2.14, *N.S*

N.S – Non-significant difference.

Table 2
Pharmacological treatment in the total sample and groups (n, %).

	Total sample ($n=29$)	*Groups*		χ^2
		Active cTBS ($n=15$)	*Sham cTBS* ($n=14$)	
Medication change before trial	18 (62.1%)	11 (73.3%)	7 (50%)	1.67, *N.S*
Antidepressants	23 (79.3%)	12 (80%)	11 (78.6%)	0.01, *N.S*
Mood Stabilizers	14 (48.3%)	8 (53.3%)	6 (42.9%)	0.32, *N.S*
Antipsychotics	14 (48.3%)	8 (53.3%)	6 (42.9%)	0.31, *N.S*

N.S – Non-significant difference.