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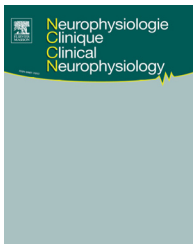

SHORT COMMUNICATION

Twice-daily neuronavigated intermittent theta burst stimulation for bipolar depression: A Randomized Sham-Controlled Pilot Study

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Summary The safety and efficacy of neuronavigated intermittent theta burst stimulation (iTBS) in patients with bipolar depression has not yet been investigated. We hypothesized the superiority of active iTBS over sham. Twenty-six patients were randomly allocated to receive

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prefrontal cortex;
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Resistant depression;
Theta burst stimulation

either active ($n = 12$) or sham ($n = 14$) iTBS. Response and remission rates according to changes in depression MADRS score were high following active iTBS (72% and 42% for response and remission rates, respectively), but no significant difference was found after sham stimulation (42%and 25%). No adverse events were observed. This study revealed the safety and tolerability of twice daily iTBS in patients with bipolar depression. Larger controlled studies are warranted to prove iTBS superiority in treatment-resistant bipolar depression.

Introduction

Bipolar disorder is a frequent and debilitating psychiatric condition affecting 1 to 3% of the general population. Despite numerous approaches and optimization strategies, more than 30% of patients with bipolar disorder have disabling treatment-resistant depression (TRD), contributing to the overall burden of disease. In such cases, repetitive transcranial magnetic stimulation (rTMS) may be proposed in addition to mood stabilizing agents and may be safer than antidepressants, which can be associated with several complications (rapid cycling, mixed or manic states, worsening of symptoms, chronic irritability). Although the clinical efficacy of rTMS over dorsolateral prefrontal cortex (DLPFC) in the treatment of TRD in patients with unipolar major depressive disorder is now well established, less is known regarding its efficacy in patients with bipolar depression.

To our knowledge, more than twenty open-label naturalistic studies investigating the efficacy of rTMS in bipolar depression have been conducted. Most of them have used high frequency (HF) rTMS and some have suggested comparable efficacy of rTMS in treating bipolar and unipolar depression (e.g. [2]). However, few controlled studies have been designed to investigate the effect of rTMS specifically in bipolar depression. Although the efficacy of HF-rTMS ($n = 20$) was suggested by Dolberg and colleagues [5], results from this seminal work were not subsequently replicated by other studies [10]. Beyond HF-rTMS over the left DLPFC, other rTMS paradigms were applied in bipolar depression (e.g. for review [11,12]), including low frequency (LF) rTMS over the right DLPFC, deep HF-rTMS (with H-coils), or accelerated TMS protocols (e.g., 4 or 5 sessions/day) with mixed results. More recent studies failed to report the efficacy of rTMS in bipolar depression using a sequential bilateral study design ($n = 49$) [7] or comparing left HF-rTMS ($n = 12$) with right LF-rTMS ($n = 13$) and sham rTMS ($n = 13$) in association with quetiapine [8]. Despite growing interest, there is no consensus regarding optimal stimulation parameters. One possible way to optimize the rTMS protocol is to employ briefer protocols such as theta burst stimulation (TBS), which is a patterned form of 50 Hz rTMS. The use of TBS in bipolar depression is still scarce. Chistyakov and colleagues showed the safety and potential antidepressant properties of continuous TBS (cTBS) protocol in an RCT including 10 bipolar patients among 29 depressed subjects [4]. On the other hand, several recent neuronavigated studies highlighted the interest of intermittent TBS (iTBS) protocol over the left DLFC in patients with major depressive disorder (MDD) [3,9]. A more recent study demonstrated the non-inferiority of 3 min iTBS versus the reference O'Reardon's HF-rTMS protocol (30 min of 10 Hz stimulation) in a large sample of 414 subjects [1], leading to recent FDA approval as ''a therapeutic option in adult patients with MDD episode who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode''. To date, no sham-controlled efficacy study has been specifically designed and conducted using iTBS for treating bipolar depression. The aim of this pilot randomized double-blind sham-controlled study was to investigate the clinical efficacy of neuronavigated iTBS applied over the left DLPFC in patients with bipolar TRD.

Methods

Participants

Twenty-six patients with treatment resistant bipolar depression (DSM IV-TR, Montgomery-Åsberg depression rating scale ($MADRS_{10}$) > 20 at inclusion despite optimized mood-stabilizing treatment at adequate duration and dosage for at least one month) were included in the study. Throughout the study period, patients were on stable mono- or bi-therapy with mood stabilizers and without antidepressants nor benzodiazepines. The study was approved by a local Ethics Committee (CPP Sud-Est VI), the French health authority (ANSM registration number: 2010-A01085-34) and recorded on ClinicalTrials.gov database (NCT02740244). The initial aim of the study was to include 40 participants, but the study was stopped prematurely because of recruitment difficulties. All patients provided written informed consent. Details on characteristics of patients are given in Table 1.

Stimulation parameters

iTBS was applied twice-daily with a 3-hours interval with a MagProX100 (MagVenture, Denmark) and a figure-of-eight coil with the following parameters: 990 pulses per session

Table 1 Socio-demographic and clinical characteristics of patients with bipolar TRD receiving either active or sham intermittent theta burst stimulation (iTBS) over the left dorsolateral prefrontal cortex.

	Active iTBS	Sham iTBS	*P*
Number of patients	12	14	
Age (years)	52.7 ± 10.8	53.1 ± 12.5	0.93
Gender Female/Male	7/5	4/10	0.23
Handedness left/right	2/10	2/12	1.0
Duration of the current episode (months)	17.3 ± 14.9	13.2 ± 10.3	0.46
Number of suicide attempts	1.4 ± 1.9	0.9 ± 0.9	0.42
Number of hospitalizations	4.2 ± 4.7	5.8 ± 4.3	0.45
Educational level (years)	13.1 ± 4.6	13.1 ± 3.8	0.97
$MADRS_{10}$ at baseline	30.0 ± 5.7	28.2 ± 5.6	0.42
BDI_{13} at baseline	20.5 ± 6.0	19.6 ± 4.3	0.65

BDI_{13}: 13-item Beck Depression Inventory; $MADRS_{10}$: 10-item Montgomery and Asberg Depression Rating Scale. Results are given as mean ± standard deviation.

(2 s train of bursts containing three pulses at 50 Hz repeated each 200 ms, every 10 s). Intensity was set at 80% of the resting motor threshold. The left DLPFC was targeted based on 3D-T1 MRI (TMS Navigator, Localite® or Syneika® systems) as the junction between Brodmann's areas 9 and 46 [15]. Sham stimulation was delivered using a commercial sham coil. Patients received 30 sessions delivered over 3 consecutive weeks. Three patients who achieved remission after 10 sessions received only 10 sessions. Remission was defined as a Beck Depression Inventory-BDI_{13} score < 10.

Clinical assessments

Our primary outcome was the number of patients in remission at end point (number of patients with a BDI_{13} score < 10 in each group after the end of stimulation sessions). The severity of depression was assessed at baseline, and then weekly (10 sessions). Severity of depression was also assessed using the $MADRS_{10}$ rated by a blinded investigator.

Statistical analysis

Socio-demographic and clinical characteristics, response and remission rates, and decreases in depression scores were compared between groups using Mann—Whitney U test and Fischer's Exact test, and Cohen's d effect size, respectively. Intra-group comparisons (pre- and post- iTBS sessions) were analysed using Wilcoxon T test.

To enhance the power of our analysis we also used a linear mixed-effect model for repeated measures (with an intention to treat approach). The evolution of BDI and MADRS scores between active and placebo groups were compared from baseline until one month after last session. Indeed, the robustness of the linear mixed effect model to missing data allowed the extension of the analysis to that point.

Results

Twice daily iTBS sessions were very well tolerated and no mood switch was observed.

According to BDI_{13} scores obtained at the end of the stimulation sessions, there was no significant difference between the number of patients who achieved remission in the active group (7 out of 12) and in the sham group (5 out of 14; $P = 0.43$).

No significant difference between active and sham groups was observed according to $MADRS_{10}$ response rates (defined as an at least 50% decrease from baseline to endpoint) with 72% of responders in the active group versus 42% in the sham group ($p = 0.2$), and to $MADRS_{10}$ remission rates (defined as $MADRS_{10} < 8$ at endpoint) with 42% of remitters in the active group vs. 25% in the sham group ($P = 1$).

In the active group, there was a significant decrease in BDI_{13} (all the subsequent values are expressed as means ± standard deviations) (−45.4% ± 26.3; $Z = -2.588$; $P = 0.009$) and in $MADRS_{10}$ scores (−53.8% ± 32.8; $Z = -2.845$; $P = 0.004$). For the sham group, there was also a significant decrease in BDI_{13} (−45.9% ± 32.7; $Z = -3.107$; $P = 0.001$) and $MADRS_{10}$ (−47.1% ± 30.5; $Z = -3.233$; $P = 0.001$) scores.

The linear mixed-effect model showed no significant difference in MADRS and BDI score changes between groups over the time ($P = 0.853$ and $P = 0.393$, respectively) (Table 1 and Fig. 1).

Discussion

For a condition as difficult to treat as bipolar depression, response and remission rates according to changes in depression MADRS score were high following active iTBS (72% and 42% for response and remission rates, respectively), with a difference of 30% with the sham group for the response rate (42%) that however failed to reach statistical significance. Furthermore, these response rates were at least as high as those typically observed in patients with unipolar TRD treated by rTMS [6]. The strengths of this study were the originality of using for the first time twice daily iTBS in bipolar disorder, strict homogeneous inclusion/exclusion criteria, optimal number of sessions (up to 30), and an accurate localization procedure with neuronavigation. Our sample size was small with a large placebo effect (nonetheless not uncommon in rTMS studies) that could be explained by higher acceptance rates provoked by having several sessions

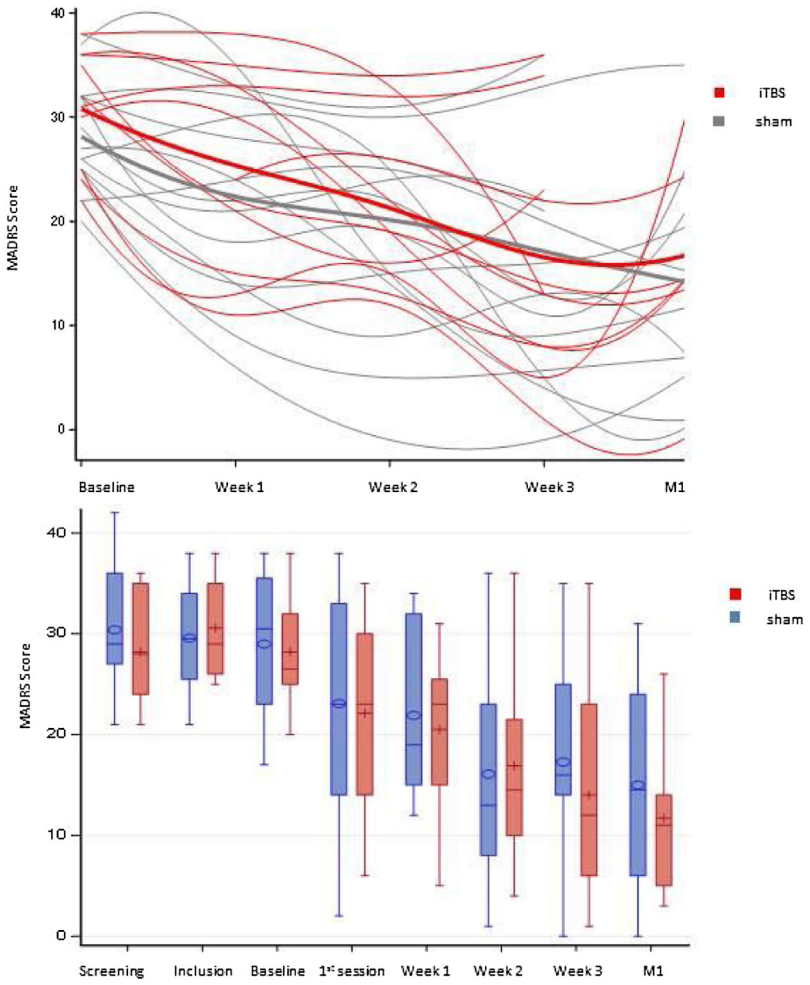

Figure 1 MADRS score evolution over time (Linear Mixed Model).

per day. This study is encouraging given the high percentage of positive outcomes for this severe, debilitating and resistant condition. On the basis of these results, 45 patients may be needed in each group to adequately power further trials aiming at assessing putative superiority of iTBS over sham (90% power with alpha set at 5%). In line with promising results for unipolar depression with accelerated iTBS (20 sessions over 4 days) [6], safety and tolerance of twice daily iTBS sessions was good with no mood switch, suggesting a favourable development for patients living with this debilitating disease. Though encouraging, further studies must be conducted before drawing any definitive conclusions regarding the clinical efficacy of accelerated iTBS in bipolar TRD. In this respect, it would be of interest to consider combining iTBS delivered to the left DLPFC with cTBS delivered to the right DLPFC (i.e. a sequential bi-hemispheric protocol) as a promising therapeutic option, as shown in several studies performed in unipolar depression [3,9,13] and also preliminary studies in bipolar depression [14].

Disclosure of interest

The authors declare that they have no competing interest.

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