

## Continuous theta burst stimulation over the supplementary motor area in refractory obsessive-compulsive disorder treatment: A randomized sham-controlled trial

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### ABSTRACT

**Background:** Obsessive-compulsive disorder (OCD) is a complex disorder with 40 to 60 % of patients resistant to treatment. Theta burst transcranial magnetic stimulation (TBS) is a promising new technique that has been shown to induce potent and long lasting effects on cortical excitability. The present study evaluated for the first time therapeutic efficacy and tolerability of continuous TBS (cTBS) over the supplementary motor area (SMA) in treatment resistant OCD patients using a double blind, sham-controlled design.

**Methods:** Thirty treatment resistant OCD outpatients were randomized to receive either active cTBS or sham cTBS for 6 weeks (5 sessions per week). Each treatment session consisted of 600 stimuli at an intensity of 70% of resting motor threshold. Patients were evaluated at baseline, at the end of treatment (week 6), and follow-up (week 12). Response to treatment was defined as at least 25% decrease on the Yale-Brown Obsessive Compulsive Scale.

**Results:** There was no significant difference between active and sham cTBS groups in treatment efficacy. Responder rates were not different between the two groups at week 6 (cTBS 28% versus sham 36%;  $p = 0.686$ ) and week 12 (cTBS 28% versus sham 36%;  $p = 0.686$ ). Depressive and anxious symptoms improvements were similar in the two groups.

**Conclusion:** This study is the first controlled trial using cTBS in treatment resistant OCD patients. The use of cTBS over the SMA is safe but not sufficient to improve OCD symptoms. Further studies are needed to identify the optimal parameters to be used in OCD patients.

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### Introduction

Obsessive-compulsive disorder (OCD) is a complex and clinically heterogeneous neuropsychiatric disorder. It is characterized by recurrent intrusive thoughts causing anxiety and compulsions, that

is, repetitive behaviours that aim to relieve distress. The prevalence of OCD is around 2–3%, and OCD symptoms usually emerge during childhood or early adulthood [1]. Association of serotonin reuptake inhibitors (SRIs) and cognitive-behavioral therapy (CBT) is the usual treatment of OCD [2]. Despite the improvement in pharmacological and behavioral treatments, 40–60% of patient remain resistant to treatment [3]. Therefore, developing alternatives to classical therapies may be useful, and neuromodulation techniques offer promising alternatives. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that has been explored in a number of clinical trials. In recent meta-analyses [4–6], it was

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found that active rTMS was significantly superior to sham rTMS for the treatment of OCD. Randomized control trials conducted to date focused on three stimulation sites; the left, right or bilateral dorso-lateral prefrontal cortex (DLPFC), the orbito-frontal cortex, and the supplementary motor area (SMA).

In spite of advances in scientific knowledge, the neurobiology of OCD remains poorly understood. The dominant neurobiological model of OCD has implicated dysfunctional cortico–striato–thalamo–cortical (CSTC) circuits in the aetiology of clinical symptoms and cognitive deficits [7]. In addition, difficulty in the inhibition process is apparent in the phenomenology of OCD, with patients being apparently unable to stop their obsessions and compulsions. Response inhibition is the ability to inhibit thought and action. It is associated with a main network including the pre-SMA, the inferior frontal gyrus, and the subthalamic nucleus [8]. De Wit et al. [9] showed an increased recruitment of the pre-SMA during inhibition task in OCD patients and their healthy siblings, suggesting that hyperactivity in the pre-SMA is a candidate neurocognitive endophenotype of OCD. In 2006, Mantovani et al. [10] showed that inhibition of the SMA has a specific effect in reducing OCD symptoms. Inhibition of the SMA might cause suppression of the hyperexcitable right hemisphere and thereby improves dysfunctional symptoms in patients with OCD.

According to Rehn et al.'s meta-analysis [6] the SMA is the most relevant cortical target for brain stimulation in OCD patients. To date, five randomized, sham-controlled studies using repeated low-frequency (1 Hz) stimulation of the SMA in treatment resistant OCD [11–15] have been reported. In these prior studies, low frequency rTMS applied over the SMA showed varying rates of clinical effectiveness. Overall, rTMS yielded a medium effect size in reducing Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores. Although encouraging, the extant evidence suggests that the treatment of OCD patients with brain stimulation could still be improved.

Over the last ten years, theta burst stimulation (TBS) has been increasingly used as an experimental and therapeutic tool [16]. TBS is a form of repetitive transcranial magnetic stimulation (rTMS) involving the use of triple-pulse bursts at 50 HZ [17] repeated five times per second (every 200 ms, 5 Hz) in either a continuous (cTBS) or intermittent fashion (iTBS). TBS is thought to induce more rapid and longer-lasting effects on synaptic plasticity than conventional rTMS protocols. It uses lower stimulation intensity and a shorter time of stimulation compared with conventional rTMS protocols [16]. cTBS consists of a 40-second train of uninterrupted TBS (600 pulses), which, when applied for 40 s, decreases cortical excitability for up to 50 min, whereas cTBS applied for 20 s decreases cortical excitability for 20 min [18,19]. Application of TBS to the treatment of psychiatric disorders is relatively new, and limited to major depression [20]. To date, there is no experimental data or double blind randomized controlled trials on the effectiveness of TBS for reducing clinical symptoms in OCD patients [21]. To the best of our knowledge, only one case report has been published so far [22]. This study concerned the efficacy and safety of 10 sessions of cTBS over the right DLPFC in one OCD patient with comorbid depressive disorder.

We report here the results of the first high-powered randomized, double blind sham-controlled trial testing the effectiveness of cTBS in patients with treatment resistant OCD. Because cTBS induces larger and longer-lasting modulation of cortical excitability than standard rTMS, we expected cTBS protocol over the SMA to reduce OCD symptoms in drug-resistant patients. To ensure a high-powered design, we took a number of methodological precautions to provide a stringent test of the hypothesis: we used magnetic resonance imaging to precisely determine in advance the position of the SMA for each patient; all patients received more sessions

than in any other trials; and, we included a follow-up period of 6 weeks.

## Method

### Study design and randomization

We performed a 6 week randomized, sham-controlled, double blind, parallel group trial that compared the effect of cTBS on OCD symptoms. This trial was conducted in the Poitiers Henri Laborit psychiatric hospital in France. Ethical approval was obtained from the Henri Laborit Ethics Committee. After reading the information sheet and reviewing the potential side effects of rTMS, patients provided their informed consent. Eligible patients were randomly allocated (1:1) to either active cTBS or sham cTBS stimulation using a computed based block randomization (block size of four). The study was conducted between August 2013 and June 2016.

### Participants

Thirty outpatients aged between 18 and 65 years, with DSM-IV-TR OCD diagnosed using the Mini-International Neuropsychiatric Interview (MINI) [23] were enrolled in the study. All patients were naïve to TMS. To be eligible, patients had to have a total Y-BOCS score of 20 or more, a total duration of the disease of at least 2 years, and they should have received at least two 12-week adequate sequences and dose of treatment with SRIs but not responding (treatment resistant). The current medication regimen was maintained throughout the treatment and follow up visits. Benzodiazepines (Lorazepam, Diazepam, or Alprazolam) were also maintained at the same dose throughout the study. Exclusion criteria were as follows: diagnosis of schizophrenia, current major depressive disorder (Montgomery Asberg Depression Rating Scale (MADRS) > 21), other psychotic disorders, bipolar I disorder, substance and alcohol dependence within the last six months, suicidal (score at 3 or more in MADRS, moderate or severe stage in MINI), metallic implant in the cranium (except teeth), severe or unstable medical conditions, history of TMS, history of epilepsy, neurological disorders leading to increased intracranial pressure, and severe cardiac disorder and/or with intracardiac lines, cardiac pacemakers and other contraindication to magnetic resonance imaging (MRI). Additionally, participants showing abnormal findings in brain MRI were excluded from the study.

### Assessment

Trained psychiatrists who were blind to the patient stimulation group completed clinical assessments. All assessments included the Y-BOCS, the Clinical Global Impression Severity (CGI-S), the MADRS, the Brief Anxiety Scale (BAS), the Global Assessment of Functioning (GAF), the Brown Assessment of Belief Scale (BABS), and the Hospital Anxiety and Depression scale (HAD).

Patients were assessed at baseline, post-cTBS treatment (after 6 weeks of treatment, W6), and at 6week follow-up (12 weeks after baseline, W12).

The primary outcome measure was the total Y-BOCS score. Responder status was defined as a 25% decrease in Y-BOCS score. The secondary outcomes measures were the MADRS, the BABS, the BAS, the CGI-S and the HAD. Before and after each session, patients were assessed for TBS side effects with a structured questionnaire.

### Treatment

Before the treatment period, each patient had an anatomical T1-weighted magnetic resonance imaging in order to set-up the

neuronavigation system (Syneika One; Syneika). The coil was positioned to target the pre-SMA as described in Pelissolo et al. [14]. All patients underwent a baseline and weekly evaluation of the motor cortex excitability by measuring the resting motor threshold (RMT). RMT was defined as the minimum magnetic flux needed to elicit a threshold EMG response (50 mV in peak-to-peak amplitude) in a resting target muscle (Abductor pollicis brevis) in 5/10 trials using single-pulse TMS administered to the contralateral primary motor cortex.<sup>1</sup>

A total of 30 rTMS sessions were delivered once a day, 5 days a week, for a total of 6 weeks. The cTBS treatment was administered with the MagPro® X100 with Option stimulator (MagVenture, Inc) using the cool B-65 Active/Placebo (A/P) coil which can be configured in active or sham mode by flipping the coil over. Active cTBS was used according to Huang et al. [17] at 70% of participants' RMT. This intensity was based on previous studies reporting that 70% of the RMT is equivalent to 80% of the AMT [24,25]. cTBS stimulation consisted of 3 single biphasic pulses separated by 0.02 s (50 Hz) repeated every 0.2 s (5 Hz) for a total of 600 pulses delivered in a 40s session.

#### Sham cTBS

The sham cTBS was administered using the MagPro® cool B65 A/P coil that is designed to support true double blinded clinical trial. Treatment allocation and parameters were recorded and encrypted in USB-keys using MagPro® MagLink Software v 2.1 for each subject. This software allows the study master to define stimulation parameters (active or sham, pulses configuration, intensity of stimulation) for each participant, to record the stimulation sessions as well as the intensities used during motor threshold and stimulation. With this system the operator cannot modify the rTMS parameters, nor know the patient's randomization arm. In order to maintain the blind condition, we excluded patients who previously received TMS stimulations and also maintained the separation between the rating clinicians and TMS operators.

#### Dimensional OCD symptoms

OCD symptom dimensions were determined using the statistical algorithm for the extraction of quantitative specific symptom dimension data from the Y-BOCS checklist developed by Schavitt et al. [26]. This validated procedure is useful to generate dimension severity rating from existing Y-BOCS severity scores.

#### Statistical analyses

Statistical analyses were performed using JASP (<https://jasp-stats.org>). The demographic and clinical characteristics at baseline were compared between the active cTBS group and sham cTBS group using independent sample t-tests (two-tailed) and chi-square tests. Responder status was compared between these two groups using chi-square. Primary and secondary outcomes were analysed using repeated-measures two-way analyses of variance with patient group (active cTBS, sham cTBS) as a between-patient factor and time (baseline, W6, W12), as a within-patient factor. Sphericity was tested using a Mauchly's test. When the assumption was rejected, the Greenhouse-Geisser adjustment was used to adjust the degree of freedom. A significant threshold of  $p < 0.05$  was chosen for all tests. When statistical significant differences

were found in the main effects, post-hoc Bonferroni corrections for multiples comparisons were performed. We also conducted a Bayesian Repeated ANOVA on the Y-BOCS scores to quantify how the observed data supported evidence in favour of the null hypothesis (the absence of difference between active cTBS and sham cTBS).

## Results

#### Participants

Two patients in the sham cTBS group withdrew after the inclusion visit and before the beginning of the stimulation, leaving 28 patients in the final sample. There were 14 patients in each group (Fig. 1). This sample size provided adequate statistical power ( $1 - \beta = 0.90$ ) to detect the expected within-between interaction in a mixed analysis of variance, based on an observed correlation of 0.60 between repeated measures, and for a medium effect size of  $f = 0.25$ , considered as the minimal clinically important difference (MCID). The statistical power was 0.99 for a large effect size of  $f = 0.40$ .

All patients completed the 30 stimulation sessions and the evaluation visits. Table 1 summarizes the sample characteristics of the study participants at baseline. Baseline demographic, dimensional OCD symptoms, Y-BOCS score and clinical characteristics were similar between groups. A DSM-IV-TR history of major depression was present in 12.5% of patients in the sham cTBS group and in 14.3% of patients in the active cTBS group.

At the beginning of the study, pharmacological treatments involved SSRIs ( $n = 27$ ), clomipramine ( $n = 10$ ), other antidepressants ( $n = 4$ ), antipsychotics ( $n = 16$ ), mood stabilisers ( $n = 5$ ), anti-histamine agents ( $n = 3$ ) and benzodiazepines ( $n = 23$ ). Patient's treatments were maintained throughout the study and were in adequate and stable dose for more than 12 weeks. Among the patients of both groups, 21 (70%) had a current augmentation treatment, with a combination of an antidepressant and either another antidepressant or an antipsychotic or mood stabiliser. Regarding history of drug treatments, 80% of patients in the active cTBS group and 87% of patients in the sham cTBS group had received clomipramine in the past or were still receiving it.<sup>2</sup>

#### Primary outcome

No differences in responder status between the two groups were found at the post-treatment assessment (active cTBS = 3/14, 21.4%, sham cTBS = 5/14, 35.7%,  $p = 0.403$ ), at the 6 weeks follow-up visit (active cTBS = 4/14, 28.4%, sham cTBS = 5/14, 35.7%,  $p = 0.686$ ) and at the 12 weeks follow-up visit (active cTBS = 4/14, 28.4%, sham cTBS = 5/14, 35.7%;  $p = 0.686$ ).

The evolution of Y-BOCS scores (Fig. 2) and sub-scores was not significantly different in the two groups between baseline, W6 and W12 (Table 2). For anxiety, depression, and CGI-S there were no significant differences between groups at baseline, W6 and W12 (Table 2).

Repeated measures two-way ANOVA showed a significant main effect of Visit ( $F(2,52) = 12.838$ ;  $MSE = 14.491$ ;  $p < 0.001$ ; partial  $\eta^2 = 0.331$ ), post hoc tests using the Bonferroni correction revealed that mean Y-BOCS scores reduced by an average of 4.214 ( $< 0.001$ ) at post-treatment visit and then reduced by an average of 4.679 ( $< 0.001$ ) at follow-up visit. No significant main effect for Group ( $F(1,26) = 1.045$ ;  $MSE = 71.082$ ;  $p = 0.316$ ; partial  $\eta^2 = 0.039$ ) and

<sup>1</sup> RMT was measured independently of subjects' handedness on the same hemisphere. Handedness was determined with the item 20 of the neurological soft signs Krebs' scale (40).

<sup>2</sup> Only one patient was left-handed. The results were the same when we excluded this patient from the analyses.

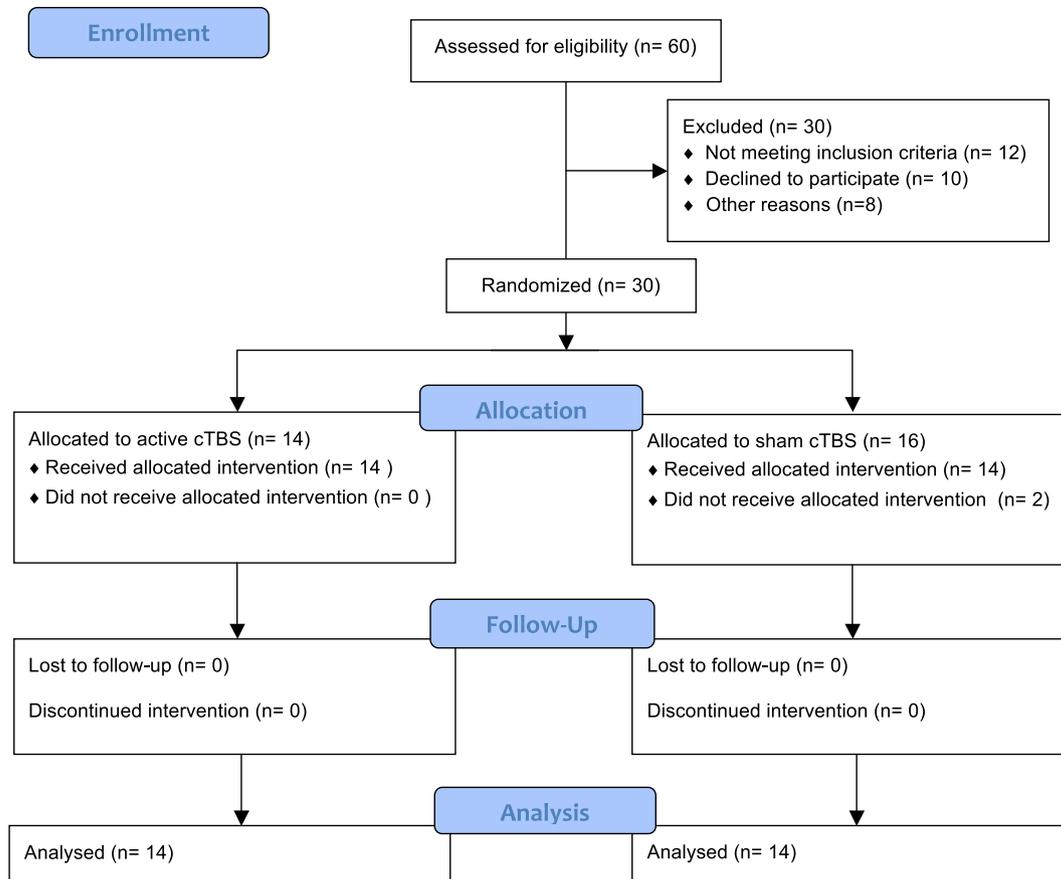


Fig. 1. The CONSORT flowchart with the number of participants in each phase.

Table 1

Baseline demographic and clinical characteristics of the participants.

Variable	Active cTBS (n = 14)	Sham cTBS (n = 14)	p-value
Gender (M/F)	5/9	8/6	0.256#
Age (years)	46.3 (10.1)	48.2 (12.9)	0.664*
Age at onset (years)	18.1 (10.1)	26.1 (15.5)	0.129*
Duration of illness (years)	29.5 (9.4)	23.9 (16.3)	0.281*
Y-BOCS score			
Total	30.1 (4.4)	29.4 (4.7)	0.681*
Obsession	14.6 (2.5)	14.4 (2.9)	0.838*
Compulsion	15.5 (2.1)	15.0 (2.5)	0.564*
Dimensional OCD symptoms			
Aggression	7.4 (5.5)	8.6 (4.3)	0.520*
Sexual/religious	1.2 (3.1)	3.2 (4.2)	0.165*
Symmetry ordering	9.1 (5.5)	10.2 (3.4)	0.541*
Cleaning contamination	8.8 (5.2)	8.1 (5.4)	0.723*
Hoarding	3.8 (5.0)	2.1 (3.5)	0.324*
CGI-S score	5.4 (0.5)	5.5 (0.8)	0.773*
MADRS score	13.8 (8.6)	12.1 (5.9)	0.563*
BAS score	11.7 (8.4)	11.9 (7.9)	0.945*
GAF score	48.6 (8.4)	44.2 (6.7)	0.140*
BABS score	4.6 (4.0)	3.7 (2.5)	0.506*
HAD score	21.7 (9.2)	21.5 (6.1)	0.943*

Notes: Data are presented as mean (SD). Y-BOCS: Yale Brown Obsessive Compulsive Disorder Scale; CGI-S: Clinical Global Impressions Severity; MADRS: Montgomery-Asberg Depression Rating Scale; BAS: Brief Anxiety Scale; GAF: Global Assessment of Functioning; BABS: Brown Assessment of Beliefs Scale; HAD: Hospital Anxiety and Depression scale.

\*The p-value was obtained by a two sample two tailed t-test.

#The p-value was obtained using a Pearson  $\chi^2$  two-tailed test.

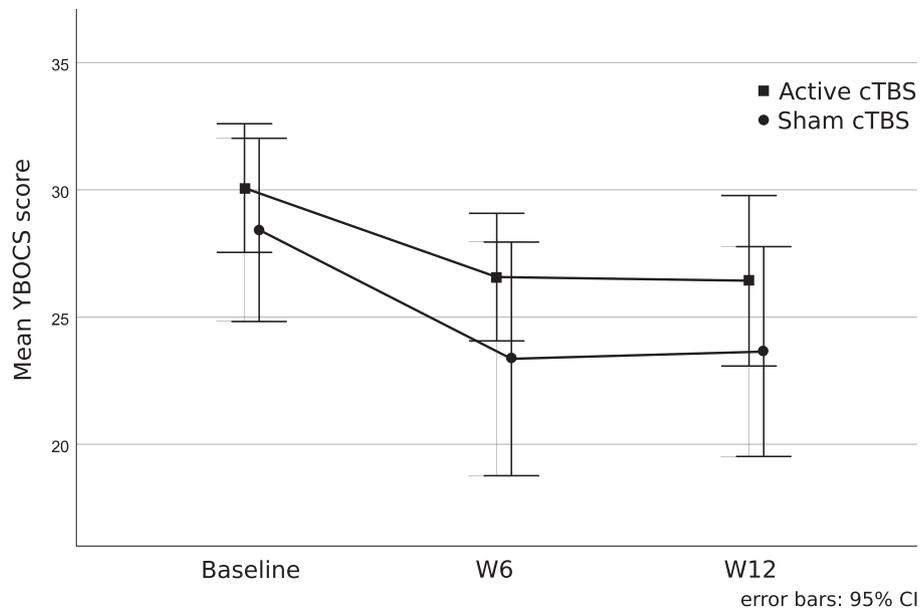


Fig. 2. Evolution of Y-BOCS scores between active and sham cTBS.

no significant interaction between Group and Visit ( $F(2,52)=0.543$ ;  $MSE=14.491$ ;  $p=0.584$ ; partial  $\eta^2=0.02$ ) (Table 2) were found. In order to quantify evidence for the null hypothesis, we performed a repeated Bayesian ANOVA (Table 3). A Bayes factor ( $BF_{01}$ ) of 3.909 was found, providing substantial evidence for the null hypothesis that there is no difference in Y-BOCS score between active cTBS and sham cTBS.

#### Secondary outcomes

An ANOVA showed no significant interaction between Group and Visit for the MADRS ( $F(2,52)=0.838$ ;  $MSE=23.921$ ;  $p=0.438$ ; partial  $\eta^2=0.031$ ), the BABS ( $F(2,50)=0.498$ ;  $MSE=4.264$ ;  $p=0.548$ ; partial  $\eta^2=0.02$ ), the BAS ( $F(2,52)=0.6$ ;  $MSE=13.403$ ;  $p=0.552$ ; partial  $\eta^2=0.023$ ), the CGI-S ( $F(2,52)=1.366$ ;  $MSE=0.27$ ;  $p=0.264$ ; partial  $\eta^2=0.05$ ) and the HAD ( $F(2,52)=0.055$ ;  $MSE=25.284$ ;  $p=0.946$ ; partial  $\eta^2=0.002$ ) (Table 2).

No severe adverse events were reported during the course of the trial. Mild headache (active cTBS 1/sham cTBS; 2) were the only side effect reported.

#### Discussion

The present study is the first randomized trial using cTBS for treating OCD symptoms in treatment resistant patients. Using a

relatively large sample of patients and a rigorous and well-controlled protocol, we found no significant difference in Y-BOCS scores between active- and sham cTBS groups. A Bayesian analysis provided stronger evidence for the null hypothesis than for the alternative hypothesis. All in all, our results clearly suggest that cTBS has no discernible efficacy in treating resistant OCD patients. In the present study, cTBS was well tolerated and not associated with side effects, confirming previous findings demonstrating safety and tolerability of cTBS in patients with major depression [20].

In 2006, Mantovani et al. [10] demonstrated that inhibition of the SMA successfully reduced OCD symptoms. Following this pioneering study, 5 randomized trials in OCD using low frequency rTMS over the SMA [11–15] reported inconsistent results. In the current trial, we used cTBS, known to induce larger and longer-lasting modulation of cortical excitability than standard rTMS [16], thus offering the promise of a potentially greater clinical efficacy. Despite this, we found no significant decrease in OCD symptoms.

In a case report, Wu et al. [22] have observed efficacy of theta burst in a 33-year-old OCD patient with depressive comorbidity. In that case report, 10 cTBS sessions (6 sessions twice a week, then 4 sessions once a week) were applied over the right DLPFC. The cTBS parameters were 3 pulses at 50 Hz with a 200 ms interval. For the cTBS paradigm, 4 continuous sessions of 20s TBS trains were given (1200 pulses) at an intensity of 80% active motor threshold (AMT).

Table 2  
Outcome comparison between active cTBS group and sham cTBS group.

Scales	Active cTBS (n = 14)			Sham cTBS (n = 14)			p-value (group*visit)
	Baseline	W6	W12	Baseline	W6	W12	
YBOCS	30.07 (4.38)	26.57 (4.35)	26.43 (5.80)	29.36 (4.70)	24.43 (7.44)	23.64 (7.14)	0.584
CGI	5.43 (0.51)	5.21 (0.43)	5.00 (0.56)	5.50 (0.76)	5.21 (0.89)	4.64 (1.01)	0.264
MADRS	13.79 (8.62)	8.21 (5.40)	9.57 (7.72)	12.14 (5.97)	9.43 (7.62)	10.93 (7.51)	0.438
BAS	11.71 (8.44)	7.29 (5.78)	7.79 (6.90)	11.93 (7.89)	8.64 (7.33)	7.00 (5.07)	0.552
BABS	4.57 (4.01)	4.36 (4.05)	3.64 (2.74)	3.69 (2.66)	4.08 (2.50)	3.69 (2.69)	0.548
HAD	21.71 (9.22)	17.07 (7.62)	17.64 (8.22)	21.50 (6.10)	17.50 (6.87)	18.29 (6.74)	0.946

Notes: Data are presented as mean (SD). YBOCS: Yale Brown Obsessive Compulsive Disorder Scale; CGI: Clinical Global Impressions; MADRS: Montgomery-Asberg depression rating scale; BAS: Brief Anxiety Scale; BABS: Brown Assessment of Beliefs Scale; HAD: Hospital Anxiety and Depression scale.

**Table 3**  
Bayesian repeated-measures ANOVA results.

Models	P(M)	P(M data)	BF <sub>M</sub>	BF <sub>01</sub>	Error %
Null model (incl. Visit, Group, subject)	0.5	0.796	3.909	1.0	
Visit*Group	0.5	0.204	0.256	3.909	2.327

Notes: P(M): indicates prior model probabilities; P(M|data): indicates the updated probabilities after having observed the data; BF<sub>M</sub>: indicates the degree to which the data have changed the prior model odds; BF<sub>01</sub>: Bayes factor in favour of the null hypothesis.

One week later, 10 sessions of iTBS were performed on left DLPFC for comorbid depression. These authors report a marked improvement in the symptoms of OCD (Y-BOCS score decreased from 19 to 8), anxiety and depression. This symptomatic improvement was represented by a lack of activation of the right orbitofrontal cortex during a challenge task symptom on MRI after treatment compared to before treatment. Building on this encouraging finding, we tried to use cTBS in order to inhibit the SMA in a relatively large sample of OCD patients. Our results did not confirm our expectations.

We believe there are at least 4 different explanations that may account for our failure to find positive effects of cTBS in the present trial. First, our parameters of stimulation (number of pulses and intensity of the RMT and AMT) may not be optimal. We delivered 600 pulses per session, as recommended by Huang et al. [17] conventional protocol. However, it might not be sufficient to inhibit the SMA. Chistyakov et al. [27] used cTBS over the right DLPFC to treat depressive patients. The result of this open label study suggested that there is a dose effect since the number of stimuli of cTBS enhanced its therapeutic effect. Chistyakov et al. used 1200 to 3600 pulses per session (600 pulses repeated and separated by a 15 min interval) and found a greater effect for the 3600 pulses [28]. In the same way, other studies used a greater number of pulses (1200–1500) than we did [11–15,22]. In our study, 600 pulses may not have been sufficient for inducing clinical effects. However, experimental studies [29] demonstrate that doubling stimulation duration of cTBS may result in a reversal of effect with regard to cortical excitability. Thus, the ideal number of stimulations for best efficacy still needs to be precisely determined.

In addition, we stimulated patients at 70% of RMT which is approximately equal to 80% of AMT used in the original protocol of Huang et al., 2005 [17]. We chose this intensity in order to guarantee a better tolerability of the treatment [30]. However, most popular paradigms used in OCD over SMA are low-frequency tonic stimulation, mostly at 1 Hz, with an intensity of 110–120% RMT, which is superior to our intensity. Stimulus intensity is a very important factor to determine plasticity [31] and highly influences the cTBS after-effects [32]. Thus, to date, the best parameters of stimulation of cTBS to obtain maximum efficacy remain largely unknown. Further studies are needed to identify the optimal parameters to be used in OCD patients.

Second, our cTBS protocol was designed after previous rTMS protocols as no previous study has examined cTBS in OCD patients. However, it is possible that these two protocols have different effects over the SMA even if they have been shown to exert similar effects on primary motor area [16]. Therefore, differences in parameters such as number of pulses, stimulus intensity and time of stimulation need further investigation in order to optimize TBS for clinical applications.

Third, individual differences might contribute to our failure to find a significant effect of cTBS in the present study. Like other methods of non-invasive brain stimulation, the response to TBS protocols is highly variable from one person to another. Genetic factors like BDNF polymorphism [33], difference in intracortical network activation [34], functional connectivity in cortical networks targeted by cTBS stimulation [35] and the effect of patient's

age [36] may contribute to explain differential responses to cTBS. In addition, almost all our participants were medicated, and there is some evidence that medication can affect TBS-induced plasticity [37,38]. This is another factor that should be considered in future studies.

Fourth, all patients included in the present study suffered from severe or very severe OCD. They had high baseline Y-BOCS median scores (30 and 29 in the cTBS and sham groups, respectively), duration of illness (29 and 24 years in the cTBS and sham groups, respectively), and most of the patients were relatively resistant with a mean of 2 SRIs trials and at least 1 augmenting agent before TBS.

The aforementioned factors may have influenced the therapeutic response, and should be taken into account in future studies. Moreover, the blinding procedures could be improved by applying a best guess questionnaire in order to check if the blinding was successfully maintained throughout the trial.

In conclusion, the results of this clinical trial suggest that cTBS over the SMA has no clinically significant effect in treating OCD, even if it was well tolerated. The potential clinical utility of cTBS in OCD should be explored in rigorous experimental designs (higher stimulation intensity and number of pulse), and with different inclusion criteria (e.g., less severe and resistant OCD patients, or drug free patients). Availability of novel coil designs ensuring stimulation of much larger and deeper brain region like the double cone-coil [39] have to be considered in future trials. Furthermore, it will be interesting in future studies to use neuroimaging and neurophysiologic techniques in addition to clinical assessments for a better understanding of cTBS neurobiological action.

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