

Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study

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Theta-burst transcranial magnetic stimulation could modulate cortical excitability and has the potential to treat refractory depression. However, there has been a lack of large randomized studies of the antidepressant efficacy of different forms of theta-burst stimulation, such as intermittent and continuous theta-burst stimulation. A randomized sham-controlled study was conducted to investigate antidepressant efficacy of theta-burst stimulation and to compare efficacy among left-prefrontal intermittent theta-burst stimulation, right-prefrontal continuous theta-burst stimulation and a combination of them in patients showing different levels of antidepressant refractoriness. A group of 60 treatment-refractory patients with recurrent major depressive disorder were recruited and randomized to four groups (Group A: continuous theta-burst stimulation; Group B: intermittent theta-burst stimulation; Group C: a combination of continuous and intermittent theta-burst stimulation; and Group D: sham theta-burst stimulation; 15 patients were included in each group). After 2 weeks of theta-burst stimulation treatment, depression improved in all groups. Groups B and C had better antidepressant responses (as reflected by % decreases in depression score) than Groups A and D ($P = 0.001$, *post hoc* analysis: $B > A$, $B > D$, $C > A$, and $C > D$), even after controlling for age and refractoriness scores. The mean antidepressant effect was highest in Group C and followed by that in Group B. Additionally, a significant placebo effect was found in patients with low refractoriness; this disappeared in patients with moderate-to-high refractoriness. A significant correlation existed between refractoriness scores and treatment responses. Treatment refractoriness was a significant factor negatively predicting efficacy of theta-burst stimulation ($P = 0.039$). This randomized sham-controlled study demonstrated that active theta-burst stimulation is a well-tolerated form of repetitive transcranial magnetic stimulation and has good antidepressant efficacy, particularly in depressed subjects within a certain range of treatment refractoriness.

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Abbreviations: CGI-S = Clinical Global Impression Scale; HDRS = Hamilton Depression Rating Scale; TBS = theta-burst stimulation; TMS = transcranial magnetic stimulation; TRD = treatment-refractory depression

Introduction

Theta-burst stimulation (TBS) is a form of repetitive transcranial magnetic stimulation (TMS). The effects of TBS on synaptic plasticity occur much more rapidly than with traditional repetitive TMS protocols, and such a swift method could produce a powerful and consistent effect, as demonstrated by studies on motor cortex excitability (Huang *et al.*, 2005). TBS is capable of inducing long-lasting effects on corticospinal excitability, which is pattern-dependent and is thought to involve long-term potentiation/depression-like effects on cortical synapses.

Intermittent TBS produces long-term potentiation-like effects, whereas continuous TBS produces a long-term depression-like reduction of cortical excitability. Continuous TBS takes as little as 20 s to produce 20 min of suppression, but traditional low-frequency repetitive TMS (e.g. 1 Hz) takes at least 20 min of continuous stimulation. The proposed theoretical mechanisms are that intermittent TBS increases postsynaptic concentration of calcium ions, or Ca^{2+} (an important factor in enhancing synaptic plasticity), by mounting presynaptic facilitatory responses. Then, continuous TBS decreases the postsynaptic Ca^{2+} level through a cumulative effect of presynaptic inhibition that outlasts facilitatory responses (Huang *et al.*, 2011).

As many as a third of patients with depression are refractory to normally adequate dosages of antidepressants (Rush, 2007; Fekadu *et al.*, 2009b) and thus may need more powerful treatment options, such as brain stimulation. In several studies, treatment-refractory depressive (TRD) patients had poor medical outcomes, resulting in a high socioeconomic burden (Greenberg *et al.*, 2003; Li *et al.*, 2012). Repetitive TMS (daily high-frequency repetitive TMS targeting the left prefrontal cortex for several weeks) is an efficacious treatment for TRD (Daskalakis *et al.*, 2008; Berlim *et al.*, 2013e; George *et al.*, 2013). However, the results of repetitive TMS studies have been inconsistent. Some reasons include the targets selected for stimulation (for example, unilateral stimulation to left or right dorsolateral prefrontal cortex or bilateral dorsolateral prefrontal cortex stimulation); suboptimal methods to target the dorsolateral prefrontal cortex (i.e. the 5-cm anterior method); different treatment durations (longer treatment duration may be more effective); and the high heterogeneity of depression populations (Daskalakis *et al.*, 2008; Lisanby *et al.*, 2009). A good example is the trial for the NeuroStar[®] TMS Therapy System (Neuronetics). To receive US Food and Drug Administration (FDA) approval for treatment of adults with major depressive disorder without psychosis who 'have not adequately responded to appropriate pharmacological treatment intervention', O'Reardon and colleagues (2007) found that active repetitive TMS targeted over the left dorsolateral prefrontal cortex for 4 to 6 weeks was more effective than was sham repetitive TMS. Careful scrutiny of the published data reveals a significant improvement in the score of the 17-item Hamilton

Depression Rating Scale (HDRS-17) at Week 2 in both active and sham repetitive TMS groups. However, no statistically significant difference between active and sham groups could be demonstrated. As most of the recruited participants were only slightly refractory to treatment (one or two failures with adequate antidepressant treatment), we questioned whether patients with lower treatment refractoriness might have higher placebo responses at Week 2. In fact, the antidepressant effects of repetitive TMS were less marked in patients with higher levels of treatment resistance (Lisanby *et al.*, 2009). However, the potential impact from the level of treatment refractoriness of the recruited patients on the repetitive TMS results is still not completely understood.

TBS seems to be a promising alternative physical treatment for depression, and it requires further investigation (Fitzgerald and Daskalakis, 2011). Although little is known about whether the application of TBS over non-motor regions causes the same modulatory effects, one research group recently applied TBS in subjects with major depressive disorder. The authors of this open-label study, which had no sham control group, reported clinical improvement after 2 weeks of treatment to the left prefrontal intermittent TBS (1200 pulses) and right prefrontal continuous TBS (1200, 1800 and 3600 pulses) (Chistyakov *et al.*, 2010). This study showed preliminary evidence that TBS is effective in treating depression, and also demonstrated some dose-dependent effects of TBS: continuous TBS (3600 pulses) was significantly more effective for lessening depression than was continuous TBS (1200 pulses). The improvement rates were 71.4% and 60%, respectively. Intermittent TBS was the least therapeutically effective approach. A recent pilot study ($n = 33$) investigated the antidepressant efficacy of the bilateral prefrontal TBS and found that active TBS was more effective than sham TBS (Plewnia *et al.*, 2014). To date, there is still a lack of large randomized and sham-controlled study to investigate the antidepressant efficacy of different forms of TBS.

Hypoactivity of the left dorsolateral prefrontal cortex and hyperactivity of the right dorsolateral prefrontal cortex are common explanations for the occurrence of major depression. Intermittent TBS to the left and right dorsolateral prefrontal cortex could be effective in the treatment of patients with TRD. Therefore, we designed a double-blind, randomized, sham-controlled study to primarily investigate antidepressant efficacy among intermittent TBS, continuous TBS, and a combination of intermittent and continuous TBS. Since most TMS studies supported that left prefrontal high-frequency TMS has good antidepressant efficacy (George *et al.*, 2013), we hypothesized that left prefrontal intermittent TBS would be more effective than right prefrontal continuous TBS. We also wanted to study whether patients showing different levels of antidepressant refractoriness might respond in different ways to TBS treatment.

Materials and methods

Subjects

Eligible subjects were adult patients 21–70 years of age, with a DSM-IV diagnosis of recurrent major depressive disorder. The diagnosis was established after taking a thorough medical history and after conducting a semi-structured interview by administering the Mini International Neuropsychiatric Interview (MINI) (American Psychiatric Association, 1994). Patients were required to have failed at least two normally adequate antidepressant treatments. In addition, the current depressive episode had to have a Clinical Global Impression Scale (CGI-S) score of at least 4 and a total score of at least 18 on the HDRS-17 (i.e. moderate to severe depression at entry) (Hamilton, 1967) before TBS treatment.

Patients were excluded if they had a lifetime psychiatric history of psychotic disorders, bipolar I or II disorders; substance abuse or dependence; personality disorders (based on DSM-IV criteria); or a lifetime medical history of major systemic illness, neurological disorders (e.g. stroke, seizure, traumatic brain injury, post-brain surgery), and brain implants (neurostimulators) or cardiac pacemakers; or if they were pregnant.

Measures of treatment refractoriness

As treatment resistance in depression involves many dimensions, degrees of refractoriness were measured by a points-based staging model, the Maudsley staging method (Fekadu *et al.*, 2009a). The Maudsley staging method incorporates three main factors: treatment (i.e. numbers of antidepressant treatment failures and if augmentation or electroconvulsive therapy had been used), severity of symptoms, and duration of presenting episode. The Maudsley refractoriness score was used as a covariate in subsequent analyses.

To investigate the treatment refractoriness in more detail, we further categorized patients into three levels of treatment refractoriness based on the Maudsley staging method score: low (Maudsley staging method ≤ 7), moderate (Maudsley staging method = 8–10), and high refractoriness (Maudsley staging method ≥ 11). Such methods could categorize most patients with only one to two treatment failures of antidepressant treatment into the low-refractoriness group and patients with more than seven treatment failures into the high-refractoriness group. Because life stress is also a known determinant of depression, a life event stress scale was also completed by each participant, and the score was used as a covariate of no interest in subsequent analyses.

Study overview

The study had three phases. First, patients underwent a 1-week screening phase, which included brain structural imaging by MRI and routine laboratory studies, including complete blood count and chemistry, and thyroid tests, to ensure that the patient was medically stable. This was followed by a 2-week acute treatment phase, which involved daily treatment with active TBS or sham. Throughout the study, patients were required to maintain their original medication regimen. Patients were randomized 1:1:1:1 to each TBS group (Groups A, B, C and D). During the acute treatment phase, TBS sessions were scheduled daily in a 5-day sequence, for a total of 10 sessions over 2 weeks. Finally, after the 2-week double-blind phase of active or sham TBS treatment, each patient visited again at the 12th week after the TBS treatment to check how many patients remained

responsive to the TBS treatment. Notably, in this 12-week follow-up phase, changes in medications were permitted based on the clinician's judgement to maximize the patient's improvement.

The study was performed in accordance with the Declaration of Helsinki and was approved by the local Ethics Review Committee. All participants provided written informed consent.

Theta-burst stimulation parameters and session procedures

The TBS sessions were delivered using the Magstim Rapid² stimulator (Magstim Company, Ltd). The TBS parameters we adopted followed the standard TBS protocols, with 3-pulse 50-Hz bursts given every 200 ms (at 5 Hz) and an intensity of 80% active motor threshold, as measured from the right first dorsal interosseous muscle by a hand-held 700-mm figure-of-eight coil (Huang *et al.*, 2005). In the continuous TBS, a 120-s train of uninterrupted bursts was given to the right dorsolateral prefrontal cortex (1800 pulses) in each session per day. In the intermittent TBS, a 2-s train of bursts was repeated every 10 s for a total of 570 s (1800 pulses) to the left dorsolateral prefrontal cortex in each session per day. To accurately target the coil placement to the dorsolateral prefrontal cortex, which was defined as a spot between the junction of Brodmann area (BA) 9 and 46 on each patient's brain MRI (Li *et al.*, 2010b). Patients in Group A received continuous TBS (1800 pulses/session \times 10 sessions); Group B received intermittent TBS (1800 pulses/session \times 10 sessions); Group C received a combination of intermittent and continuous TBS (intermittent TBS-1800 + continuous TBS-1800 pulses/session \times 10 sessions; randomly assigned order starting from intermittent TBS or continuous TBS); and Group D received a sham TBS (bursts given as continuous TBS or intermittent TBS, randomly assigned; 1800 pulses/session \times 10 sessions) with the coil set at 90° against the skull.

Procedures to improve the blinding process

All patients were instructed that they were to be treated by TBS, but would be blind to the individual group assignment. All efficacy outcome measures were assessed by blinded study personnel (raters) who were not permitted access to the treatment sessions. Patients were instructed not to disclose any details of the treatment session with the raters, and the whole rating period was monitored by a research assistant to ensure that the procedure was blinded. We questioned all patients about the group assignment at Week 2; none of the recruited patients admitted that they knew for sure which group they had been assigned to.

Efficacy and safety assessments

Ratings were administered at baseline (Week 0, before TBS treatment), at the end of Week 1 and Week 2 of the TBS treatment, and at the 12-week follow-up after the TBS treatment (Week 14). The primary efficacy outcome was improvement in depression, measured by percentage of change in HDRS-17 score before and after 2 weeks of TBS treatment among the groups receiving continuous TBS, intermittent TBS, continuous + intermittent TBS, and sham TBS. Responders were defined as those who had at least 50% reduction at Week 2 from their baseline HDRS-17 score. As a *post hoc* analysis, patients in different groups of treatment refractoriness were studied with regard to the HDRS-17 scores over time (Week 0, Week 1 and Week 2). Safety was assessed at every treatment session by recording spontaneous

Table 1 Demographic data, clinical variables and treatment outcomes

	A cTBS	B iTBS	C cTBS + iTBS	D Sham	F/ χ^2	P
<i>n</i>	15	15	15	15	–	–
Demographics and clinical variables						
Age (range in years)	49.2 (27–64)	42.4 (25–61)	42.5 (23–60)	46.9 (25–58)	1.397	0.254
Female	10	8	11	11	2.080	0.556
Maudsley refractoriness	9.9 (1.9)	9.0 (1.5)	9.2 (1.7)	9.1 (1.6)	1.498	0.587
Life stress	88.8 (71.2)	140.0 (118.4)	136.9 (125.9)	120.6 (93.1)	0.596	0.621
CGI-S	4.7 (0.7)	4.8 (0.7)	5.0 (0.8)	4.6 (0.5)	1.006	0.397
HDRS-17 (BL)	24.3 (5.5)	23.1 (3.9)	25.4 (5.1)	23.8 (3.2)	0.649	0.587
Comorbidity (PD/SP/GAD)	2/0/5	1/1/5	2/0/6	2/0/5	1.154/3.860/ 0.776	0.764/0.277/ 0.855
Medications						
Drug-free	5	4	4	2	1.689	0.639
SSRI/SNRI/ Other ATDs	4/3/3	4/4/3	4/2/5	3/7/3	0.267/4.770/ 1.120	0.966/0.189/ 0.773
APDs/BZDs	8/10	5/11	7/11	5/11	1.357/0.267	0.716/0.966
Outcomes						
% HDRS-17 changes, mean (range)	–22.5% (+13.3% ~ –70.0%)	–42.3% (+4.3% ~ –88.9%)	–52.5% (–15.0% ~ –92.3%)	–17.4% (+30.0% ~ –84.6%)	6.166	0.001**
Responders (%; Week 2)	3 (25.0%)	6 (40.0%)	10 (66.7%)	2 (13.3%)	11.4	0.010*
Remain responsive at Week 14, n/n (%)	2/3 (66.7%)	5/6 (83.3%)	4/10 (40.0%)	1/2 (50.0%)	3.03	0.387

CGI-S = Clinical global impression – severity; HDRS-17 (BL) = 17-item Hamilton depression rating scales (Baseline); PD = Panic disorder; SP = Social phobia; GAD = Generalized anxiety disorder; SSRI = Serotonin-specific reuptake inhibitors; SNRI = Serotonin-norepinephrine reuptake inhibitors; Other antidepressants (ATDs): bupropion or mirtazapine; APDs = Antipsychotics; BZDs = Benzodiazepines.

adverse events and inquiring about pre-identified symptoms such as seizure, headache, and dizziness. Various cognitive measures were collected, to be reported elsewhere.

Statistical methods

Statistical analysis of demographic and clinical data was performed using SPSS 16.0 (SPSS Inc). One-way ANOVA (or Student's *t*-test) and Fisher's chi-square test (or Yate's correction) were used to compare the continuous and categorical variables among groups, respectively. $P < 0.05$ was deemed statistically significant. To investigate relationships between clinical ratings (i.e. HDRS-17, CGI-S, Maudsley refractoriness scores, and life event stress scores), Pearson's correlation analysis between the variables was applied and correlation coefficient (*r*) was reported with $P < 0.05$ (two-sided tests) as statistically significant. Multivariate linear regression was done with % HDRS-17 changes in 2 weeks as the dependent factor and age, sex, baseline HDRS-17, TBS groups (active or sham), and Maudsley refractoriness scores as independent factors. Repeated-measure ANOVA was further carried out, with time (i.e. HDRS-17 scores at Weeks 0, 1 and 2) as within-subject factors and TBS groups (i.e. Groups A, B, C and D), and three levels of treatment refractoriness (i.e. low, moderate and high) as between-subject factors. Main effects of time and group were determined by ANOVA and Student's *t*-test, and were reported with $P < 0.05$ (two-sided tests) as statistically significant. The least significant difference was used for *post hoc* analyses. Finally, logistic regression was carried out, with age, sex, life stress scores, baseline HDRS-17 scores, psychiatric comorbidities of anxiety disorders, refractoriness levels (high-refractoriness as reference group), and TBS groups (Group D as reference group) treated as independent factors. Responses to 2-week TBS (>50% reduction in HDRS-17 scores) was the dependent factor. Adjusted odds ratio predicting TBS's antidepressant efficacy and its 95% confidence intervals (CI) were reported. Factors with an odds ratio value > 1 predicted good

responses to TBS, while factors with an odds ratio value < 1 predicted poor responses to TBS. A P -value < 0.05 (2-sided tests) was deemed statistically significant.

Results

A total of 60 subjects were randomized to four TBS groups (15 per group) (Supplementary Fig. 1). All subjects completed the entire study. Baseline demographic and clinical features (i.e. age, gender, Maudsley refractoriness scores, life stress scores, CGI-S scores, and HDRS-17 scores) were similar in the four groups (Table 1). The CGI-S severity score of 4.8 (mean) and HDRS-17 score of 24.2 (mean) for the whole study cohort corresponded to a depression severity of at least moderate illness. The degree of life stress and treatment resistance did not differ among the four groups. There also was no difference in the prescribed medications and comorbidities of anxiety disorders between groups (Table 1). The degree of functional impairment in the study cohort was high, because 83.3% of the sample was unemployed or had temporarily stopped work.

Antidepressant outcomes

The main outcome measures of % HDRS-17 changes from baseline (Week 0) to the end of 2-week TBS treatment (Week 2) differed significantly among the four groups (F -value = 6.166; $P = 0.001$). The *post hoc* least significant difference analysis demonstrated that intermittent TBS (Group B) and a combination of continuous and intermittent TBS (Group C) had better antidepressant responses than continuous TBS (Group A) and sham TBS (Group D) ($B > A$, $B > D$, $C > A$, and $C > D$) (Table 1 and Fig. 1). After adjusting for

age and refractoriness scores by the analysis of covariates, Groups B and C still had better antidepressant responses than Groups A and D ($F = 5.440$, $P = 0.002$). There were significantly more responders in Group B (40.0%) and Group C (66.7%) than in Group A (25.0%) and Group D (13.3%) ($P = 0.010$, Table 1).

During the follow-up phase (open label), the mean (standard deviation, SD) HDRS-17 scores in the active and sham group were similar [active versus sham = 16.8 (9.7) versus 17.0 (6.6), $P = 0.939$]. The mean (SD) HDRS-17 changes from Week 0 to the end of Week 2 and Week 14 did not differ in the active TBS group [(Week 2 – Week 0)/Week 0 versus (Week 14 – Week 0)/Week 0 = -37.4% (27.8%) versus -40.6% (33.0%), $P = 0.807$], supporting the durability of the TBS treatment. There were 19 responders in the follow-up phase, including 16 responders from the active TBS groups and three responders from the sham group. Around 40% to 83.3% of the responders in the four groups remained good responders at Week 14 (Table 1). Seven patients (Group A = 2, Group B = 2, Group C = 1, and Group D = 2) who did not fulfil the response criterion after the 2 weeks of acute TBS treatment reached the response criterion at

the 14th week follow-up assessment. A delayed response to TBS treatment at Week 14 was observed in 17.9% (7/39) of the patients who did not fulfil the response criterion after the 2-week TBS treatment.

Correlations between clinical variables

Pearson's correlation demonstrated no correlations of life stress and refractoriness scores, as well as presenting depression severity scores (i.e. HDRS-17 and CGI-S). However, there were significant correlations between Maudsley refractoriness scores and HDRS-17 ($r = 0.277$; $P = 0.034$) and between Maudsley refractoriness scores and CGI-S ($r = 0.262$; $P = 0.045$) (Table 2). Additionally, a significant correlation between CGI-S and HDRS-17 scores existed ($r = 0.678$; $P < 0.001$). These findings supported treatment refractoriness as an important factor in the assessment of depression severity.

Treatment refractoriness on the antidepressant efficacy of theta-burst stimulation

Multivariate linear regression [$F(6,59) = 4.272$; $P = 0.002$] demonstrated that baseline Maudsley refractoriness scores ($t = 3.356$; $P = 0.002$) and TBS group (-2.268 ; $P = 0.029$), but not age (0.350; $r = 0.728$), gender (-0.853 , $P = 0.399$), life stress scores (-0.898 ; $P = 0.374$), and baseline HDRS-17 scores (-1.062 ; $P = 0.294$), could better predict 2-week % HDRS-17 changes. The findings supported treatment refractoriness as an independent factor in the treatment outcomes of TBS. As seen in Table 3 and Supplementary Fig. 2A–C, it is notable that in patients with lower refractoriness, sham TMS (Group D) was also effective in the treatment of TRD, but the sham responses disappeared gradually as the level of treatment refractoriness rose. Figure 2 illustrates that sham TBS was effective for treating patients with lower refractoriness levels. However, in patients with higher refractoriness levels (i.e. moderate and high refractoriness), intermittent TBS (Group B) and a combination of intermittent TBS and continuous TBS (Group C) were statistically more effective. Continuous TBS (Group A) seemed to have antidepressant efficacy in the treatment of patients with moderate refractoriness (Table 3). Regarding the HDRS-17 scores of Day 10 (Week 2) in patients with moderate refractoriness and high refractoriness, there were statistical significances between four TBS groups and both demonstrated an advantage of Group C (intermittent + continuous TBS) over Group D

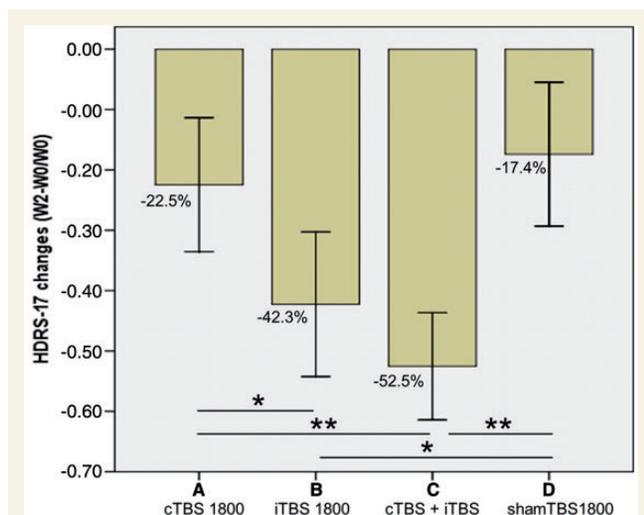


Figure 1 The antidepressant effects of TBS among different paradigms. Note the mean (SD) changes of HDRS-17 following 2-weeks of TBS treatment in the four TBS groups (post hoc least significant difference analysis; * $P < 0.05$, ** $P < 0.01$). cTBS = continuous TBS; iTBS = intermittent TBS; W0 = Week 0; W2 = Week 2.

Table 2 Correlations between clinical variables

Correlation coefficient ^a , r (P)	Stress level ^b	Maudsley refractoriness scores	HDRS-17 scores	CGI-S
Stress level	–	0.071 (0.626)	0.136 (0.357)	–0.005 (0.974)
Maudsley refractoriness scores	0.071 (0.626)	–	0.277* (0.034)	0.262* (0.045)
HDRS-17 scores	0.136 (0.357)	0.277* (0.034)	–	0.262* (0.045)
CGI-S	–0.005 (0.974)	0.262* (0.045)	0.678** (0.000)	–

^aPearson's correlation.

^bRated by life event stress questionnaire.

* $P < 0.05$, ** $P < 0.01$.

Table 3 Changes in depression scores (HDRS-17) over 2-week TBS treatment in patients with different levels of treatment refractoriness

HDRS-17 scores	A cTBS1800	B iTBS1800	C cTBS + iTBS	D Sham	F/P (group)
Low refractoriness					
Day 0 (Baseline)	– (–) ^a	22.5 (4.9)	24.5 (6.4)	24.7 (1.5)	0.182/0.840
Day 5	– (–) ^a	12.0 (4.2) ^b	19.5 (2.1)	13.0 (3.6) ^b	2.854/0.170
Day 10	– (–) ^a	10.5 (4.9) ^b	17.0 (1.7)	9.7 (5.5) ^b	1.663/0.298
F/P (time)	–/–	513.00/0.002**	2.778/0.344	13.189/0.046*	
Moderate refractoriness					
Day 0 (Baseline)	23.4 (5.4)	21.7 (3.5)	25.3 (5.0)	23.5 (4.7)	0.956/0.428
Day 5	15.9 (8.4) ^b	14.6 (6.4) ^b	16.0 (6.9) ^b	19.8 (5.1)	0.674/0.575
Day 10	13.6 (5.5) ^b	13.1 (8.0) ^b	10.3 (5.7) ^{b,c}	19.5 (3.4)	3.125/0.049*
F/P (time)	6.626/0.018*	10.623/0.002**	41.377/0.000**	3.169/0.126	
High refractoriness					
Day 0 (Baseline)	26.4 (5.1)	25.4 (3.9)	26.3 (6.7)	23.7 (2.4)	0.474/0.704
Day 5	24.0 (6.2)	22.4 (4.4)	18.0 (5.3) ^b	23.0 (3.4)	1.055/0.394
Day 10	25.0 (6.6)	17.0 (5.1) ^{b,d}	15.7 (7.4) ^{b,c,d}	23.8 (1.7)	3.723/0.032*
F/P (time)	1.315/0.304	19.007/0.001**	43.538/0.002**	0.220/0.799	

^aNo subject in group A was randomized to this subgroup of low refractoriness.

^bPost hoc LSD analysis for the main effect of time; $P < 0.05$ (versus Day 0).

^cPost hoc LSD analysis for the main effect of group; $P < 0.05$ (versus Group D).

^dPost hoc LSD analysis for the main effect of group; $P < 0.05$ (verses Group A).

* $P < 0.05$; ** $P < 0.01$.

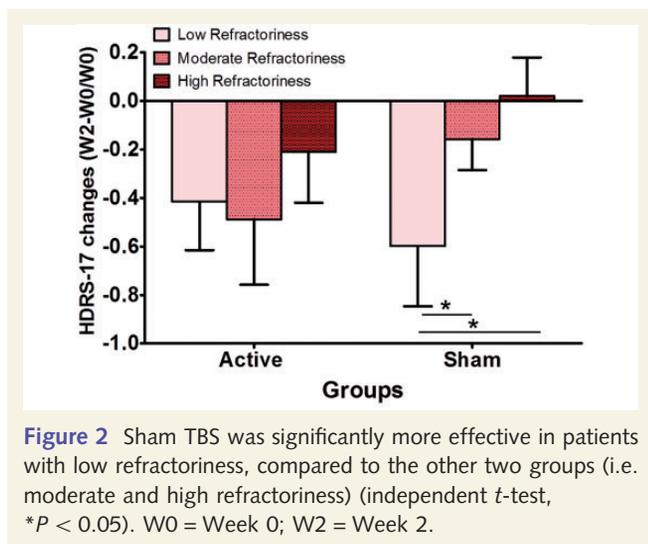


Figure 2 Sham TBS was significantly more effective in patients with low refractoriness, compared to the other two groups (i.e. moderate and high refractoriness) (independent *t*-test, * $P < 0.05$). W0 = Week 0; W2 = Week 2.

(sham) in the *post hoc* analysis (Table 3). There was a strong correlation between higher Maudsley refractoriness scores and less %HDRS-17 changes in the study population (Fig. 3), particularly in the patients treated by sham TBS ($r = 0.844$; $P < 0.001$) (Fig. 3) as compared to that by active TBS ($r = 0.338$; $P = 0.023$) (Fig. 3). Most responders at Week 2 who remained responsive at Week 14 were with moderate refractoriness (9/12, 75.0%), whereas the other three patients with lasting responsiveness included two with low refractoriness and one with high refractoriness. The level of treatment refractoriness at baseline was not a significant factor mediating the durability of antidepressant responsiveness ($\chi^2 = 0.856$, $P = 0.652$). Seven of 39 non-responders at Week 2 (2/4: low refractoriness and 4/16: moderate

refractoriness, but 1/19: high refractoriness) became responders at the 14 week follow-up assessment. The results suggested that patients with lower refractoriness (i.e. low or moderate) had a higher chance of delayed response to TBS as compared to those with high refractoriness ($\chi^2 = 4.05$, $P = 0.044$). Group was not a significant factor mediating the delayed responsiveness to TBS ($\chi^2 = 0.197$, $P = 0.978$).

Finally, logistic regression showed that the refractoriness level [moderate versus high refractoriness: odds ratio (CI) = 12.347 (1.760–86.604); $P = 0.011$] and the TBS group [Group C versus Group D: odds ratio (CI) = 12.906 (1.809–109.879); $P = 0.013$], but not age, sex, life stress, baseline HDRS-17 score, or psychiatric comorbidity, were the most important variables in predicting responders to 2-week TBS (Supplementary Table 1).

Safety outcomes

No seizures were recorded throughout the study. There were more events of headache, dizziness, and palpitations or nausea with active TBS than with sham TBS, yet no statistical significance existed among groups (Supplementary Table 2). All of the events were generally reported as mild or moderate, tolerable, and all diminished gradually after treatment with TBS. It is notably that more patients in Group C, a combination of intermittent and continuous TBS, complained of dizziness (Group C versus Group D = 5:1, $\chi^2 = 3.33$; $P = 0.068$). After careful evaluation, it was found that most patients with dizziness had received a sequence from continuous to intermittent TBS (4/7, 57.1%), whereas only a small portion of patients suffered from dizziness when intermittent TBS was given first and followed by continuous TBS (1/8, 12.5%). There were no differences on the main outcome measure of % HDRS-17 changes (Week 2 versus Week 0) between these two sequences. Because dizziness had the potential to compromise

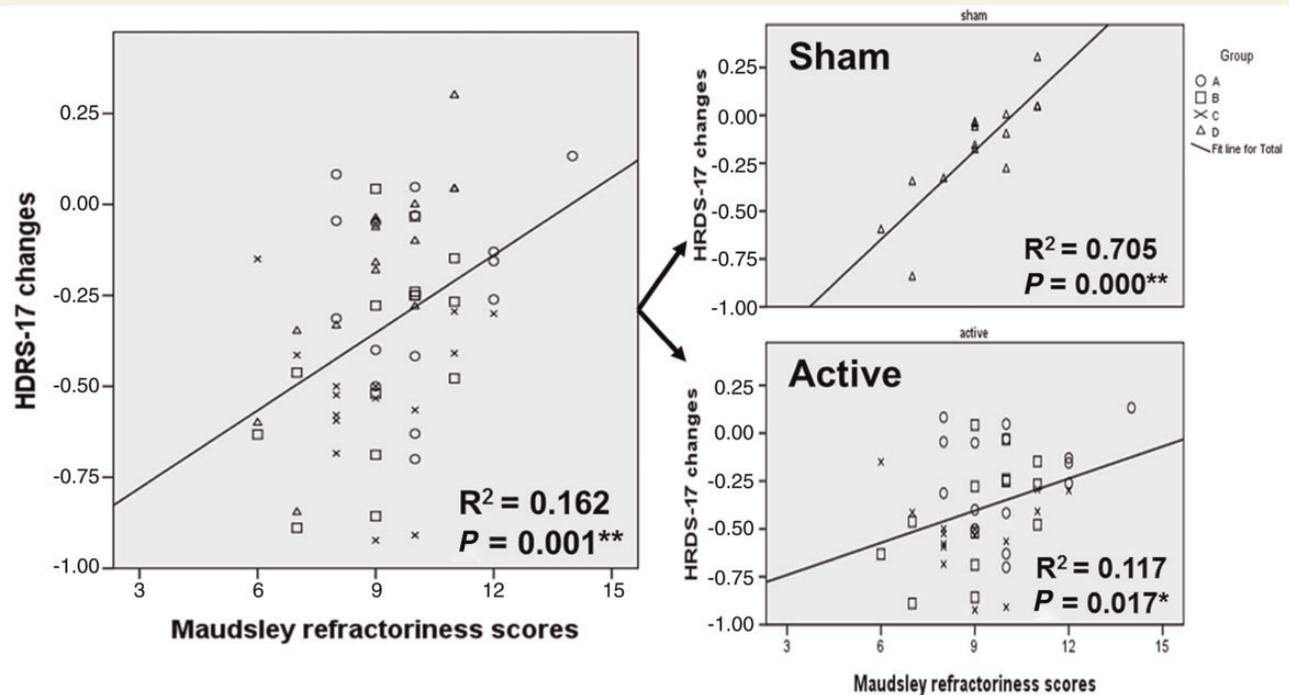


Figure 3 Significant correlations existed between baseline scores of treatment refractoriness (by Maudsley staging method) and changes of HDRS-17 scores after 2 weeks of TBS treatment (*left*). The correlation was even stronger in patients receiving sham TBS treatment (*right, top*) than in those receiving active TBS treatment (*right, bottom*). Pearson's correlations were conducted (* $P < 0.05$, ** $P < 0.01$). Group A (continuous TBS), Group B (intermittent TBS), Group C (continuous TBS + intermittent TBS), and Group D (sham TBS).

blinding, a separate analysis was conducted to study the association between treatment responses and the occurrence of side effects. Dizziness was not associated with treatment response ($\chi^2 = 4.778$; $P = 0.189$). There also was no association between other side effects and HDRS-17 changes.

Discussion

This is the first large, randomized controlled trial of daily prefrontal TBS in patients with TRD. Our results showed that daily TBS for a period of 2 weeks is a safe and well-tolerated option for antidepressant treatment for patients with TRD and the antidepressant effect is sustainable. As hypothesized, left prefrontal intermittent TBS (Group B or C) was more effective than right prefrontal continuous TBS (Group A) and sham TBS (Group D) (Table 1 and Fig. 2). We also found that treatment refractoriness at baseline was an important and independent variable in predicting TBS's antidepressant responses. Patients with lower refractoriness levels responded better to TBS, and this was particularly true for those with moderate refractoriness (Supplementary Table 1). Sham TBS was also effective for treating a subgroup of patients with TRD (i.e. those with low refractoriness) and the correlation between baseline refractoriness (by Maudsley staging method) and antidepressant responses to a 2-week TBS treatment was impressively strong in the group treated by sham TBS. Patients with lower refractoriness (i.e. low or moderate refractoriness), whether they

received active or sham TBS, also had a higher chance of a delayed response to TBS during the follow-up.

Antidepressant effects of theta burst stimulation

We found that the paradigms involving left prefrontal intermittent TBS (Groups B or C) were significantly more effective than was sham TBS. The results were in line with those from previous studies adopting repetitive TMS, in which one of the most effective parameters in the repetitive TMS studies seemed to include left prefrontal high-frequency repetitive TMS (e.g. 10 Hz) (Daskalakis *et al.*, 2008; Berlim *et al.*, 2013e; George *et al.*, 2013). In addition, the finding of a better but non-significant antidepressant effect associated with bilateral TBS stimulation (Group C) than left intermittent TBS (Group B) was not surprising, as bilateral repetitive TMS stimulation was also effective (Berlim *et al.*, 2013b), but did not seem superior to left repetitive TMS stimulation (Dumas *et al.*, 2012). The selection of a total of 3600 pulses (intermittent TBS: 1800 pulses + continuous TBS: 1800 pulses) for the bilateral stimulation group here was to make the between-group comparisons more reasonable [i.e. intermittent TBS (1800) versus intermittent TBS (1800) + continuous TBS (1800) and continuous TBS (1800) versus intermittent TBS (1800) + continuous TBS (1800)]. However, whether bilateral TBS is more effective than left-sided TBS warrants further investigation, since the finding of the better antidepressant effects associated with

Group C here might be due to dosing effects (3600 pulses in Group C versus 1800 pulses in Group B). A dose-dependent antidepressant effect has been suggested (i.e. right prefrontal continuous TBS: 3600 pulses/day > 1200 pulses/day) by an open-labelled study (Chistyakov *et al.*, 2010), yet a recent study investigating TBS's effects on motor cortex reported that TBS-induced plasticity cannot be enhanced simply by prolonging the stimulation duration. Instead, they observed some interesting findings that when stimulating for too long, the after-effects were reversed (Gamboa *et al.*, 2010). Therefore, whether TBS's antidepressant effects are dose-dependent remains elusive and warrants further investigations.

Our follow-up data also revealed that 57.9% of the TBS responders (11/19) remained showing symptomatic relief at a 12-week follow-up, which was very close to the TMS result, ~58%, as reported by a recent TMS review (George *et al.*, 2013). More well-controlled studies are needed to examine the durability of the active TBS-related antidepressant effect.

Efficacy and potential mechanisms of intermittent theta-burst stimulation on depression

Theoretically, intermittent TBS can induce lasting central effects through long-term potentiation-like effects on neuronal synapses. Based on studies from the human motor cortex, intermittent TBS could increase cortical excitability, while continuous TBS could decrease cortical excitability (Huang *et al.*, 2005). In an investigation of intermittent TBS mechanisms with function MRI that measures blood perfusion, it has been found that intermittent TBS targeting the motor cortex could not only affect blood perfusions at the stimulated motor cortex, but could also affect motor-related remote brain regions (Cardenas-Morales *et al.*, 2011). Although the TBS mechanisms operating in the human motor cortex may not be completely transferred to other brain regions, such observations of an influence both on stimulated cortical regions and the remote regions connected to them are consistent with what we had learned from repetitive TMS in the treatment of major depression (Baeken and De Raedt, 2011). High-frequency repetitive TMS working in human left dorsolateral prefrontal cortex can be considered as a 'top-down' augmentation, and successful repetitive TMS treatment seems to result in a cascade of neurobiological changes in limbic regions linked with the stimulated prefrontal cortex, such as the anterior cingulate cortex, amygdala, and associated temporal cortical regions (Li *et al.*, 2010b; Baeken and De Raedt, 2011). Recently, we have also found that successful treatment of left prefrontal repetitive TMS involves a reversal of prefronto-thalamic dysconnection (Li *et al.*, 2013). At the molecular level, TBS might impact depressive symptoms through its effects on the glutamatergic, GABAergic systems, gene expression, and protein levels (Cardenas-Morales *et al.*, 2010). Dorsolateral prefrontal cortex has been found to be closely associated with major depression (Lemogne *et al.*, 2010; Samson *et al.*, 2011; Sibille *et al.*, 2011) and is functionally involved in cognition and emotion regulations (Ruchow *et al.*, 2008). The structural and functional impairments of dorsolateral prefrontal cortex, particularly left-side,

were more involved in drug-resistant major depression (Li *et al.*, 2010a, b).

Continuous theta-burst stimulation's efficacy and potential mechanisms on depression

Despite conflicting results across studies, review and meta-analytic evidence have supported that low-frequency repetitive TMS targeting right dorsolateral prefrontal cortex is an effective treatment paradigm (Berlim *et al.*, 2013d). This idea came from the assumed antidepressant effects associated with restoration of asymmetrical frontal cortical activity (i.e. relatively greater right prefrontal cortex activity), which has been implicated in the experience and expression of emotions and motivations (Allen *et al.*, 2004).

A pattern of prefrontal cortex asymmetry with relatively right predominance (e.g. frontal alpha asymmetry) has been proposed as an endophenotype for depression (Allen *et al.*, 2004). However, our study found no evidence that right continuous TBS was more effective than sham treatment. There are some possible explanations. First, asymmetrical frontal cortical activity could be a trait characteristic for depression as proposed, but may not be critically associated with antidepressant responses. For example, recent repetitive TMS studies in combination with electroencephalography (Spronk *et al.*, 2008) or magnetoencephalography (Li *et al.*, 2013) consistently found that antidepressant-resistant depressives who responded to left prefrontal repetitive TMS (10 Hz) did not have significant changes in the frontal alpha asymmetry. Second, continuous TBS might only be effective for a subgroup of patients with major depressive disorder. Our results revealed that continuous TBS was only effective for patients with lower treatment refractoriness (Table 2). In fact, patients with higher treatment refractoriness could be more likely to have 'bilateral' prefrontal cortex hypofrontality. The idea could be supported by the observations that decreased glucose metabolism in the bilateral prefrontal cortex was significantly correlated with higher rating scores on the depression scales in major depressive disorder populations (Kimbrell *et al.*, 2002), and indirect evidence that TRD may have more prominent hypofrontality than non-TRD (Levinson *et al.*, 2010).

Different levels of treatment refractoriness and theta-burst stimulation outcomes

Although repetitive TMS is indicated for patients with major depressive disorder who have failed to receive satisfactory improvement from previous antidepressant medication, one of the factors found to confound repetitive TMS antidepressant results is treatment refractoriness (Fregni *et al.*, 2006; Brakemeier *et al.*, 2008). That is, a positive history of treatment refractoriness was associated with worse repetitive TMS results. However, such linkage would be quite confusing to clinicians who are deciding whether or not to refer a patient with TRD, and when to refer them. Our data indicated that lower treatment refractoriness associated with TRD was a significant predictor for better TBS responses, and the

best response occurred in the group of patients with moderate refractoriness. Most previous studies only adopted qualitative, instead of quantitative, measures of treatment refractoriness. One strength of our study was the use of quantitative measure of refractoriness by the Maudsley staging method (Fekadu *et al.*, 2009a), and we also categorized patients into three levels of treatment refractoriness. Our findings not only echo previous findings of high treatment refractoriness as a predictor of worse repetitive TMS responses, but also suggest that patients with moderate treatment refractoriness may have an underlying brain dysfunction that is more treatable by active repetitive TMS. Whether the Maudsley staging method could reliably measure treatment refractoriness in all patients with major depressive disorder warrants further investigation. However, as compared with other staging methods such as the Antidepressant Treatment History Form (ATHF), the Thase and Rush model, the European staging model, and the Massachusetts General Hospital staging model, and the Maudsley staging method, the predictive utility has been assessed as being best for the Maudsley staging method (Ruhe *et al.*, 2012). The Maudsley staging method scores could be used as a continuous variable and have been found to predict the persistence of a depressive episode and the functional impairment associated with TRD (Fekadu *et al.*, 2009b).

On the other hand, a group of patients with low refractoriness also responded to sham TBS and the association was impressively robust. There was no real stimulation applied to the patients receiving sham TBS and also no medication changes during the sham treatment. Such antidepressant responses occurred spontaneously and were observed more in patients with lower refractoriness. Furthermore, we also observed that patients with lower refractoriness had a significantly higher chance of having a delayed response to TBS, since six non-responders at Week 2 ($n = 3$: low refractoriness and $n = 3$: moderate refractoriness) became responders at Week 14. These findings implied that many inconsistent results from the previous TMS studies may have been confounded by the heterogeneity of the recruited depressives. In other words, when patients with lower refractoriness were recruited, more sham effects could be expected, and it was more likely that the differences between active and sham would be smaller and statistically non-significant.

Age effects and theta-burst stimulation outcomes

In our TBS study, we found no evidence to support that age limited the antidepressant effects of the TBS treatment. It has been suggested that antidepressant efficacy of repetitive TMS decreases with the age of the patient, yet the data are contradictory. For example, a meta-analysis aimed to find out predictors of antidepressant response to high-frequency repetitive TMS of left dorsolateral prefrontal cortex and after pooling data from six separate clinical trials, they found that age and treatment refractoriness were significant negative predictors of depression improvement (Fregni *et al.*, 2006). A recent trial also found a negative effect of age on the antidepressant response to

low-frequency repetitive TMS of right dorsolateral prefrontal cortex (Aguirre *et al.*, 2011). However, there were also studies indicating that age did not limit repetitive TMS effect. A multi-centre study investigated the antidepressant effects of high-frequency repetitive TMS of left dorsolateral prefrontal cortex on moderate-to-severe depression and found no interaction effect of age with repetitive TMS efficacy (Herwig *et al.*, 2007). Likewise, a recent study investigated the antidepressant effects of both high-frequency repetitive TMS over left dorsolateral prefrontal cortex and low-frequency repetitive TMS over right dorsolateral prefrontal cortex and also found no evidence of the age affecting repetitive TMS's antidepressant outcome. They pointed out that the antidepressant effects did not differ between the two age groups (<65 and ≥ 65 years) (Ciobanu *et al.*, 2013). In addition, if we divided patients into two age groups (<45 and ≥ 45 years), we also found that the antidepressant responses (responders: <45 versus ≥ 45 years = 41.6% versus 30.5%) did not differ significantly between these two groups ($\chi^2 = 0.781$, $P = 0.377$). The logistic regression model also revealed that age was not a significant variable in predicting the antidepressant efficacy (Wald = 0.015, $P = 0.903$, Supplementary Table 1). Furthermore, the main findings of the % HDRS-17 changes from Week 0 to Week 2 remained the same with a significant difference among the four groups [ANOVA, $F(3,53) = 6.064$, $P = 0.002$; *post hoc* least significant difference: $B > A$, $B > D$, $C > A$, and $C > D$] if we calculated the results of the 57 of 60 subjects (95%) who were aged under 60 years. Because it has been suggested that the increased distance from coil to prefrontal cortex in the aged brain was associated with ineffective responses to repetitive TMS (Kozel *et al.*, 2000), we excluded subjects aged over 70 years in the current study to minimize the potential concern of the coil-cortex distance on the TBS responses. Indeed, most of our recruited patients (59/60, 98.3%) were aged 24 to 61 years and the oldest was a 64-year-old female (Table 1).

Limitations

Two limitations should be considered in the interpretation of our study. Firstly, the current study was an add-on TBS study, in spite of the randomized and sham-controlled design. It has been reported that add-on repetitive TMS treatment could enhance the clinical responses to antidepressants (Berlim *et al.*, 2013c). Therefore, the observed responses to TBS could partly result from modulation of the effects of the medications or psychotherapeutic interventions that patients were using during the TBS treatment. However, before we have solid evidence to support the antidepressant efficacy of TBS on refractory depression, the add-on design is more ethically sounded and could provide more naturalistic data. Additionally, none of our recruited patients were concomitantly receiving psychotherapeutic interventions during the TBS treatment. The concomitant medications were also not allowed to be changed and were their original medication regimen which they had failed to respond to. It is notable that there were no differences in the medications across groups and we found no correlation between the TBS responses and the antidepressant medications. Therefore, the add-on design did not change the main finding that left prefrontal intermittent TBS (Group B or C)

was more effective than right prefrontal continuous TBS (Group A) and sham TBS (Group D) but it is possible that some of the TMS effects were a consequence of modulation of the response to medication. Secondly, the sham condition we adopted was not optimal. However, we attempted to minimize the potential bias in the study procedures. The results turned out to be acceptable, since a significant portion of patients in the sham group seemed to have antidepressant effects in response to the sham condition. For example, 73.3% (11/15 patients) were found to have at least 15% decreases in the HDRS-17 scores and two subjects were classified as responders at the end of 2-weeks of TBS treatment. In addition, even without a real stimulation effect on the scalp, some patients in the sham condition still reported having side effects like headache (2/15, 13.3%) and dizziness (1/15, 6.7%). The actual stimulating effect of TBS on the scalp is minimal, as it uses much lower power (i.e. 80% active motor threshold) than does traditional repetitive TMS (i.e. 100–120% resting motor threshold). To support this, only five subjects (5/45, 11.1%) who received active TBS had temporary headache. Furthermore, a recent systemic review and meta-analysis that searched the literature from January 1995 to July 2012 found that the use of angulation (non-sham coil) and sham coil in previous repetitive TMS trials had similar results, and concluded that the existing sham repetitive TMS interventions seem to result in acceptable levels of blinding (Berlim *et al.*, 2013a).

Conclusion

The results of this double-blind sham-controlled study provide evidence that TBS is a safe, well-tolerated, and effective treatment for TRD. Paradigms involving left prefrontal intermittent TBS were most effective. Patients with different levels of treatment refractoriness responded differently to either active or sham TBS.

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Supplementary material

Supplementary material is available at *Brain* online.

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