Egyptian Journal of Psychiatry

Vol. 44, No. 1, 2023
ISSN: 1110-1105 (print)
ISSN: 2090-2425 (online)
DOI: 10.21608/ejpsy.2023.315356

ORIGINAL ARTICLE

Effectiveness of theta-burst and high-frequency transcranial magnetic stimulation in treatment of depression: a double-blinded sham-controlled trial

Nashaat A.M. Abdel-Fadeel, Mohamed Abdel-Azem, Heussin M. Saeed, Mostafa M. Abdelnaeem
Department of Neurology and Psychiatry, Faculty of Medicine, Minia University, Minia, Egypt.

Correspondence to *Nashaat A.M. Abdel-Fadeel, MD, Department of Neurology and Psychiatry, Faculty of Medicine, Minia University, Minia 61111, Egypt*
E-mail: nashaatadel2014@gmail.com, nashaat.adel@mu.edu.eg

Background

Major depressive disorder (MDD) is a leading cause of disability worldwide. Almost a third of patients diagnosed with MDD do not respond to antidepressants. Transcranial magnetic stimulation (TMS) is a novel option for these patients. The first approved and most frequently used protocol for TMS in patients with MDD is the 10-Hz high-frequency repetitive TMS (rTMS) over the left dorsolateral prefrontal cortex. Intermittent theta-burst stimulation (iTBS) is a recently developed FDA-approved rTMS technique with relatively short session duration (3 min) compared with the standard 10-Hz high-frequency rTMS treatment session (37.5 min).

Patients and Methods

In this double-blinded, sham-controlled trial, we recruited 51 participants aged 18–60 years, diagnosed with a current episode of treatment-resistant MDD, who were receiving stable antidepressant medication doses for at least 4 weeks before the start of sessions and had moderate to severe depression. Participants were randomly assigned 1:1:1 to treatment groups (10-Hz rTMS, iTBS, or sham). Sessions were conducted by delivering iTBS, 10-Hz rTMS, or sham parameters to the left dorsolateral prefrontal cortex as of once daily sessions (i.e. five sessions a week for at least 4 weeks, which may be extended to 6 weeks). The TMS sessions were delivered through a figure-of-eight coil connected to the Neurosoft TMS system. Primary outcome was improvement in depression, measured by changing score of Hamilton depression rating scale-17 before, each week, and after the end of sessions among the three groups, asking about adverse effects, assessed safety, and tolerability of intervention.

Results

In this RCT, the improvement in depression symptoms measured by change of Hamilton depression rating scale-17 scores between baseline score and primary end point (4 weeks) was highly statistically significant, favoring 10-Hz rTMS (14.53 points; 49.75%) over sham (5.6; 21.87%) (P<0.004). There was also a significant difference between iTBS (15.9 points; 56.68%) versus sham (5.6 points; 21.87%), with a highly significant difference in depression outcome, in favor of the active iTBS group (P=0.001). Response rates were significantly higher for 10-Hz rTMS (73.3%) and iTBS (66.7%) versus the sham (13.3%). Regarding the remission rates for the 10-Hz rTMS (20%), iTBS (40%), and sham (6.7%), the difference was statistically significant between iTBS and sham, but the 10-Hz rTMS comparison with sham has failed to show a statistically significant difference. Regarding adverse effects, there was a nonsignificant difference in reported adverse effects between different study groups. Headache was the most frequently reported adverse effect in all sample (62.2%).

Conclusions

Both conventional 10 HZ rTMS and iTBS are effective, efficacious, and tolerable for management of treatment-resistant MDD. However, iTBS is preferable than 10-HZ rTMS regarding shorter session time, which leads to increased treatment capacity.

Keywords

Repetitive transcranial magnetic stimulation, Sham and depression, Theta-burst stimulation.

Egyptian Journal of Psychiatry 2023,
44:25–33

INTRODUCTION

Major depressive disorder (MDD) represents a global challenge and is a leading cause of disability worldwide (Organization, 2017). Psychosocial interventions may be effective in mild forms of depression, whereas pharmacological interventions are recommended in moderate to severe forms (Middleton *et al.,* 2005). Despite adequate psychosocial and pharmacological interventions, 10–30% of patients diagnosed with MDD experience a chronic and debilitating course (Kessler and Bromet, 2013).

New emerging treatment modalities have been proposed for this group of patients including noninvasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS), which uses a magnetic field to modulate brain activity holding a promise in treatment-resistant depression (George and Aston-Jones, 2010).

rTMS delivers focused and powerful magnetic field pulses to induce changes in the activity of specific brain regions that are involved in and known to be affected in depression (Pascual-Leone *et al.,* 1996). Functional neuroimaging studies of MDD showed reduction of activity in specific brain regions, particularly the left dorsolateral prefrontal cortex (DLPFC) (Pizzagalli, 2011). Stimulation of left DLPFC by rTMS showed significant mood improvement in patients with treatment-resistant depression (George *et al.,* 1997).

rTMS has become clinically approved, accepted, and recognized therapeutic intervention for treatment-resistant depression (Voigt *et al.,* 2019). The most used rTMS protocol is high-frequency (10 Hz) stimulation of the left DLPFC (Brunoni *et al.,* 2017). The treatment course typically involves a daily session that lasts for 37.5 min, 5 days a week for 4–6 weeks (Berlim *et al.,* 2017).

Theta-burst stimulation (TBS) is a new modality of rTMS that has been investigated for potential therapeutic effects in treatment of depression. Intermittent theta-burst stimulation (iTBS) is a special form of TBS that has the ability to stimulate the cerebral cortex in a much shorter duration than conventional methods with the advantageous enhancement of neuroplasticity (Bakker *et al.,* 2015).

iTBS lasts for about 3 min and induces a similar or more potent stimulation than conventional 10-Hz rTMS (Di Lazzaro *et al.,* 2011). Moreover, iTBS was suggested to be significantly superior to sham in MDD treatment (Berlim *et al.,* 2017; Brunoni *et al.,* 2017).

A large multicenter trial conducted by Blumberger *et al.,* (2018) has shown that iTBS was noninferior to the standard 10-Hz rTMS in the management of treatment-resistant depression. However, several limitations existed in their trial including the absence of sham-controlled condition. In clinical trials, testing the potential therapeutic effects of any TMS method requires a valid controlled condition (Lisanby *et al.,* 2001).

Therefore, we conducted this sham-controlled trial to compare the effectiveness of iTBS and conventional 10-Hz rTMS (10 Hz rTMS) with sham in patients with MDD who had failed to achieve a significant response from one prior adequate antidepressant treatment trial in the current episode.

PATIENTS AND METHODS

Study design

The study design was a randomized sham-controlled double-blinded study. The study site was Minia University Hospital in Minia Governorate, Egypt. The patients have been referred from the psychiatry outpatient clinics during the period from December 1, 2018, to October 1, 2019.

We recruited adults aged 18–60 years; both males and females were included. The diagnosis of MDD was stated according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria using Structured Clinical Interview for DSM-5 (SCID-5) as a single or recurrent episode (American Psychiatric Association, 2013).

Regarding severity of depressive symptoms, we recruited patients with moderate to severe symptoms during the current depressive episode who showed a 17-item Hamilton Rating Scale for Depression (HRSD-17) score of at least 18 (Hamilton, 1967).

Previous treatment failure was defined according to Antidepressant Treatment History Form (Sackeim, 2001) either by failure of response to a previous antidepressant treatment trial of adequate dose and duration (Antidepressant Treatment History Form score of 3 or higher) or intolerance to at least two separate antidepressant treatment trials of inadequate dose and duration (score 1 or 2).

The patients were allowed to receive a stable antidepressant regimen for at least 4 weeks before TMS without change of their antidepressant before intervention, which continued during the study, whereas patients who were unable to tolerate two previous trials were allowed to receive TMS without concomitant antidepressant medications.

We excluded patients with a current or past history of psychotic symptoms, substance use disorder, and bipolar affective disorder. We also excluded patients with MDD who failed to respond to adequate electroconvulsive therapy course (eight sessions or more) or with a history of previous TMS treatment or a vagus nerve stimulator implant.

In addition, general contraindications of TMS have been ruled out before starting intervention such as personal history of epilepsy or a family history of epilepsy in a first degree relative, presence of metal in or close to the patient's

head, or unstable medical or neurological condition (e.g. seizures, stroke, brain tumor, and brain surgery).

Ethical approval was granted by the research ethical committee of Minia University. The participants participated in the study voluntarily after taking their consent and after informing them about the purpose and procedures of the study, and they were told that they may receive active (rTMS or iTBS) or sham treatment.

Randomization

Simple random sampling was used. Randomization of the current study was ensured by random allocation of participants (1:1:1) to each study group (10-Hz rTMS, iTBS, or sham). Additionally, the three groups were balanced regarding the number of antidepressant trials in the current episode, as this variable was found significantly correlated with rTMS-induced improvement (the lower the number of failed antidepressant trials, the better the response to rTMS (Lisanby *et al.,* 2009). The groups were randomized into two categories (more than one failed antidepressant trials vs. one or less than one antidepressant trial).

Blinding

Participants were informed that they will be treated with TMS but they did not know the type of stimulation they received or the differences between multiple techniques. Assessment of patients before, during, and after the course of stimulation was performed by a trained psychologist (rater). This rater did not know which type of stimulation the patient received or whether the patient received a real TMS or sham. The rater and the participants were instructed not to share any information about details of the sessions.

Initial assessment of all participants including assessment of contraindications of TMS were conducted by a psychiatrist along with a full psychiatric interview using the Structured Clinical Interview for DSM-5 (SCID-5) to state the diagnosis of MDD, as a single or recurrent episode and to screen for disease-specific exclusion criteria based on Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The assessment of depression severity was conducted by a trained investigator before enrollment, every week, and after the end of the sessions.

Transcranial magnetic stimulation procedures

The TMS sessions were delivered through a figure-of-eight coil connected to Neuro-MS/D magnetic stimulator (Neurosoft LLC, Ivanovo, Russia). Resting motor threshold (RMT) was determined by use of visual observation according to the latest guidelines (McClintock *et al.,* 2018). The coil was advanced 5.5 cm anterior to the MT location along a right superior oblique plane with a rotation point about the tip of the patient's nose to locate left DLPFC.

Conventional 10-Hz rTMS was delivered according to conventional FDA-approved protocol and parameters (120% RMT stimulation intensity; 10 Hz frequency; 4 s on and 26 s off; 3000 pulses per session; and total duration of 37.5 min) (O'Reardon *et al.,* 2007; George *et al.,* 2010).

iTBS was delivered at the same site and intensity (120% RMT). It differs from 10-Hz rTMS in pattern of stimulation and total number of pulses (triplet 50 Hz bursts, repeated at 5 Hz; 2 s on and 8 s off; 600 pulses per session; and total duration of 3 min 9 s) (Huang *et al.,* 2005).

Sham TMS was delivered through tilting the figure of eight coil 90° from tangential as recommended by Lisanby *et al.,* (2001) as it was proven to be devoid of biological effects.

The sessions were scheduled daily, 5 days a week for at least 4 weeks (20 sessions). It may be extended for another 2 weeks (10 supplementary sessions) in patients who showed improvement in Hamilton depression rating scale (HDRS-17) score more than 30% from baseline but did not achieve remission, in accordance with current guidelines (McClintock *et al.,* 2018).

Study parameters

The primary efficacy outcome was improvement in depression, measured by change in HDRS-17 score before, after each week, and after end of sessions within the three groups (10 Hz rTMS, iTBS, and sham).

Secondary outcome measures were also recorded at baseline and after end of sessions. These measures included Hamilton Anxiety Rating Scale and quality-of-life scale (both evaluated by the same person who assessed HDRS scores).

Patient response was defined by 50% reduction in depression score at baseline, which was in consistence with published results (O'Reardon *et al.,* 2007; George *et al.,* 2010). Remission was defined by HRSD-17 total score less than 7 (Frank *et al.,* 1991). Safety and tolerability were assessed by asking about adverse effects during and after each session, guided with previously identified rTMS adverse effects such as headache, tinnitus, and seizures.

Statistical Analysis

Data analysis was done by the Statistical Package for the Social Sciences (SPSS), version 25.0 for Windows (IBM Corporation, New York, USA). Regarding descriptive statistics, frequencies and percentages were calculated for categorical variables, whereas means and SDs were calculated for continuous variables. Analytical statistics such as *t* tests were used to compare outcome variables within the three groups. χ^2 tests were used in comparing the three groups on categorical variables. Wilcoxon signed-rank test and Kruskal–Wallis test were used for comparing two or more independent samples of equal sample size with nonparametric distribution.

RESULTS

From December 1, 2018, to October 1, 2019, 51 participants with MDD were enrolled, of whom six discontinued treatments (two from 10 Hz rTMS group, three from iTBS group, and one from sham). In the follow-up of patients in the outpatient clinic, all of them stopped the treatment course because of difficulty of commitment to daily sessions.

Sample characteristics

The three groups were comparable regarding demographic and clinical features: the study participants did not show significant differences regarding age, sex, residence, marital status, duration of illness, new or recurrent episodes, and presence of environmental precipitant among the three groups. Baseline scores of depression, anxiety, and quality of life scales were also balanced and comparable to each other, as shown in Table 1.

Randomization was successful with respect to the distribution of participants with similar previous treatment failure across groups (Table 1). The three groups were balanced regarding the level of medication resistance (more than one vs. one or fewer adequate trials in which the patient did not respond to treatment).

Continuous efficacy outcome measures

The improvement in depression symptoms was measured by change of HDRS-17 scores, with highly statistically significant difference in depression scores between baseline and after end of sessions in each of the three study groups ($P<0.001$) (Table 2).

In comparison of each group with the other (Table 3), we found that change of depression scores between baseline score and primary end point (4 weeks) was in favor of active arms (10 Hz rTMS and iTBS) against sham, but it was nonsignificant between the two active arms.

As shown in Table 3, participants who received 10-Hz rTMS showed an average change of 14.53 points on the depression scale (49.75%) in comparison with only 5.6 points for those who received sham (21.87%) ($P=0.004$). Similarly, in iTBS, the mean improvement was 15.9 (56.68%) points, in comparison with 5.6 points for sham ($P=0.001$).

Regarding the comparison between 10 Hz rTMS and iTBS, although the results were statistically nonsignificant ($P=0.755$), the change in mean depression scores after the primary end point after 4 weeks was in favor of the iTBS technique (Table 3).

Interestingly, in the first 3 weeks of sessions, the pattern of change of depression scores over time was similar among the three groups, but it sharply decreased after 3 weeks in the two active arms, whereas it reached a plateau phase of change in sham, as illustrated in Fig. 1.

Categorical outcomes

Response rates

As shown in Fig. 2, the response rate (defined by decrease in HDRS-17>50%), after primary end point (4 weeks) was 60% in the 10-Hz rTMS, 66.7% in iTBS, and only 6.7 in sham. The same differences were sustained through sessions until the secondary efficacy time point at week 6.

Moreover, the comparison between response rates in the two active arms (10 Hz and iTBS) after 4 or 6 weeks failed to achieve statistically significant results ($P=0.705$ and 0.690, respectively).

Remission rates

Regarding remission of depression after primary end point of 4 weeks (defined by HDRS-17<8), two (15.4%) participants achieved remission in the 10-Hz rTMS group in comparison with six (40%) in the iTBS group and one (6.7%) in the sham group (Fig. 3).

Notably, although the difference was in favor of active techniques, the comparison between 10-Hz rTMS and sham groups regarding remission rates showed nonstatistically significant difference ($P=0.291$). However, the difference between iTBS and sham has successfully achieved statistically significant difference ($P=0.034$) (Table 4).

Adverse effects

As shown in Table 3, the frequencies of reported adverse effects in TMS treatment were as follows: the most frequently reported adverse effect was headache (37.7%) followed by local pain (26.6%). There was no statistically significant difference in reported adverse effects between different study groups, with P values of 0.293, 0.092, 0.360, 0.844, and 0.760 for headache, local pain, anxiety, dizziness, and tinnitus, respectively.

DISCUSSION

To the best of our knowledge, this is the first randomized double-blinded sham-controlled trial in which the effectiveness of conventional 10-Hz rTMS (10 Hz rTMS) and iTBS is tested against sham in patients with MDD, who have failed to achieve a satisfactory response from one prior adequate antidepressant treatment trial in the current episode.

In the current study, the mean age of participants was 35.44±10.4 years, ranging from 18 to 55 years, which is close to but relatively lower than rTMS trials in depression, such as Fitzgerald *et al.,* (2012) (43–44 years), and Blumberger *et al.,* (2018) (41–43 years). This may be attributed to the relatively wider acceptance of the new treatment modalities (such as brain stimulation) among young adults in our culture. This also addresses the challenges that may limit the adoption of such treatment modalities among elderly populations in our subcultural background and may need further investigation.

Table 1: Sociodemographic and clinical characteristics of different study groups:

	10 Hz rTMS (*N*=15)	iTBS (*N*=15)	sham (*N*=15)	*P* value
Age (years)				
Mean±SD	33.20±10.073	39.07±11.145	34.07±9.640	0.254
Range	22–51	18–51	19–55	
Sex [*n* (%)]				
Male	8(53.3)	5(33.3)	7(46.7)	0.533
Female	7(46.7)	10(66.7)	8(53.3)	
Residence [*n* (%)]				
Urban	4(26.7)	8(53.3)	9(60.0)	0.153
Rural	11(73.3)	7(46.7)	6(40.0)	
Marital status [*n* (%)]				
Married	12(80.0)	7(46.7)	7(46.7)	0.095
Widowed	–	3(20.0)	–	
Divorced	–	1(6.7)	1(6.7)	
Never married	3(20.0)	4(26.7)	7(46.7)	
Duration of marriage (years)				
Mean±SD	9.80±9.770	11.00±12.154	6.93±10.292	0.574
Range	0–30	0–30	0–28	
Duration of illness (years)				
Mean±SD	7.13±7.170	8.27±5.946	5.47±3.871	0.423
Range	1–28	1–20	1–11	
New or recurrent episode [*n* (%)]				
New	1(6.7)	2(13.3)	3(20.0)	0.562
Recurrent	14(93.3)	13(86.7)	12(80.0)	
Environmental factors [*n* (%)]				
No environmental precipitant	3(20.0)	4(26.7)	5(33.3)	0.711
Environmental precipitant	12(80.0)	11(73.3)	10(66.7)	
Hamilton depression score-17				
Mean±SD	27.47±5.668	28.20±5.519	24.47±6.081	0.159
Range	18–39	18–37	18–35	
Hamilton anxiety score				
Mean±SD	24.00±4.488	24.27±6.419	±3.852 26.53	0.229
Range	16–32	16–37	20–32	
Quality of life score				0.198
Mean±SD	39.20±6.428	7.345 35.67±	38.27±4.906	
Range	28–49	24–54	33–50	
Unable to tolerate two inadequate antidepressant trial	5	2	5	
+	+	+	+	
One failed adequate antidepressant trial	6	9	6	
one or less than failed antidepressant trials	11	11	11	
Two failed antidepressant trials	4	4	4	

iTBS, intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation.

Table 2: Comparison between depression scores before and after intervention in each study group:

	10 Hz rTMS (*N*=15)	iTBS (*N*=15)	sham (*N*=15)
Baseline (mean±SD)	27.47±5.66	28.20±5.519	24.47±6.081
After end of sessions (mean±SD)	11.47±5.069	11.20±6.63	18.87±7.53
P value	<0.001	<0.001	<0.001
HDRS-17 improvement after 4 weeks (mean±SD)	14.53±8.55	15.93±7.62	5.60±7.13
HDRS-17 improvement after 4 weeks percentage (%) (mean±SD)	49.75±26.83	56.68±27.20	21.87±23.33

HDRS, Hamilton depression rating scale; iTBS, intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation.

Table 3: Comparison between study groups regarding improvement in depression as measured by score change of Hamilton depression rating scale before and after interventions:

	10 Hz rTMS vs. sham	iTBS vs. sham	10 Hz rTMS vs. iTBS
HDRS-17 improvement after 4 weeks (mean±SD)	14.53±8.55 vs. 5.60±7.13	15.93±7.62 vs. 5.60±7.13	14.53±8.55 vs. 15.93±7.62
P value	0.004	0.001	0.755

HRDS, Hamilton depression rating scale; iTBS, intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation.

Table 4: Comparison betweenReported adverse effects in each group:

	10 Hz rTMS (*N*=15)	TBS (*N*=15)	Sham (*N*=15)	χ^2	*P*	Significance
Headache	7	11	10	2.458	0.293	NS
Local pain	5	6	1	4.773	0.092	NS
Anxiety	1	0	0	2.045	0.360	NS
Dizziness	3	2	2	0.338	0.844	NS
Tinnitus	1	1	2	0.549	0.760	NS

rTMS, repetitive transcranial magnetic stimulation; TBS, theta-burst stimulation.

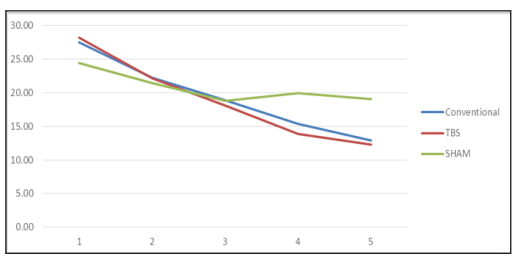

Figure 1: Changes in Hamilton depression score throughout the weeks of treatment in each group.

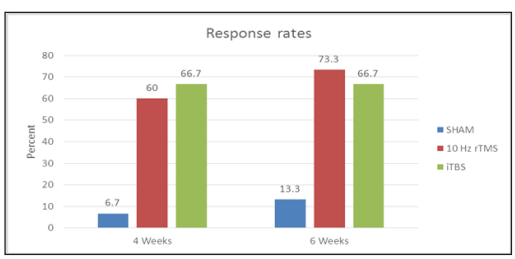

Figure 2: Response rates in different study groups after primary end point at 4 weeks and after end of sessions at 6 weeks.

Although it has been postulated that the antidepressant effect of rTMS decreases with increasing age, the results of previous studies are contradictory. Although a meta-analysis (Fregni *et al.,* 2006) found that in management of depression, old age is considered a poor prognostic factor, a multicenter study found no effect of age on the efficacy of TMS in patients with moderate to severe depression (Herwig *et al.,* 2007).

Figure 3: Remission rates in different study groups after primary end point at 4 weeks and after end of sessions at 6 weeks.

In this RCT, conventional 10-Hz rTMS and iTBS (active arms) significantly decreased depression scores against sham (*P*=0.004 and 0.001, respectively). This pattern of symptom improvement was consistent in both continuous and categorical outcomes. Response rates (defined by 50% reduction of HDRS-17 baseline score) were 73.3% in 10 Hz rTMS, 66.7% in iTBS, and 13.3% only for sham.

The response rate in the existing study was much higher than the pivotal trial done by O'Reardon *et al.,* (2007), whose response rates in HAMD-17 was 20.5% for active arm versus 11.6% for sham. This could be explained

by their relatively more treatment-resistant sample, with up to four failed adequate antidepressant trials in the current episode (mean=1.6 failed antidepressant trials) versus our trial with much lower mean number of failed antidepressant treatment trials (mean=1.00 failed trial). The number of failed antidepressant trials is a significant prognostic factor of response in different previous clinical trials (Fregni *et al.,* 2006; O'Reardon *et al.,* 2007; Cohen *et al.,* 2010).

Regarding remission of depression after primary endpoint (4 weeks) (defined by 17-HDRS<8), two (15.4%) participants achieved remission in the 10-Hz rTMS group in comparison with six (40%) in the iTBS group and one (6.7%) in the sham group.

Remission rates differed significantly between iTBS and sham (P=0.034). However, the difference in remission rates between 10 Hz rTMS and sham groups failed to achieve significant difference (P=0.291). This result is similar to the results of O'Reardon *et al.,* (2007), who did not detect a significant difference in rates of remission between 10-Hz rTMS and sham. This may be attributed to the relatively small sample size in which continuous measures were significant but categorical ones were not in some comparisons between the active and sham methods.

The comparison of remission rates between the 10-Hz rTMS group and iTBS group was statistically nonsignificant (P=0.232); however, it was in favor of iTBS (40%) over 10-Hz rTMS (20%).

Comparison of differences in depression scores at baseline and after end of sessions in each group separately showed statistically significant differences in both active (10 Hz rTMS and iTBS) groups and also in the sham group (P<0.001, P<0.001, and P=0.009 ,respectively).

Absolutely, this may be translated into weakness in sham conditions that we have used in our trial (i.e. tilting the figure of eight coil 90° from tangential). More precisely, other sham TMS coils were designed to be similar in appearance to active coil but with an embedded magnetic shield that blocks the magnetic field. These sham TMS coils were used in multicenter large-sized trials such as O'Reardon *et al.,* (2007) and George *et al.,* (2010). In contrast to the sham TMS approach used in our trial, the attenuation of the magnetic field ensures that no real brain stimulation occurs (Duecker and Sack, 2015).

However, the substantial treatment response that occurs in sham stimulation is not an exceptional phenomenon. A recent meta-analysis and systematic review (Razza *et al.,* 2018) found that the sham response in rTMS trials of depression was large and significant.

Tilting TMS coil from 45 to 90° from the scalp to direct the magnetic field away from the brain is the most frequently used method of sham stimulation in rTMS controlled trials (Sommer *et al.,* 2006), and it was found to be devoid of biological effects (Lisanby *et al.,* 2001).

It is true that the sham group reached a statistically significant change in depression scores, but this change did not indicate a substantial response (defined by decrease in HRDS >50%) and after 4 weeks; only one participant showed response in sham group, whereas nine patients achieved response in the 10 Hz rTMS group and 10 patients in the iTBS group.

Similarly, it appears that adding 2 weeks of rTMS beyond the initial 4-week stimulation in patients who do not achieve remission after 4 weeks of treatment can lead to an important clinical effect, as consistent with published previous trials (O'Reardon *et al.,* 2007; Levkovitz *et al.,* 2015).

The reason for this conclusion is that the mean difference in Hamilton depression scores between 4 and 6 weeks of treatment in patients who received additional 10 sessions was significant in our total sample (P=0.008).

Dropout occurred in six (11.7%) patients. There was no considerable difference across groups (13.3% of 10 Hz rTMS, 13.3% of iTBS, and 6.6% of sham). The reason for discontinuation was not related to adverse effects, and all patients reported that the cause was the difficulty in commitment to regular daily sessions.

To make sure that the effect of TMS was not affected by another confounding factors, we included patients with stable antidepressant regimens for at least 4 weeks before treatment; these regimens continued unchanged during TMS courses to prevent any effect of medication-change that may affect results of the study.

Those who were unable to tolerate two trials of antidepressants of inadequate dose and duration before TMS (n=12 patients) were allowed to receive sessions without concomitant antidepressant medications, and this was in favor of ensuring that TMS was the only active factor.

In a large number of TMS studies, patients were on stable medications throughout TMS courses (Chistyakov *et al.,* 2010; Paillere Martinot *et al.,* 2010; Hernandez-Ribas *et al.,* 2013; Blumberger *et al.,* 2018). However, some other studies (Avery *et al.,* 2006; O'Reardon *et al.,* 2007; Duprat *et al.,* 2016) involved three phases: a lead-in phase (withdrawal of antidepressants), acute treatment phase (daily TMS or sham treatment), and a taper phase (reduced frequency of TMS or sham+restart of antidepressants).

Although medications washout before entering the study ensures that the outcome results are solely from TMS and ameliorates the effects of confounding factors, we found it as ethically problematic especially in the sham-controlled studies.

As DSM-5 separates bipolar disorder from depressive disorders, thus we decided not to include patients with bipolar depression in our study. Yet patients with bipolar depression were involved in other studies (Hernandez-Ribas *et al.,* 2013; Rachid *et al.,* 2017).

Previous preclinical data suggested that doubling the number of pulses of iTBS does not increase the excitatory effect and in fact might have an inhibitory effect (Gamboa *et al.,* 2010).

To avoid such reversal effect and to maximize the advantage of the iTBS shorter duration, we applied iTBS with a single standard run of 600 pulses. Second, 120% RMT stimulation intensity was matched in both groups because inadequate stimulation intensity was identified as a potential reason for lower efficacy in earlier trials of rTMS, and current guidelines recommend using stimulation of at least 110% RMT for conventional protocols (Milev *et al.,* 2016; McClintock *et al.,* 2018).

Despite the strengths of the current study, several limitations should be considered: the localization of left DLPFC was done by advancing the figure-of-eight coil 5.5 cm anterior to the MT location along a right superior oblique plane.

Localization of DLPFC for TMS coil positioning included a variety of techniques: placing the coil 5, 5.5, or 6 cm anterior to the motor cortex, the 10–20 system, stereotactic frames, and a MRI-based neuro-navigation (McClintock *et al.,* 2018).

In the early trials of rTMS in depression, the placement was 5 cm anterior to the motor threshold spot (O'Reardon *et al.,* 2007). Data suggest that this '5-cm rule' was doubted, and further studies suggested that the coil placement to be 5.5–6 cm anterior to the MT location (Herbsman *et al.,* 2009).

Although neuroimaging (as MRI)-guided positioning techniques offer the greatest accuracy, the method is expensive requiring a specific brain MRI scan and there is limited evidence for its routine use in clinical trials (Fitzgerald *et al.,* 2009). Another limitation is that sham stimulation was delivered using the two-wing 90° method through tilting the coil 90° off the scalp in double wing tilting position, rather than using the magnetic shield embedded sham coils.

For the existing study, we suggest that an extension phase of the study should continue to follow-up the participants for long-term effects of rTMS to assess the long-lasting effects and the need for maintenance sessions to prevent relapse. Furthermore, to clarify the differential therapeutic effects of these two stimulation techniques, addition of a functional neuroimaging component to clinical treatment trials may be helpful.

In conclusion, we have found that both conventional 10-Hz rTMS and iTBS are effective, efficacious, and tolerable for management of treatment-resistant MDD. We found that iTBS and 10-Hz rTMS have a similar efficacy and adverse effect profile in treatment-resistant depression, and their efficacy is much greater than the efficacy of sham (placebo) stimulation.

Absolutely, these findings highlight the efficacy of iTBS (just 3-min protocol), which proved to act comparably to the standard 37.5 min for 10-Hz rTMS as an intervention for treatment-resistant depression. These findings, undoubtedly, call attention to the use of iTBS, with the advantage of much shorter duration, in facilitating wider use and acceptance of TMS in the management of treatment-resistant depression.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCE

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders: DSM-5. Vol. 5. Washington, DC: American Psychiatric Association.

Avery DH, *et al*. (2006). A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biol Psychiatry 59:187–194.

Bakker N, *et al*. (2015). rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. Brain Stimulat 8:208–215.

Berlim MT, *et al*. (2017). Efficacy of theta burst stimulation (TBS) for major depression: an exploratory meta-analysis of randomized and sham-controlled trials. J Psychiatr Res 90:102–109.

Blumberger DM, *et al*. (2018). Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet 391:1683–1692.

Brunoni AR, *et al*. (2017). Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis. JAMA Psychiatry 74:143–152.

Chistyakov AV, *et al*. (2010). Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. Int J Neuropsychopharmacol 13:387–393.

Cohen RB, *et al*. (2010). Clinical predictors associated with duration of repetitive transcranial magnetic stimulation treatment for remission in bipolar depression: a naturalistic study. J Nerv Ment Dis 198:679–681.

Di Lazzaro V, *et al*. (2011). Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation. J Neurophysiol 105:2150–2156.

Duecker F, AT Sack (2015). Rethinking the role of sham TMS. Front Psychol 6:210.

Duprat R, *et al*. (2016). Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: a fast road to remission? J Affect Disord 200:6–14.

Fitzgerald PB, *et al*. (2009). A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. Neuropsychopharmacology 34:1255–1262.

Fitzgerald PB, *et al*. (2012). A double blind randomized trial of unilateral left and bilateral prefrontal cortex transcranial magnetic stimulation in treatment resistant major depression. J Affect Disord 139:193–198.

Frank E, *et al*. (1991). Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 48:851–855.

Fregni F, *et al*. (2006). Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. Int J Neuropsychopharmacol 9:641–654.

Gamboa O, *et al*. (2010). Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp Brain Res 204:181–187.

George MS, *et al*. (1997). Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 154:1752–1756.

George MS, *et al*. (2010). Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 67:507–516.

George MS and G Aston-Jones (2010). Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Neuropsychopharmacology 35:301–316.

Hamilton M (1967). Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 6:278–296.

Herbsman T, *et al*. (2009). More lateral and anterior prefrontal coil location is associated with better repetitive transcranial magnetic stimulation antidepressant response. Biol Psychiatry 66:509–515.

Hernandez-Ribas R, *et al*. (2013). Identifying brain imaging correlates of clinical response to repetitive transcranial magnetic stimulation (rTMS) in major depression. Brain Stimul 6:54–61.

Herwig U, *et al*. (2007). Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. Br J Psychiatry 191:441–448.

Huang Y-Z, *et al*. (2005). Theta burst stimulation of the human motor cortex. Neuron 45:201–206.

Kessler RC and EJ Bromet (2013). The epidemiology of depression across cultures. Annu Rev Public Health 34:119–138.

Levkovitz Y, *et al*. (2015). Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry 14:64–73.

Lisanby SH, *et al*. (2001). Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. Biol Psychiatry 49:460–463.

Lisanby SH, *et al*. (2009). Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. Neuropsychopharmacology 34:522–534.

McClintock SM, *et al*. (2018). Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry 79:1.

Middleton H, *et al*. (2005). NICE guidelines for the management of depression. BMJ 330:267–268.

Milev RV, *et al*. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. Can J Psychiatry 61:561–575.

Organization WH (2017). Depression and other common ment al disorders: global health estimates. World Health Organization.

O'Reardon JP, *et al*. (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62:1208–1216.

Paillere Martinot ML, *et al*. (2010). Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: a [(18)F]-fluorodeoxyglucose PET and MRI study. Int J Neuropsychopharmacol 13:45–59.

Pascual-Leone A, *et al*. (1996). Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 348:233–237.

Pizzagalli DA (2011). Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology 36:183–206.

Rachid F, C Moeglin, O Sentissi (2017). Repetitive transcranial magnetic stimulation (5 and 10 Hz) with modified parameters in the treatment of resistant unipolar and bipolar depression in a private practice setting. J Psychiatr Pract 23:92–100.

Razza LB, *et al*. (2018). A systematic review and meta-analysis on placebo response to repetitive transcranial magnetic stimulation for depression trials. Prog Neuropsychopharmacol Biol Psychiatry 81:105–113.

Sackeim HA (2001). The definition and meaning of treatment-resistant depression. J Clin Psychiatry 16:10–17.

Sommer J, *et al*. (2006). Transcranial magnetic stimulation--a sandwich coil design for a better sham. Clin Neurophysiol 117:440–446.

Voigt J, L Carpenter, A Leuchter (2019). A systematic literature review of the clinical efficacy of repetitive transcranial magnetic stimulation (rTMS) in non-treatment resistant patients with major depressive disorder. BMC Psychiatry 19:13–13.