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ORIGINAL PAPER

Antidepressant effects of prolonged intermittent theta-burst stimulation monotherapy at the bilateral dorsomedial prefrontal cortex for medication and standard transcranial magnetic stimulation-resistant major depression: a three arm, randomized, double blind, sham-controlled pilot study

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Abstract

The dorsomedial prefrontal cortex (DMPFC) plays a pivotal role in depression and anxiosomatic symptom modulation. However, DMPFC stimulation using a double-cone coil has demonstrated inconsistent results for antidepressant efficacy. No study thus far has investigated the antidepressant and anti-anxiosomatic effects of prolonged intermittent theta-burst stimulation (piTBS) bilaterally over DMPFC. Furthermore, head-to-head comparisons of antidepressant effects between standard iTBS and piTBS warrant investigation. This double-blind, randomized, sham-controlled trial recruited 34 patients with highly treatment-resistant depression (TRD) unresponsive to antidepressants and standard repetitive transcranial magnetic stimulation (rTMS)/piTBS. These patients were randomly assigned to one of three monotherapy groups (standard iTBS, piTBS, or sham), with treatment administered bilaterally over the DMPFC twice per day for 3 weeks. The primary outcome was the overall changes of 17-item Hamilton Depression Rating Scale (HDRS-17) over 3-weeks intervention. The changes in Depression and Somatic Symptoms Scale (DSSS) as the secondary outcome and the anxiosomatic cluster symptoms as rated by HDRS-17 as the post-hoc outcome were measured. Multivariable generalized estimating equation analysis was performed. Although no differences in overall HDRS-17 changes between three groups were found, the antidepressant efficacy based on DSSS was higher in piTBS than in iTBS and sham at week 3 (group effect,$p=0.003$, post-hoc: piTBS > iTBS, $p=0.002$; piTBS > sham, $p=0.038$). In post-hoc analyses, piTBS had more alleviation in anxiosomatic symptoms than iTBS (group effect, $p=0.002$; post-hoc, $p=0.001$). This first randomized sham-controlled study directly compared piTBS and iTBS targeting the DMPFC using a figure-of-8 coil and found piTBS may fail to demonstrate a significant antidepressant effect on overall depressive symptoms, but piTBS seems superior in alleviating anxiosomatic symptoms, even in depressed patients with high treatment resistance. This *Trial registration* (Registration number: NCT04037592). URL: https://clinicaltrials.gov/ct2/show/NCT04037592.

Keywords Dorsomedial prefrontal cortex · Prolonged intermittent theta-burst stimulation · Repetitive transcranial magnetic stimulation · Treatment refractory depression · Anxiosomatic cluster symptoms

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Background

Repetitive transcranial magnetic stimulation (rTMS) is a Food and Drug Administration–cleared treatment option for treatment-resistant depression (TRD). The standard protocol involves high-frequency (e.g., 10-Hz) rTMS targeting of the left dorsolateral prefrontal cortex (DLPFC) and has been found to have a response rate of 40–60% and a remission rate of approximately 30% [1–3]. Theta-burst stimulation (TBS), a pattern-specific form of rTMS, has been found to achieve a more rapid and intensive plasticity effect on the synapses than conventional rTMS [4, 5]. Both the standard protocol (i.e., intermittent TBS [iTBS]; 600 pulses for 6 weeks) and the prolonged iTBS protocol (i.e., piTBS; 1800 pulses for 2 weeks) over the left DLPFC have demonstrated similar antidepressant effects compared with the standard 10 Hz rTMS protocol [2, 3, 6].

Although the DLPFC is reported to play an important role in treatment refractoriness [1, 7, 8], the pathophysiology of TRD remains largely unknown. Compared to the DLPFC, the dorsomedial prefrontal cortex (DMPFC) is considered another, and perhaps more important, core brain region in major depressive disorder (MDD). For instance, extensive gray matter reduction has been observed in the DMPFC of patients with multiple depressive episodes [9, 10], and more severe depression has been noted in patients with brain lesions in the DMPFC [9, 11, 12]. Moreover, misplacing the deep brain stimulation electrode to inhibit the DMPFC region has been found to elicit immediate dysphoric responses [9, 13]. Ketamine administration rapidly increased synapse formation in the medial prefrontal cortex (PFC), which were associated with the rapid antidepressant effects of ketamine [14]. However, the effects were blocked if the medial PFC was infused with rapamycin, a selective mTOR inhibitor [14]. Many large resting-state functional MRI (rsfMRI) studies have also shown that patients with MDD have a dysregulated DMPFC, a critical hub anteriorly located in the default mode network(DMN), especially those with recurrent depressive episodes [15–17]. Recently, the DMPFC, proposed to be an antidepressant target, is likely to be correlated with anxiosomatic symptoms in depression [9, 18]. By analyzing the correlation between rsfMRI and each item in different depression symptom scales, Siddiqi et al. divided depression symptom maps into two distinct clusters and found that the DMPFC is the distinct circuit-based target for treating anxiosomatic symptoms [18].

Several case reports and open-label studies have demonstrated the preliminary antidepressant effectiveness of bilateral DMPFC stimulation in TRD patients, but the few related sham-controlled trials have failed to demonstrate the antidepressant effects of DMPFC stimulation in TRD patients [19–24]. More sham-controlled studies were warranted to confirm the clinical efficacy of DMPFC stimulation. MDD is a heterogeneous disorder, and the refractoriness might be caused by different pathophysiology. In literature, MDD could be further defined as two or four connectivity-based bio-subtypes, such as mainly DLPFC-related or DMPFC-related dysregulation [18, 25], which might respond distinctly to the different neuromodulation treatments. Moreover, previous positron emission tomography (PET) findings have indicated that TRD patients resistant to standard DLPFC- rTMS treatment demonstrate low glucose metabolism in the DMPFC region [1]. Whether TRD patients resistant to antidepressants and standard DLPFC-rTMS/piTBS respond to bilateral DMPFC stimulation warrants further investigation. Last, to our knowledge, whether piTBS (i.e., 1800 pulses) outperforms standard iTBS (i.e., 600 pulses) has yet to be evaluated in a sham-controlled study.

In this double-blind, randomized, sham-controlled trial, we compared the antidepressant and anti-anxiosomatic efficacy among standard iTBS, piTBS, and sham protocols applied bilaterally to the DMPFC in TRD patients resistant to antidepressants and standard DLPFC stimulation. We hypothesized that piTBS two times per day for 3 weeks would provide higher clinical efficacy than iTBS and sham treatment.

Methods and Materials

Subjects

Adults aged 21 to 70 years and diagnosed with recurrent MDD based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria were eligible in the current double-blind, sham-controlled trial. Depressed patients with the failed response to adequate dose and duration of antidepressant treatments as well as one complete left-sided DLPFC rTMS/piTBS treatment course [1, 3, 6] in the current episodes and with at least moderate severity defined by the Clinical Global Impression – Severity score (CGI-S) and ≥ 18 of the 17-item Hamilton Depression Rating Scale (HDRS-17). The psychiatric comorbidity diagnoses would be established after thorough medical history taking and a semistructured interview by administering the Mini-International Neuropsychiatric Interview (MINI) [26]. We excluded schizophrenia, bipolar, organic brain and neurological disorders. During the study period and one week before receiving brain stimulation treatment, the recruited patients were required to be antidepressant-free for at least one week. There was no patient receiving fluoxetine before entering the trial. The study was performed under the Declaration of Helsinki and was approved by the local Ethics

Review Committee. All participants had provided written informed consent. The study was preregistered in the ClinicalTrials.gov (Registration number: NCT04037592). Sample size calculation was performed using the G*Power (version 3.1.9.2) [27]. The estimated parameters used to reject the null hypothesis included the population means of the experimental and sham groups being equal with a probability (power) of 0.8, and the type I error probability associated with this test's null hypothesis was 0.1. The expected effect size of 0.82 was based on the literature [6, 22]. The number of twenty participants required in each group was predetermined before the study.

Study overview and brain stimulation parameters

The study included two phases. First, a one-week screening period was performed to ensure the patients met the recruitment criteria and were medically stable. Second, those patients were randomized 1:1:1 to each intervention group (Group A standard iTBS; Group B, piTBS; Group C, sham iTBS). An independent research assistant conducted a computerized random number generator with block randomization methods (block size of 9).

Treatment sessions were given twice every weekday over three weeks. Each session would start at stimulating left DMPFC and then right DMPFC. The intersession interval was 15 min [19, 28, 29]. The parameters of standard iTBS (group A, 600 pulses) and piTBS (group B, 1800 pulses) followed the published protocols [6]. In short, the iTBS parameters were three-pulse 50 Hz bursts administered at 5 Hz with 80% active motor threshold. In the sham group (group C) patients were randomly assigned to receive the same parameter as standard iTBS or piTBS groups but all delivered by a sham coil, which improved the blinding process by mimicking the somatosensory and auditory effects of active protocols without actual stimulation of the brain [3]. All treatment coils were 70-mm figure-of-8 coils (Magstim® Double 70-mm Stimulating Coil 9925–00 and Magstim® Placebo Coil). Neuro-navigation computer software with an infrared system (Brainsight, Rogue Research, Inc., Montreal, QC) was used to guide the coil to target the bilateral DMPFC, following the location coordinate (X 0, $Y+30$, $Z+30$) from the literature [22, 30].

Study goals and efficacy assessments

Symptomatic ratings of participating patients were collected using HDRS-17 [31], Depression and Somatic Symptoms Scale (DSSS) [32], Young Mania Rating Scale (YMRS) [33] and CGI severity[34], which were applied at baseline (W0; before the first brain stimulation) and at the end of treatment weeks 1 (W1), 2 (W2), and 3 (W3). The primary outcome was the changes of the HDRS-17 score after 3 week intervention.

On the basis of previous studies, in the further post-hoc analysis, we divided HDRS-17 symptoms into two distinct clusters of symptoms—namely anxiosomatic and dysphoric—to analyze the anti-anxiosomatic effect of DMPFC stimulation [18]. The anxiosomatic cluster symptoms comprised nine items derived from HDRS-17: early insomnia, middle insomnia, slowness or retardation, psychic anxiety, autonomic anxiety, gastrointestinal symptoms, somatic symptoms, genital symptoms, and hypochondriasis. The remaining eight HDRS items were clustered as dysphoric symptoms. Percent improvement of anxiosomatic symptom at each time-point relative to the baseline value was analyzed. Previous research team found that symptom change, but not baseline symptom severity, resulted in a two-cluster solution [18].

For patient-reported outcomes, the depression subscales of the DSSS were assessed to determine subjective antidepressant efficacy as the secondary outcome. Safety was evaluated at each treatment session by recording adverse events and inquiring about preidentified symptoms such as headache, dizziness, seizure, or manic shifting.

The DSSS is a simple and self-administered scale with 22 items, and it has been demonstrated to have good reliability and validity for depression, with high correlation with HDRS outcomes [32] (detail in Supplementary material). Compared to the conventional scales, the DSSS evaluates somatic symptoms more accurately [32, 35]. DSSS items were grouped into two domains: a depression subscale (DS) and somatic subscale (SS). The DS score was analyzed as the dependent variable, and the SS score was evaluated as the covariate.

Other clinical measurement and covariates evaluation at baseline

The treatment resistance may influence the antidepressant response, not only on sham treatment but active rTMS/TBS treatment [6]. The impact of the following refractory factors on the efficacy of DMPFC stimulation was analyzed. Maudsley Staging Method (MSM) was used to measure the degree of refractoriness [6, 36]. In addition, the history of previous three antidepressant treatment failures compared with ≤ 2 antidepressant failures was confirmed as a significantly poor predictor for standard rTMS/iTBS intervention [37, 38].The number of comorbid anxiety disorders, i.e., generalized anxiety disorder, panic disorder and agoraphobia, diagnosed by MINI evaluation, was summed for each participant. Comorbid anxiety can reduce treatment efficacy in TRD patients across different modalities, including TMS [37–40]. Last, suicidality was measured by the suicidal scale of the MINI [37], and categorized by low (suicidal score ≤ 5), moderate

(score 6–9), and high (score ≥ 10) in the further post-hoc analysis.

Statistical methods

One-way ANOVA and Fisher's chi-square test compared the continuous and categorical (sex, education, lifetime antidepressant failure, and MINI_Suicidality) baseline characteristic variables among groups for a relatively small sample. For primary and secondary outcomes measures, generalized estimating equations (GEE) methods were done for longitudinal, repeated and within-subject correlated data [41]. An autoregressive model of order 1 (AR-1) was set regarding the working correlation matrix. The dependent variables were the total score of HDRS-17, the percentage improvement of anxiosomatic cluster symptoms and the depression subscale of DSSS, while the independent factors were time (baseline, week 1, week 2 and week 3). The percentage improvement of dysphoric cluster symptoms and somatic subscales of DSSS, and CGI severity were considered as within-subject factors. Moreover, dysphoric cluster symptoms, somatic subscales of DSSS and CGI severity were treated as time-varying covariates correlated with one of our main outcomes: improvement of anxiosomatic symptoms or depression subscales of DSSS. Group was set as a between-subject factor. The least significant difference (LSD) correction was used for post-hoc analyses when the main effect of the group was significant. All statistical analysis of demographic and clinical data was performed using IBM SPSS Statistics 21 (IBM Corp., Armonk, NY). A value < 0.05 was considered statistically significant.

Results

In total, 45 patients with severe TRD who had failed responses to antidepressants (the median of antidepressant failures of 4.5 trials) and one completed left-sided DLPFC-rTMS or DLPFC-piTBS treatment course for current episodes were recruited (Figure S1). Of these, only 34 patients agreed to enter the study; they were randomized to three treatment groups: standard iTBS ($n = 11$), piTBS ($n = 12$), and sham ($n = 11$). All the patients completed treatments between August 2019 and December 2020 and could tolerate the active or sham treatments. Six patients experienced temporary headaches, for which analgesic intervention was not required (standard iTBS, $n = 2$; piTBS, $n = 3$; sham, $n = 1$; $p = 0.606$). Five patients reported temporary dizziness (standard iTBS, $n = 1$; piTBS, $n = 3$; sham, $n = 1$; $p = 0.457$). No events of seizure or manic shifting were reported. Total YMRS scores of each group at baseline and W3 were 0.0 ± 0.0 and 0.4 ± 0.8 in the standard iTBS, 0.1 ± 0.3 and 0.3 ± 0.8 in the piTBS, as well as 0.0 ± 0.0 and 0.0 ± 0.0 in the sham group.

The baseline demographic variables did not differ between the three groups; these included depression

Table 1 Demographic and clinical characteristics at baseline

	Total	600iTBS	1800iTBS	Sham	*p* value
Age	46 ± 16	46 ± 15	46 ± 18	47 ± 16	$p = 0.995$
Sex (female, %)*	20 (58.8%)	6 (54.5%)	7 (58.3%)	7 (63.6%)	$p > 0.999$
Education (≤ 12 / > 12 Years)*	12/22	4/7	4/8	4/7	$p > 0.999$
MSM severity	10 ± 2	10 ± 2	10 ± 2	10 ± 1	$p = 0.916$
Duration of illness, years	11 ± 10	11 ± 12	14 ± 9	10 ± 8	$p = 0.622$
Lifetime Antidepressant failure ≥ 3*	30 (88.2%)	8 (72.7%)	12 (100.0%)	10 (90.9%)	$p = 0.121$
MINI suicidality* (low/moderate/high)	22/3/9	8/1/2	7/1/4	7/1/3	$p = 0.971$
80% aMT, left, %	62 ± 10	61 ± 10	62 ± 9	62 ± 12	$p = 0.963$
80% aMT, right, %	63 ± 11	64 ± 10	62 ± 11	62 ± 12	$p = 0.898$
HDRS-17 (BL)	24 ± 5	24 ± 5	25 ± 6	24 ± 4	$p = 0.625$
Anxiosomatic subscale (BL)	13 ± 3	12 ± 4	14 ± 3	12 ± 3	$p = 0.142$
Dysphoric subscale (BL)	12 ± 3	12 ± 2	12 ± 4	12 ± 3	$p = 0.832$
DSSS_DS (BL)	22 ± 7	22 ± 4	21 ± 9	23 ± 7	$p = 0.853$
DSSS_SS (BL)	12 ± 7	9 ± 6	14 ± 8	14 ± 7	$p = 0.112$
CGI-S	5 ± 1	5.00 ± 1	5.00 ± 1	5 ± 1	$p = 0.951$
Comorbidity (GAD/panic disorder/agoraphobia)	20/4/2	7/1/0	6/1/0	7/2/2	

iTBS intermittent theta burst stimulation, *MSM* maudsley staging method for refractoriness, *MINI* mini international neuropsychiatric interview, *aMT* active motor threshold, expressed as a percentage of maximum stimulator output, *HDRS-17 (BL)* 17-item Hamilton depression rating scales (Baseline), *DSSS* depression and somatic symptoms scale, *DS* depression subscale, *SS* somatic subscale, *CGI-S* clinical global impression–severity, *GAD* generalized anxiety disorder

*Fisher's chi-square test

refractoriness, number of lifetime antidepressant treatment failures(≥ 3), and several depression scale scores (Table 1). Our patients had a mean age of 46.2 years and a female preponderance and all had moderate-to-severe treatment refractoriness (100%, 34/34, MSM score ≥ 7). Most of the patients also had considerable clinical illness severity, three or more antidepressant treatment failures (88.2%, 30/34), and a high prevalence of comorbid anxiety disorder (64.7%, 22/34).

Clinician-rated depression change during the 3-week treatment period as the primary outcome

A GEE analysis was performed to evaluate antidepressant efficacy between Group (G) and Time (T) on the HDRS-17 total score during the 3-week treatment period after adjustments for MSM refractoriness, CGI severity, MINI suicidality, antidepressant failure ≥ 3 and the number of anxiety disorder. The result revealed a significant main effect of T and a significant interaction between G and T (G × T, $p = 0.020$; T, $p < 0.001$; G, $p = 0.375$). However, post-hoc comparison with LSD correction indicated no differences in the estimated HDRS score at W3 between the three groups (Fig. 1).

Improvement in anxiosomatic-related HDRS symptoms during the 3-week treatment period as the post-hoc outcomes

On the basis of the findings of Siddiqi et al. [18], we further analyzed the improvement in anxiosomatic and dysphoric cluster symptoms after bilateral DMPFC stimulation. Our GEE analysis results demonstrated no interaction between G and T (G × T, $p = 0.965$) but a significant G effect ($p = 0.002$) and a trend T effect ($p = 0.073$) on percent improvement in anxiosomatic symptoms after adjustments for MSM refractoriness, CGI severity, MINI suicidality, antidepressant failure ≥ 3, and percentage improvement of dysphoric symptoms. The results of the post-hoc comparison with LSD correction demonstrated piTBS led to a larger anti-anxiosomatic effect than iTBS did ($p = 0.001$), but this effect was not statistically larger than that of the sham treatment ($p = 0.108$; Fig. 2).

Self-reported depression change during the 3-week treatment period as the secondary outcomes

Another GEE analysis was applied for the antidepressant efficacy between G and T on the DS scores of DSSS during the 3 week treatment after adjustments for SS score, MSM refractoriness, CGI severity, MINI suicidality, antidepressant failure ≥ 3 and the number of anxiety disorder. The results revealed a significant main effect of G and T (G, $p = 0.003$; T, $p = 0.034$) but not of interaction between G and T (G × T, $p = 0.395$). Post hoc comparison after LSD correction indicated that the estimated DS score after piTBS was significantly lower than that after

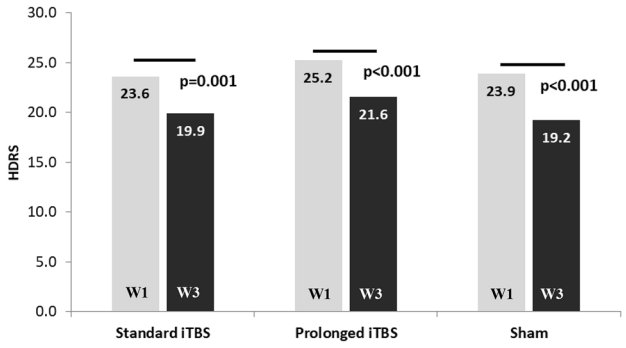

Fig. 1 HDRS-17 scores before and after 3 week DMPFC stimulation among the three patient groups no significant difference was found in estimated HDRS score at week 3 among the three groups[a]. Each group demonstrated improvement after receiving DMPFC stimulation. Analyzed by GEE with adjustment of MSM refractoriness, suicidal risk level, CGI, the number of anxiety disorder, and lifetime antidepressant failure. *HDRS* Hamilton depression rating Scale, *DMPFC* dorsomedial prefrontal cortex, *GEE* generalized estimating equation, *MSM* Maudsley staging method, *CGI* clinical global impression

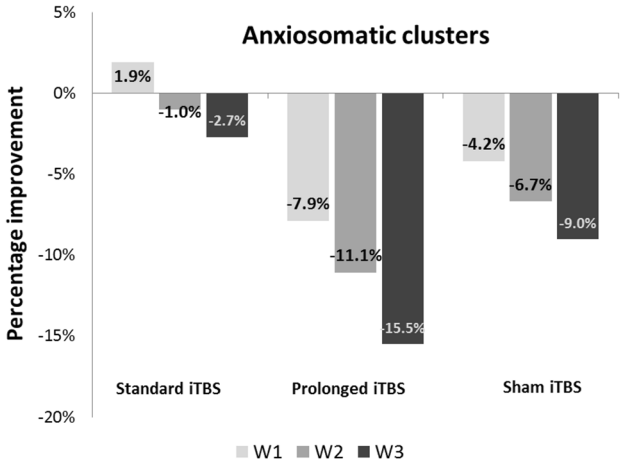

Fig. 2 Percent improvement in anxiosomatic cluster symptoms after 3 week DMPFC stimulation among the three patient groups The percent improvement in anxiosomatic symptoms relative to baseline values demonstrated a significant group effect ($p = 0.002$). Overall, prolonged iTBS led to much more anxiosomatic symptom improvement than did standard iTBS ($p = 0.001$), and demonstrated a non-significant reduction of the anxiosomatic symptoms compared with sham intervention($p = 0.108$) [a]. Standard iTBS presented a more minor improvement of anxiosomatic symptoms than sham treatment ($p = 0.015$) [a]. [a]: Analyzed by GEE with adjustment of MSM refractoriness, suicidal risk level, CGI, lifetime antidepressant failure, and the changes of dysphoric cluster symptoms. *DMPFC* dorsomedial prefrontal cortex, *GEE* generalized estimating equation, *MSM* Maudsley Staging Method, *CGI* Clinical Global Impression

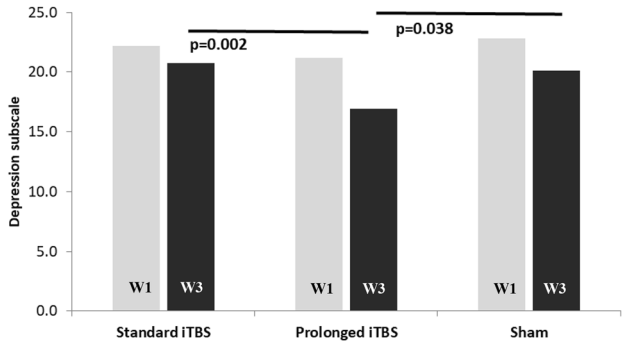

Fig. 3 Baseline depression subscale of DSSS and estimated depression subscale after 3 week DMPFC stimulation among the three patient groups Prolonged iTBS demonstrated improved antidepressant efficacy compared with the standard iTBS and sham interventions[a]. [a] Analyzed by GEE with adjustment of MSM refractoriness, suicidal risk level, CGI, the number of anxiety disorder, lifetime antidepressant failure, and the changes of somatic subscale of DSSS. *DSSS* depression and somatic symptoms scale, *DMPFC* dorsomedial prefrontal cortex, *GEE* generalized estimating equation, *MSM* Maudsley Staging Method, *CGI* Clinical Global Impression

standard iTBS ($p = 0.002$) or sham treatment ($p = 0.038$) after 3 weeks (Fig. 3). In addition, covariates such as the number of anxiety disorders ($p = 0.035$), antidepressant failure ≥ 3 ($p = 0.022$), MINI suicidality ($p = 0.002$), CGI severity ($p < 0.001$), and SS score ($p < 0.001$), but not MSM treatment refractoriness ($p = 0.172$), had effects on the estimated DS score.

Effects of the covariate on antidepressant efficacy in the piTBS group as the post-hoc outcomes

To further evaluate the influence of these covariates in the antidepressant effect of piTBS, another GEE analysis was conducted in the piTBS group. All participants in the piTBS group experienced at least three antidepressant treatment failures; therefore, we could not evaluate the impact of antidepressant treatment experience for this group. The number of anxiety disorders ($p = 0.001$),MSM refractoriness($p < 0.001$),CGI severity ($p < 0.001$),and MINI suicidality($p < 0.001$) showed significant effects on antidepressant efficacy. Mild baseline suicidality was associated with higher antidepressant efficacy than were moderate and severe baseline suicidality(both $p < 0.001$;estimated DS scores after piTBS: mild = 16.69 ± 10.74; moderate = 26.12 ± 9.78; severe = 26.59 ± 9.52). TRD comorbid with one anxiety disorder benefited more from piTBS intervention than TRD without a comorbid anxiety disorder (estimated DS scores after piTBS: 21.98 ± 10.05 vs. 24.28 ± 9.97, respectively, $p = 0.001$).

Discussion

This is the first randomized, double-blind, and sham-controlled study to bilaterally modulate the DMPFC using the piTBS protocol (1800pulses/session) with a figure-of-8 coil in high-resistant depressed patients who have failed to respond to antidepressants and one complete standard DLPFC- rTMS or piTBS treatment. The behavioral effects related to standard iTBS and piTBS were also compared directly. Although the study failed to demonstrate a difference in the primary outcome regarding overall clinician-rated antidepressant effect, the self-reported antidepressant effect in the piTBS group was superior to the standard iTBS and sham group. Compatible with our hypothesis and the findings of Siddiqi et al., patients who received two daily piTBS sessions demonstrated much more alleviation of their anxiosomatic and depressive symptoms than did those receiving standard iTBS over 3 weeks. However, in these highly refractory patients, moderate-to-high suicidality was a poor predictor for DMPFC-piTBS intervention. In general, DMPFC-piTBS with a relatively low stimulus strength and relatively focal stimulation was well tolerated and safe in the TRD patients.

Our findings are in line with the rsfMRI results of Siddiqi et al. and those of recent trials on patients with psychiatric disorders other than TRD: the anti-anxiosomatic effect of DMPFC stimulation is much better than its anti-dysphoric effect [18, 42, 43]. In their pilot trial for anorexia nervosa, Woodside et al. found that DMPFC-rTMS led to significant improvements on the eating disorders examination global scales and comorbid anxiety severity on the Beck Anxiety Inventory, but no such improvement was noted for depression measured using the HDRS-17 [42]. In the earlier trial for refractory binge–purge behaviors, the same research team observed similar results: the responders exhibited considerable anxiety-related improvements, but to a lesser extent improvement to depression symptoms [43].

Other studies found that compared with the sham intervention, DMPFC-piTBS did not lead to a considerable HDRS improvement [19–21]. Dunlop and colleagues found that compared with sham stimulation, two daily sessions of 20 Hz or 1 Hz stimulation on bilateral DMPFC over 3 weeks did not improve depressive symptoms, as defined by the HDRS-17 [20]. Moreover, Bodén et al. found that twice-daily standard iTBS bilaterally targeting the DMPFC over 10 days did not lead to more reduction in the self-reported Montgomery Åsberg Depression Rating Scale (MADRS) score than sham treatment [19]. Different scales might reveal varied treatment outcomes to some extent. For instance, an early 10-Hz-rTMS randomized controlled trial using 5-cm defined DLPFC as

the stimulation location method, which was recently found to be a relatively anxiosomatic neuromodulation target, found that the modality provided a greater reduction in HDRS score than in MADRS scores. This difference may be indicative of a non-significant superiority of rTMS compared with a sham intervention if the MADRS is used [18, 44]. Hence, a suitable measurement for depression and somatic symptoms in TRD patients is needed to appropriately evaluate the clinical efficacy of bilateral DMPFC stimulation, the anxiosomatic circuit-based treatment, to prevent false-negative results [18]. The MADRS is a unidimensional scale focused on dysphoric symptoms, and the HDRS is a relatively multidimensional scale combining the evaluation of anxiety and somatic symptoms [45]. Compared to MADRS and HDRS, the DSSS emphasizes depression and somatic symptoms simultaneously and reasonably resolves the limitation of the poor evaluation of somatic symptoms [35]. In the current study, using the DSSS scales, we found that piTBS exhibited higher antidepressant efficacy than either the standard iTBS or sham intervention did. In particular, we noted that piTBS might benefit TRD patients with a comorbid anxiety disorder more than those without an anxiety disorder. We also found that piTBS delivered a superior anti-anxiosomatic effect to standard iTBS. Our findings supported the role of bilateral DMPFC stimulation in symptom-specific treatment targets in the literature [18]. Additional randomized controlled trials on bilateral DMPFC stimulation to validate our findings are warranted.

In contrast to other DMPFC stimulation studies, we used figure-of-8 coil instead of double-cone coil, which was believed to stimulate the anterior cingulated cortex or deeper regions of the DMPFC [19–24]. As mentioned before, the composite targeting atlas derived through rsfMRI and depressive symptoms indicated that a focal superficial figure-of-8 coil targeting DMPFC might have effect in treating depression [18]. Our previous PET findings also supported this conjecture: TRD patients exhibited significantly more decreased glucose metabolism in the bilateral superficial DMPFC than non-TRD and healthy participants [8]. Patients who didn't respond to DLPFC-rTMS demonstrated lower baseline metabolic activity at the bilateral superficial DMPFC than the responders [1]. Compared to the figure-of-8 coil, the double-cone coil exhibits a considerably deep electrical field penetration, which may simultaneously modulate the DMN (i.e., the MPFC) and salience network (i.e., dorsal anterior cingulate). Our results provide evidence that only stimulating a superficial area of the DMPFC leads to antidepressant and anti-anxiosomatic effects, without the expense of higher and broader induced electrical fields in the superficial cortical regions and the risk of optical nerve excitation [46]. Whether DMPFC stimulation using a double-cone coil can demonstrate higher clinical efficacy than stimulation using a figure-of-8 coil needs further investigation.

We found that the higher the total number of pulses was, the higher was the clinical efficacy (600 pulses v.s. 1800 pulses) even in patients with severe TRD. However, the patients' depression refractoriness might limit the degree of improvement. Compared to previous studies, the patients in current study had a higher treatment refractoriness [2, 19–24]. Our piTBS patients all had a history of ≥ 3 antidepressant treatment failures that were confirmed to have considerably decreased antidepressant efficacy in the Three-D trial. [37, 38, 47]. These patients were requested not to take antidepressants during the DMPFC trial. However, this potential synergistic interaction between TMS and pharmacological interventions remains elusive because of the heterogeneity of concomitant TMS studies [48, 49]. Notably, the DLPFC-piTBS monotherapy in our previous study exhibited similar antidepressant efficacy with add-on DLPFC-standard iTBS in the Three-D trial [2, 3]. Moreover, our recruited participants had experienced $<25\%$ HDRS-17 improvements in their previous DLPFC-rTMS or DLPFC-piTBS treatment. Following the lesson of limited improvements in switching between medications from the STAR*D trial, except for further optimization of DMPFC-TMS parameters, these highly refractory patients might need to find another brain target for TMS stimulation or receive other intensive therapies beyond TMS.

The dropout rate was low in our study, echoing that rTMS treatment is a treatment with relatively high tolerability and acceptability. In the literature, the dropout rates of active or sham rTMS were around 7.5% [50]. Detailed informed study process, re-checking the patients' availability before trial, encouragement during the trial, the property of self-pay rTMS treatment without insurance coverage in Taiwan, and the high motivation if participants decide to receive the treatment during the COVID-pandemic might further lower the dropout rate.

Surprisingly, the standard iTBS demonstrated lower anxiosomatic symptoms reduction than the sham treatment, which might imply the DMPFC-standard iTBS protocol used in the current study might some extent exacerbate the anxiosomatic symptoms or inhibit the anti-anxiosomatic placebo effect. Using a similar protocol of twice-a-day subthreshold standard iTBS targeting at DMPFC, Struckmann et al. found active standard iTBS decreased the functional connectivity between left DLPFC and right insula compared with the sham intervention [19, 51]. However, another study found the strength of functional and structural connectivity between left DLPFC and insula was positively correlated with the antidepressant efficacy of rTMS [52]. The results of the two studies mentioned above echo our finding of less anti-anxiosomatic efficacy of standard iTBS than sham intervention. Additionally, previous studies found that

placebo response might be associated with DMN activity [53–55]. Whether standard iTBS and piTBS have distinct contributions to the neurocircuitry within DMN needs further investigation.

The current pilot study has some limitations. First, no consensus on the symptom components of anxiosomatic cluster symptoms exists; nonetheless, here, we combined all HDRS-17 items mentioned in anxiosomatic clustering–response maps across HDRS-24 and HDRS-28 datasets as anxiosomatic cluster symptoms [18]. Second, the current sample size was relatively small, which may have affected the results and reduced the between-group difference. Patient recruitment was mainly limited by the COVID-19 pandemic. Recruiting TRD patients without pharmacological intervention and maintaining the scheduled treatment frequency were difficult. Further research with a larger sample size to confirm the present results is warranted. Third, regarding the blinding process, none of the participants reported they surely knew which study group they were assigned to, although quantitative analysis did not perform. Finally, the twice-daily session design and intersession interval of 15 min to promote plasticity were validated based on the literature [19, 20, 23, 28, 29]. However, whether longer intersession intervals or more intensive protocols (e.g., 10 sessions per day) would yield improved clinical effects remains unknown [56, 57]. Additional systematic studies optimizing the intersession interval and number of sessions per day are needed.

Conclusion

This randomized sham-controlled study, for the first time, directly compared the clinical efficacy of piTBS and standard iTBS targeting the DMPFC using a figure-of-8 coil. PiTBS may fail to demonstrate a clinician-rated antidepressant effect, but piTBS seems superior in alleviating anxiosomatic symptoms and self-reported depressive symptoms than standard iTBS and sham, even in depressed patients with high treatment resistance. TRD patients with severe anxiosomatic symptoms or even comorbid eating disorders may benefit from this circuit-based neuromodulation. However, TRD patients with moderate-to-severe suicidality may require a more powerful treatment modality.

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Data availability statement The data are not publicly available due to restrictions of local IRB regulations.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest. All authors have no financial relationships relevant to this article to disclose.

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