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Antidepressant Efficacy of Prolonged Intermittent Theta Burst Stimulation Monotherapy for Recurrent Depression and Comparison of Methods for Coil Positioning: A Randomized, Double-Blind, Sham-Controlled Study

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ABSTRACT

BACKGROUND: Prolonged intermittent theta burst stimulation (piTBS) with triple doses of the standard protocol is an updated form of repetitive transcranial magnetic stimulation, and it is an effective add-on intervention for major depressive disorder. In the present study, our objective was to investigate the antidepressant efficacy of piTBS monotherapy. Efficacy between the standard 5-cm method and magnetic resonance imaging (MRI)–guided coil positioning to the left dorsolateral prefrontal cortex method was also compared.

METHODS: In the present double-blind, randomized, sham-controlled trial, 105 patients with recurrent depression who exhibited no responses to at least one adequate antidepressant treatment for the prevailing episode were assigned randomly to one of three groups: piTBS monotherapy (n = 35), repetitive transcranial magnetic stimulation monotherapy (n = 35), or sham stimulation (n = 35). The acute treatment period was 2 weeks. Half of the patients were randomized to MRI navigation in each group.

RESULTS: No serious adverse events were observed. The piTBS group exhibited significantly greater decreases in depression scores than the sham group at week 2 (−40.0% vs. −13.9%; $p < .001$ after correcting for multiple comparisons by Bonferroni [effect size (Cohen's d) = 1.12]), and the odds ratio for responses was high. The MRI navigation method (−32.4%) did not yield better antidepressant effects than the standard method (−40.6%). Brain stimulation and 17-item Hamilton Depression Rating Scale changes in the first week were the most important variables for predicting antidepressant responses.

CONCLUSIONS: Left prefrontal piTBS monotherapy is effective for the treatment of recurrent depression, and the MRI-guided method of coil targeting is not better than the standard method.

Keywords: Coil positioning, Magnetic resonance imaging, Major depressive disorder, Prefrontal cortex, Theta burst stimulation, Transcranial magnetic stimulation

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Repetitive transcranial magnetic stimulation (rTMS) is a U.S. Food and Drug Administration–approved treatment option for medication-resistant depression, and the antidepressant efficacy of high-frequency (e.g., 10-Hz) rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) has been demonstrated by numerous large international studies (1–3). However, not all patients respond to rTMS interventions (1,2,4), and the antidepressant effects of rTMS are less marked in patients with higher levels of treatment resistance (1,5).

Theta burst stimulation (TBS) exerts powerful and rapid effects on synaptic plasticity (6). Experiments on the motor cortex have revealed that intermittent TBS (iTBS) increases cortical excitability, whereas continuous TBS (cTBS) decreases it (7), and the effects of TBS are greater than those of traditional rTMS. In a recent meta-analysis, Berlim *et al.* (8) revealed that active TBS is significantly more effective than sham TBS in the treatment of depression. Subgroup analysis further revealed that iTBS, as opposed to cTBS, is one of the most promising and effective protocols for the treatment of depression (8). In addition, Blumberger *et al.* (9) recently reported that add-on iTBS for 3 minutes was not inferior to 10-Hz rTMS for the treatment of depression. Similarly, in our previous randomized, double-blind, sham-controlled study, we investigated the antidepressant efficacy of 2-week add-on prefrontal TBS therapy for refractory depression and observed that strategies involving prolonged iTBS (piTBS) (i.e., three times

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longer than standard iTBS; 1800 pulses vs. 600 pulses) were significantly more effective than sham treatment in the treatment of depression (10). We selected 1800 pulses because the aftereffects of TBS critically depend on the total stimulation pulses (6), and 1200 pulses of iTBS (iTBS-1200) exhibited suboptimal antidepressant efficacy (cTBS-3600 > cTBS-1800 > cTBS-1200 > iTBS-1200) (11). A recent study applying 10 sessions of piTBS in combination with medications per day (i.e., each session lasted for 10 minutes followed by a 50-minute intersession interval) observed that such spaced TBS for 5 days was an effective treatment strategy for highly refractory patients with depression who had failed to respond to electroconvulsive therapy (12). The evidence available so far supports that such add-on piTBS is a well-tolerated and effective antidepressant treatment option (13).

Studies have demonstrated the efficacy of high-frequency rTMS (10-Hz) monotherapy in patients with depression (14,15). However, there is still a lack of large sham-controlled trials to investigate whether piTBS monotherapy is also effective for the treatment of depression. In addition, although it may take 4 weeks for rTMS to achieve optimal efficacy, a large double-blind, sham-controlled, multicenter study revealed that numerous rTMS responders display initial improvement during the first 2 weeks (15). In patients who do not respond to one form of brain stimulation in clinical settings, early changes in treatment parameters are warranted. Therefore, the primary objective of the present study was to evaluate the antidepressant efficacy of 2-week piTBS monotherapy compared with sham treatment for the treatment of patients with major depressive disorder with a history of poor responses to at least 1 adequate trial of antidepressants for the current episode. The aim was to recruit patients with lower refractoriness levels compared with treatment-resistant depression, which is often defined as a failure to respond to at least 2 classes of adequate antidepressant trials (16). We hypothesized that the piTBS monotherapy has more antidepressant efficacy than sham treatment.

In addition, it remains unclear whether neuronavigation using individual magnetic resonance imaging (MRI) to localize the DLPFC is better than the standard procedure of coil positioning (i.e., 5 cm anterior to the primary motor cortical representation of the hand). Consequently, the second objective was to investigate antidepressant efficacy between the standard procedure of coil positioning and MRI-guided coil targeting. We hypothesized that the MRI-guided coil positioning has better antidepressant effects than the standard method.

METHODS AND MATERIALS

Patients

Eligible patients were adult patients 21 to 70 years of age diagnosed with recurrent major depressive disorder based on the DSM-IV criteria (17). Patients qualified to participate in the study if they failed to respond to at least 1 adequate antidepressant treatment for their current episode (e.g., failed to achieve 50% improvement in depression to an equivalent daily dose of 10–20 mg of escitalopram for at least 8 weeks). The recruited patients had to be antidepressant free for at least 1 week prior to the present trial. In addition, all recruited participants were required to have a Clinical Global Impression-Severity scale score of at least 4 and a total score of at least 18 on the 17-item Hamilton Depression Rating Scale (HDRS-17) (18). Patients with psychotic disorders, bipolar disorders, organic mental disorders, and a prevailing strong suicidal risk were excluded. Refer to the Supplement for additional details.

This 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, and the study was preregistered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000020892), which is one of the largest clinical trial registries in Asia and is a member of the World Health Organization registry network.

Study Overview and Sample Size Determination

This study comprised 3 phases. First, patients underwent 1-week screening to ensure that they were medically stable and satisfied the recruitment criteria. Second, patients were randomized 1:1:1 to each treatment group (group A: piTBS; group B: 10-Hz rTMS; group C: sham). The rTMS group was included as an active comparison group to enhance assay sensitivity, with the aim of validating the study methodology and patient population, and compare neuroimaging differences between piTBS and rTMS in a sham-controlled trial (the results will be reported elsewhere). During the acute treatment phase, patients were required to be antidepressant free, and treatment sessions were scheduled daily in a 5-day sequence for 10 sessions over 2 weeks. Third, after the 2-week double-blind phase of the intervention, each patient visited again on the 12th week following the 2-week treatment (week 14 [W14]).

The number of participants required was determined using the Power and Sample Size Program v3.0.43 (19). To enhance the blinding process and to avoid the limitations of the sham procedure identified in our previous study (10), the present study used a sham coil, which could mimic the auditory and somatosensory effects of active magnetic stimulation without the actual stimulation of the brain. In addition, one half of the patients in the sham group received the same piTBS parameter stimulation (sham-piTBS) and the other half received the same rTMS parameter stimulation using a sham coil (sham-rTMS), which also enhanced the blinding process. Blinded study personnel (raters), without authorized access to the treatment sessions, assessed all the efficacy outcome measurements. All participants were asked about their treatment experiences at W2; however, none of them was confident about their group assignments. Refer to the Supplement for additional details.

Brain Stimulation (TBS/TMS) Parameters and Session Procedures

The piTBS and rTMS parameters were mainly selected according to our previous published protocols that had demonstrated antidepressant efficacy in a 2-week treatment course (10,20) and were delivered using the Magstim Rapid^2 stimulator (Magstim Co., Ltd., Whitland, United Kingdom). The piTBS parameters we adopted were also in line with the standard iTBS protocol, excluding the increase in the number of pulses from 600 to 1800 (6). The left DLPFC was the treatment site for all groups, and this site was identified using 2 methods (~1:1 in each group): MRI-guided targeting to the left

Table 1. Demographic Data and Clinical Variables

	Group A: piTBS (n = 35)	Group B: rTMS (n = 35)	Group C: Sham (n = 35)	F/χ^2	p Value
Age, Years	47.1 ± 14.2	47.1 ± 13.8	47.1 ± 12.4	F = 0.000	1.000
Female	23	24	24	χ^2 = 0.087	.957
EST/NAVI	20/15	20/15	20/15	–	–
MSM Refractoriness Score	8.7 ± 2.0	8.9 ± 2.6	8.4 ± 2.3	F = 0.389	.678
Life Stress	145.5 ± 89.4	195.8 ± 180.8	146.1 ± 106.4	F = 1.681	.191
CGI-S	4.4 ± 0.6	4.7 ± 0.9	4.6 ± 0.8	F = 1.270	.285
HDRS-17 (BL)	22.5 ± 3.5	22.9 ± 3.8	23.1 ± 3.5	F = 0.185	.831
Psychiatric Comorbidity					
Dysthymia	7	10	6	χ^2 = 1.408	.580
Panic disorder	3	6	4	χ^2 = 1.200	.661
Agoraphobia	5	7	6	χ^2 = 0.453	.947
Social phobia	2	3	0	χ^2 = 2.920	.366
Generalized anxiety disorder	27	24	27	χ^2 = 0.895	.751

Values are mean ± SD or n.

EST, 5-cm estimation method; BL, baseline; CGI-S, Clinical Global Impression-Severity scale; HDRS-17, 17-item Hamilton Depression Rating Scale; MSM, Maudsley Staging Method; NAVI, magnetic resonance imaging navigation method; piTBS, prolonged intermittent theta burst stimulation; rTMS, repetitive transcranial magnetic stimulation.

DLPFC using a procedure similar to the one in our previous study (10) and the standard procedure (5 cm anterior to the motor cortex) (14,15). In summary, group A patients received piTBS treatment (1800 pulses/session × 10 sessions), group B received rTMS treatment (1600 pulses/session × 10 sessions), and group C received a sham treatment (parameters given as piTBS or rTMS, randomly assigned; 10 sessions) using a sham coil (Magstim Placebo Coil; Magstim Co., Ltd.) (Supplemental Figure S1). T1 images were acquired using a 3.0 GE Discovery 750 whole-body high-speed imaging device (GE Healthcare, Milwaukee, WI). Notably, several patients who were allocated to the MRI navigation group withdrew before treatment because most of them (n = 6) failed to comply with the scheduled MRI scanning time (Supplemental Figure S2).

Efficacy and Safety Assessments

Symptomatic ratings were administered at baseline (W0, before brain stimulation), at the end of W1 and W2 brain stimulation treatments, and at the 12-week follow-up after the treatment (W14). The primary efficacy outcome was improvement in depression and was measured based on the percentage change in the HDRS-17 score before and after 2 weeks of brain stimulation treatment (% HDRS-17 change) between the piTBS and sham groups. In addition, we calculated the response rate (defined as ≥50% reduction compared with the baseline HDRS-17 score) and the remission rate (defined as HDRS-17 score ≤7). Safety was assessed in every treatment session by recording spontaneous adverse events and inquiring about preidentified symptoms such as seizure, headache, and dizziness. The degree of refractoriness was measured using the Maudsley Staging Method (MSM) (21), and the details are presented in the Supplement.

Statistical Methods

All statistical analyses were performed using IBM SPSS Statistics 21 (IBM Corp., Armonk, NY). The primary efficacy outcome (% HDRS-17 changes before and after 2 weeks of treatment among the 3 groups) and the secondary outcome measures (% HDRS-17 changes between the standard method and MRI-guided coil targeting) were analyzed using the analysis of covariance model, with baseline HDRS-17 scores and the MSM refractoriness score as covariates. Least squares mean scores of % HDRS-17 changes for each group and for the differences between the piTBS and sham groups and between the rTMS and sham groups were reported. The Bonferroni was used for post hoc analysis when the main effect on the brain stimulation group was significant. For the secondary outcome measures, the antidepressant effects of the 3 brain stimulation groups were compared between the 5-cm standard method and the MRI navigation method. Analysis of covariance models were also performed separately in the 2 coil targeting groups. Fisher's exact test was used to compare categorical variables (e.g., responders at W2 between brain stimulation groups). Effect sizes (Cohen's d) were calculated for the mean differences between groups.

Logistic regression was performed for age, sex, targeting methods (MRI navigation as reference group), education levels, duration of illness, MSM scores, life stress, baseline Clinical Global Impression-Severity scale scores, handedness, baseline HDRS-17 scores, HDRS-17 changes at W1, types of previous antidepressants (selective serotonin reuptake inhibitor as reference), and brain stimulation groups (sham group as reference group), which served as independent factors. Responses to 2 weeks of brain stimulation (>50% reduction in HDRS-17 scores) were the dependent factors. Adjusted odds ratios predicting the antidepressant efficacy of brain stimulation and their 95% confidence intervals were reported. Statistical significance was set at $p < .05$ (2-sided tests).

RESULTS

Demographic/Clinical Data at Baseline and Safety Reports to Brain Stimulation

A total of 105 patients were randomly assigned to 3 treatment groups over a 3-year period. All participants in the piTBS

Table 2. Clinical Outcomes in Response to Brain Stimulation Treatment by Analysis of Covariance, Adjusting for Baseline HDRS-17 Scores and MSM Refractoriness Score

	Group A: piTBS	Group B: rTMS	Group C: Sham	F/χ^2	*p* Value	Post Hoc (Bonferroni)
HDRS-17 (BL)	22.5 ± 3.5	22.9 ± 3.8	23.1 ± 3.5	$F = 0.185$	.831	–
LS % Change at W1	−22.6 ± 3.3	−23.0 ± 3.3	−12.8 ± 3.3	$F = 3.092$	.049[a]	A<C, B<C
LS mean difference from sham	−9.8 ± 4.6	−10.2 ± 4.6				
p Value	.037[a]	.030[a]				
Responders at W1	6 (17.1)	3 (8.6)	1 (2.9)	$\chi^2 = 3.918$	.151	
Remitters at W1	3 (8.6)	2 (5.7)	0 (0)	$\chi^2 = 2.920$	.366	
LS % Change at W2	−40.0 ± 4.2	−34.0 ± 4.2	−13.9 ± 4.2	$F = 10.712$	<.001[b]	A<C, B<C
LS mean difference from sham	−26.2 ± 5.9	−20.2 ± 5.9				
p Value	<.001[b]	.001[b]				
Responders at W2	16 (45.7)	14 (40.0)	1 (2.9)	$\chi^2 = 21.458$	<.001[b]	
Remitters at W2	9 (25.7)	5 (14.3)	1 (2.9)	$\chi^2 = 7.597$	.026[a]	

Values are mean ± SE or *n* (%).

BL, baseline; HDRS-17, 17-item Hamilton Depression Rating Scale; LS, least squares; MSM, Maudsley Staging Method; piTBS, prolonged intermittent theta burst stimulation; rTMS, repetitive transcranial magnetic stimulation; W, week.

[a]$p < .05$.

[b]$p < .005$.

(*n* = 35), rTMS (*n* = 35), and sham (*n* = 35) groups completed the entire study procedure (Supplemental Figure S2). Demographic and clinical variables as well as the distribution of psychiatric comorbidities did not differ among the 3 groups at baseline (Table 1). Overall, the recruited patients tolerated the active treatment well. Fifteen patients reported temporary headaches that did not require analgesic intervention (piTBS, *n* = 5; rTMS, *n* = 6; sham, *n* = 4 [$\chi^2_2 = 0.465$, $p = .793$]), 13 patients reported temporary dizziness (piTBS, *n* = 4; rTMS, *n* = 5; sham, *n* = 4 [$\chi^2_2 = 0.175$, $p = .916$]), and 1 patient (rTMS condition) reported the exacerbation of tinnitus. No event of seizure or mania was reported.

Antidepressant Efficacy of piTBS Monotherapy

As shown in Table 2 and Figure 1, analysis of the primary outcome revealed that the % HDRS-17 change at W2 was significantly greater for the piTBS group than for the sham group (−40.0% vs. −13.9% [mean difference = 26.2%]; $p < .001$ after correcting for multiple comparisons through Bonferroni [effect size (Cohen's *d*) = 1.12]). The % change in HDRS-17 scores at W2 was also significantly greater for the rTMS group than for the sham group (−34.0% vs. −13.9% [mean difference = 20.2%]; $p = .003$ [effect size (Cohen's *d*) = 0.87]). Post hoc analysis revealed no significant mean differences in HDRS-17 changes between the piTBS and rTMS groups. In addition, baseline HDRS-17 scores ($F = 0.182$, $p = .180$) and MSM scores ($F = 0.327$, $p = .568$) were not significant factors influencing % HDRS-17 changes at W2.

In addition, 31 responders in total were found at W2 (Table 2), and most of the piTBS responders (*n* = 12 of 16, 75%) and rTMS responders (*n* = 7 of 14, 50%) remained responders 3 months after treatment (W14). A total of 15 remitters were found at W2 (Table 2), and 9 of them (7 of 9 [77.8%] in the piTBS remitters and 2 of 5 [40%] in the rTMS remitters) remained remitters 3 months after treatment (W14). The refractoriness levels of the recruited patients ranged mostly from mild (MSM score ≤7) to moderate (MSM score 8–10) (10). The only responder (W2) in the sham group exhibited a low refractoriness level (MSM score 6). Most of the 19 patients who remained responsive at W14 exhibited low (*n* = 9 of 19, 47.4%) or moderate (*n* = 8 of 19, 42.1%) refractoriness levels.

Targeting Methods and Antidepressant Efficacy

Analysis of the secondary outcomes revealed that the % HDRS-17 change at W2 was not significantly better in patients who were allocated to the MRI navigation method (Figure 2).

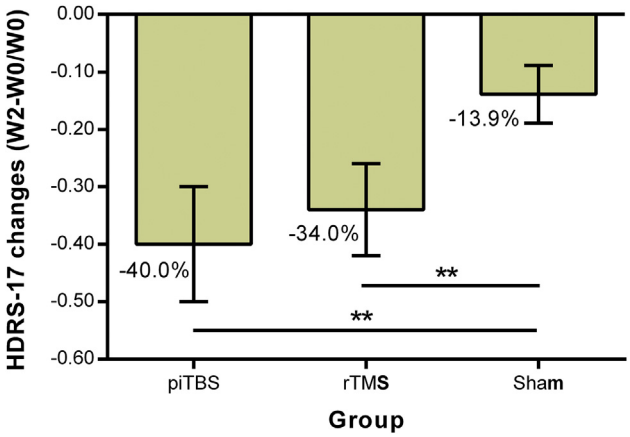

Figure 1. Bar charts of 17-item Hamilton Depression Rating Scale (HDRS-17) changes in response to a 2-week prefrontal prolonged intermittent theta burst stimulation (piTBS) (group A), repetitive transcranial magnetic stimulation (rTMS) (group B), and sham treatment (group C), showing that the piTBS monotherapy was significantly more effective than sham treatment ($p < .001$). The rTMS monotherapy was also effective than sham treatment ($p = .003$). **$p < .005$. W, week.

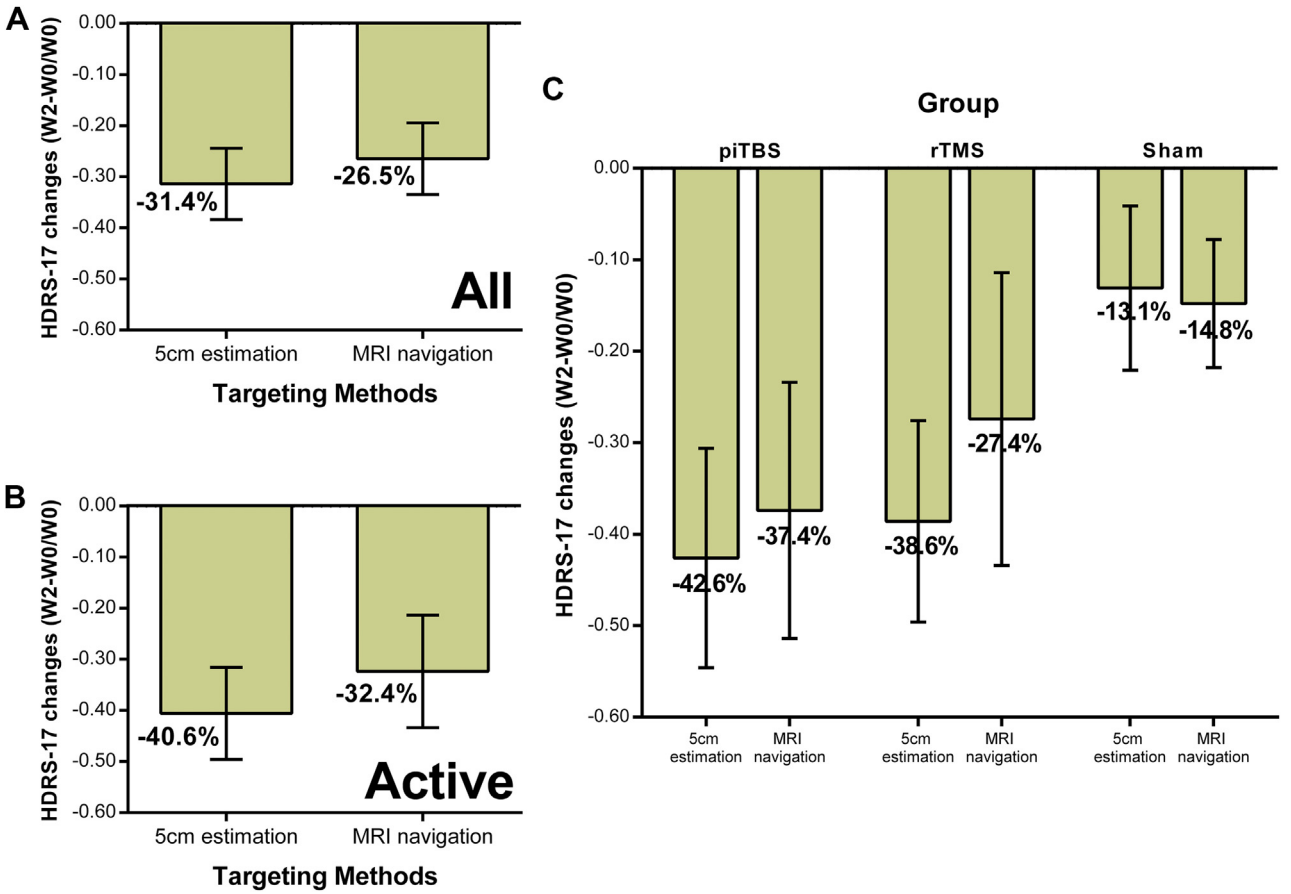

Figure 2. Comparisons of 17-item Hamilton Depression Rating Scale (HDRS-17) changes over 2 weeks of brain stimulation **(A)** between the standard 5-cm method and the magnetic resonance imaging (MRI)–navigated method of coil positioning for all patients, **(B)** for patients receiving active brain stimulation, and **(C)** separately for each stimulation group. No difference between different coil positioning methods was observed. piTBS, prolonged intermittent theta burst stimulation; rTMS, repetitive transcranial magnetic stimulation; W, week.

For example, in patients receiving active treatment (Figure 2B), the MRI navigation method (−32.4%) did not yield better antidepressant effects than the standard method (−40.6%). Subgroup analysis revealed that piTBS had a better antidepressant effect than sham treatment in patients receiving the standard 5-cm estimation method ($p < .001$) and that rTMS treatment was effective in decreasing depression scores (Supplemental Figure S3).

Factors Reliably Predicting Antidepressant Responses

The results of logistic regression demonstrated that brain stimulation group (piTBS vs. sham [odds ratio, 76.2; $p = .002$]; rTMS vs. sham [odds ratio, 19.3; $p = .005$]) and HDRS-17 changes in the first week ($p < .001$) were the most important variables for predicting responders to the 2-week brain stimulation (Table 3), but the variables age, sex, MSM refractoriness score, life stress, baseline Clinical Global Impression-Severity scale, baseline HDRS-17 score, duration of illness, handedness, education levels, previous antidepressants, and targeting methods were not.

As early improvements following brain stimulation are one of the most important factors predicting the final antidepressant outcome, in a post hoc analysis, we further plotted receiver-operating characteristic (ROC) curves for assessing the most optimal early improvement (10%, 20%, 30%, 40%, and 50%) to predict the responses at W2 and calculated the area under the ROC curve (22). The 20% improvement at W1 had the largest area under the ROC curve (0.827; $p < .001$) (Supplemental Figure S4).

DISCUSSION

The present study, which represents the first large randomized, double-blind, sham-controlled study, revealed that piTBS monotherapy was well tolerated and was effective for the treatment of recurrent depression in patients who did not exhibit adequate responses to antidepressants. Our findings are potentially applicable in clinical settings because the piTBS program required lower levels of intensity (lower stimulus strength) and less time to achieve effects similar to those of rTMS treatment. In addition, our prolonged protocol could decrease total treatment sessions considerably because the antidepressant efficacy of our 2-week piTBS protocol was very close to the efficacy of the standard iTBS protocol for 4 to 6 weeks (9). In addition, the present study failed to reveal that MRI-guided coil positioning was better than the standard

Table 3. Logistic Regression That Investigated Variables Predicting Antidepressant Responses to Brain Stimulation Treatment

Independent Variable	Nonresponders (W2)	Responders (W2)	*p* Value	OR (95% CI)
Age, Years	47.7 ± 13.5	45.7 ± 13.0	.690	1.015 (0.942–1.094)
Sex			.223	
Female	51 (68.9)	20 (64.5)	–	0.171 (0.010–2.934)
Male	23 (31.1)	11 (35.5)	–	Reference
Education, >12/≤12 Years	33/41	6/25	.278	1.854 (0.608–5.648)
Targeting Method			.143	
5-cm estimation	38 (63.3)	22 (36.7)	–	6.132 (0.541–69.578)
MRI navigation	36 (80.0)	9 (20.0)	–	Reference
MSM Refractoriness Score	8.7 ± 2.3	8.4 ± 2.3	.949	1.017 (0.597–1.733)
Life Stress	157.2 ± 142.1	175.0 ± 107.2	.082	1.010 (0.999–1.021)
CGI-S	4.7 ± 0.8	4.3 ± 0.6	.210	0.187 (0.014–2.575)
HDRS-17 (BL)	23.3 ± 3.4	21.7 ± 3.9	.103	0.635 (0.368–1.097)
Duration of Illness, Years	11.6 ± 10.0	10.8 ± 10.6	.074	1.119 (0.993–1.261)
Left Handedness	2 (2.7)	1 (3.2)	.419	0.209 (0.005–9.299)
Type of Previous Antidepressant			.921	
SSRI	32 (43.2)	15 (48.4)	–	Reference
SNRI	13 (17.6)	8 (25.8)	.993	0.988 (0.052-18.591)
Other	28 (37.8)	8 (25.8)	.488	0.374 (0.023–6.002)
Group			.007[a]	
piTBS	19 (54.3)	16 (45.7)	.002[b]	76.2 (2.8–207.2)
rTMS	21 (60.0)	14 (40.0)	.005[a]	19.3 (1.8–39.6)
Sham	34 (97.1)	1 (2.9)	–	Reference
% HDRS-17 Change (W1)	−11.1 ± 12.0	−39.4 ± 20.9	<.001[b]	0 (0–0.001)

Values are mean ± SE or *n* (%).

BL, baseline; CGI-S, Clinical Global Impression-Severity scale; CI, confidence interval; HDRS-17, 17-item Hamilton Depression Rating Scale; MRI, magnetic resonance imaging; MSM, Maudsley Staging Method; OR, odds ratio; piTBS, prolonged intermittent theta burst stimulation; rTMS, repetitive transcranial magnetic stimulation; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; W, week.

[a] $p < .05$.

[b] $p < .005$.

method. Overall, we demonstrated that the most important factors predicting the final antidepressant response were active brain stimulation treatment and HDRS-17 changes within the first week.

Regarding the piTBS protocol in the present study (1800 pulses/session: three times longer than the standard iTBS protocol), we previously performed a double-blind trial to demonstrate its antidepressant efficacy and safety (10). The novelty of the present study is the confirmation of the efficacy of piTBS monotherapy in patients with medication-resistant depression. The response rate following piTBS monotherapy was 40% in our previous study and 45.7% in the present study, which are not lower than the overall response rate of 35.6% reported in a meta-analysis by Berlim *et al.* (8). Although the standard iTBS parameter for motor cortical experiments has been reported to be 600 pulses/session (6), the optimal treatment protocol for depression is yet to be determined (8). Notably, the antidepressant effects of piTBS monotherapy administered for 2 weeks in the present study (mean HDRS-17 scores improved from 22.5 to 13.7) are comparable to those of iTBS for 4 to 6 weeks (mean scores improved from 23.6 to 13.4). Time is valuable, and shorter treatment periods with comparable antidepressant efficacy are of great clinical importance. Our previous and present studies have demonstrated that no seizures or switching to mania occurred, nor was there a statistically significant difference in headache, dizziness, nausea, or other side effects between the active and sham TBS groups (10). The safety of the prolonged iTBS protocol has also been demonstrated in studies adopting a relatively aggressive approach referred to as spaced TBS (12,13).

Treatment using the active comparator 10-Hz rTMS was associated with significant end point improvements in the HDRS-17 score; 10-Hz rTMS has been previously reported to be effective as monotherapy for resistant depression (23), and the parameters adopted in the present study were based on our previous studies that demonstrated the antidepressant efficacy of 10-Hz rTMS in comparison with sham treatment (1,20). A response rate of 40% at W2 in the present study is consistent (i.e., ~50%) with that in our previous findings (1,20). We used a 100% motor threshold. Although it seems suboptimal, meta-analytical evidence has indicated that the intensity of rTMS does not significantly influence antidepressant effects (24). For example, the effect sizes between studies using intensities <100% MT and 100% to 120% MT were not significantly different (24). Between-group efficacy testing was exploratory and not our primary study aim. According to the results of post hoc analysis, no statistically significant differences were observed in HDRS-17 changes between the piTBS and the rTMS groups. Our results are consistent with the

findings of a recent noninferiority study demonstrating that iTBS and 10-Hz rTMS have similar antidepressant effects (9).

The finding that the MRI-guided coil positioning was not better than the standard method with regard to antidepressant efficacy was unexpected because previous studies have suggested that the inaccuracy of the "standard" procedure partly explains the between-study variability of antidepressant effects (25). For example, Ahdab *et al.* (25) compared the locations of the DLPFC by the 5-cm method of coil positioning and by using a neuronavigation system integrating individual MRI, revealing that the "standard" procedure failed to accurately locate DLPFC targets. The navigation method could be more costly and time-consuming compared with the estimation method. The supporting evidence was that there were significantly more patients in the MRI navigation group who withdrew their consent before treatment (Supplemental Figure S2), mainly because they failed to comply with the MRI scanning schedule and asked for early rTMS availability. Based on our findings, the coil positioning method is not a key factor influencing the antidepressant outcome of rTMS and piTBS. The results also suggest that the antidepressant mechanisms of rTMS and piTBS are still not understood exhaustively, and they may involve mechanisms that are not associated with the locus of stimulation.

The optimal DLPFC target of rTMS for depression remains unknown. The ideal target of DLPFC may be more posteriorly located. For example, medication-resistant patients have been reported to have more impaired glucose metabolism not only in the bilateral DLPFC, but also in a posteriorly located frontal region, the supplementary motor area, compared with nonresistant depression patients (26). In addition, an effect on the brain connectivity network (27), instead of just a local effect at the stimulation site, is potentially responsible for the effects of rTMS. Recently, a similar finding was made in chronic tinnitus patients, in which the coil localization method was not a critical factor influencing the rTMS treatment outcome (28).

Notably, the HDRS-17 change in the first week was found to be one of the most important factors predicting the final antidepressant response to brain stimulation. The finding was in line with many of the rTMS studies, showing that the most prominent improvement of depression occurred in the early course of treatment (5,15). Despite the preliminary results, the ROC analysis demonstrated that the 20% improvement at W1 had the largest area under the ROC curve (0.827; $p < .001$) (Supplemental Figure S4), which indicated that if we aim for antidepressant responses at W2, it is critical to achieve at least 20% improvement at W1. The identification of reliable early outcome predictors facilitates the selection of appropriate stimulation parameters and the maximization of the outcomes of clinical treatments. Future studies with larger sample sizes are still warranted to determine the most optimal cutoff value.

The present study had a few limitations. Whether the antidepressant efficacy of piTBS is better than that of standard iTBS should be confirmed using further large-scale, sham-controlled studies. In addition, the follow-up period was open label, and antidepressant use was allowed for nonresponders, which from a design perspective may not truly reflect delayed responses to piTBS. However, delayed responses were not the primary focus of the present study. As we did not alter the medication administered to the responders during follow-up, the study design facilitated the observation of the duration of rTMS and piTBS effects up to 3 months following active treatment. The "standard" 5-cm rule applied during the targeting the DLPFC may be suboptimal, potentially diminishing the therapeutic effects of rTMS (29). However, head shapes in Chinese populations are rounder than those of their Caucasian counterparts, who feature a flatter back and forehead (30). Berlim *et al.* (23) reviewed 29 randomized controlled trials using high-frequency rTMS and observed that an average of 29.3% of patients with depression were responders. Using the 5-cm method to target the DLPFC, the present study detected an above-average response rate of up to 50%. Finally, because the results of meta-analytic studies suggest that rTMS treatment over longer periods of stimulation (e.g., >2 weeks) have better clinical effects (31), we are in the course of conducting another piTBS study with a longer treatment period for further comparison.

Conclusions

The present study, which represents the first randomized, sham-controlled trial, confirmed the antidepressant effects of 2-week piTBS monotherapy, and its antidepressant effects were consistent with those of the standard iTBS protocol performed over 4 to 6 weeks. In addition, the coil positioning method is not a key factor influencing the antidepressant outcomes of piTBS and rTMS.

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UMIN-CTR Clinical Trial: Antidepressant Efficiency of Prefrontal Trasncranial Magnetic Stimulation Monotherapy in Non-drug responsive Major Depression: a Randomized Case-control Study; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000024104; UMIN000020892.

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