


# Task-Modulated Brain Activity Predicts Antidepressant Responses of Prefrontal Repetitive Transcranial Magnetic Stimulation: A Randomized Sham-Control Study

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## Abstract

**Background:** Prolonged intermittent theta-burst stimulation (piTBS) and repetitive transcranial magnetic stimulation (rTMS) are effective antidepressant interventions for major depressive disorder (MDD). Cognition-modulated frontal theta (frontal $\theta$ ) activity had been identified to predict the antidepressant response to 10-Hz left prefrontal rTMS. However, whether this marker also predicts that of piTBS needs further investigation.

**Methods:** The present double-blind randomized trial recruited 105 patients with MDD who showed no response to at least one adequate antidepressant treatment in the current episode. The recruited patients were randomly assigned to one of three groups: group A received piTBS monotherapy; group B received rTMS monotherapy; and group C received sham stimulation. Before a 2-week acute treatment period, electroencephalography (EEG) and cognition-modulated frontal theta changes ( $\Delta$ frontal $\theta$ ) were measured. Depression scores were evaluated at baseline, 1 week, and 2 weeks after the initiation of treatment.

**Results:** The  $\Delta$ frontal $\theta$  at baseline was significantly correlated with depression score changes at week 1 ( $r = -0.383$ ,  $p = 0.025$ ) and at week 2 for rTMS group ( $r = -0.419$ ,  $p = 0.014$ ), but not for the piTBS and sham groups. The area under the receiver operating characteristic curve for  $\Delta$ frontal $\theta$  was 0.800 for the rTMS group ( $p = 0.003$ ) and was 0.549 for the piTBS group ( $p = 0.619$ ).

**Conclusion:** The predictive value of higher baseline  $\Delta$ frontal $\theta$  for antidepressant efficacy for rTMS not only replicates previous results but also implies that the antidepressant responses to rTMS could be predicted reliably at baseline and both piTBS and rTMS could be effective through different neurobiological mechanisms.

## Keywords

frontal cortex, major depression, theta, theta burst stimulation, transcranial magnetic stimulation

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## Background

High-frequency (e.g., 10-Hz) repetitive transcranial magnetic stimulation (rTMS) to the left dorsolateral prefrontal cortex (DLPFC) is an effective method for treating medication-resistant depression.<sup>1–3</sup> Studies also demonstrated the efficacy of 10-Hz left prefrontal rTMS monotherapy in patients with depression.<sup>4</sup> In addition, theta-burst stimulation (TBS), as a new form of rTMS, has more powerful and rapid effects on synaptic plasticity than traditional rTMS protocols<sup>5</sup> and has been

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demonstrated to be effective for treating depression. For example, Berlim and colleagues revealed that active TBS has significantly more antidepressant effects than sham TBS. Subgroup analysis further identified that intermittent TBS (iTBS), but not continuous TBS (cTBS), was one of the most promising and effective protocols for treating depression.<sup>6</sup> Likewise, in one of our randomized double-blind sham-controlled studies, we investigated the antidepressant efficacy of 2-week add-on therapy of prefrontal TBS for refractory depression and found that paradigms involving prolonged iTBS (piTBS with 1800 pulses/session; 3 times longer than the standard TBS protocol) were significantly more effective than sham TBS.<sup>7</sup> 1800 pulses were used because the after-effects of TBS critically depend on the total stimulation pulses,<sup>5</sup> and 1200 pulses of iTBS exhibited suboptimal antidepressant efficacy.<sup>8</sup> Furthermore, Blumberger et al. conducted a large head-to-head comparison trial and found that iTBS and 10-Hz rTMS for 4 to 6 weeks had similar antidepressant effects for treatment-resistant depression.<sup>9</sup> Recently, we further demonstrated in a sham-controlled trial that in patients with medication-resistant depression, piTBS monotherapy for two weeks was more effective than sham treatment and had comparable antidepressant effects to 10-Hz left prefrontal rTMS.<sup>10</sup> The advantages of piTBS protocol include no prominent side effects and a decrease of total treatment sessions considerably.<sup>10</sup>

Determining how to accurately predict the response to brain stimulation in treating refractory depression is an important clinical lesson that may facilitate further modification of treatment regimens. However, a dearth of data exists on whether the neurobiological predictors of response to prefrontal rTMS align with those of the response to TBS intervention. In our previous study, we used a rostral anterior cingulate cortex (rACC)-engaging cognitive task (RECT) to engage task-related neurons before 10-Hz left prefrontal rTMS,<sup>1,11</sup> and found that frontal theta differences (baseline vs. post-RECT) significantly differed between rTMS responders and non-responders.<sup>12</sup> Likewise, Bailey et al. performed a working memory (WM) task while electroencephalography (EEG) was recorded, demonstrating that rTMS responders had higher levels of WM-related fronto-midline theta power as compared to non-responders at baseline.<sup>13</sup> Whether task-modulated frontal theta activity predicts the antidepressant responses of iTBS needs further investigation. It may be possible since we previously found that prefrontal TBS protocols primarily modulated fronto-cingulate circuit of the depression-related network<sup>11,14,15</sup> and our RECT task was designed to engage rostral ACC. The present randomized, double-blind, sham-controlled study reported results of the EEG part from our recently-published clinical trial.<sup>10</sup> Measuring EEG signals from scalp electrodes, we

hypothesized that post-RECT changes in frontal $\theta$  activity (frontal $\theta$  differences between pre-RECT and post-RECT,  $\Delta$ frontal $\theta$ ) could predict the antidepressant effects of rTMS and/or piTBS monotherapy.

## Methods and Materials

### Subjects

Eligible subjects were adult patients aged from 21 to 70 years and diagnosed with recurrent MDD on the basis of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria. Patients were qualified if they failed to respond to at least one adequate antidepressant treatment in their current episode (for example, failed to achieve 50% improvement of depression to an equivalent daily dose of 10 to 20 mg of escitalopram for at least 8 weeks). The recruited patients were required to be antidepressant-free for at least 1 week prior to this double-blind, sham-controlled trial. All recruited participants had to have a Clinical Global Impression – Severity score of at least 4 and a total score of at least 18 on the Hamilton Depression Rating Scale (HDRS-17).<sup>16</sup>

Patients were excluded if they had a lifetime psychiatric history of psychotic disorders, bipolar disorders, and organic mental disorder. Finally, regarding to potential safety issues during the monotherapy period of brain stimulation, patients with a current strong suicidal risk (i.e., a score of 4 on item 3 of the HDRS-17) were excluded.

The study was performed in accordance with 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 University Hospital Medical Information Network Clinical Trials Registry (Registration number: UMIN000020892).

### Study Overview and Efficacy Assessments

The study comprised three phases. First, patients underwent a 1-week screening to ensure that they were medically stable and met recruitment criteria. Second, patients were randomized 1:1:1 to each treatment group (group A, piTBS; group B, 10-Hz rTMS; and group C, sham). Covariate adaptive randomization was used to make sure the ratio of sex and gender in each group is balanced.<sup>17</sup> There were totally 10 treatment sessions over 2 weeks (one session/day). During the treatment phase, patients were required to be antidepressant free. Third, each patient visited again at the 12th week after the 2-week treatment (week 14). To improve the blinding process, we used a sham coil (Magstim<sup>®</sup> Placebo Coil; Magstim Co., Ltd,

Wales United Kingdom), which could mimic the auditory and somatosensory effects of active magnetic stimulation without actual stimulation of the brain. In addition, half of the patients in the sham group received the same iTBS parameter stimulation (sham-iTBS), and the other half received the same rTMS parameter stimulation using a sham coil (sham-rTMS). All efficacy outcome measurements were assessed by blinded study personnel (raters) who were not permitted access to the treatment sessions. HDRS-17 was used to measure depression severity and was administered at baseline (W0, before brain stimulation), at the end of week 1 (W1) and week 2 (W2) brain stimulation treatments, and at the 12-week follow-up after the treatment (week 14 [W14]). Response rate was defined as  $\geq 50\%$  reduction compared with the baseline HDRS-17 score. The degree of refractoriness was measured using the Maudsley Staging Method (MSM).<sup>18</sup> The aim of the present study was to determine whether the post-RECT changes in frontal $\theta$  power ( $\Delta$ frontal $\theta$ ) might predict the antidepressant efficacy of TBS and/or rTMS monotherapy. Other details of the methodology had been published.<sup>10</sup>

### **Brain Stimulation (TBS/TMS) Parameters and Session Procedures**

The piTBS and rTMS protocols were delivered using the Magstim Rapid<sup>2</sup> stimulator (Magstim Co., Ltd., Wales United Kingdom). The piTBS parameters we adopted also followed the standard iTBS protocol (tripulse 50-Hz bursts administered every 200 milliseconds; 80% active motor threshold (MT); a 2-second train of bursts was repeated every 10 seconds),<sup>5</sup> except for a total of 570 seconds (1800 pulses). The rTMS parameters exactly followed the protocol we published before and was 10 Hz at 100% resting MT.<sup>12</sup> The left DLPFC was the treatment location for all groups (5-cm estimation method: MRI navigation method for targeting DLPFC=4: 3 in each group<sup>10</sup>) Both treatment and sham coils were 70-mm figure-of-eight coils (Magstim® Double 70-mm Stimulating Coil 9925-00) with exactly the same appearance to improve the blinding process. The sham coil could mimic the auditory and somatosensory effects of active coil stimulation without actual stimulation of the brain.

### **Electroencephalography**

**Task-Modulated EEG.** The present study utilized a computerized rACC-engaging cognitive task (RECT) in combination with EEG to study potential biomarkers predicting responses to brain stimulation treatment and had been reported in details elsewhere.<sup>12</sup> Resting-state EEG datasets were acquired before and after performing RECT (i.e. baseline RECT and post-RECT),

and then followed by the first session of brain stimulation. The RECT program was primarily based on the flexibility task of the Tests for Attentional Performance<sup>19</sup> and had been found to induce and modulate brain activities in the rACC.<sup>12</sup> During the task, competing stimuli (sharp and round forms) were presented simultaneously on the left and right side of the computer screen, and the patients were asked to press a response key indicating the correct side of the screen containing the target stimuli with their index finger. The shape task, instead of a color task, was used for the target stimuli of the RECT program because the former had found to be associated with more frontal theta engagement than the latter.<sup>20</sup> After the pre-test trials, the patients performed 10-minutes of continuous testing trials under the supervision of a trained research assistant to maximize full engagement on the program. Notably, prolonged flexibility program was easy but had high demands on sustained attention and working memory for alternating target stimuli (sharp vs. round). The present study used the RECT program to engage ACC neurons temporarily and to test post-RECT frontal theta activity. We have found that the 10-minute RECT program alone have no lasting effects on frontal theta and cognitive functions, even if it was applied on a daily basis for 10 days.

**EEG Data Acquisition and Analysis.** We followed the same procedures as described in our previous publication.<sup>12</sup> To summarize here, EEG data were acquired in a dim, electrically shielded quiet room, while patients were seated in a comfortable arm-chair with eyes closed in a maximally alert state. A standard 32-channel digital EEG cap (Quik-Cap) with Ag/AgCl sintered electrodes was placed according to the international 10/20 system, and all scalp EEG electrode impedances were kept below 5k $\Omega$ . Neuroscan amplifiers (Nuamps) and Neuroscan 4.3 software were used for EEG recording. During each 3-min EEG recording, the alertness was controlled. If patterns of drowsiness appeared in the EEG, the subjects were aroused by acoustic stimuli. The 32-channel EEG electrodes were referenced to the linked mastoids. An electrode was placed between FP1 and FP2 for ground. The data sampling rate was 1000 Hz and the acquired signals were filtered with digital high-and low-pass filtering at 0.15 and 50 Hz, respectively. Vertical and horizontal eye movements were recorded by electrooculogram electrodes placed in the superior and inferior orbit of the right eye and in the outer canthi. After acquisition, epochs with movement, eye blinks, decreases in alertness, and muscle artifacts were removed by automatic artifact rejection for voltage deflections greater than  $\pm 75 \mu\text{V}$ , followed by visual inspection by an EEG reviewer blind to the treatment. For the remaining EEG artifacts, independent

component analysis (ICA) was further applied using EEGLAB running under MATLAB 7.1 (The Mathworks Inc., Sherborn, MA, USA).

The off-line artifact-free epochs were obtained and tapered with a Hanning window, and then submitted to a power spectral analysis using Fast Fourier Transform (FFT). FFT was used to calculate absolute and relative power in each of five frequency bands:<sup>21</sup> delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–35 Hz), and gamma (35–50 Hz). Relative power was calculated as the amount of the absolute power in one specific band divided by the sum of that in the five frequency bands (i.e., relative theta power = (theta power)/[(delta power)+(theta power)+(alpha power)+(beta power)+(gamma power)]). For each separate EEG record, relative theta power in the frontal region (FP1, F7, F3, Fz, F4, F8, and FP2) was averaged and used as our main variable of interest (i.e., frontal $\theta$ ). The selected sensors in the frontal region should be able to cover frontal midline theta and other sources of theta activity from the frontal area.

### Statistical Methods

One-way analysis of variance (ANOVA), Fisher's exact test, and/or Yates's correction were used to compare the continuous (e.g., age and MSM) and categorical variables (e.g., responders at W2) between brain stimulation groups. Analysis of covariates (ANCOVA) was used to compare % HDRS-17 changes over 2 weeks among 3 groups, adjusting for baseline HDRS-17 scores and MSM scores. Multivariate linear regressions were performed with %HDRS-17 changes at W2 as the dependent factors and brain stimulation groups as independent factors after adjusting for age, sex, MSM refractoriness scores, and  $\Delta$ frontal $\theta$ . The Bonferroni was used for *post-hoc* analysis when the main effect on the brain stimulation group was significant. Receiver operating characteristic (ROC) curves were plotted for assessing the accuracy of predictions of antidepressant responses at W2 by baseline frontal $\theta$ . We set 1 as a

positive antidepressant response at W2 (i.e.,  $\geq 50\%$  reduction of the HDRS-17 score from baseline) as the state variable. Area under the ROC curve (AUC) and the optimal cutoff with maximum sum of sensitivity and specificity were calculated.<sup>22</sup> To investigate relationships between EEG variables and clinical symptomatic improvement (i.e., %HDRS-17 changes), Pearson's correlation analysis was applied. All statistical analyses were performed using SPSS 21.0 (IBM, Armonk, NY, USA). Statistical significance was set at  $p < 0.05$  (two-sided tests).

### Results

One hundred and five patients in the iTBS ( $n = 35$ ), rTMS ( $n = 35$ ) and sham ( $n = 35$ ) groups completed the entire study procedures. The demographic variables (i.e., age and gender), the refractoriness degree (i.e., MSM score) and depression severity (i.e., HDRS-17 scores) did not differ between the three groups at baseline (Table 1). The HDRS-17 scores at baseline were 22.5 (3.5), 22.9 (3.8), and 23.1 (3.5) in the piTBS, rTMS, and sham groups, respectively.

The HDRS-17 scores after treatment were significantly different among three groups at W1, W2, and W14 (Table 1). The %HDRS-17 changes from baseline decreased significantly more in the piTBS and rTMS groups than in the sham group at W1 ( $p = 0.049$ ; *post-hoc*: piTBS = rTMS > sham) and W2 ( $p < 0.001$ ; piTBS = rTMS > sham). After the 2-week acute treatment phase, there were 31 responders in total at W2 (16 in the piTBS group and 14 in the rTMS group), and most of them (75% of piTBS responders and 50% of rTMS responders) remained responders 3 months after the treatment (W14) (Other clinical details please refer to our previous publication<sup>10</sup>).

### Brain-Stimulation Responses and Frontal Theta Activity

Calculating the mean of the RECT-modulated frontal $\theta$  resulted in a characteristic amplification of the activity

**Table 1.** Antidepressant outcomes in response to brain stimulation treatment.

	A. piTBS	B. rTMS	C. sham	F-value	p-value	Post-hoc (Bonferroni)
Age in years	47.1 (14.2)	47.1 (13.8)	47.1 (12.4)	0.00047	1.000	–
Female, N	23	24	24	0.087	0.957	–
MSM Refractoriness score	8.7 (2.0)	8.9 (2.6)	8.4 (2.3)	0.389	0.678	–
HDRS-17 (BL)	22.5 (3.5)	22.9 (3.8)	23.1 (3.5)	0.185	0.831	–
HDRS-17 (W1)	17.6 (5.9)	17.7 (5.8)	20.3 (5.3)	2.620	0.078	A < C*
HDRS-17 (W2)	13.7 (7.1)	15.2 (7.0)	20.0 (5.8)	8.658	0.00034**	A < C** B < C**
HDRS-17 (W14)	13.5 (6.6)	15.6 (7.2)	20.1 (5.8)	9.207	0.00021**	A < C** B < C*

Note. Values are mean (SD), if not otherwise specified. MSM, Maudsley Staging Method; BL, baseline; HDRS-17, 17-item Hamilton Depression Rating Scale; W1, week 1; W2, week 2; W14, week 14.

\* $p < 0.05$  \*\* $p < 0.005$ .

of rACC,<sup>12</sup> with the RECT-modulated results at expected levels (post-RECT frontal $\theta$ , min=0.07, max=0.42; after-versus-before frontal $\theta$  difference, as the  $\Delta$ frontal $\theta$ , min = -0.15, max= 0.16). The AUC for pre-RECT frontal $\theta$  was 0.497; for post-RECT frontal $\theta$ , it was 0.578; and for after versus before, it was 0.614 (Figure S1). When frontal $\theta$  was analyzed separately in the piTBS and rTMS groups, the RECT-modulated frontal $\theta$  differences had good predictive values for the rTMS group (AUC = 0.800,  $p$  = 0.003), but not for the iTBS group (AUC = 0.549,  $p$  = 0.619) (Figure 1). In addition, we calculated Brier scores<sup>23</sup> for  $\Delta$ frontal $\theta$  in the prediction of treatment responses at W2. The result for rTMS responses (0.160) was better than that for iTBS responses (0.255). Furthermore, the post-RECT frontal $\theta$  (AUC = 0.768,  $p$  = 0.044) and RECT-modulated frontal $\theta$  differences (AUC = 0.869,  $p$  = 0.006) still had good predictive values for the rTMS group using 5-cm targeting method. The lack of significance for those using MRI-navigation method could be attributed to the small sample size in the rTMS group ( $n$  = 14); therefore, future studies with larger sample sizes are still warranted.

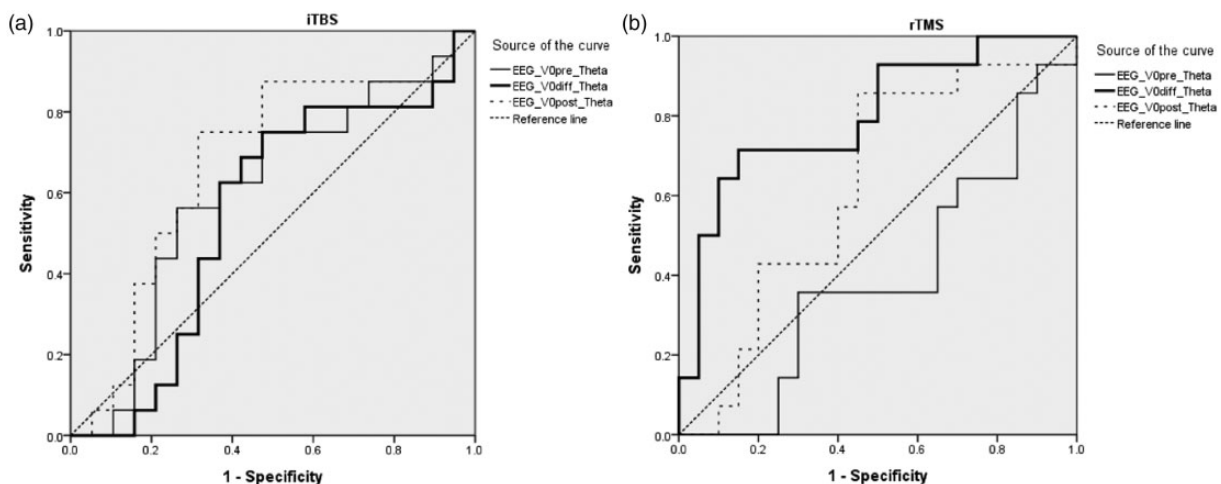
However, the multivariate regression model showed the strongest predictive variable for %HDRS-17 changes in response to the 2-week brain stimulation treatment was the brain-stimulation group ( $\beta$  = 0.406,  $t$  = 4.500,  $p$  < 0.001), but not the  $\Delta$ frontal $\theta$  ( $\beta$  = -0.075,  $t$  = -0.816,  $p$  = 0.417), the MSM score ( $\beta$  = 0.135,  $t$  = 1.490,  $p$  = 0.139), age ( $\beta$  = 0.104,  $t$  = 1.152,  $p$  = 0.252), or sex ( $\beta$  = 0.075,  $t$  = 0.810,  $p$  = 0.420). If the targeting method was entered into the regression model as an independent factor, the main result did not change and

the strongest predictive variable for depression improvement was still the brain-stimulation group ( $\beta$  = 0.407,  $t$  = 4.500,  $p$  < 0.001), but not the targeting method ( $\beta$  = 0.073,  $t$  = 0.794,  $p$  = 0.429) and the other factors.

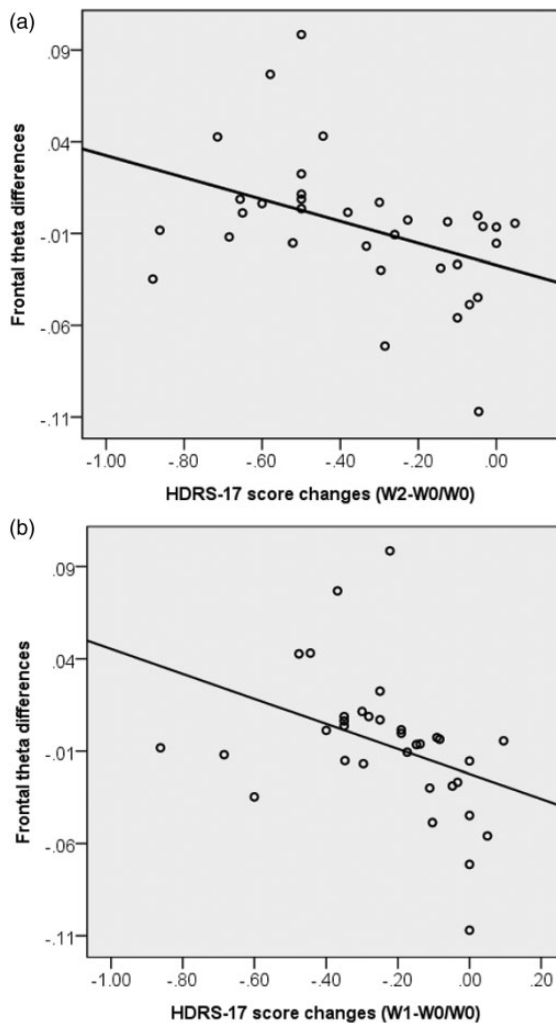
As for the rTMS group, the AUC for pre-RECT frontal $\theta$  was 0.393 ( $p$  = 0.294); for post-RECT frontal $\theta$ , it was 0.612 ( $p$  = 0.234); and for  $\Delta$ frontal $\theta$ , it was 0.800 ( $p$  = 0.003). The results indicated that  $\Delta$ frontal $\theta$  was highly predictive of rTMS responses at W2. (When we arbitrarily thresholded at 0.0039 for the before-versus-after frontal $\theta$  differences, sensitivity and specificity for accurately predicting antidepressant responses were 71.5% and 85.0%, respectively.) Furthermore, all of the frontal $\theta$  values failed to predict treatment responses at W14.

### Correlations Between Depression Changes and Baseline $\Delta$ frontal $\theta$

The results of the correlation analysis were in line with the ROC findings. We found that %HDRS-17 changes at W2 were significantly correlated with  $\Delta$ frontal $\theta$  for rTMS group ( $r$  = -0.419,  $p$  = 0.014) (Figure 2(a)), but not for the iTBS ( $r$  = -0.086,  $p$  = 0.625) and sham groups ( $r$  = 0.212,  $p$  = 0.221). In addition, %HDRS-17 changes at W1 were significantly correlated with  $\Delta$ frontal $\theta$  for rTMS group ( $r$  = -0.383,  $p$  = 0.025) (Figure 2(b)), but not for the iTBS ( $r$  = -0.018,  $p$  = 0.919) and sham groups ( $r$  = 0.258,  $p$  = 0.134) (Table 2).



**Figure 1.** Receiver operating characteristic curves. (a) None of the baseline non-modulated frontal theta activity (thin solid line), RECT-modulated frontal theta differences (thick solid line), or post-RECT-modulated frontal theta activity (dashed line) predicted antidepressant response to 2-week piTBS treatment. (b) The RECT-modulated frontal theta differences at baseline (thick solid line), but not non-modulated frontal theta activity (thin solid line) or post-RECT-modulated frontal theta activity (dashed line), predicted antidepressant responses to 2-week rTMS treatment.



**Figure 2.** Correlations between depression changes and baseline  $\Delta$ frontal $\theta$ . (a) The %HDRS-17 changes at W2 were significantly correlated with  $\Delta$ frontal $\theta$  for rTMS group ( $r = -0.419$ ,  $p = 0.014$ ). (b) The %HDRS-17 changes at W1 were significantly correlated with  $\Delta$ frontal $\theta$  for rTMS group ( $r = -0.383$ ,  $p = 0.025$ ).

## Discussion

The present randomized, double-blind, sham-controlled study used a large sample size and confirmed that the task (i.e., RECT) modulated frontal theta activity can have a predictive value for 10-Hz rTMS antidepressant efficacy. The result of the present study composed of a separate cohort of patients with MDD is consistent with our previous findings.<sup>12</sup> Furthermore, the additional finding of no predictive value of frontal theta activity for the antidepressant efficacy of iTBS implies that the antidepressant mechanism of iTBS could be different from that of rTMS. That is, the antidepressant mechanism of iTBS could be less dependent on the pretreatment activity of rACC, which had been demonstrated to be correlated with the antidepressant effects of rTMS.<sup>1,24,25</sup>

**Table 2.** Correlation between baseline  $\Delta$ frontal $\theta$  and depression changes in response to brain stimulation.

Correlation to $\Delta$ frontal $\theta$	$\Delta$ HDRS-17% after 1 week	$\Delta$ HDRS-17% after 2 weeks
piTBS (group-A)	-0.018 (0.919)	-0.086 (0.625)
rTMS (group-B)	-0.383* (0.025)	<b>-0.419* (0.014)</b>
sham (group-C)	0.258 (0.134)	0.212 (0.221)

Note. Values are  $r$  ( $p$ -value).

HDRS-17, 17-item Hamilton Depression Rating Scale; piTBS, prolonged intermittent theta burst stimulation; rTMS, repetitive transcranial magnetic stimulation.

\*  $p < 0.05$ ; Values in bold represent statistical significance after correcting for multiple comparisons.

Higher glucose uptake or neuronal activity in the rostral anterior cingulate cortex (rACC) and the prefrontal cortex (PFC) have been revealed to be reliable biomarkers that could predict antidepressant responses in MDD across several treatment types (e.g., antidepressants, sleep deprivation, and neurostimulation).<sup>11</sup> Frontal EEG theta activity during consecutive mental tasks has been shown to be generated by activity of the PFC and ACC.<sup>26</sup> In our previous study, we found that task-modulated frontal theta had a stronger correlation with baseline rACC activity and antidepressant efficacy following rTMS than non-modulated frontal theta.<sup>12</sup> Using the same task-modulated method in the present study, we further demonstrated that the predictive value of RECT-modulated frontal theta for antidepressant efficacy was found only for rTMS, not for piTBS. Our findings supported that rACC activity is involved in the antidepressant response of rTMS treatment. However, rACC activity is also associated with antidepressant responses to various kinds of pharmacological, non-pharmacological,<sup>11</sup> and even placebo interventions.<sup>27</sup> Future studies should investigate EEG predictors specific to each kind of antidepressant interventions using sophisticated computational analytical methods. In contrast, Arns et al. found that increased fronto-central theta power was linked to non-response to left or right prefrontal rTMS treatment,<sup>28</sup> whereas Bailey et al. reported no difference of frontal theta between rTMS responders and non-responders in a trial with a limited number of responders ( $N = 12$ ).<sup>29</sup> Fronto-central theta at rest does not reflect the activity of rACC and increased fronto-central theta has been found to be associated with sleepiness.<sup>30</sup>

A putative similar pattern of underlying mechanisms of rTMS and iTBS has been established in both animal and human models, such as direct and indirect neurochemical effects of  $\gamma$ -aminobutyric acid and/or glutamate concentrations, modulation of local/broader functional neural networks, modulation through long-term potentiation, and long-term depression-like

effects.<sup>6,31–34</sup> Although the exact mechanisms of prefrontal TBS for depression remain elusive and require further investigation, selectively targeting brain neurons/circuits with specific oscillatory frequencies (i.e., theta-wave in the case of TBS) might play a unique role in the brain regions where strong theta signals could be detected at rest (i.e., ACC and medial PFC).<sup>34–38</sup>

In addition, higher rACC theta activity before treatment in patients with MDD has been found to reliably predict antidepressant responses to antidepressant drugs.<sup>39–41</sup> A coupling between theta electrical activity (by EEG) and ACC metabolic activity (by positron-emission-tomography, PET) has been confirmed in research simultaneously using EEG and PET recordings.<sup>42</sup> Mayberg et al. first pointed out the association between pretreatment glucose metabolism of the rACC at baseline and subsequent antidepressant responses.<sup>43</sup> Afterwards, pretreatment activity in the rACC was repeatedly reported to be correlated with antidepressant responses to various medications<sup>11</sup> and the rTMS's antidepressant effects.<sup>1,24,25</sup> All these support that fronto-cingulate dysfunction plays an important role in the treatment response in depression.<sup>11</sup> Taken together, based on the findings of the present study, a predictive value of pretreatment frontal theta activity only for rTMS not only indicates that better baseline function in the fronto-cingulate circuit could be essential for rTMS to be effective, but also suggests that iTBS might be a better choice than rTMS for patients with more impaired fronto-cingulate dysfunction. However, this is speculative and further investigation in patients with depression is required to confirm this hypothesis. Our regression result showed that stimulation group, but not  $\Delta$ frontal $\theta$ , predicted the antidepressant responses. Our finding indicated that rTMS and piTBS have better antidepressant efficacy than sham treatment, independent of the frontal theta changes. However, we further did a regression analysis within the active groups, finding that only the  $\Delta$ frontal $\theta$  ( $\beta = -0.243$ ,  $t = -1.826$ ,  $p = 0.073$ ), but not the stimulation group ( $p = 0.587$ ), had a trend significance predicting antidepressant responses at W2. Taken together, the results from the present study supported that task-modulated frontal theta plays an important role in the antidepressant response of brain stimulation.

This study had a few limitations. First, we did not apply other neuroimaging tools in combination with electroencephalography; however, we had investigated the correlation of frontal theta and brain activities in our previous research,<sup>12</sup> and the present study was an extension trial using the same EEG design. Second, we used a 100% MT (motor threshold) for rTMS treatment, which was determined based on our previous studies that demonstrated the antidepressant efficacy of 10-Hz rTMS in comparison with sham treatment.<sup>1,12</sup> Although it

seems suboptimal, meta-analytical evidence has indicated that antidepressant effects between studies using intensities <100% MT and 100–120% MT were not significantly different.<sup>44</sup> Third, the present study investigated frontal $\theta$  from scalp electrodes, but did not directly measure rACC activity. However, our previous study combining EEG and PET had shown that the RECT-modulated increases in frontal $\theta$  correlated with rACC glucose uptakes.<sup>12</sup> Finally, treatment duration for 2 weeks could be too short. The standard duration of rTMS treatment is 4 to 6 weeks and meta-analytic evidence suggests that rTMS treatment over longer periods of stimulation (e.g., more than two weeks) may have better antidepressant effects,<sup>45</sup> we are conducting another piTBS study with a longer treatment period for further comparison.

## Conclusion

This first large randomized, sham-controlled trial confirmed that the task-modulated frontal theta activity could predict the treatment efficacy of rTMS but not piTBS, suggesting that antidepressant mechanisms of TBS might differ from those of rTMS.

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## Supplemental Material

Supplemental material for this article is available online.

## References

- Li CT, Wang SJ, Hirvonen J, et al. Antidepressant mechanism of add-on repetitive transcranial magnetic stimulation in medication-resistant depression using cerebral glucose metabolism. *J Affect Disord.* 2010; 127(1–3): 219–229.
- Berlim MT, Van den Eynde F, Daskalakis ZJ. Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. *Depress Anxiety.* 2013; 30(7): 614–623.
- Berlim MT, Van den Eynde F, Daskalakis ZJ. A systematic review and Meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. *Psychol Med.* 2013; 43(11): 2245–2254.
- George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry.* 2010; 67(5): 507–516.
- Huang YZ, Edwards MJ, Rouinis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron.* 2005; 45(2): 201–206.
- Berlim MT, McGirr A, Rodrigues Dos Santos N, Tremblay S, Martins R. Efficacy of theta burst stimulation (TBS) for major depression: an exploratory meta-analysis of randomized and sham-controlled trials. *J Psychiatr Res.* 2017; 90: 102–109.
- Li CT, Chen MH, Juan CH, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. *Brain.* 2014; 137(Pt 7): 2088–2098.
- Chistyakov AV, Rubicsek O, Kaplan B, et al. Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. *Int J Neuropsychopharmacol.* 2010; 13(3): 387–393.
- Blumberger DM, Vila-Rodriguez F, Thorpe KE, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet.* 2018; 391(10131): 1683–1692.
- Li CT, Cheng CM, Chen MH, et al. 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. *Biological Psychiatry.* 2020; 87(5): 443–450.
- Pizzagalli DA. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology.* 2011; 36(1): 183–206.
- Li CT, Hsieh JC, Huang HH, et al. Cognition-modulated frontal activity in prediction and augmentation of antidepressant efficacy: a randomized controlled pilot study. *Cereb Cortex.* 2016; 26(1): 202–210.
- Bailey NW, Hoy KE, Rogasch NC, et al. Responders to rTMS for depression show increased fronto-midline theta and theta connectivity compared to non-responders. *Brain Stimul.* 2018; 11(1): 190–203.
- Li CT, Chen MH, Juan CH, et al. Effects of prefrontal theta-burst stimulation on brain function in treatment-resistant depression: a randomized sham-controlled neuroimaging study. *Brain Stimulation.* 2018; 11(5): 1054–1062.
- Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. *Lancet.* 2012; 379(9820): 1045–1055.
- Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol.* 1967; 6(4): 278–296.
- Frane JW. A method of biased coin randomization, its implementation, and its validation. *Drug Information J.* 1998; 32(2): 423–432.
- Fekadu A, Wooderson S, Donaldson C, et al. A multidimensional tool to quantify treatment resistance in depression: the Maudsley staging method. *J Clin Psychiatry.* 2009; 70(2): 177–184.
- Zimmermann P, Fimm B. *Test for Attentional Performance (TAP)*. 1.5th ed. Freiburg, Germany: Psytest Press; 1997.
- Min BK, Park HJ. Task-related modulation of anterior theta and posterior alpha EEG reflects top-down preparation. *BMC Neurosci.* 2010; 11: 1–8.
- Nuwer MR, Lehmann D, da Silva FL, Matsuoka S, Sutherling W, Vibert JF. IFCN guidelines for topographic and frequency analysis of EEGs and EPs. The international federation of clinical neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl.* 1999; 52: 15–20.
- Soreide K, Korner H, Soreide JA. Diagnostic accuracy and receiver-operating characteristics curve analysis in surgical research and decision making. *Ann Surg.* 2011; 253(1): 27–34.
- Rufibach K. Use of brier score to assess binary predictions. *J Clin Epidemiol.* 2010; 63(8): 938–939; author reply 9.
- Teneback CC, Nahas Z, Speer AM, et al. Changes in prefrontal cortex and paralimbic activity in depression following two weeks of daily left prefrontal TMS. *J Neuropsychiatry Clin Neurosci.* 1999; 11(4): 426–435. (4):
- Langguth B, Wiegand R, Kharraz A, et al. Pre-treatment anterior cingulate activity as a predictor of antidepressant response to repetitive transcranial magnetic stimulation (rTMS). *Neuro Endocrinol Lett.* 2007; 28(5): 633–638.
- Asada H, Fukuda Y, Tsunoda S, Yamaguchi M, Tonoike M. Frontal midline theta rhythms reflect alternative activation of prefrontal cortex and anterior cingulate cortex in humans. *Neurosci Lett.* 1999; 274(1): 29–32.
- Rette D, McDonald E, Iosifescu DV, Collins KA. Neural predictors of the antidepressant placebo response. *Pharmaceuticals (Basel).* 2019; 12(4): 158.
- Arns M, Drinkenburg WH, Fitzgerald PB, Kenemans JL. Neurophysiological predictors of non-response to rTMS in depression. *Brain Stimul.* 2012; 5(4): 569–576.
- Bailey NW, Hoy KE, Rogasch NC, et al. Differentiating responders and non-responders to rTMS treatment for



- depression after one week using resting EEG connectivity measures. *J Affect Disord.* 2019; 242: 68–79.
30. De Gennaro L, Marzano C, Veniero D, et al. Neurophysiological correlates of sleepiness: a combined TMS and EEG study. *Neuroimage.* 2007; 36(4): 1277–1287.
  31. Iwabuchi SJ, Raschke F, Auer DP, Liddle PF, Lankappa ST, Palaniyappan L. Targeted transcranial theta-burst stimulation alters fronto-insular network and prefrontal GABA. *Neuroimage.* 2017; 146: 395–403.
  32. Hoogendam JM, Ramakers GM, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimul.* 2010; 3(2): 95–118.
  33. Dubin MJ, Mao X, Banerjee S, et al. Elevated prefrontal cortex GABA in patients with major depressive disorder after TMS treatment measured with proton magnetic resonance spectroscopy. *J Psychiatry Neurosci.* 2016; 41(3): E37–E45.
  34. Li CT, Huang YZ, Bai YM, Tsai SJ, Su TP, Cheng CM. Critical role of glutamatergic and GABAergic neurotransmission in the Central mechanisms of theta-burst stimulation. *Hum Brain Mapp.* 2019; 40(6): 2001–2009.
  35. Cavanagh JF, Frank MJ. Theta as a mechanism for cognitive control. *Trends Cogn Sci.* 2014; 18(8): 414–421.
  36. Cooper PS, Wong AS, Fulham WR, et al. Theta frontoparietal connectivity associated with proactive and reactive cognitive control processes. *Neuroimage.* 2015; 108: 354–363.
  37. Romei V, Thut G, Silvanto J. Information-Based approaches of noninvasive transcranial brain stimulation. *Trends Neurosci.* 2016; 39(11): 782–795.
  38. Noh NA, Fuggetta G, Manganotti P, Fiaschi A. Long lasting modulation of cortical oscillations after continuous theta burst transcranial magnetic stimulation. *PLoS One.* 2012; 7(4): e35080.
  39. Mulert C, Juckel G, Brunmeier M, et al. Rostral anterior cingulate cortex activity in the theta band predicts response to antidepressive medication. *Clin EEG Neurosci.* 2007; 38(2): 78–81.
  40. Baskaran A, Milev R, McIntyre R. The neurobiology of the EEG biomarker as a predictor of treatment response in depression. *Neuropharmacology.* 2012; 63(4): 507–513.
  41. Pizzagalli DA, Webb CA, Dillon DG, et al. Pretreatment rostral anterior cingulate cortex theta activity in relation to symptom improvement in depression: a randomized clinical trial. *JAMA Psychiatry.* 2018; 75(6): 547.
  42. Pizzagalli DA, Oakes TR, Davidson RJ. Coupling of theta activity and glucose metabolism in the human rostral anterior cingulate cortex: an EEG/PET study of normal and depressed subjects. *Psychophysiology.* 2003; 40(6): 939–949.
  43. Mayberg HS, Brannan SK, Mahurin RK, et al. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport.* 1997; 8(4): 1057–1061.
  44. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a Meta-analysis. *Psychol Med.* 2009; 39(1): 65–75.
  45. Dell’osso B, Camuri G, Castellano F, et al. Meta-Review of metanalytic studies with repetitive transcranial magnetic stimulation (rTMS) for the treatment of major depression. *Clin Pract Epidemiol Ment Health.* 2011; 7: 167–177.