

Cognition-Modulated Frontal Activity in Prediction and Augmentation of Antidepressant Efficacy: A Randomized Controlled Pilot Study

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Higher rostral anterior cingulate cortex (rACC) activity correlated with frontal theta power (frontal θ) is associated with better antidepressant responses. The antidepressant efficacy of repetitive transcranial magnetic stimulation (rTMS) varied widely; however, the effects of TMS might be modulated by manipulating the pretreatment neural states. Therefore, we conducted a pilot study to investigate whether manipulated frontal θ before rTMS treatment could predict and augment antidepressant responses. A computerized rACC-engaging cognitive task (RECT) was exploited continuously for 10 min to patients with major depressive disorder. In total, 36 patients were randomized to 3 groups (Group-A: RECT[active] + rTMS[active]; Group-B: RECT[sham] + rTMS[active]; Group-C: RECT[active] + rTMS[sham]). Frontal θ and whole-brain glucose uptakes were assessed. We found that the RECT-modulated increases in frontal θ correlated well with rACC glucose uptakes. The treatment responders demonstrated a significant increase in frontal θ after RECT. Post-RECT frontal θ had good sensitivity/specificity in predicting antidepressant responses to rTMS. Group-A had more reduction in total depression scores, had more responders, and was more likely to achieve remission than other groups (Group-A [41.6%] > Group-B [16.6%] > Group-C [0%], $P < 0.05$). A significant enhancement in the post-1st-rTMS frontal θ was observed in Group-A responders but not in Group-B responders, supporting the argument that RECT-modulated rTMS augmented rTMS efficacy. In conclusion, this study suggests that manipulating pre-rTMS neural activity could predict and augment antidepressant effects to rTMS treatment.

Keywords: anterior cingulate cortex, electroencephalography, major depression, positron emission tomography, repetitive transcranial magnetic stimulation, state-dependent, theta

Introduction

Higher glucose uptakes or neuronal activity in rostral anterior cingulate cortex (rACC) is considered as a reliable biomarker predicting better antidepressant responses in major depressive disorder (MDD) across treatment choices (e.g., antidepressants, sleep deprivation, and neurostimulation) (Pizzagalli 2011). The link between increased pretreatment rACC activity and medication responses has been examined irrespective of whether the rACC activity/metabolism was measured at rest, in response to emotional stimuli, or in a response inhibition task (Pizzagalli 2011). rACC activity as a key indicator in the treatment outcome could be due to its hub position in the default network (Pizzagalli 2011). Anterior cingulate cortex is structurally and functionally connected to both prefrontal cortex (PFC)

and several limbic structures including amygdala (Devinsky et al. 1995). Adequate rACC activity might facilitate adaptive self-referential processing and help to recalibrate relationships between the default network and a “task-positive network.” The task-positive network comprises brain regions implicated in cognitive control such as dorsolateral PFC and dorsal ACC regions (Pizzagalli 2011). rACC also plays a critical role in the limbic-cortical network associated with depression (Mayberg et al. 1997; Mayberg 2002).

Frontal electroencephalography (EEG) theta activity during consecutive mental tasks is a manifestation of activity of the medial PFC and ACC (Asada et al. 1999). Frontal theta (frontal θ) power not only increases in the working memory task conditions when compared with rest but is also modulated by task difficulty (Brookes et al. 2011). Notably, increased resting rACC theta current density before treatment has been found to predict a positive response to antidepressant drugs in patients with MDD (Mulert et al. 2007; Baskaran et al. 2012), but not to placebo (Korb et al. 2009). Another study by using simultaneous EEG and positron-emission-tomography (PET) recordings in human subjects confirmed a coupling between theta electrical activity (EEG) and ACC metabolic activity (PET) at rest (Pizzagalli et al. 2003).

The relationship between antidepressant treatment outcomes and baseline EEG theta activity, particularly in frontal EEG, has been proposed (Baskaran et al. 2012). For example, pretreatment frontal θ activity was reported to differentiate responders from non-responders after open-labeled paroxetine treatment for 6 weeks (Knott et al. 2000). Likewise, a recent study reported the association between higher pretreatment frontal θ power and better treatment response to a variety of antidepressants (Spronk et al. 2011). However, the use of baseline resting-state EEG theta activity to predict treatment responses is also limited due to inconsistent results (Iosifescu et al. 2009). Therefore, a more sensitive and reliable method is needed.

Therefore, in the present study, an rACC-engaging cognitive task (RECT) (which highly depends on sustained attention and working memory during performance) was designed to engage the task-related neurons and presented to a group of MDD patients before active-repetitive transcranial magnetic stimulation (rTMS) treatment. Repetitive transcranial magnetic stimulation was selected here as the antidepressant treatment of choice since a link between pretreatment rACC glucose uptakes and antidepressant responses to rTMS has also been established (Li et al. 2010; Pizzagalli 2011).

Functional abnormalities in the PFC, the target of the rTMS treatment, have been found as a major cause leading to the development of depression (Baxter et al. 1989). However, a growing body of evidence indicated that the brain effects from left prefrontal rTMS are widespread, not only in the target brain regions but also in the remote cortical and subcortical brain regions such as striatum, temporal cortex, hippocampus/parahippocampus, thalamus, and amygdala (Teneback et al. 1999; Speer et al. 2000; Li et al. 2010, 2013). Furthermore, baseline activity/function in the rACC, instead of the dorsolateral PFC, was consistently reported to be correlated with the rTMS's antidepressant effects (Teneback et al. 1999; Langguth et al. 2007; Li et al. 2010). The correlation of resting rACC activity at baseline with clinical responses to various kinds of antidepressant interventions was highly based on the results of a recent meta-analysis (see reviews by Pizzagalli 2011). Such results were also in line with Dr Helen Mayberg's original finding on the association between pretreatment glucose metabolism of the rACC at baseline and subsequent antidepressant responses (Mayberg et al. 1997), in which glucose metabolism in the rACC, but not in other brain regions, discriminated the treatment responders and non-responders.

We set out to investigate 2 issues in the current study. First, we aimed to probe whether more post-RECT changes in frontal θ power may reflect higher rACC activity at baseline and thus predict better responses to rTMS antidepressant treatment. Second, we wanted to explore the possibility of using the RECT program repeatedly for 10 days to increase baseline rACC activity and further enhance rTMS antidepressant efficacy. The rationale of this experimental design is conceptually similar to those investigating state-dependent TMS effects on perception and cognitive functions. By manipulating neural activation states before TMS application, one might be able to selectively target specific neural populations within a region (Silvanto et al. 2008; Pasley et al. 2009) and, in turn, lead to behavioral enhancement (Banissy and Muggleton

2013). Many TMS studies have successfully demonstrated such effects in various cognitive functions (Silvanto et al. 2007, 2008; Cattaneo et al. 2009). It has been proposed that state-dependent TMS effects could be applicable to the clinical context (Pasley et al. 2009; Banissy and Muggleton 2013). Besides, daily prefrontal TMS in combination with cognitive training for a short period (e.g., 5 consecutive days) was able to induce long-term enhancement of cognitive and brain functions (Snowball et al. 2013). However, it remains to be tested whether a manipulation of the network pivotal to the antidepressant effects (i.e., to prime the system consisting of the rACC) may enhance rTMS antidepressant efficacy. To answer our second question, a randomized sham-controlled pilot study was performed to compare rTMS antidepressant effects between MDD groups with and without pretreatment frontal θ modulations.

Material and Methods

Study Design

The study involved a three-group (A, B, and C), double-blind, randomized, sham-controlled trial ($n = 12$ for each group) (see Supplementary Fig. S1 for subject recruitments). The study design is illustrated in detail in Figure 1. To study whether manipulated frontal θ power could be of predictive value for antidepressant responses, 3 separate resting-state EEG datasets were acquired on the first day of the rTMS course, including 2 baselines (i.e., pre-RECT and post-RECT) acquired before rTMS treatment and a third one acquired immediately after the first session of rTMS treatment. To study whether frontal θ changed after the 2-week RECT (active or sham) combined with rTMS (active or sham) treatment, the last EEG data were acquired right before the tenth rTMS session.

Baseline psychiatric ratings, attentional performance, EEG frontal theta power, and PET scans were obtained from the medication-free MDD patients with details described in the respective method sections. Structural (magnetic resonance imaging, MRI) imaging scans were acquired on the same day or, due to clinical limitations, at most within 5 days of the study day.

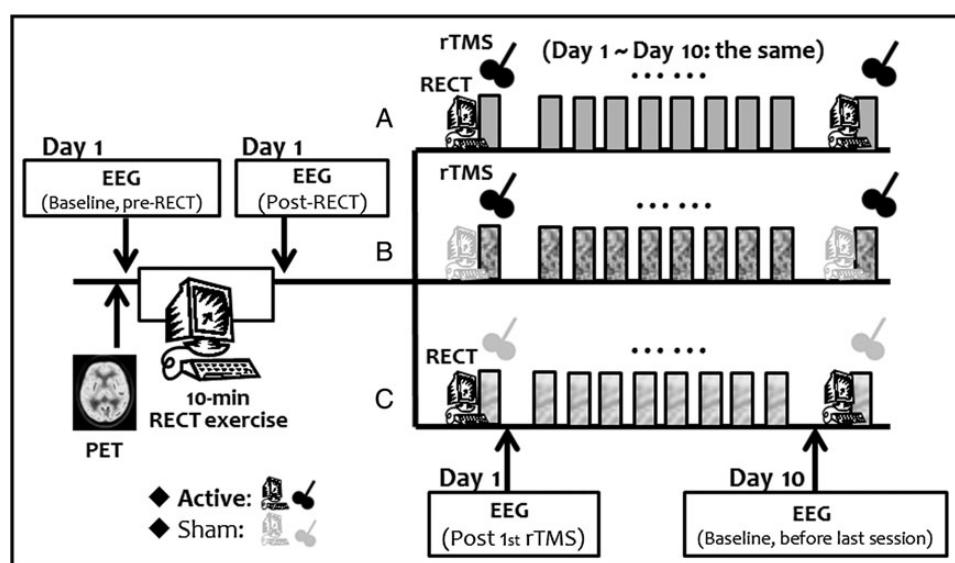


Figure 1. Study design. A computerized RECT program was performed by all participants continuously for 10 min to manipulate frontal theta activity. Pre-RECT, post-RECT, and post-1st-rTMS resting-state EEG data on the first day of rTMS treatment were analyzed for each patient. The only between-group difference before the first rTMS was the procedure for the first rTMS (A: active RECT + active rTMS; B: sham RECT + active rTMS; C: active RECT + sham rTMS). In Group-A, a 10-min RECT was re-presented every day right before the active-rTMS treatment. In Group-B, a 10-min sham RECT was presented every day right before the active-rTMS treatment. In Group-C, a 10-min active RECT was re-presented but was followed by a sham rTMS treatment every day for 10 days. Another EEG recording right before the last rTMS session was also obtained.

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

Study Subjects

All recruited patients were MDD without major physical illnesses and substance abuse. All patients presented with moderate severity scores of ≥ 18 on the 17-item Hamilton Depression Rating Scale (HDRS-17) before rTMS treatment (see Supplementary material for other details).

rTMS Procedures

The detailed rTMS procedures were carried out largely as has been described previously (Li et al. 2010). To summarize, brain-navigation computer software and an infrared system were used to accurately guide the figure-8-shaped stimulating coil to target the left dorsolateral PFC, based on each patient's brain MRI. Ten daily rTMS treatment sessions were administered for 2 consecutive weeks (parameters: 10 Hz, 100% motor threshold, 4-s on and 26-s off, 40 times/session, and 5 sessions/week). Patients received active (with the angle of coil being tangential to the skull) or sham rTMS (90° off the skull) during the course of rTMS treatment (Fig. 1). Patients who showed >50% improvement in depression rating scores were defined as responders.

Psychiatric Evaluations

Demographic and clinical characteristics were obtained by a thorough history-taking. Psychiatric ratings for mood and somatic severity were taken at baseline (pre-rTMS, W0), the end of the first week of rTMS treatment (W1), and the end of the second week of rTMS treatment (W2). Objective assessments were done by an experienced psychiatrist (T.-P. Su) who was blind to the study design and the randomization results, including ratings for HDRS-17 and Young Mania Rating Scales (YMRS). Subjective assessments of somatic painful symptoms were evaluated by using a 10-cm Visual Analogue Scale (VAS) pain and VAS-unpleasantness scale.

Neurocognitive Tests for Attentional Performance

Neurocognitive tests were performed at W0 and W2 by a trained research assistant. Attentional function was measured by Tests for Attentional Performance (Zimmermann and Fimm 1997) with visual task (detection of a square among crosses) used to measure visual attention function. Reaction times (mean and standard deviations [SD]) and omissions were recorded for further analyses. Longer reaction times and more omissions represented poorer attentional performance (see Supplementary material for details).

Computerized rACC-Engaging Cognitive Task

The RECT program was primarily based on the flexibility task of the Tests for Attentional Performance (Zimmermann and Fimm 1997). During the task, competing stimuli (sharp and rounded in form) were presented simultaneously on the left and right side of the computer screen and patients were asked to press a response key indicating the correct side of the screen containing the target stimuli with their index finger as long as the target stimuli appeared. The shape task, instead of a color task, was used for the target stimuli of the RECT program here since the former takes higher levels of attention and has been found to be associated with more frontal θ engagement than the latter (Min and Park 2010). After the pretest trials, patients performed 10-min of continuous testing trials under the supervision of a trained research assistant to maximize full engagement on the program (see Supplementary material for details). Notably, this modified, prolonged flexibility program is easy but has high demands on sustained attention and working memory for alternating target stimuli (sharp vs. rounded). In contrast, the sham-RECT computer program included a 10-min slideshow with different forms alternately appearing on the screen, but patients only needed to watch the stimuli without taking any action during the presentation. Subjects were prenotified that the sham-RECT computer program was aimed to enhance their brain activity

essentially for rTMS efficacy. Active (or sham) rTMS treatment was applied immediately after the active (or sham) RECT training at every session for every patient.

EEG Data Acquisition and Analysis

EEG data were acquired in a dimly lit, electrically shielded quiet room. To summarize, 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 5 k Ω (other details in Supplementary material). Neuroscan amplifiers (Nuamps) and Neuroscan 4.3 software were used for EEG recording, while patients were seated in a comfortable arm-chair with eyes closed in a maximally alert state. During each 3-min EEG recording, the alertness was controlled. 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. Fast Fourier transform was used to calculate absolute and relative power in each of 5 frequency bands (Nuwer et al. 1999): 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 1 specific band divided by the sum of that in the 5 frequency bands. 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 θ). The selected sensors in the frontal region should be able to cover frontal midline theta, which is closely related to dorsal ACC and cognitive domain of attention function, and other sources of theta activity from the frontal area.

Imaging Studies

MRI and PET Data Acquisition

T1-weighted images (T1-images; repetition time [TR] = 2530 ms, echo spacing = 7.25 ms, echo time [TE] = 3 ms, flip angle = 7°, FOV = 256 × 256 mm, and isotropic 1 × 1 × 1 mm voxels) were acquired mainly for improving spatial registration and normalization of PET data, on a 3T MR system (GE Discovery 750 whole-body high-speed imaging device). ¹⁸F-FDG PET scans of glucose utilization at rest were acquired on a PET/CT scanner (Discovery VCT; GE Healthcare) with a 3D brain mode. Patients fasted for at least 8 h before the PET examination. PET images were acquired in 45 min after an intravenous injection of about 370 MBq of ¹⁸F-FDG. The brain acquisition time was 15 min. Detailed procedures were identical to our previously published paper (Li et al. 2012).

PET Data Analysis

All preprocessing and analyses of images were performed on using statistical parametric mapping software (SPM8; Wellcome Department of Imaging Neuroscience; available online at <http://www.fil.ion.ucl.ac.uk/spm>) (Friston et al. 1995). Each subject's images were normalized to a study-specific MRI-aided ¹⁸F-FDG template (for details, please see Supplementary material) and smoothed with a 3D Gaussian kernel (FWHM = 12 × 12 × 12 mm). Voxel-based partial correlations were performed for investigating the associations between the glucose uptakes of the ACC and the improvement in depressive symptoms (% HDRS change), the baseline frontal θ , and the % frontal θ differences between baseline and post-RECT frontal θ , after covarying for age, gender, and total brain glucose uptakes (Friston 1997); the statistical threshold was set at voxel-level family-wise errors -corrected $P < 0.05$ or voxel-level uncorrected $P < 0.005$ with a small volume correction for multiple comparisons with an 8-mm radius sphere on the peak voxel in the a priori region-of-interest of ACC (Li et al. 2010).

Statistics for Demographic Data, Clinical Variables, and Neuro-Electrical Signals

Demographic data as well as clinical variables and neuro-electrical signals were analyzed using SPSS 16.0 software (SPSS, Inc.). One-way ANOVA and chi-square tests were applied to compare the continuous and categorical variables among independent groups, respectively. A post hoc LSD analysis was done to determine significant between-groups differences ($P < 0.05$). Before the ANOVA analysis, we used Levene's test

Table 1

Baseline characteristics and clinical variables over time

	A	B	C	F/χ^2	<i>P</i> -value	Non-parametric analysis ^a (χ^2/P -value)
Age (years)	43.4 (9.0)	39.4 (13.2)	42.4 (12.5)	1.098	0.347	(2.048/0.359)
Sex, male/female (N/N)	4/8	5/7	6/6	0.686	0.710	—
Education (years)	12.8 (4.2)	13.3 (3.3)	12.2 (4.4)	0.206	0.815	(0.188/0.910)
Duration (years)	12.8 (9.5)	9.1 (9.8)	10.1 (10.2)	0.426	0.657	(1.510/0.470)
MDEs (times)	7.2 (3.0)	4.7 (3.0)	6.5 (3.2)	0.186	0.174	(3.713/0.156)
Current episode (months)	5.2 (4.1)	6.3 (4.7)	6.9 (11.1)	0.156	0.856	(0.509/0.775)
VAS-pain (W0)	5.0 (3.7)	4.8 (2.1)	4.8 (2.1)	0.025	0.975	(0.198/0.906)
VAS-pain (W1)	3.7 (3.1)	4.0 (2.1)	5.1 (3.1)	0.742	0.485	(1.386/0.500)
VAS-pain (W2)	3.8 (3.6)	4.4 (2.5)	5.2 (2.0)	0.714	0.498	(0.928/0.629)
YMRS (W0)	2.3 (3.5)	1.0 (1.8)	0.9 (1.0)	1.314	0.284	(1.895/0.388)
YMRS (W1)	1.0 (1.3)	0.8 (1.3)	1.2 (1.4)	0.205	0.816	(0.638/0.727)
YMRS (W2)	1.1 (1.4)	1.0 (1.8)	1.4 (1.8)	0.138	0.871	(0.452/0.798)
HDRS-17 (W0)	22.5 (6.7)	22.8 (5.0)	21.9 (4.9)	0.072	0.931	(0.337/0.845)
HDRS-17 (W1)	12.6 (9.5)	14.5 (6.1)	19.3 (7.7)	2.074	0.143	(3.866/0.145)
HDRS-17 (W2)	11.6 (9.0)	14.0 (7.6)	19.6 (4.7)	3.473	0.044*	6.173/0.046*
Responders, <i>N</i> (%)	7 (58.3%)	5 (41.7%)	1 (8.3%)	6.742	0.034*	—
Remitters, <i>N</i> (%)	5 (41.6%)	2 (16.6%)	0 (0.0%)	6.739	0.034*	—

Note. Data presented as mean (SD). MDE, major depressive episodes; VAS, 10-cm Visual Analogue Scale; YMRS, Young Mania Rating Scale; HDRS-17, 17-item Hamilton Depression Rating Scale; W0, the day before the initiation of rTMS treatment; W1, the day after the 1-week rTMS treatment; W2, the end of the 2-week rTMS treatment.

^aIf the homogeneity assumption has been violated, non-parametric analysis was applied (i.e., Kruskal–Wallis test for continuous variables; χ^2 values were reported).

^bMore than 50% improvement of HDRS-17 after the 2-week rTMS treatment.

^cHDRS-17 scores ≤ 7 after the 2-week rTMS treatment.

* $P < 0.05$.

for homogeneity of variances to ensure that the homogeneity assumption has not been violated. If the results from Levene's test were significant ($P < 0.05$), non-parametric analysis were applied by Kruskal–Wallis test and Mann–Whitney *U*-test for the 3-group and the 2-group comparisons, respectively. Paired *t*-tests were used to compare within-subject frontal θ changes between 2 different time-points (e.g., pre-RECT vs. post-RECT). A partial correlation test (2-tailed) was chosen to examine the relationship between baseline attentional performance and baseline frontal θ power, controlling for age and gender. As for the sub-analysis comparing theta changes over time in the responders and non-responders, non-parametric analysis with Wilcoxon Signed Ranks tests (2 related data, e.g., baseline vs. post-RECT) was performed due to the small sample size and non-spherical distributions. The significance level was set at a *P*-value of < 0.05 . Receiver operating characteristic (ROC) curves were plotted for assessing the accuracy of predictions of antidepressant responses by pretreatment EEG frontal θ . Area under the ROC curve (AUC) and the optimal cutoff with maximum sum of sensitivity and specificity were calculated (Soreide et al. 2011).

Results

Demographic Characteristics and Clinical Variables among Groups

The 3 groups were similar for demographic and disease-related characteristics such as age, sex, education level, duration of illness, past major depressive episodes, and duration of current episode (Table 1). Baseline scores of HDRS-17, YMRS, and pain-related variables were also comparable. The active-rTMS treatment (Group-A and Group-B) for 2 weeks had significant antidepressant effects compared with the sham rTMS effect (Group-C), as demonstrated by significant decreases in the HDRS-17 scores over 2 weeks and the fact that more subjects in the Group-A and Group-B were responders and remitters than in Group-C (Table 1). In total, 41.6% of patients in Group-A and 16.6% of patients in Group-B met the symptomatic remission criteria (i.e., remitters in Table 1). The results also indicated that pure RECT for 2 weeks (Group-C) did not improve depression. The mean % HDRS-17 decrease after 2 weeks among the 3 groups was significantly different (ANOVA,

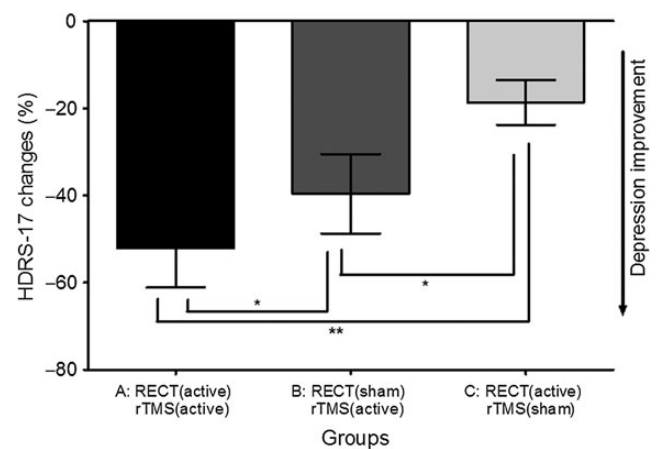


Figure 2. Mean (\pm SD) changes of total depression scores as rated by HDRS-17 in the 3 groups (Kruskal–Wallis test, chi-square = 7.329, $P = 0.026$), indicating that RECT-modulated rTMS (Group A) had better clinical effects. Group-A had significantly better antidepressant effects than Group-B and Group-C (by Mann–Whitney *U*-tests; Group-A vs. Group-B, $Z = -2.449$, $P = 0.014$ and Group-A vs. Group-C, $Z = -3.098$, $P = 0.001$). * $P < 0.05$, ** $P < 0.005$.

$F_{df=2, 33} = 5.226$, $P = 0.011$; Kruskal–Wallis test, chi-square = 7.329, $P = 0.026$) and was highest in Group-A (mean \pm SE = $-52.1\% \pm 9.0\%$), followed by Group-B ($-39.6\% \pm 9.1\%$) and then Group-C ($-18.6\% \pm 4.8\%$) (Fig. 2). Group-A had better antidepressant effects than Group-B ($P = 0.014$) (Fig. 2). Most HDRS-17 domains improved in the active-rTMS groups and Group-A showed best performance in some domains (e.g., HDRS-17 item-1: depression) (see Supplementary Fig. S2).

Neurocognitive Profiles and EEG Variables among Groups

Baseline scores of neurocognitive performance and EEG relative spectral power in each frequency band were comparable (see Supplementary Table S1). No significant difference in the

neurocognitive performance and EEG signals was observed between the W0 and W2 measures in each group. There was a significant positive correlation ($r=0.395$, $P<0.05$) between baseline frontal θ and mean response time for the visual attention task (see Supplementary Fig. S3).

Modulated frontal θ and Antidepressant Responses to 2 weeks of rTMS Treatment

Post-RECT frontal θ and the differences between pre-RECT and post-RECT frontal θ were significantly different between responders and non-responders (all $P<0.05$, Fig. 3A), despite no difference in the baseline frontal θ . Neither in the Group-A nor

Group-B could baseline frontal θ reliably differentiate responders from non-responders. No frontal θ change was observed before and after 2 weeks of rTMS treatment (W0 vs. W2) (Fig. 3B). The RECT immediately before rTMS further augmented post-RECT frontal θ , as demonstrated by an enhanced post-1st-rTMS frontal θ in Group-A responders (Wilcoxon Signed Ranks tests; $Z=-2.366$, $P=0.018$, see the first and third column in Fig. 3C), but not in the Group-B responders ($Z=-1.483$, $P=0.138$, see the first and third column in Fig. 3D). Likewise, if all subjects in each group were all included, a significant increase of the post-1st-rTMS frontal θ was observed in the Group-A, but not in Group-B (data not shown).

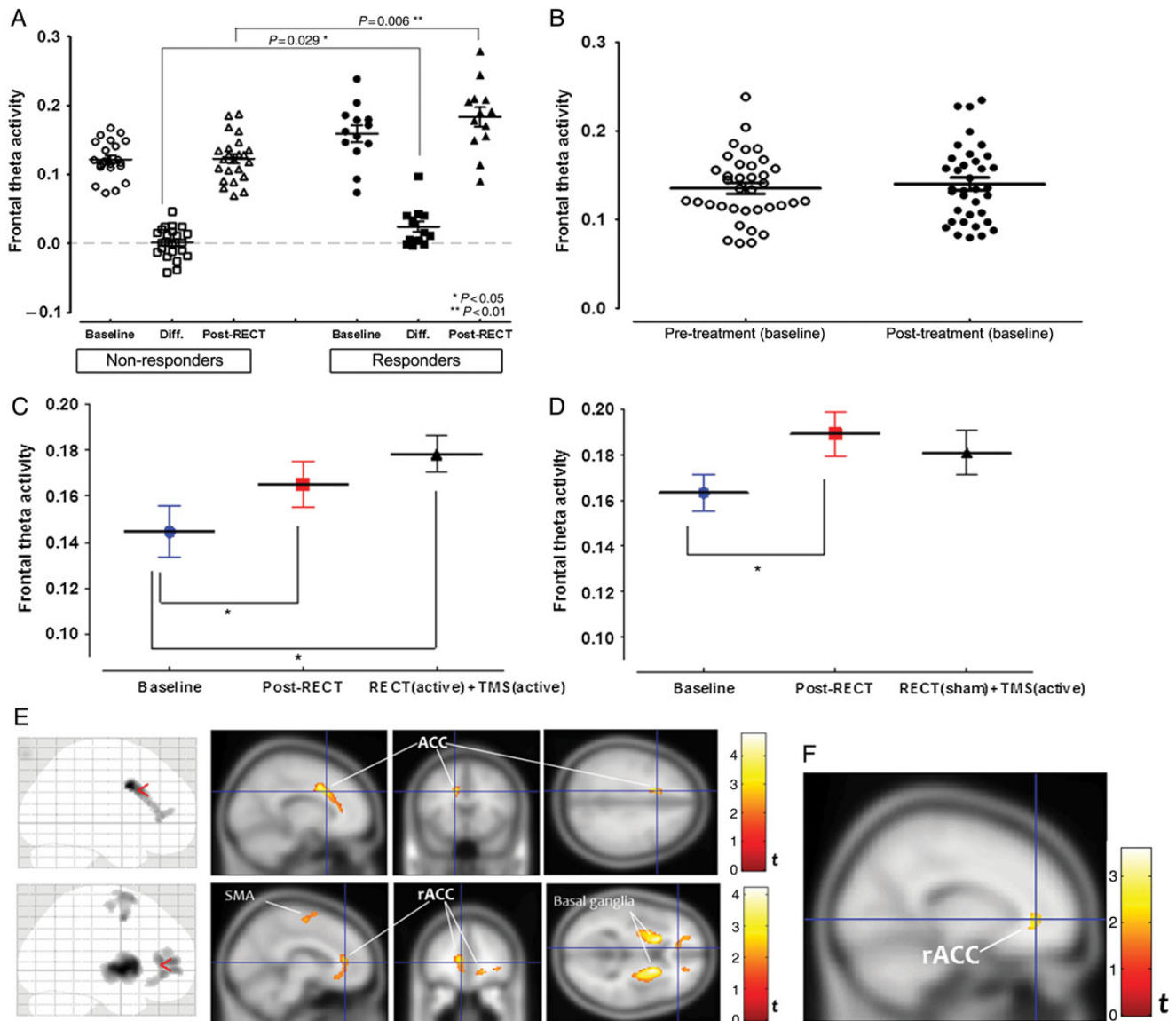


Figure 3. Baseline and modulated frontal theta activity and correlations with baseline glucose uptakes as measured by ^{18}F -FDG PET. (A) RECT-modulated frontal theta activity differed significantly between the rTMS responders and the non-responders; the difference (Diff.) of frontal theta activity between baseline and post-RECT was significantly higher in the rTMS responders than in the non-responders. (B) Frontal theta activity at baseline showed no changes between pre- and post-2-week rTMS treatment; (C) Frontal theta activity increased significantly in response to RECT (Wilcoxon signed ranks test; $Z=-2.023$, $P=0.043$) and was further enhanced after active-RECT and active-rTMS treatment in Group-A responders ($Z=-2.366$, $P=0.018$); (D) frontal theta activity also increased significantly in response to RECT ($Z=-2.197$, $P=0.028$) but showed no significant increase after sham-RECT or active-rTMS treatment in the Group-B responders ($Z=-1.483$, $P=0.138$); (E) upper panel: Frontal theta activity correlated significantly with baseline anterior cingulate cortex (ACC) glucose uptake (maximum correlation: dorsal ACC); lower panel: Frontal theta activity after RECT modulation correlated significantly with rostral ACC glucose uptakes; (F) rostral ACC glucose uptakes correlated significantly with % HDRS-17 decreases in response to 2-week rTMS treatment. Correlation of relative frontal theta power and brain glucose uptake was performed at the voxel level after controlling for age, gender, and total brain uptake. Contrast bars represented t -values, statistical significance thresholded at corrected $P<0.05$.

Correlations between Pretreatment Frontal θ and Baseline Glucose Uptakes

Correlation analysis demonstrated that baseline frontal θ was significantly correlated with glucose uptakes in a cluster consisting of dorsal ACC and part of rACC (peak MNI coordinate: [-16, 8, 36], 54 voxels, $t=4.76$, corrected $P=0.023$) (Fig. 3E, upper panel; see Supplementary Fig. S4), whereas the post-RECT % increases of the frontal θ correlated with that in the rACC (left: [-10,46,8], 377 voxels, $t=3.55$, $P=0.032$; right: [14,46,2], 403 voxels, $t=2.95$, $P=0.044$) (see Supplementary Fig. S4), as well as some non-a priori areas responsible for motor planning and execution such as supplementary motor area ([18, 2, 50], 470 voxels, $t=2.81$), right basal ganglia ([24, 0, 2], 1315 voxels, $t=4.22$), and left basal ganglia ([-18, 12, 6], 1147 voxels, $t=3.92$) (Fig. 3E, lower panel). If the analyses of correlations between frontal θ and glucose uptakes were done separately in each group, there would be no significant findings.

Baseline rACC Glucose Uptake and Responses to 2 weeks of rTMS Treatment

Whole-brain analysis demonstrated that glucose uptakes in the rACC (peak coordinate = [16, 39, 1], cluster size = 273 voxels, $t=3.21$, $P=0.032$) were significantly correlated with % HDRS-17 changes after 2 weeks of treatment (Fig. 3F). There was no significant correlation if analysis was done separately in each group. Furthermore, we also investigated whether baseline PFC activities at the target (i.e., left dorsolateral PFC) could predict antidepressant effects in the present study. We found such an association to be absent (AUC = 0.516, 95% CI = 0.318–0.715, $P=0.873$). The results from the present study with a separate cohort of MDD patients are consistent with the findings from our previous study (Li et al. 2010), confirming that rACC pretreatment activity could have a predictive value for 2-week rTMS treatment efficacy.

Predicting rTMS Responses by Frontal Theta Activity

Area under the ROC curve for baseline frontal θ was 0.673 and for post-RECT frontal θ was 0.799 (Fig. 4). If we arbitrarily thresholded at 0.1483 (post-RECT frontal θ), the sensitivity and specificity to accurately predict antidepressant responses are 83.3% and 77.3%, respectively. As for the other frequency bands, none were predictive of the antidepressant responses. When frontal θ was analyzed separately in different rTMS groups (i.e., Group-A and Group-B), post-RECT frontal θ also had better predicting values than baseline frontal θ for Group-A (AUC; post-RECT frontal θ vs. baseline frontal θ = 0.886 vs. 0.723) and Group-B (0.829 vs. 0.741). These results indicate that pretreatment, RECT-modulated frontal θ could be a more useful biomarker in predicting subsequent antidepressant outcomes than baseline frontal θ without any modulation.

Discussion

The present study is the first to demonstrate the potential to predict and augment rTMS antidepressant efficacy by manipulating the pretreatment brain states.

As hypothesized, the cognition-modulated frontal θ (i.e., post-RECT frontal θ) had the potential to predict antidepressant responses to the 2-week rTMS treatment with acceptable sensitivity and specificity (Fig. 4), possibly because the RECT-modulated frontal θ better reflected pretreatment rACC

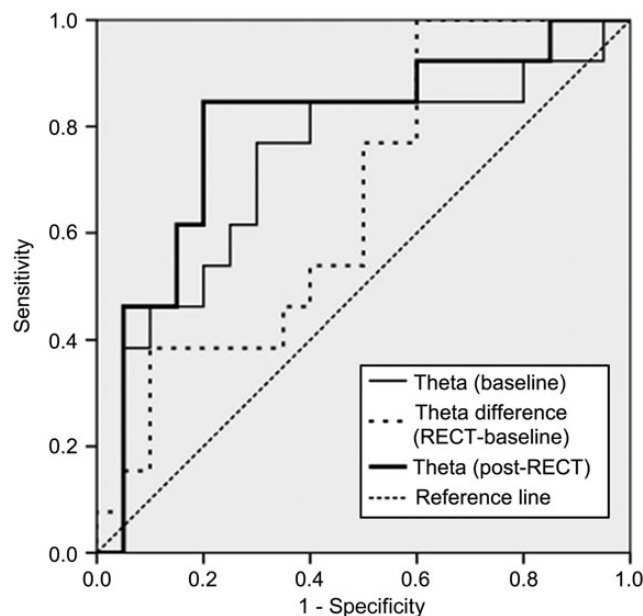


Figure 4. Receiver operating characteristic curves. The RECT-modulated frontal theta activity at baseline (thick solid line) better predicted antidepressant responses to 2-week rTMS treatment, than non-modulated frontal theta at baseline (thin solid line) and the differences between RECT-modulated and non-modulated frontal theta (dashed line).

neuronal activity than did the unmodulated EEG data. We also found that post-RECT frontal θ had better predicting values than baseline frontal θ for both active-rTMS groups, including Group-A (active rTMS combined with RECT) and Group-B (active rTMS without RECT). High-frequency rTMS targeting the left PFC for several weeks is effective in the treatment of antidepressant-resistant MDD (Daskalakis et al. 2008; Berlim et al. 2014; George et al. 2013). However, the reported antidepressant results in the previous studies have been inconsistent and not every subject responded well to rTMS. Therefore, how to predict rTMS's antidepressant effect is clinically important. Since the rTMS parameters adopted in the present study (e.g., 10 Hz, 100% MT, and 1600 pulses/session) are widely used for clinical treatment of depression, the findings of a good predictive value by RECT-modulated frontal θ before rTMS treatment might therefore benefit the population suffering from depression.

As for our second aim, we found that the RECT-modulated rTMS had better antidepressant performance than non-modulated rTMS (Fig. 2). One may argue that the sham condition was perhaps not ideal, yet it was a conventional way and we tried to minimize potential procedural bias by selecting only patients who did not have rTMS experiences, assigning randomization groups by a research assistant who was blind to the study design, and performing psychiatric assessments by a psychiatrist who was also blind to the study design. Most importantly, the most crucial comparison in this study was the one between Group-A and Group-B, both of whom received active rTMS but only Group-A underwent active-RECT modulation. Therefore, our finding that there were significant differences between 2 active-rTMS groups ruled out the more simple explanations in terms of sham not being ideal. The augmentation of rTMS efficacy may be due to the activities of rACC immediately after RECT-modulated rTMS. Supporting evidence comes from the augmentation of the frontal θ power after the

first session of rTMS was seen in Group-A responders (Fig. 3C) but not in Group-B responders (Fig. 3D), and higher pretreatment rACC activity was associated with better outcome to antidepressant treatment (Mulert et al. 2007; Pizzagalli 2011; Baskaran et al. 2012). Likewise, recent evidence indicated that higher pre-TMS neural activity predicts greater post-TMS responses (Pasley et al. 2009). The behavioral effects of TMS are state-dependent and determined by initial neural activation state (Silvanto et al. 2008; Pasley et al. 2009). Despite the experimental designs and purposes differing across studies, the concept that the final TMS responses are highly dependent on the pretreatment neural states is in line with our findings. In addition, previous experiments of motor cortex stimulation revealed that time intervals between finger movements and paired associative brain stimulation, and physical activity during noninvasive brain stimulation had an impact on resulting cortical excitability and motor performance (Huang et al. 2008; Jung and Ziemann 2009). We tried to control these confounding factors by applying rTMS treatment immediately after the RECT training at every session and reminding patients to stay awake during the whole process of rTMS application. However, the most optimal protocol to modulate frontal theta and to augment antidepressant responses (e.g., exercising RECT during rTMS) remains to be determined.

Since frontal θ activity is increased as the task difficulty is increased (Brookes et al. 2011) and frontal θ increased after RECT in the rTMS responders, the increased frontal θ may reflect that the RECT was challenging and not an easy task for these subjects. Thus, we argue that, in the rTMS responders, the ACC neurons originally in a less-active state may have been “revived” and engaged temporarily following the RECT program. This notion could be supported by the observation that higher frontal θ at baseline was correlated with increased mean response times for visual attention (see Supplementary Fig. S3). But, since we did not measure ACC activity immediately after the RECT exercise, further studies are warranted to confirm such speculations.

Although we did not measure cognitive functions directly after the 10-min RECT, the temporarily increased frontal θ activity might reflect some cognitive-related effects (e.g., an enhancement of general vigilance or motivation-related mental effort to suppress negative emotions). For example, a recent fMRI study investigated the role of frontal θ oscillation during the cognitive reappraisal of aversive pictures in human subjects (Ertl et al. 2013). The investigators found an increase in frontal θ oscillation during emotional regulation and a relationship between frontal θ activity and the subjective success of emotion regulation. Theta oscillations have been involved in mediating the influence of the PFC on the amygdala (Lesting et al. 2011). In a basic study investigating fear memory and extinction processes, theta oscillations occurred specifically in the amygdala–hippocampus–PFC network where the theta coupling increased during retrieval of conditioned fear and declined during extinction learning (Lesting et al. 2011). These findings suggest that theta activities play an important role in the mood-regulating pathway involving the PFC–amygdala circuit. We found no changes in theta activity and cognitive performance after 10 sessions, and RECT alone did not have antidepressant effects. Therefore, the enhanced antidepressant response in the RECT-modulated rTMS group could not be attributed to cognitive effects alone, but it could have been mediated by the RECT’s temporarily facilitating effect on the theta oscillations and such effects may, in turn, enhance

rTMS’s antidepressant effects by improving the communications between PFC and amygdala. However, whether RECT could temporarily change cognitive functions remains elusive and warrants further study to investigate.

Our data also suggested a potential switch of non-responders to responders by pretreatment brain manipulation. The baseline level of rACC activity could be elevated if we exercise it rigorously. However, the effect of frontal θ changes after RECT seems to be short-lived, because no significant elevation of the baseline frontal θ was found in the last session of rTMS treatment (Fig. 3B).

Mapping incoming sensory stimuli onto correct responses relies on specific neuronal circuits responsible for cognitive control. ACC is involved in such a cognitive-control network to accomplish even simple stimulus-response tasks (Womelsdorf et al. 2010). The RECT program as designed in the present study seems to be consistent with this, since we found the RECT-modulated frontal θ increases correlated with ACC (Fig. 3E, upper). Brain regions responsible for motor planning and execution (i.e., SMA and basal ganglia) were also involved (Fig. 3E, lower). The findings of separate non-significant correlation in Group-A and Group-B could be due to small sample size in each group.

Two limitations of this approach might be worth considering. First, the purpose of the RECT program was to engage and exercise the attention system. However, for some subjects, this version of the RECT program might be too easy and 10 min might be insufficient. This notion was supported by the finding that most non-responders had no frontal theta elevation after the RECT program. Therefore, in the future, different levels of cognitive tasks should be developed to account for the different baseline cognitive functions across individuals. Second, the sample size in the present study was not large, so caution should be exercised in interpreting the results from this pilot study. However, this was a hypothesis-driven clinical trial with frontal theta and ACC activity with and without RECT modulation as our a priori research interests. Our hypotheses were, in part, statistically supported by the findings from the present study. Furthermore, there are different types of frontal theta (e.g., widespread frontal theta that is related to drowsiness and vigilance). Here, we focused only on frontal midline theta, and different theta measures might lead to different findings and thus warrant further investigations.

Conclusion

Cognition-modulated frontal theta at baseline has the potential to predict antidepressant responses to 2 weeks of high-frequency rTMS treatment. Manipulating initial neural activity before rTMS treatment augments antidepressant effects and potentially switches non-responders into responders.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>

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Notes

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