It is illegal to post this copyrighted PDF on any website. Frontostriatal Connectivity Changes in Major Depressive Disorder After Repetitive Transcranial Magnetic Stimulation: A Randomized Sham-Controlled Study

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ABSTRACT

Objective: The aim of this randomized, sham-controlled study was to investigate the therapeutic effects of underlying neurobiological changes after 2-week repetitive transcranial magnetic stimulation (rTMS) treatment using functional connectivity magnetic resonance imaging in patients with major depression.

Methods: Twenty-four patients with major depressive disorder diagnosed with *DSM-IV-TR* criteria were randomly assigned to the active rTMS (n = 13) or sham (n = 11) groups from January 2009 to June 2011. rTMS was given for 2 weeks at 110% of the motor threshold for 10 minutes at 10 Hz over the left dorsolateral prefrontal cortex (DLPFC). Resting state functional connectivity was evaluated before and after rTMS. The 17-item Hamilton Depression Rating Scale (HDRS) was administered, and neurocognitive tasks were performed. We examined between-group differences in functional connectivity changes from the bilateral DLPFC.

Results: Participants in the active rTMS group showed significant clinical improvement in HDRS scores compared to those in the sham group (P < .001). After 2-week rTMS, there were significant differences in changes in DLPFC–left caudate connectivity (corrected P < .05): the active group showed a greater reduction of connectivity strength between the DLPFC and left caudate compared to the sham group. Reduced levels of DLPFC–left caudate connectivity predicted improvement in depressive symptoms (r = 0.58, P = .001). Additionally, a positive correlation between residual depressive symptoms and connectivity strength after 2-week rTMS was found (r = 0.46, P = .023).

Conclusions: High-frequency rTMS over the left DLPFC showed therapeutic effects in patients with major depression. The therapeutic effect of rTMS is related to the modulation of functional connectivity in the frontostriatal network.

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*Corresponding author: Eun Lee, MD, PhD, Department of Psychiatry, Yonsei University College of Medicine, Yonsei-ro 50, Seodaemun-gu, Seoul 03722, South Korea (leeeun@yuhs.ac). **T** ranscranial magnetic stimulation (TMS) is a noninvasive technique to stimulate the human brain.¹ It involves the delivery of magnetic pulses through the skull to focused regions of the cortex and induces a focal electrical current in the underlying tissue and localized neuronal depolarization. The induced TMS field is estimated to be 2 cm below the scalp, reflecting the local stimulation effects of the underlying cortex near the gray-white junction² and the remote effects of related neurocircuitry by propagating transynaptically to functionally interconnected brain areas.^{3,4} Through these effects, repetitive TMS (rTMS) is able to alter brain neurophysiology⁵ and thus may be a promising modality for modulating neurobiological abnormalities in neuropsychiatric disorders, particularly in major depression.

Data from controlled trials and meta-analyses suggest that rTMS is an effective treatment tool for major depression.^{6,7} Notably, rTMS can be a propitious treatment option for patients with treatment-resistant depression who do not benefit from pharmacologic approaches.⁸ The dorsolateral prefrontal cortex (DLPFC) has been targeted in most rTMS trials for depression because it has been implicated in the pathophysiology of major depression.⁹ In particular, the left DLPFC, which has lower metabolic activity,⁶ has been considered a valid rTMS target site. Clinical evidence has shown substantial antidepressant effects from high-frequency stimulation over the left DLPFC in major depression.^{10,11} However, the neurobiological mechanisms underlying the antidepressant effect of rTMS over the DLPFC remain unclear.

Previous functional neuroimaging studies demonstrated that an impaired frontostriatal network is an essential deficit in treatment-resistant depression.^{12,13} A recent study showed that impaired frontostriatal connectivity predicted a better outcome after rTMS treatment.¹⁴ Additionally, an impaired frontostriatal network is also observed in drug-naive early depression patients.¹⁵ Other studies that evaluated the therapeutic mechanism of rTMS focused on the DLPFC and subgenual anterior cingulate cortex.^{16–19} However, as suggested by Mayberg et al,²⁰ the therapeutic effects of antidepressant treatment have some placebo effects regardless of the mode of treatment. Most previous studies examining the mechanisms of rTMS on depression did not use a sham-controlled design.^{14,17–19} Therefore, we conducted a randomized, rater-blind,

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- **Clinical Points**
- Repetitive transcranial magnetic stimulation (rTMS), a noninvasive brain stimulation technique, is a promising modality for patients with major depression, but the neurobiological mechanisms underlying the antidepressant effect of rTMS remain unclear.
- High-frequency rTMS over the left dorsolateral prefrontal cortex is an effective treatment modality for patients with major depression, and the therapeutic effects of rTMS may be mediated by recovering the impaired frontostriatal network functional connectivity.

sham-controlled study to evaluate the specific treatment effects of rTMS.^{16–19,21}

Moreover, there is little evidence regarding the therapeutic effects of rTMS with a seed region of DLPFC. The antidepressant effects of rTMS may be associated with a cascade of neurobiological changes in brain regions that are linked with the stimulated area. Based on the anatomic and functional brain connectivity, the left DLPFC receives input from specific sensory cortices and has dense interconnections with the subcortical areas involved in emotional and cognitive modulation, such as the limbic area and the striatum.^{22,23} Thus, the evaluation of changes in their connectivity from the stimulated area would provide clinical evidence for rTMS of the DLPFC in treatment-resistant depression.

The purpose of the present randomized, sham-controlled study was to investigate the possible therapeutic effects of and the underlying neurobiological changes with a 2-week highfrequency rTMS treatment on the left DLPFC in patients with treatment-resistant major depression. We hypothesized that changes in functional connectivity of the frontostriatal circuitry are critical for the pathophysiology and therapeutic effects of rTMS intervention in major depression. To address this, we performed whole-brain voxel-wise functional connectivity analyses to generate functional connectivity maps of the DLPFC for the resting-state data.

METHODS

Study Design

Participants with major depressive disorder (MDD) were randomly assigned with stratification to either the active or the sham group based on age, gender, and severity of depression symptoms. The participants and raters (K.R.K. and K.J.) were blind to the expected effects of each condition. However, the clinicians (J.M.K. and H.J.Y.) administering rTMS were aware of the treatment groups. Considering the potential risk of interaction between subjects and the nonblinded treater, limited interaction between them was requested during rTMS sessions. Power computations show that this study requires a sample size of 10 in each group, assuming 80% power with a 2-sided significance level of $\alpha = .05$ if the effect size is supposed to be 1.4 from a previous study.²⁴ The study was registered at ClinicalTrials. gov (NCT01325831).

Via postings in the hospital and local newspaper advertisements, 28 right-handed outpatients were recruited from the depression clinic at Severance Hospital in Seoul, South Korea from January 2009 to June 2011. Trained psychiatrists (K.R.K. and K.J.) confirmed the DSM-*IV-TR*²⁵ diagnostic criteria for MDD in patients presenting with a current major depressive episode using the Mini-International Neuropsychiatric Interview.²⁶ Participants ranged in age from 20 to 75 years and had failed to achieve adequate improvement (less than 50% improvement evaluated by the 17-item Hamilton Depression Rating Scale [HDRS]²⁷⁾ after at least 8 weeks of treatment with at least 1 serotonin reuptake inhibitor. Participants were excluded if they presented with any current psychiatric disorder other than MDD, including anxiety disorder and substance use disorder (except nicotine). We also excluded any participants having a current or past history of psychotic disorder, seizure, mental retardation, high risk of suicide, cognitive impairment (score < 24 on the Mini-Mental State Examination),²⁸ or contraindications for general functional magnetic resonance imaging (fMRI) experiments. While all participants were taking antidepressants for at least 8 weeks before the MRI scan, the pharmacologic regimen did not change during the study period. To confirm the preservation of blinding, we asked 2 questions after the 10 sessions of rTMS: "Do you know the treatment condition you've received?" and "Which condition do you think you received?" The institutional review board of Severance Hospital approved the study, and written informed consent was obtained from all participants before participation.

Stimulation Parameters

A Magstim rapid magnetic stimulator with a 70-mm figure-of-eight coil (Whitland, UK) was used for the treatment. Patients received 10 daily rTMS sessions for 2 weeks. Before the first session, the resting motor threshold (RMT) was determined over the primary motor cortex by determining the minimal intensity required to elicit at least 5 motor-evoked potentials of 50 µV out of 10 stimulations of the abductor pollicis brevis. For the active group, rTMS over the left DLPFC was administered at the intensity of 110% of the RMT, a frequency of 10 Hz for 5 seconds per train, and 20 trains with an intertrain interval of 25 seconds for 10 minutes (1,000 stimuli/d). The rTMS was conducted at a point 5 cm anterior to the point at which the RMT was determined. For the sham group, stimulation was applied with D70-mm α coil with a double, figure-of-eight shape produced by Magstim Co (Whitland, UK), which makes no difference in terms of scalp sensations and sound generated by the active and sham rTMS coil.²⁹

Assessment of Clinical Symptoms and Neurocognitive Function

Clinical and neurocognitive evaluations were performed 4 days before the first rTMS session and 4 days after the final rTMS session. Depressive symptoms were evaluated using

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the HDRS. "Response" to rTMS was defined by at least 50%

improvement from the baseline HDRS score. "Remission" was defined as a final HDRS score below 9.

Neurocognitive function, particularly frontal lobe function, was assessed using the Rey Auditory Verbal Learning Test,³⁰ the Stroop test,^{31,32} and the backward digit span and digit symbol tests from the Wechsler Adult Intelligence Scale, Third Edition.³³

Functional Connectivity MRI Procedures and Data Analyses

Full methodological details of the functional connectivity MRI (fcMRI) data are described in eAppendix 1. Preprocessing and statistical analyses of the fcMRI data were performed using the Analysis of Functional NeuroImages software.³⁴ After preprocessing, individual functional connectivity maps were produced by correlation analysis between the average blood oxygen level-dependent time course extracted from the seed region of interest (ROI) of bilateral DLPFC and the time courses from all other brain voxels. The seed region is shown in Figure 1. Then, we obtained individual contrast maps that demonstrated changes in functional connectivity strength before and after rTMS sessions. To examine group differences, we performed 2-sample t tests on contrast maps between the active and the sham groups. Statistically defined clusters of activation were identified at corrected P < .05. In the post hoc analysis, we examined hemispheric effect of the seed ROI on results of the group difference of the functional connectivity. In addition, Spearman correlation analyses were conducted to explore how functional connectivity changes on the survived clusters in group analyses were related to the depression severity or neurocognitive function. To verify the accuracy and robustness of the results, jackknife procedures were used.

RESULTS

Demographic and Clinical Characteristics

After the screening interview, 2 participants did not reach the criteria of a current major depressive episode. Another 2 participants had comorbid anxiety disorder and alcohol use disorder. Therefore, a total of 24 eligible patients with treatment-resistant major depression were randomly assigned to the active rTMS (n=13) or sham (n=11)groups. One participant withdrew the informed consent after 1 stimulation session due to headache. Another 2 participants failed to complete the 10 sessions of rTMS due to malfunction of the rTMS machine. Thus, the final analyses included 12 patients in the active group and 9 in the sham group. Among the 21 subjects, most of them (n = 16) were on selective serotonin reuptake inhibitor (SSRI) monotherapy (7 escitalopram, 6 fluoxetine, 1 sertraline, and 2 paroxetine), and 5 patients were taking an SSRI in combination with another antidepressant: escitalopram + bupropion (n = 4)and escitalopram + venlafaxine (n = 1). There were no significant differences at baseline in the demographic and

Table 1. Baseline Demographic and Clinical Characteristics of Participants^a

	Active rTMS	Sham rTMS	
	(n=12)	(n=9)	Р
Age, y	42.8 (19.1)	52.2 (20.1)	.29
Sex, male/female, n	3/9	1/8	.42
Education, y	12.9 (3.2)	9.9 (4.0)	.07
Duration of illness, y	7.4 (10.6)	9.9 (14.2)	.66
HDRS score	24.1 (6.4)	20.0 (4.6)	.12
Neurocognitive function			
Digit span (backward)	11.9 (1.8)	11.0 (1.2)	.24
Digit symbol	10.2 (2.8)	10.6 (2.2)	.69
Stroop test (color, reaction time)	67.1 (38.2)	75.3 (34.7)	.65
Rey Auditory Verbal Learning Test (recall)	10.8 (2.5)	10.5 (2.1)	.82
Rey Auditory Verbal Learning Test (recognition)	11.1 (3.2)	10.3 (2.0)	.52

^aAll data except sex are shown as mean (SD).

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Abbreviations: HDRS = 17-item Hamilton Depression Rating Scale,

rTMS = repetitive transcranial magnetic stimulation.

clinical variables between participants in the active and sham groups (Table 1). For the response to the blindness awareness questions, no difference was found between the 2 groups.

Regarding tolerability and safety, there were no seizures observed in any participant. With the exception of the 1 participant who dropped out due to transient headache, no serious side effects were reported during the session. The withdrawal rate due to all reasons during the study was 4.5%.

Clinical Effect of rTMS Treatment

For the 2-week rTMS treatment, repeated-measures analyses of variance on all participants showed a significant time effect on depression severity (F=96.2, P<.001) within subjects. A significant group-by-time interaction was observed for depression severity (F=24.1, P<.001). Specifically, the active group showed greater improvement in depressive symptoms compared to the sham group. Among the active group, 9 of 12 participants showed responses to rTMS, whereas no participants responded to the sham stimulation (P<.001). The remission rate was 25% (n=3) in the active group and 0% in the sham group; however, the group difference did not reach statistical significance (P=.229). Performance on all neurocognitive tasks did not show group-by-time interactions (Table 2).

Effect of rTMS on Functional Connectivity

Changes in the functional connectivity from the DLPFC were significantly different in the left caudate (peak at Montreal Neurological Institute and Hospital [MNI] coordinates: -14, 14, 18; cluster size: 296 mm³) between the active and the sham groups (Figure 1). The post hoc analysis revealed no significant interaction effect by seed hemisphere and groups in the left caudate (F=3.056, P=.097), which reflects no hemispheric effect of the seed ROI to results of the group difference. The active group showed a significantly greater reduction in connectivity strength between the DLPFC and left caudate compared to the sham group (see Figure 1). The significant difference was still robust in the 2-sample *t* test using a jackknife approach (see Figure 1).

Kang et al <u>It is illegal to post this copyrighted PDF on any website</u> Table 2. Clinical Effects of 2-Week rTMS Treatment

			Group × Time ^b		Within-Subject Time Effect ^b	
Measure	Active ^a	Sham ^a	F	Р	F	Р
HDRS score			24.1	<.001	96.2	<.001
Week 0	24.1 (6.4)	20.0 (4.6)				
Week 2	10.1 (3.8)	15.3 (4.3)				
Digit span			1.04	.32	0.32	.58
Week 0	11.9 (1.8)	11.0 (1.2)				
Week 2	12.4 (2.0)	10.8 (2.3)				
Digit symbol			0.88	.36	0.88	.36
Week 0	10.2 (2.8)	10.6 (2.2)				
Week 2	10.9 (2.8)	10.8 (2.9)				
Stroop (color)			0.00	.99	4.78	.043
Week 0	67.1 (38.2)	75.3 (34.7)				
Week 2	51.6 (29.0)	62.9 (28.1)				
RVLT (recall)			0.002	.96	2.6	.124
Week 0	10.8 (2.5)	10.5 (2.1)				
Week 2	11.5 (3.3)	11.8 (3.5)				
RVLT (recognition)			0.02	.90	0.98	.34
Week 0	11.1 (3.2)	10.3 (2.0)				
Week 2	11.4 (3.2)	11.3 (3.2)				

^aValues shown as mean (SD).

^b*F* scores and *P* values are presented for repeated-measures analyses of variance. Abbreviations: HDRS = 17-item Hamilton Depression Rating Scale, rTMS = repetitive

transcranial magnetic stimulation, RVLT = Rey Auditory Verbal Learning Test.

Spearman analyses showed that reduced functional connectivity strength between the left caudate and the DLPFC (pre-TMS minus post-TMS) predicted improvement in depression severity (jackknife estimated r = 0.58, P = .001). Moreover, the residual depressive symptoms after 2-week rTMS were significantly positively correlated with the connectivity strength between the left caudate and the DLPFC (jackknife estimated r = 0.46, P = .023). Changes in functional connectivity strength within the groups were not related to the changes in neurocognitive function.

DISCUSSION

This randomized, sham-controlled study examined the therapeutic effects and underlying neurobiological effects of rTMS in patients with treatment-resistant major depression using fcMRI. The present study demonstrated the therapeutic mechanism of high frequency rTMS over the left DLPFC, which is mediated via modulation of the frontostriatal network.

In our study, the active group exhibited greater improvement in depressive symptoms compared to the sham group. The fcMRI results showed that changes between the DLPFC and left caudate revealed a significant difference between active and sham groups, and the connectivity change significantly correlated with improved HDRS scores during the 2-week rTMS treatment. These findings suggest that the therapeutic effect of rTMS over the left DLPFC in major depression is related to the recovery of impaired connectivity between the DLPFC and left caudate. Moreover, residual depressive symptoms after the 2-week rTMS correlated with connectivity strength between the left caudate and the bilateral DLPFC. This result provides clinical implications for the altered functional connectivity between the DLPFC and the caudate as a neural correlate of treatment-resistant major depression. However, this result could be narrowly interpreted as one of the various connectivity changes that occur while the therapeutic process is

ongoing. Because this study targeted patients with inadequate response to medication, our results may simply reflect the therapeutic mechanisms of the subpopulation with MDD that is unresponsive to pharmacologic treatment. Additional studies may be required to verify whether changes in frontostriatal connectivity are the general therapeutic mechanism of rTMS for depression.

Our findings have implications for clinical importance of the caudate in patients with major depression. The caudate is known to be involved in reward-related learning and motivation.35 Neuroanatomically, the caudate is a major receptive part of the striatum with neural innervation from various cortical areas, including the prefrontal cortex and thalamus.³⁶ Converging lines of evidence from clinical studies also support the role of the caudate in depression. A study of the resting-state default mode network in drug-naive individuals showed that decreased connectivity between the caudate and the precuneus/posterior cingulate cortex was a neural correlate of major depression.¹⁵ Recently, 2 studies demonstrated that an increased functional connectivity between the DLPFC and caudate correlated with depression severity.37,38 One study was conducted in young, medicationfree, depressed patients.³⁸ Moreover, the association between frontostriatal atrophy and poor outcome of treatment was found,39 and reduced gray matter volumes in the caudate were reported in the patients with treatment-resistant depression,¹³ which suggested the involvement of the caudate in treatment resistance and chronicity of major depression. A recent prospective rTMS trial showed that abnormal frontostriatal connectivity predicted clinical improvement after rTMS treatment over the dorsomedial PFC.¹⁴ Collectively, these findings indicate that frontostriatal circuit abnormalities may be the core deficits involved in the determination of treatment response as well as a neural correlate of major depression.

Our significant finding was confined only to the left caudate. The left-lateralized caudate effect may be derived from the administration of leftlateralized prefrontal rTMS treatment. Substantial evidence implicates left hemisphere involvement in pathophysiology and symptomatic correlation in major depression. A proton magnetic resonance spectroscopy study showed that left-lateralized abnormalities in the caudate were involved in adolescents with major depression.40 A structural MRI study in adults with major depression found that baseline depressive symptoms are inversely correlated with left caudate volume.41 Moreover, change in regional cerebral blood flow of the left caudate and left prefrontal cortex correlated with the emergence of depressive symptoms after interruption of SSRI

It is illegal to post this copyrighted PDF on any websi Figure 1. Group Difference Maps of Changes in Functional Connectivity During 2-Week rTMS and the Relationship Between DLPFC-Left Caudate Connectivity Strength and Depressive Symptoms^a



^aThe significance level of the group difference map was a corrected cluster threshold of *P* < .05. The anatomic image was obtained from a study-specific anatomic template.

Abbreviations: DLPFC = dorsolateral prefrontal cortex, HDRS = 17-item Hamilton Depression Rating Scale, MNI = Montreal Neurological Institute and Hospital coordinate system, rTMS = repetitive transcranial magnetic stimulation.

treatment.⁴² Taken together, these findings suggest the potential role of the left-lateralized caudate and prefrontal cortex in the pathophysiology and treatment response of depression.

On the other hand, no difference in connectivity to the subgenual cingulate cortex was found between the 2 groups. Unlike our findings, some studies reported that the subgenual anterior cingulate cortex is a crucial neural substrate for therapeutic response to rTMS in depression.^{16,17,19} Connectivity changes in the subgenual cingulate cortex may be related to nonspecific beneficial effects in depression, considering that subgenual anterior cingulate changes reflect a common pathway for the treatment response in depression.^{17,20,43} In addition, because the anterior cingulate cortex for depression,²⁰ the placebo effects in the sham group may negate the potential changes in the subgenual cingulate cortex in our sham-controlled study.

It should be noted that the clinical improvement in our depressed patients was independent of cognitive performance changes. In addition, changes in neurocognitive function were not related to the changes in the frontostriatal connectivity strength. Based on a recent review,⁴⁴ it is still difficult to draw clear conclusion about neurocognitive effects and the underlying mechanism of rTMS, although there have been many studies supporting the beneficial effect on cognitive functions. Several reports revealed that cognitive improvement during the rTMS treatment period could not be explained by mood improvement.^{45,46} The potential effects of rTMS on neurocognitive function may be mediated through different neural circuits from those predicting improvement of depressive symptoms.^{44,46}

Several limitations of our study should be mentioned. First, the sample size of each group was relatively small. The small sample size may have led to false-negative errors and limited our statistical power to detect subtle connectivity abnormalities, including anterior cingulate, thalamus, and other limbic areas, as well as correlations with clinical or cognitive symptoms. Second, participants enrolled in our study had a wide range of ages. However, there were no significant differences between the active and the sham groups. Age-related declines in neural plasticity may reduce the therapeutic effects of rTMS treatment. Third, the standard 5 cm target may be less effective than the individualized positioning methods or TMS positioning based on anatomic coordinates.^{17,47} Advanced techniques for optimal TMS targeting should help enhance the targeting accuracy and reduce intersubject variability in placement. Fourth, in the present design with sham stimulation at the same location as a control, we cannot conclude whether

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It is illegal to post this copyr the finding of the frontostriatal change is specific to rTMs over the left DLPFC or whether they would have been also related to rTMS to different cortical targets. Finally, the present findings using 2-week rTMS protocol should be interpreted with caution and their application restricted to the acute effects of prefrontal rTMS. In future research, a longer treatment period would be required for greater clinical benefits or long-lasting effects.

In summary, high-frequency rTMS treatment over the left DLPFC had therapeutic effects in patients with

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Drug names: bupropion (Wellbutrin and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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Supplementary material: See accompanying pages.

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treatment-resistant major depression. The neurobiological mechanism of the therapeutic effects was associated with changes in the resting functional connectivity between the DLPFC and the left caudate. This finding suggests that the antidepressant effects of rTMS may be mediated by the modulation of the frontostriatal network. Our results have implications for understanding the efficacious clinical application of rTMS for patients with major depression as well as the underlying neural correlates involved in neurobiological changes after rTMS treatment.

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Supplementary material follows this article.



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Supplementary Material

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List of Supplementary Material for the article

1. <u>eAppendix 1</u> Supplementary Method

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

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eAppendix 1. Supplementary Method

fMRI procedures and data analyses

Functional MRI data were acquired using a 1.5 T MR scanner (Sigma Eclipse, GE Medical Systems, Waukesha, WI, USA). Scans were performed on the same day as the clinical and neurocognitive assessments. Subjects were instructed to remain still during the scan with their eyes fixed on the crosshairs of a slide with a black background. The participants' heads were cushioned with attached earmuffs. Thirty contiguous 5-mm-thick axial slices covering the entire brain were collected using the T2-weighted echo planar imaging sequence depicting the blood-oxygenation-level-dependent (BOLD) signal (TE = 22 ms; TR = 2000 ms; flip angle = 90°; field of view = 240 mm; 5-mm slice thickness; a matrix, $64 \times 64 \times 30$; and spatial resolution, $3.75 \times 3.75 \times 5$). Next, high-resolutionT1-weighted fast spoiled gradient echo sequence MR images (116 coronal slices with 1.5-mm slice thickness; TE = 18 ms; TR = 85 ms; flip angle = 12°; field of view = 240 mm; a matrix, $256 \times 256 \times 116$; and spatial resolution, $0.94 \times 0.94 \times 1.5$) were collected.

Preprocessing and statistical analyses of the fMRI data were performed using the Analysis of Functional NeuroImages (AFNI, <u>http://afni.nimh.nih.gov/</u>, Ver. 2011_05_26_1457)¹ software. The first 14 volumes were discarded to allow for the BOLD signal equilibration. Corrections for the differences in slice acquisition time and head movements were performed for all slices within a volume. Corrected images were normalized to the standard 152 T1 template of the Montreal Neurological Institute (MNI) space provided by AFNI, using the parameters from spatial normalization of T1-weighted images. All voxels were resampled as $2 \times 2 \times 2$ mm size by linear

interpolation. Normalized images were smoothed with a 6-mm full-width at half-maximum Gaussian filter. A temporal band-pass filtering was applied at 0.01 Hz < f < 0.08 Hz.^{2, 3} The time courses representing large ventricle, white matter and global signal were regressed out during analyses to reduce the confound effects related physiological processes. The six head motion parameters and the zero-order through fourth-order trends in the BOLD time series were also regressed out.

For the purposes of ROI placement for sampling in functional connectivity analyses, we used the seed ROI of bilateral DLPFC, which was defined as a 20mm radius sphere (centered at x, y, z coordinates \pm 41, 16, 54). Reference time series were obtained by averaging the fMRI time series within the DLPFC ROIs. Individual functional connectivity maps were produced by computing the correlation coefficient between the average BOLD time course extracted from the seed regions and the time courses from all other brain voxels. In order to avoid extraneous contribution by probable large ventricle voxels, we excluded voxels in the large ventricle from the functional connectivity maps using the large ventricle mask. The functional connectivity strengths were generated by converting the correlation coefficients to z values as a normal distribution using Fisher's z transformation. Next, we obtained the individual contrast maps that demonstrated changes in the functional connectivity strength between before and after rTMS sessions (i.e., pre-TMS minus post-TMS). To examine group differences, we performed two-sample t-tests on contrast maps between the active and the sham groups. Statistically-defined clusters of activation were identified using the whole-brain Monte Carlo simulations (Alpha-Sim program by AFNI) to achieve a corrected cluster threshold of p < 0.05. Specifically, clusters reaching a contiguous volume of at least 296 mm³ at a voxel-wise threshold of p < 0.001 were considered significant at corrected p < 0.05. In order to refine a location of clusters, we constructed a study-specific anatomical template by averaging spatial normalized T1-weighted image across all participants.

In addition, the individual connectivity strength values before (pre-TMS) and after the 2week rTMS (post-TMS) were extracted by averaging across all voxels based on the survived clusters in group analyses. To assess the potential influence of subject outliers on the group difference, we conducted a two-sample t-test using a (n - 1) jackknife approach for the reduction degree values of functional connectivity. In the post hoc analysis, to examine hemispheric effect of the seed ROI to results of the group difference of the functional connectivity, we obtained the reduction degree values of functional connectivity derived from each left and right DLPFC seed region in the clusters from the between-group differences. We performed a repeated measure analysis of variance with factors of seed hemisphere and two groups using these values.

For the statistical analyses of clinical and demographic data, we used t-tests on continuous variables and Fisher's exact tests on categorical variables to evaluate between-group differences. To examine if there was an effect of group or time for the outcome measures of HAMD and neurocognitive tasks, repeated measure analyses of variance were performed. In addition, Spearman's correlation analyses were conducted to explore how functional connectivity changes were related to the depression severity or neurocognitive function and were further tested using a jackknife approach and a bootstrap procedure with replacement in 10000 samples to obtain the estimates of statistical accuracy of correlation coefficients. Statistical analyses were performed using the SPSS v.21.0 (SPSS, Chicago, IL, USA). All tests were two-tailed, and significance was accepted at p < 0.05.

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