Changes in Regional Cerebral Blood Flow After Repetitive Transcranial Magnetic Stimulation of the Left Dorsolateral Prefrontal Cortex in Treatment-Resistant Depression

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High-frequency repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex is effective in treatment-resistant depression, although its mechanism is still not completely elucidated. To clarify the neuroanatomical alteration of function elicited by rTMS, single photon emission computed tomography (SPECT) with ^{99m}Tc-ECD was performed on 12 male inpatients with treatment-resistant unipolar depression before and after high-frequency rTMS of the left dorsolateral prefrontal cortex. These results suggest that the manifestation of the antidepressant effect of high-frequency rTMS is associated with changes in the neuroanatomical function of the left dorsolateral prefrontal cortex as well as of the limbic-paralimbic region, including the ipsilateral subgenual cingulate, and the basal ganglia.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2008; 20:74–80)

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method that can stimulate the cerebral cortex and alter cortical and subcortical functions.[1–3] This method was reported by Barker et al.[4] in 1985. It has been utilized for neurological examination and studies on cerebral function and was applied to the treatment of drug-resistant depression for the first time by Höflich et al.[5] in 1993. Since then, many studies have been implemented on the antidepressant effect of rTMS. Most of these studies were done by stimulating the left dorsolateral prefrontal cortex with a 5–20 Hz (high-frequency) rTMS[6–8] or by stimulating the right dorsolateral prefrontal cortex with a 1 Hz (low-frequency) rTMS.[9–10] There are many reports on the effectiveness of high-frequency rTMS of the left dorsolateral prefrontal cortex for treatment-resistant depression,[6,10–12] and past studies have proven that more intensive rTMS showed a higher antidepressant effect.[13] Although rTMS is known to modulate mesolimbic and mesostriatal dopaminergic systems[14] and affect cortisol and thyroid-stimulating

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hormones,[15,16] the mechanism of the antidepressant action is not yet clarified.

Imaging studies in patients with depression have shown both an abnormal functioning of the frontal lobe, especially the dorsolateral prefrontal cortex and the anterior cingulate,[17–19] and changes in regional cerebral blood flow (rCBF) and metabolism that accompany improvement in symptoms of depression.[20–22] However, there are only a few studies on the effect of high-frequency rTMS on rCBF and metabolism in patients with treatment-resistant depression, and the results are not consistent.[23,24]

The aim of the present study was to evaluate the changes in rCBF by using ^{99m}Tc-ECD single photon emission computed tomography (SPECT) to reveal any alteration of neuroanatomical function that was associated with the manifestation of an antidepressant effect of rTMS over the left dorsolateral prefrontal cortex in male patients with treatment-resistant unipolar depression.

METHOD

Subjects

Twelve right-handed male inpatients who met DSM-IV criteria for major depressive disorder (unipolar depression) participated in the study (Table 1). Inclusion criteria were a 17-item Hamilton Depression Rating Scale (HAM-D)[25] score of greater than 18. Exclusion criteria included significant medical illnesses or neurological disorders, a history of substance abuse or dependence, convulsive disorders, active suicidal ideation, and previous rTMS or ECT treatments. All patients had failed to respond to a minimum of two distinctly different classes of antidepressant medications (stage II or III, definition of Thase and Rush[26]), and 4 of 12 patients also had not responded to lithium augmentation. Patients were not deliberately withdrawn from medication before the trial, but their medical treatments were not allowed to have changed in the 6 weeks before the commencement of the study or during the trial. All patients were taking medication during the trial: 7 patients were taking a tricyclic antidepressant (3 were receiving amoxapine; 2, clomipramine; and 2, amitriptyline); 1, a selective serotonin reuptake inhibitor (paroxetine); 1, a serotonin-noradrenaline reuptake inhibitor (milnacipran); 1, another class of medication (sulpiride); and 2 patients were taking a combination of antidepressants (mianserin and clomipramine or paroxetine). Three patients were taking lithium carbonate, 2 were taking clonazepam, and 4 patients were taking antipsychotic medications (2, levomepromazine; 1, risperidone; and 1, olanzapine). Ten patients were receiving benzodiazepines such as hypnotic or anxiolytic agents.

After a complete description of the study had been given to the patients and their families, written informed consent was obtained from all patients on a form

TABLE 1. Clinical Characteristics of 12 Depressed Male Patients Receiving rTMS

		Depression							
					HAM-D Score				
Subject	Age (years)	Age at Onset (years)	Number of Previous Episodes	Duration of Current Episode (months)	Baseline	Week 1	Week 2	Week 4	Decrease (%)
1	49	47	1	6	19	13	10	13	47
2	35	32	2	7	21	13	6	4	71
3	60	40	3	12	23	18	18	18	22
4[a]	32	23	2	2	18	14	5	4	72
5	70	69	2	4	25	13	11	2	56
6	48	44	3	5	29	14	9	6	69
7	43	39	2	5	22	18	9	12	59
8	25	22	3	8	24	19	17	15	29
9[a]	38	37	2	2	19	7	1	1	95
10[a]	45	38	3	4	19	12	4	3	79
11	43	42	1	6	22	17	8	4	64
12[a]	50	48	3	5	28	20	18	18	36
Total									
Mean	44.83	40.08	2.25	5.50	22.42	14.83	9.67	8.33	58.25
SD	12.16	12.30	0.75	2.71	3.58	3.69	5.57	6.40	21.49

[a] Patient had not responded to lithium augmentation
Decrease (%) = (Score at Baseline − Score at Week 2) / Score at Baseline

approved by the Ethics Committee of the Kyorin University School of Medicine.

rTMS Treatment

rTMS was administered by using a Magstim Super Rapid magnetic stimulator (Magstim Company, Whitland, UK) with hand-held 70-mm figure-of-8 coils that were interchanged to allow cooling at times during the treatment sessions. At the first rTMS treatment session, single-pulse TMS was used to determine the resting motor threshold in the right hand by using a visualization of movement method.[27] The stimulation site during the rTMS treatment sessions was defined as a 0.5 cm anterior in a parasagittal line to the motor cortex. Twenty-five-second trains were applied at 10 Hz (total of 1000 stimuli per session) and at 100% of the resting motor threshold over the left dorsolateral prefrontal cortex. Ten treatment sessions were administered within a 2-week period.

Clinical Assessment and Data Analysis

All patients were assessed with the 17-item HAM-D at 4 time points: before rTMS (baseline), at week 1, at week 2, and at week 4 (2 weeks after the rTMS treatment). These measures were rated at same time in each patient by an expert investigator. Response criteria were defined as a >25% decrease in the score of the HAM-D from baseline to week 2. One-way repeated-measures analysis of variance (ANOVA) was used to compare the scores of the HAM-D and to estimate the main effect of time (baseline, week 1, week 2, and week 4). Statistical analysis was conducted using SPSS for Windows 14.0 (SPSS Inc., Chicago) and the level of statistical significance was set at $p<0.05$.

SPECT Procedure and Analysis

SPECT images were acquired within 48 hours before the first rTMS treatment and within 48 hours after the last rTMS treatment after injection of 600 MBq ^{99m}Tc-ECD in the resting state via a venous cannula previously inserted in the right arm. Patients rested supine in a quiet room before the injection was administered with their eyes closed and their ears unplugged. Image acquisition started 10 minutes after the injection was given, by using a triple-detector gamma camera GCA-9300A/HG (Toshiba Corporation, Tokyo) with low energy super high resolution fan beam collimators. The matrix size was 128×128, and data were collected in 30 frames at 4° steps over 120° with a pixel width of 1.72 mm and a slice thickness of 3.45 mm. Scanned data were prefiltered by using a Butterworth filter (order 8 and a cutoff at 0.08–9 cycle/pixel) and reconstructed with a Ramp filter. Scatter and attenuation corrections were performed, respectively, by the triple-energy window correction and Sorenson method.

Statistical analysis was conducted on a voxel-by-voxel basis by using statistical parametric mapping (SPM2, http://www.fil.ion.ucl.ac.uk/spm). SPECT images were realigned and spatially normalized to the standard stereotactic space, which was based on the Montreal Neurological Institute template, and smoothed with an isotropic 12-mm full-width half-maximum Gaussian filter to improve the signal-to-noise ratio. rCBF comparisons between patients before and after rTMS treatment were performed by using the paired t test. The height threshold was set a priori to $p<0.01$, and the extent threshold was set to $p<0.05$ after correction for multiple comparisons by SPM2. To evaluate changes in rCBF that correlated with the improvement of depressive symptoms, we analyzed the scans within responders using the scores of the HAM-D at baseline and week 2 as covariates of interest. Brain regions were identified as a cluster level of $p<0.05$ and significant at a threshold of $p<0.01$ (corresponding to Z score equal to or greater than 2.33). Stereotactic coordinates were based on Talairach and Tournoux atlas coordinates,[28] converted from Montreal Neurological Institute coordinates.[29]

RESULTS

ANOVA for the score of the HAM-D showed a significant main effect of time [$F(3, 33)=54.2$, $p<0.001$]. Multiple comparisons using Bonferroni's correction showed that the mean of the scores of the HAM-D significantly decreased to 14.83 (SD = 3.69) after 1 week ($p<0.001$), to 9.67 (SD = 5.57) after 2 weeks ($p<0.001$), and to 8.33 (SD = 6.40) after 4 weeks ($p<0.001$) from the baseline of 22.42 (SD = 3.58). However, there was no significant difference between the scores at week 2 and week 4 (Table 1).

A significantly increased rCBF occurred in left dorsolateral prefrontal cortex, the region stimulated by the rTMS treatment and premotor area (Figure 1), whereas no significant relative decrease of the rCBF was found. As shown in Table 2 and Figure 2, among 11 responders (91.7%), areas of significant negative correlations between rCBF and the change of the scores of the HAM-D were

observed in the left dorsolateral prefrontal cortex, the ventrolateral prefrontal cortex, the right-dominant orbitofrontal cortex, the anterior cingulate, the left subgenual cingulate, the anterior insula, and the right putamen/pallidum. No region showed a significant positive correlation between rCBF and the change of the scores of the HAM-D.

Two subjects out of 12 complained of discomfort in the stimulated region during the rTMS treatments; however, after the completion of the stimulation the discomfort disappeared. No serious adverse events that could discontinue the treatment occurred in this trial.

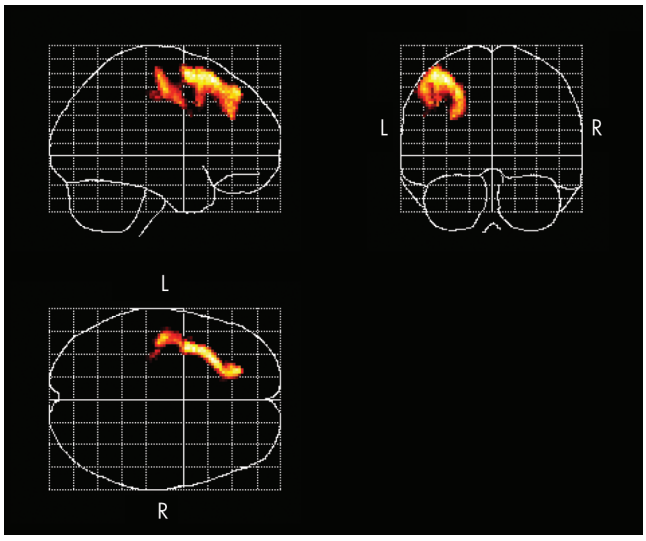
DISCUSSION

The present study of high-frequency rTMS of the left dorsolateral prefrontal cortex in 12 patients with treatment-resistant depression measured changes in rCBF by SPECT before and after the treatment. After the rTMS treatment, the HAM-D score decreased significantly (mean of −58.25%) and an improvement in the symptoms of depression was observed.

Changes in rCBF

Successful rTMS treatment was associated with a significant increase in rCBF in the left dorsolateral prefrontal cortex in the stimulated region. Furthermore, the present study revealed that there was a relationship between the improvement in symptoms of depression and the increase in rCBF in the left dorsolateral prefrontal cortex, the ventrolateral prefrontal cortex, the orbitofrontal cortex, the anterior cingulate, the left subgenual cingulate, the anterior insula, and the right putamen/pallidum.

FIGURE 1. Statistical Parametric Mapping of Areas of Significant Increase in Regional Cerebral Blood Flow Observed after Treatment of Depressed Male Patients with rTMS



It has been suggested that TMS has different effects on neuroanatomical function depending on its frequency, that is, the excitement of the cerebral cortex is enhanced by stimulation from high-frequency TMS and suppressed by stimulation from low-frequency TMS.[10,30] The activation of the cortex is not limited to the stimulated region but can be transferred to remote regions via the intracerebral networks.[30,31] According to a study on healthy male subjects after stimulation of the left dorsolateral prefrontal cortex with fast and slow rTMS, increases in CBF in the stimulated regions were observed in both cases. Slow rTMS induced an increase in CBF in the contralateral right caudate body and the anterior cingulate and a decrease in CBF in the ipsilateral orbitofrontal cortex. Fast rTMS applied over the right dorsolateral prefrontal cortex was associated with an increase in the CBF in the stimulated region, the bilateral orbitofrontal cortex, and the left medial thalamus.[32] Speer et al.[30] reported increases in the rCBF in the left-dominant bilateral prefrontal and the limbic and paralimbic regions after a high-frequency rTMS of the left dorsolateral prefrontal cortex in patients with depression. Some studies of high-frequency rTMS for treatment-resistant depression have shown inconsistent results,[23,24] partly because these studies used different designs in patient selection and treatment methods.

Functional imaging studies show decreases in rCBF and metabolism in the dorsolateral prefrontal cortex[17,19] and in the left-dominant hypofrontality[18] in patients with depression, and also show changes in rCBF and metabolism according to improvement in symptoms of depression.[20,22] The results obtained in the present study support those of previous reports, and it is assumed that the direct activation of the cerebral cortex through high-frequency rTMS and the resultant changes in neuroanatomical function associated with the improvement in depressive symptoms are responsible for increasing the rCBF of the left dorsolateral prefrontal cortex after rTMS treatment. Previous studies have demonstrated that the limbic-paralimbic regions are reciprocally connected with the prefrontal and the subcortical regions and are

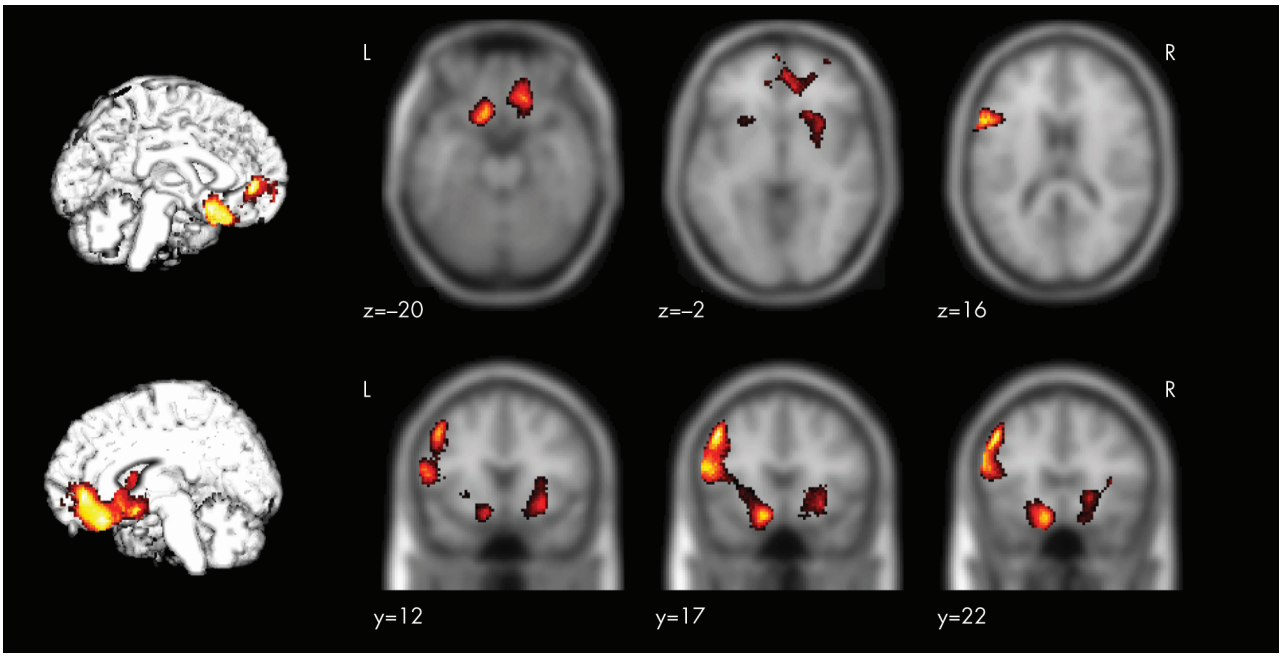
involved in the regulation of mood and affect.[21,33,34] In the present study, among patients who responded to rTMS treatment, significant relative increases of rCBF occurred in the ipsilateral dorsolateral prefrontal cortex toward the stimulated region, the limbic-paralimbic regions including the left subgenual cingulate (Brodmann

TABLE 2. Locations of Regional Cerebral Blood Flow Changes with Significant Correlations to HAM-D Score in 11 Depressed Male Patients Who Responded to rTMS Treatment

Brain Region	Talairach and Tournoux Coordinates			Brodmann Area	Z score
	x	y	z		
Areas of rCBF increase					
Lt. dorsolateral prefrontal	−48	17	38	8 / 9	4.87
	−42	10	47		2.48
Lt. ventrolateral prefrontal	−57	18	18	45	4.11
Rt. ventrolateral prefrontal	36	58	−3	10	2.99
	34	56	−10	10	2.52
Lt. orbitofrontal	−2	60	−11	11	3.15
Rt. orbitofrontal	18	28	−18	47	3.83
	8	30	−25	11	3.44
	26	48	−16	11	3.38
Rt. medial frontal	22	47	1		2.41
Lt. anterior cingulate	−8	44	−4	32	2.61
Rt. anterior cingulate	2	49	−1	32	3.26
	10	40	−7	32	3.07
Lt. subgenual cingulate	−12	17	−16	25	4.00
Lt. anterior insula	−40	16	7		2.63
	−30	15	−2		2.56
Rt. anterior insula	38	24	8		2.77
Rt. putamen/pallidum	30	−7	6		3.23
	20	19	−6		2.88
	24	8	11		2.77
	28	12	5		2.63

z scores greater than 2.33 correspond to $p < 0.01$

FIGURE 2. Changes in Regional Cerebral Blood Flow in Areas Showing Significant Correlations with Score of HAM-D Observed after Treatment of Depressed Male Patients Who Responded to rTMS Treatment



area 25), and the right basal ganglia, whereas no region showed significant relative decrease of rCBF that was correlated with the change of the scores of the HAM-D. Drevets et al.[35] reported a decrease in rCBF and glucose metabolism in the subgenual prefrontal cortex (Brodmann area 25) and a decrease in the volume of the left subgenual prefrontal cortex in patients with familial bipolar and unipolar depression. In addition, there is a report in which marked decreases in the blood flow in the paralimbic regions, especially in the inferior frontal and cingulate cortex, were noted in patients with severe treatment-resistant depression, but there was no decrease in CBF in the parietal or occipital lobe.[36] The anterior cingulate (Brodmann areas 24 and 32) is reciprocally connected with the prefrontal and the limbic-paralimbic regions, and previous reports show that rCBF and metabolism in the anterior cingulate decrease in patients with depression and increase with an improvement in symptoms of depression.[20,22] In addition, the activation of the rostral anterior cingulate may predict treatment response in depression.[37,38] The present study showed an increase in rCBF in the anterior cingulate and an improvement in symptoms of depression after successful rTMS treatment of the left dorsolateral prefrontal cortex. Several studies[22,34,39] have reported that decreases in rCBF and metabolism in the subgenual cingulate (Brodmann area 25) and the limbic-paralimbic regions such as the anterior insula and the putamen/pallidum are associated with improvement of depression. Acting on the postulation that the subgenual cingulate region is metabolically overactive in treatment-resistant depression, Mayberg et al.[40] reported that deep brain stimulation resulted in a decrease in metabolic activities in this region and in the limbic-paralimbic regions and improved symptoms in these patients. Our findings of increased rCBF in the subgenual cingulate and the limbic-paralimbic regions after successful rTMS treatment are different and have not been previously reported. In most previous studies, rCBF and metabolism were evaluated 6 weeks after the commencement of the trials, whereas in the present study, the rCBF was measured with the SPECT within 48 hours after the completion of the rTMS treatment. Hence, the difference in the timing of the evaluation of the neuroanatomical function during the convalescence from the depression and the manner of the antidepressant treatment may have influenced the findings obtained in the present study.

There are several limitations in the present study. First, a placebo effect due to rTMS treatment cannot be excluded because of the nonblinded design. Second, because pharmacologic treatment was continued during rTMS, the effects of these medications on depression and rCBF should be considered. We believe further studies are necessary to clarify whether the results of the present study are specific findings of the treatment of depression with high-frequency rTMS over the left dorsolateral prefrontal cortex or are due to changes in neuroanatomical function during the time course of convalescence from depression.

In conclusion, we conducted high-frequency rTMS over the left dorsolateral prefrontal cortex in patients with treatment-resistant depression and found changes in rCBF associated with a reduction in symptoms of depression. The results of this study suggest that the manifestation of an antidepressant effect of high-frequency rTMS of the left dorsolateral prefrontal cortex in patients with treatment-resistant depression is related to changes in the neuroanatomical function of the left dorsolateral prefrontal cortex as well as of the ipsilateral subgenual cingulate (Brodmann area 25), the ventrolateral prefrontal cortex, the orbitofrontal cortex, the anterior cingulate, the anterior insula, and the right putamen/pallidum.

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