Regional Cerebral Blood Flow Changes after Low-Frequency Transcranial Magnetic Stimulation of the Right Dorsolateral Prefrontal Cortex in Treatment-Resistant Depression

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Key Words

Transcranial magnetic stimulation · Depression · Brain imaging

Abstract

Several studies have proved that low-frequency transcranial magnetic stimulation (TMS) of the right dorsolateral prefrontal cortex (DLPFC) showed an antidepressant effect, although its mechanism is still not completely elucidated. The aim of the present study was to clarify the alteration in neuroanatomical function elicited by low-frequency TMS of the right DLPFC in treatment-resistant depression and to detect the difference between responders and nonresponders to TMS. Single-photon emission computed tomography with ^{99m}Tc -ethyl cysteinate dimer was performed in 14 right-handed male patients with treatment-resistant unipolar depression before and after low-frequency TMS of the right DLPFC. Five 60-second 1-Hz trains were applied and 12 treatment sessions were administered within a 3-week period (total pulses, 3,600). The Hamilton Rating Scale for Depression was administered and the regional cerebral blood flow (rCBF) was analyzed using statistical parametric mapping (SPM2). After TMS treatment in 14 patients, the score on the Hamilton Rating Scale for Depression decreased significantly, and considerable decreases in rCBF were seen in the bilateral prefrontal, orbitofrontal, anterior insula, right sub-

genual cingulate, and left parietal cortex, but no significant increase in rCBF occurred. Additionally, as compared with 8 nonresponders, 6 responders showed significant increases in rCBF at baseline in the left hemisphere including the prefrontal and limbic-paralimbic regions. These results suggest that the antidepressant effect of low-frequency TMS of the right DLPFC is associated with a decrease in rCBF in the limbic-paralimbic regions via the ipsilateral subgenual cingulate, and increased rCBF at baseline in the left hemisphere may be involved in the response to low-frequency TMS treatment.

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Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive method that can stimulate the cerebral cortex and alter cortical and subcortical functions [1–3]. Alterations in cortical and subcortical functions differ, depending on the frequency and site of the stimulation; and as for the cortex, the sites include the original as well distant ones as the stimulation spreads through the intracerebral network [4, 5]. Functional imaging studies have clarified abnormalities in neuroanatomical functions of the dorsolateral prefrontal cortex (DLPFC) in patients with depression [6, 7] and have revealed changes in the regional

cerebral blood flow (rCBF) and metabolism with improved symptoms of depression [8, 9]. It follows that the DLPFC was selected as the stimulation site in the treatment of depression by TMS.

Many of the studies have been conducted by a method to stimulate the left DLPFC with 5- to 20-Hz high-frequency TMS [10–15], and several reports have shown that a greater antidepressive effect can be achieved with more intensive TMS [14, 15]. Furthermore, the efficacy of high-frequency TMS of the left DLPFC for treatment-resistant depression has been supported [10, 12, 13, 15]. Studies on the antidepressive effects of TMS revealed that TMS modulated the mesolimbic and mesostriatal dopaminergic systems [16] and affected cortisol and thyroid-stimulating hormone [17, 18]. In brain imaging studies on depression with high-frequency TMS of the left DLPFC, Speer et al. [4] reported an increase in rCBF in the left-dominant bilateral prefrontal, cingulate and limbic-paralimbic regions of 10 patients with depression, and Kito et al. [19] found an increase in rCBF in the left DLPFC stimulation site, as well as in the left premotor area, orbitofrontal cortex, anterior cingulate, left subgenual cingulate, anterior insula and right basal ganglia of 12 patients with treatment-resistant depression; and they also described that changes in neuroanatomical functions not only of the left DLPFC but also of the limbic-paralimbic regions including the ipsilateral subgenual cingulate were involved in the onset of the antidepressive effect of high-frequency TMS.

Recently several studies proved that low-frequency TMS of the right DLPFC with 1 Hz showed an antidepressant effect [12, 20]. In another report, low-frequency TMS of the right DLPFC of patients with depression revealed decreases in the rCBF of the right prefrontal area of the stimulation site, the left basal ganglia, left amygdala and left medial temporal cortex [4], but its mechanism is still not completely elucidated. Since alterations in cortical and subcortical functions depend on the frequency and site of stimulation, brain imaging studies on depression with TMS could contribute to the clarification of its action mechanism and the pathophysiology of depression. To determine more appropriate TMS conditions based on abnormalities in cortical and subcortical functions associated with depression, further studies are needed, measuring rCBF or cerebral metabolism in patients with depression.

The aim of the present study was to clarify the alteration in neuroanatomical function elicited by low-frequency TMS of the right DLPFC of patients with treatment-resistant depression and to detect the difference in

rCBF between responders and nonresponders to TMS by using ^{99m}Tc -ethyl cysteinate dimer single-photon emission computed tomography (SPECT).

Materials and Methods

Subjects

Right-handed male patients who met the DSM-IV criteria for major depressive disorder (unipolar depression) participated in the study. The inclusion criteria were as follows: male patients, 25–65 years old at the time of enrollment with a Hamilton Rating Scale for Depression [21] score greater than 18 and nonresponse to treatment for stage II or III depression [22] utilizing a minimum of antidepressant medications in different chemical classes for episodes occurring at the time of enrollment or earlier. The exclusion criteria were: organic brain disorder, convulsive disorder, alcoholism, significant suicidal tendency, metal devices such as pacemakers or intracranial clips, diseases like hypertension and diabetes or the taking of medications for these diseases, history of electroconvulsive therapy and noncompliance or change in the type or dose of antidepressant medications within 6 weeks before enrollment.

The study was approved by the ethics committee of Kyorin University School of Medicine. The subjects participating in the study gave their informed consent after receiving oral and written descriptions on the aim of the study.

TMS Treatment

A Magstim Super Rapid magnetic stimulator (Magstim Company, Whitland, UK) with 70-mm figure-of-8 coil was used. At the first TMS treatment session, single-pulse TMS was applied to determine the resting motor threshold in the left hand by using a visualization of movement method [23]. The stimulation site during the TMS treatment sessions was defined as a point 5 cm anterior in a parasagittal line to the motor cortex. Five 60-second 1-Hz trains, at 100% of the resting motor threshold, were applied daily in stimulus intervals of 60 s for 4 days (Monday, Wednesday, Thursday and Saturday). Twelve treatment schedules were administered within a 3-week period (total pulses, 3,600). Treatment was consistently applied during the period.

Clinical Assessment and Analysis

All subjects were assessed with the Hamilton Rating Scale for Depression by trained psychiatrists at 3 time points: before TMS (baseline), in week 3 (completion of the treatment) and in week 5 (2 weeks after the completion of the treatment). These measures were rated at the same time for each subject by an expert investigator. The subjects who showed an improvement rate greater than or equal to 50% on the Hamilton Rating Scale for Depression from baseline to week 5 compared to baseline were defined as responders and those with an improvement rate of less than 50% were considered as nonresponders. One-way repeated-measures analysis of variance was used to compare the Hamilton Rating Scale for Depression scores and to estimate the main effect of time. Statistical analysis was conducted by SPSS for Windows 14.0 (SPSS Inc., Chicago, Ill., USA) and the level of statistical significance was set at $p < 0.05$.

SPECT Procedure and Analysis

SPECT images were acquired after the injection of 600 MBq ^{99m}Tc -ethyl cysteinate dimer in the resting state via a venous cannula previously inserted in the right arm within 48 h at baseline and within 48 h in week 3. The subjects rested supine in a quiet room before the injection was administered with their eyes closed and their ears unplugged. The image acquisition started 10 min after the injection had been given, by using a triple-detector γ -camera GCA-9300A/HG (Toshiba Corporation, Tokyo, Japan) with low-energy super-high-resolution fan beam collimators. The matrix size was 128×128 , and data were collected in 30 frames at 4-degree 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 0.08–0.09 cycles/pixel) and reconstructed with a Ramp filter. Scatter and attenuation corrections were performed by the triple-energy window correction and Sorenson methods, respectively.

The statistical analysis was conducted on a voxel-by-voxel basis with statistical parametric mapping (SPM2, <http://www.fil.ion.ucl.ac.uk/spm>). The 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 the subjects before and after TMS treatment were performed by using the paired *t* test. To detect the difference in rCBF at baseline between the responders and nonresponders to TMS treatment, we examined the scans by analysis of covariance with age as a covariate. The height threshold was set a priori to $p < 0.05$ and the extent threshold to $p < 0.05$ after correction for multiple comparisons by SPM2. Brain regions were identified with a cluster level of $p < 0.05$ and significant at a threshold of $p < 0.01$ (corresponding to a *Z* score equal to or greater than 2.33). Stereotactic coordinates were based on Talairach atlas coordinates [24], converted from Montreal Neurological Institute coordinates [25].

Results

Fourteen right-handed male patients with unipolar depression who met the diagnostic criteria for major depressive disorder participated in the present study (table 1). Two patients were excluded, as one had received electroconvulsive therapy and the other proved to have manic episodes. All subjects continued to take their antidepressant medications at the time of enrollment, and the type and dose of the medications remained unchanged throughout TMS treatment, from baseline to week 5. Of the 14 subjects, 4 were taking tricyclic antidepressants (3 amoxapine, 1 amitriptyline), 4 were using a selective serotonin reuptake inhibitor (2 fluvoxamine and 2 paroxetine), 1 was taking a selective serotonin-noradrenaline reuptake inhibitor (milnacipran) and 5 were utilizing a plurality of antidepressants (2 milnacipran and sulpiride, 2 milnacipran and mianserin and 1

Table 1. Clinical characteristics of 14 male patients with depression receiving low-frequency right-sided TMS

Subject	Age years	Number of previous episodes	Duration of current episodes months	Score on the Hamilton Rating Scale for depression			
				base-line	week 3	week 5	decrease %
1	60	4	7	21	12	11	48
2	50	3	6	18	8	8	56
3	46	4	5	19	15	13	32
4	59	2	4	26	18	19	27
5	34	3	13	19	17	16	16
6	53	3	16	18	13	12	33
7	58	2	15	21	16	15	29
8	46	1	11	27	8	1	96
9	36	4	9	19	7	6	68
10	56	3	30	26	18	12	54
11	30	3	8	24	15	16	33
12	34	2	18	18	16	15	17
13	35	4	5	23	11	8	65
14	56	4	21	27	15	12	56
Total							
Mean	46.64	3.00	12.00	21.86	13.50	11.71	45.00
SD	10.86	0.96	7.42	3.55	3.76	4.71	22.40

Decrease (percent) = (score at baseline – score in week 5)/score at baseline.

amitriptyline and trazodone). Additionally, 4 out of the 14 participants were taking lithium carbonate, 1 clonazepam and 1 olanzapine, along with their antidepressant medication. Twelve of the 14 subjects were using benzodiazepine hypnotics or antianxiety agents. One out of the 14 subjects complained of discomfort on the stimulation site; however, the symptoms were not serious enough to discontinue the treatment and disappeared after the completion of the stimulation. A one-way repeated-measures analysis of variance for the total scores on the Hamilton Rating Scale for Depression at baseline, at 3 weeks and at 5 weeks showed a significant main effect of time [$F(2, 26) = 38.1$, $p < 0.001$]. Multiple comparison using Bonferroni's method showed that the total scores on the Hamilton Rating Scale for Depression significantly decreased from the baseline score of 21.86 ($SD = 3.55$) to 13.50 ($SD = 3.76$) at 3 weeks and 11.71 ($SD = 5.57$) at 5 weeks, respectively ($p < 0.001$). Six out of the 14 patients were responders who showed an improvement rate greater than or equal to 50%, and 8 participants were nonresponders (table 1). After low-frequency right-sided TMS treatment in the 14 male pa-

Table 2. Locations of rCBF Changes in 14 male patients with depression after low-frequency right-sided TMS treatment

Brain region	Talairach coordinates			Brodmann area	Z score
	x	y	z		
<i>Areas of rCBF decrease</i>					
Left premotor	-50	-4	33	6	3.15
	-57	-10	39	6	2.85
	-53	-1	15	6	2.45
Right premotor	32	16	53	6	2.78
Left dorsolateral prefrontal	-30	29	35	9	3.29
	-53	5	27	9	3.10
	-32	47	14		2.72
	-46	40	15	46	2.70
	-42	46	18	10	2.65
Right dorsolateral prefrontal	-40	37	4		2.39
	32	27	39	8/9	3.77
	44	37	9	46	3.48
	34	29	28	9	3.18
	44	32	26		2.61
	53	28	19	46	2.54
	26	51	20	10	2.39
Left medial prefrontal	-2	63	12	10	3.67
Right medial prefrontal	2	59	19	10	3.52
	6	56	3	10	2.82
Left orbitofrontal	-24	33	-8	47	2.89
	22	52	-11	10/11	2.62
Right orbitofrontal	36	50	-11		2.60
Left anterior cingulate	-16	44	-4	32	3.15
	-10	47	9	10/32	2.53
Right subgenual cingulate	17	16	-14	25/47	3.35
Left anterior insula	-42	21	3		2.63
Right anterior insula	30	20	12	13	2.36
	32	16	1	13	2.33
Left somatosensory area	-34	-36	59	2	3.86
	-48	-19	43	2	3.25
Left inferior parietal	-46	-29	49	40	3.48
	-36	-40	46	40	2.90
	-53	-35	48	40	2.41

tients, significant decreases in rCBF were seen in the bilateral premotor area, DLPFC, medial prefrontal cortex, orbitofrontal, left anterior cingulate, right subgenual cingulate, bilateral anterior insula, left somatosensory and inferior parietal regions, but no significant increase in rCBF was observed (fig. 1, table 2). Furthermore, as compared with the 8 nonresponders, the 6 responders showed significant increases in rCBF at baseline in the left hemisphere of the prefrontal cortex, orbitofrontal, subgenual cingulate, anterior insula, temporal lobe including parahippocampus and amygdala, and inferior parietal regions (fig. 2, table 3).

Table 3. Locations of rCBF differences at baseline between 6 responders and 8 nonresponders to TMS treatment

Brain region	Talairach coordinates			Brodmann area	Z score
	x	y	z		
<i>Areas of rCBF difference (responders > nonresponders)</i>					
Left primary motor	-61	-3	15	4	3.43
	-40	-18	38	4	2.85
Left premotor	-42	-8	37	6	2.33
Left middle prefrontal	-24	36	17		2.73
	-28	35	-2		2.59
Left medial prefrontal	-2	64	0	10	2.44
Left orbitofrontal	-10	49	-21	11	3.62
Left subgenual cingulate	-16	21	-11		2.92
Left anterior insula	-32	21	1	13	3.50
Left superior temporal	-59	-32	15	22/42	4.10
	-59	4	2	22	3.88
Left middle temporal	-61	-31	-2	21	3.69
Left inferior temporal	-55	-45	-11	20	2.83
Left parahippocampus	-40	-47	-6		4.47
Left amygdala	-30	-7	-13		3.98
Left inferior parietal	-46	-27	36	2/40	2.90
Left angular	-51	-56	12	39	2.51

Discussion

In the present study, we performed low-frequency TMS of the right DLPFC of 14 patients with treatment-resistant depression and investigated changes in rCBF by using SPECT. After TMS treatment, the total scores on the Hamilton Rating Scale for Depression significantly decreased, and 6 out of 14 subjects were responders and 8 nonresponders. Furthermore, in order to evaluate the relationship between the rCBF at baseline and the response to low-frequency TMS treatment, we compared the difference between the rCBFs of the responders and nonresponders at baseline.

Changes in rCBF after Low-Frequency TMS Treatment

After low-frequency TMS of the right DLPFC of the 14 patients with treatment-resistant depression, significant decreases in rCBF were observed not only in the right DLPFC, which was the stimulation site, but also in wider regions including the bilateral prefrontal cortex and limbic-paralimbic regions such as the orbitofrontal, left anterior cingulate and right subgenual cingulate, and the left parietal cortex.

Fig. 1. Areas of significant decrease in rCBF in 14 male patients with depression after low-frequency right-sided TMS treatment.

Fig. 2. Areas of significant differences in rCBF at baseline between 6 responders and 8 nonresponders to TMS treatment.

Earlier studies on the effects of TMS on neuroanatomical function have suggested that the outcome of TMS differs, depending on its frequencies: the excitement of the cerebral cortex is enhanced by high-frequency TMS and suppressed by low-frequency TMS. The actions of TMS on the cortex is not only limited to the stimulation site but can also spread to remote regions [4, 5]. There are many reports on functional imaging that reveal abnormalities in rCBF and metabolism in patients with depression, and decreases in rCBF and metabolism in the DLPFC [6, 7], left-predominant hypofrontality [26] and changes in these accompanied by an improvement in symptoms of depression [8, 9]. According to these findings, an increase in the rCBF of the left DLPFC accompanied by an improvement in symptoms of depression was expected; however, it was not confirmed in the present study. On the other hand, the finding that low-frequency TMS of the right DLPFC resulted in a decrease in the rCBF of the stimulation site is consistent with the previous report [4]. It is considered that the decrease in the rCBF of the right DLPFC is brought about by the direct action of the stimulation of the right DLPFC with low-frequency TMS in the cortex rather than by the neuroanatomical change accompanied by an improvement in symptoms of depression.

The anterior cingulate (Brodmann areas 24 and 32) is reciprocally associated with the prefrontal and the limbic-paralimbic regions and conventional studies have shown that a decrease in rCBF and metabolism corresponds to symptoms of depression and an increase in these indicates an improvement in symptoms [8, 9]. These findings were obtained by treatment with antidepressants. Moreover, Kito et al. [19] reported that high-frequency TMS of the left DLPFC of patients with treatment-resistant depression showed an increase in the rCBF of the anterior cingulate accompanied by an improvement in symptoms of depression. However, we did not find an increase in the rCBF of the anterior cingulate after TMS treatment in the present study, but a decrease in the rCBF of the medial prefrontal cortex and anterior cingulate. This discrepancy may be accounted for by a remote effect via stimulation from the right DLPFC, which could decrease the rCBF in the anterior cingulate.

In addition, as for the SPECT study, the scan was taken within 48 h after the last TMS at 3 weeks. It is possible that TMS might have directly acted on the cortex and subcortex in addition to causing a change in rCBF accompanied by an improvement in symptoms of depression. It is difficult to distinguish between the immediate effects

of low-frequency TMS and the long-term consequences (a change in rCBF accompanied by the improvement of depression), as they are intermingled, and to evaluate each of them separately in patients with treatment-resistant depression. It is reported that an increase in the rCBF of the DLPFC and anterior cingulate is related to an improvement in depression [4, 8, 9, 19]. However, this was not found in our study, which may be attributable to the timing of the SPECT, taken within 48 h after the last TMS at 3 weeks.

In the present study, we observed a decrease in the rCBF of the bilateral orbitofrontal cortex, anterior insula, and the ipsilateral subgenual cingulate of the stimulation site after TMS treatment. According to existing research, the limbic-paralimbic regions are reciprocally associated with the prefrontal and the subcortical regions and are involved in the regulation of mood and emotion [27–29]. Drevets et al. [30] identified a decrease in rCBF and glucose metabolism in the subgenual prefrontal cortex (Brodmann area 25) and a reduction in the volume of the left subgenual prefrontal cortex in patients with familiar bipolar and unipolar depression. Several studies have reported a decrease in rCBF and metabolism in the limbic-paralimbic area such as the subgenual cingulate and anterior insula and putamen/pallidum regions accompanied by an improvement in symptoms of depression [9, 29, 31]. Mayberg et al. [32] found a decrease in metabolism of the subgenual cingulate region (Brodmann area 25) and limbic-paralimbic regions accompanied by an improvement in symptoms of depression by setting the subgenual cingulate region as the target area for the deep brain stimulation in treatment-resistant depression, based on the assumption that the region is metabolically overactive. Even though these modalities in the treatment of depression are different from that of the present study, they support our findings in that low-frequency TMS of the right DLPFC resulted in a decrease in the rCBF of the limbic-paralimbic regions such as the bilateral orbitofrontal cortex and anterior insula via the ipsilateral subgenual cingulate of the stimulation site with an improvement in symptoms of depression.

Pascual-Leone et al. [10] reported that high-frequency TMS of the left DLPFC and low-frequency TMS of the right DLPFC were effective but low-frequency TMS of the left DLPFC and high-frequency TMS of the right DLPFC were not successful in their studies on antidepressive effects [33]. These clinical findings and functional imaging studies based on therapies for depression including medical treatments and TMS raise the possibility that high-frequency TMS of the left DLPFC contributes to an im-

provement in symptoms of depression through an increase in rCBF on the side of the DLPFC stimulation site, the ipsilateral subgenual cingulate and anterior cingulate. However, low-frequency TMS of the right DLPFC contributes to an improvement in symptoms of depression by decreasing the rCBF in the limbic-paralimbic region such as the orbitofrontal cortex and anterior insula through the subgenual cingulate on the side of the stimulation site.

There was a decrease in the rCBF of the left somatosensory and inferior parietal regions in the present study. The reduction in the rCBF of the left somatosensory area seems to be due to the remote effect of low-frequency TMS on the contralateral side rather than due to an improvement in symptoms of depression.

Differences in rCBF at Baseline between Responders and Nonresponders to TMS Treatment

To detect the difference in rCBF associated with the response to low-frequency TMS treatment, we compared the rCBF at baseline between 6 responders and 8 nonresponders.

As compared with the 8 nonresponders, the 6 responders showed increases in rCBF in several brain regions in the left hemisphere (fig. 2, table 3), but there was no decrease in rCBF. Concerning the antidepressant response to TMS with brain imaging studies, Kimbrell et al. [34] administered TMS at 20 or 1 Hz to 13 patients with depression over the left prefrontal cortex and showed that a better response to 20-Hz TMS was associated with global hypometabolism at baseline, whereas a response to 1-Hz TMS tended to be related to hypermetabolism at baseline using positron emission tomography, and the authors suggest that the antidepressant response to TMS may depend on cerebral metabolism before pretreatment. In the present study, the responders receiving low-frequency TMS treatment have shown significant increases in rCBF at baseline in comparison with the nonresponders. These findings are consistent with the previous report by Kimbrell et al. [34] and interestingly were observed only in the left hemisphere, providing further evidence that the antidepressant response to the frequency or site of TMS treatment may depend on rCBF or cerebral metabolism before pretreatment. Furthermore, since nonresponders participated in this study, who are also likely to show decreased rCBF at baseline in the left hemisphere, high-frequency TMS that resulted in an increase in the rCBF of the left-dominant cortex, subcortex and limbic-paralimbic regions [4, 19] may contribute to an improvement in depressive symptoms in nonresponders.

Additionally, compared with the nonresponders, significant increases in rCBF in the responders were observed in the left medial temporal lobe including the parahippocampus and amygdala. In the present study we did not find a significant decrease in the rCBF of the left medial temporal region after low-frequency TMS of the right DLPFC, but Speer et al. [4] reported a decrease in rCBF in the left amygdala and left medial temporal cortex, which were not on the side of the stimulation.

Limitations

There are several limitations in the present study. The enrolled subjects were right-handed males with a similar degree of treatment-resistant depression and not necessarily a sample from the general population of patients with depression. Additionally, a placebo effect due to low-frequency TMS treatment of depression cannot be excluded because of the nonblinded design. Pharmacological therapy was continued during the TMS treatment; therefore, the effects of these medications on depression and rCBF cannot be completely excluded.

To the best of our knowledge, this study is the first to investigate changes in rCBF and the difference between responders and nonresponders to low-frequency TMS of the right DLPFC in treatment-resistant depression. Low-frequency TMS of the right DLPFC improved the symptoms of depression and resulted in decreases in rCBF not only in the stimulation site but also the bilateral prefrontal cortex and limbic-paralimbic regions such as the ipsilateral subgenual cingulate, bilateral orbitofrontal, anterior insula, and left parietal cortex. The results of the present study suggest that the antidepressant effect of low-frequency TMS of the right DLPFC is associated with a decrease in rCBF in the limbic-paralimbic regions via the ipsilateral subgenual cingulate. Additionally, as compared with nonresponders, responders show increases in rCBF at baseline in the left hemisphere including the prefrontal and limbic-paralimbic regions, raising the possibility that the increased rCBF in the left hemisphere may be involved in the response to low-frequency right-sided TMS treatment.

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