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Time course of cerebral blood flow changes following electroconvulsive therapy in depressive patients—measured at 3 time points using single photon emission computed tomography

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Abstract. Although electroconvulsive therapy (ECT) has been employed for treating depression for more than 60 years, its mechanisms of action are yet unknown. To clarify the ECT effects on brain function, we examined cerebral blood flow (CBF) using single photon emission computed tomography at 3 time points—few days before an ECT course (Pre) and approximately 5 days (Post 1) and 1 month (Post 2) after the last ECT session. Eight depressive patients completed the study. In all the patients, the depressive symptoms improved after the ECT course, and major cognitive impairment was not observed at any time point. At Pre, the regional CBF (rCBF) in the widespread areas in the frontal lobe and limbic regions including cingulate cortex and parahippocampal gyrus was lower in the patients than in the normal controls. At Post 1 and Post 2, the rCBF in the frontal and limbic regions continued to be lower in the patients than in the controls although the successive recovery of decreased rCBF in the frontal region was observed. Regarding the time course among the patients, the rCBF in the right medial frontal region significantly increased (toward normal) at Post 2, not at Post 1. These findings suggest that depressive patients have decreased CBF in the frontal and limbic regions, and the medial frontal region plays a crucial role in ECT and recovery from depression. Further, patients who have undergone ECT treatment for depression should be carefully observed because brain functions continue to change even after a successful ECT course. (Keio J Med 55 (4) : 153–160, December 2006)

Key words: depression, electroconvulsive therapy (ECT), single photon emission computed tomography (SPECT), brain mapping

Introduction

Depression is one of the most common mental disorders and is mainly characterized by depressive mood and loss of interest or pleasure. It has been reported as one of the most burdensome diseases worldwide[1] and could frequently be fatal due to acts of suicide committed by the depressive patients. While depression can be effectively treated in the majority of patients by administering either antidepressant medication or some types of psychotherapy, up to 20% of the patients fail to respond to these therapies.[2]

On the other hand, electroconvulsive therapy (ECT) has been employed in the treatment of depression for more than 60 years. The safety of this therapy has been improved with the introduction of some techniques such as succinylcholine-induced muscle relaxation, barbiturate-induced anesthesia, oxygenation, and brief-pulse stimulation. It is estimated that every year, more than 1 million patients receive ECT worldwide.[3] ECT has been clearly mentioned in the therapeutic guidelines for depression,[4] and a recent meta-analysis reconfirmed

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its efficacy and safety.[5] Despite its established utility, the mechanisms of action of ECT remain to be clarified.

Functional neuroimaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) have revealed a biological basis underlying depression. Most of these studies have indicated decreased frontal activity in the depressive state under resting conditions.[6,7] Most importantly, the medial frontal region that includes the anterior cingulate cortex was of particular concern because considerable data support the involvement of this area in mood regulation and depression. However, previous reports on changes in the cerebral blood flow (CBF) and metabolism following an ECT course (short-term; within several days to 1 week after the last session) have presented conflicting results.[8] Although most reports have suggested the involvement of the frontal areas of the brain, some reports have indicated an increase in the frontal activity, [9–11] some have indicated a decrease,[12–14] whereas a few reports have showed no change.[15,16] Furthermore, although short-term follow-up findings after an ECT course have been widely studied, there are only a few studies that have analyzed the mid-term or long-term follow-up observations.

In this study, aiming to clarify the time course of ECT effects on the brain function, we investigated changes in the clinical symptoms and measured the CBF by using SPECT at 3 time points — before a course of ECT, approximately 5 days after the course, and 1 month after the last ECT session.

Subjects and Methods

Subjects

Patients who fulfilled the criteria for a major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed.)[17] were selected for this study on the basis of careful clinical diagnostic examinations. Each patient provided a written informed consent prior to the participation in the study. Of the 10 patients who first agreed to participate, 8 inpatients (5 males and 3 females, mean age ± standard deviation (SD): 48.9 ± 16.2 years) completed the study. Of the 2 drop-out subjects, 1 patient showed no improvement after several ECT treatments and refused to continue with the therapy. The other patient responded to ECT once; however, this patient's condition was aggravated during the follow-up period, and he refused to undergo further examination. Patients were referred to the Keio University Hospital for ECT because they showed an inadequate response to their previous therapies. All patients were right-handed; those who had a history of major medical illnesses, cognitive disorders, psychoactive substance abuse or dependence, or those who had received ECT up to 6 months prior to the study were excluded from the study. All the patients underwent brain magnetic resonance imaging (MRI) or computed tomography (CT); the results of these investigations were normal, except for the observation of minimum cerebral atrophy.

Clinical assessments were performed at 3 time points — few days (2.8 ± 2.4 days) before the first ECT (Pre), approximately 5 days (4.8 ± 1.5 days) after the completion of the treatment course (Post 1), and 1 month (31.9 ± 3.2 days) after the last ECT session (Post 2). The severity of depressive symptoms was rated on the 17-item Hamilton Depression Scale (HAM-D),[18] and Mini-Mental State Examination (MMSE)[19] was performed in order to examine the general mental status. Concurrently, the regional CBF (rCBF) was measured by SPECT.

All patients received a few psychotropic drugs, including antidepressants. The medications remained unchanged from the first (Pre) to the last (Post 2) assessment, i.e., during the entire study period; however, benzodiazepines or neuroleptics were provided for insomnia and anxiety, as required. Table 1 shows the demographics of the patients.

Regarding the SPECT images for CBF, 12 healthy subjects (6 males and 6 females; age 55.9 ± 5.6 years) served as normal controls (no significant difference was observed in the age between the patients and normal controls by unpaired *t*-test at $p < 0.05$). This study was approved by the ethical committee of the hospital.

Electroconvulsive therapy

ECT was generally administered in accordance with the guidelines of the American Psychiatric Association.[20] The patients were treated with bifrontotemporal ECT using a brief-pulse square-wave ECT device (Thymatron system IV device; Somatics, Inc., Lake Bluff, IL, USA). ECT treatments were performed 3 times a week, and they were continued until a stable response was obtained. General anesthesia was induced by intravenous administration of sodium thiopental (4 mg/kg), and succinylcholine (1 mg/kg) was used to induce muscle relaxation. Electroencephalogram (EEG) seizure manifestations were monitored to ensure adequate seizure duration. The titration method[20] was applied for determining the stimulus intensity of the first ECT session. The patients were restimulated at a higher intensity when the seizure duration was less than 25 seconds.

Single photon emission computed tomography

Patients were injected with 740 MBq of Tc-99m-hexamethyl propyleneamine oxime (^{99m}Tc-HMPAO; Nihon Mediphysics, Tokyo, Japan), and SPECT imaging was performed 30 minutes after administering the injection. A 3-headed rotating gamma camera (Toshiba GCA-

Table 1 Characteristics of the Patients

Patient	Age	Sex	No Episo	Dur	Psycho	Antidepressants taken (mg/day)	HAM-D		
							Pre	Post 1	Post 2
1	27	F	2	2		amoxapine (100)	17	10	7
2	33	M	1	30		nortriptyline (100)	20	5	6
3	40	M	3	3		clomipramine (50)	26	9	7
4	41	M	5	12		amoxapine (100), mianserin (30)	20	7	9
5	53	F	3	38		trazodone (100)	23	4	3
6	58	M	3	1		amoxapine (100), mianserin (30)	24	7	9
7	68	F	2	2	+	milnacipran (105), trazodone (100)	39	12	13
8	71	M	2	21		clomipramine (25)	21	6	8

Abbreviations: No Episo: the number of depressive episodes, Dur: duration of the current episode and duration of medication in the current episode, Psycho: with psychotic features, HAM-D: Hamilton Depression Scale, Pre: at several days before electroconvulsive therapy, Post 1: at approximately 5 days after the last electroconvulsive therapy session, Post 2: at 1 month after the last electroconvulsive therapy session, F: female, M: male

9300A/DI; Toshiba Corporation, Tokyo, Japan) mounted with ultra high-resolution fanbeam collimators was used for data acquisition, and a medical image processor (GMS5500; Toshiba Corporation, Tokyo, Japan) was employed for image processing. The energy window for acquisition was set at 140 keV with a width of 20%. The gamma camera was rotated continuously for 16 minutes, and SPECT data were arranged into 90 projections over 360°. Images were reconstructed in a 128 × 128 matrix using a ramp filter after the data was processed with a Butterworth filter (order 8, 0.11 cycles/pixel).

Image analyses

Image analyses were carried out using a three-dimensional stereotactic surface projection (3D-SSP) method.[21] In brief, all CBF images were globally normalized and transformed to correspond to the size and shape of the standard brain[22] by linear and nonlinear parameters. Maximum cortical activity was extracted to the adjacent predefined surface pixels on a pixel-by-pixel basis. In order to compare the CBF between the patients and normal controls, pixel-by-pixel Z scores were used. Here, the Z scores were defined as follows:

Z = (mean counts per pixel of the patients – mean counts per pixel of the normal controls)/SD of normal controls.

Moreover, in order to evaluate the relative rCBF values, the mean counts for each gyrus level classification were calculated by the stereotactic extraction estimation (SEE) method,[23] and the mean value of the counts per pixel of the whole brain was adjusted to 50.

Data analyses

Statistical analyses were carried out by using the SPSS software, version 14.0 J (SPSS Inc, Tokyo, Japan). Repeated measures of analysis of variance (ANOVA) were used for the analysis of data over time, and Bonferroni correction was used for multiple comparisons; significance was set at a level of 0.05.

Results

Clinical evaluations

ECT was performed 7.3 ± 1.2 times (range: 5-10 times) for each patient. As shown in Table 1, one patient had psychotic features and responded well to ECT, but her depressive symptoms did not remit when remission was defined as a total HAM-D score of less than 8 points. The total HAM-D score changed significantly between the 3 time points (repeated measures of ANOVA, $p = 0.000$). Post-hoc analysis by Bonferroni correction revealed significant differences between the Pre and Post 1 observations as well as the Pre and Post 2 observations. Compared to the HAM-D scores at Pre, the scores at Post 2 were reduced by more than 50% in all the patients. This finding is indicative of the clinical efficacy of the treatment and the sustained improvement. Furthermore, no significant correlations were observed between the ratio of HAM-D at Post 1/at Pre and the clinical variables on depression including the number of depressive episodes, the duration of the current episode, and the duration of medication in the current episode (Pearson's coefficient, $p < 0.05$). In contrast, as shown in Table 2, the total MMSE score was at least 25 in all the patients, and repeated measures of ANOVA demonstrated no sig-

Table 2 Results of the Mini-Mental State Examination

	Pre	Post 1	Post 2
MMSE	28.3 ± 1.7	28.3 ± 1.4	29.3 ± 0.9
	(25-30)	(26-30)	(28-30)

Upper rows: Data are presented as mean ± standard deviation.
Lower rows: the numbers denote the range of the total score

nificant changes in MMSE before and after ECT.

CBF measured by SPECT

1. Comparison between the patients and normal controls

At Pre, the relative rCBF in the widespread areas in the frontal lobe and limbic regions, including the anterior and posterior cingulate cortices, parahippocampal gyrus, thalamus, and uncus, was lower in the depressive patients than in the normal controls (Fig. 1; A). On the other hand, the relative rCBF in the widespread areas in the occipital, parietal, posterior temporal lobes, and the cerebellum was higher in the depressive patients than in the normal controls. At Post 1 and Post 2, the rCBF in the frontal areas (particularly the inferior frontal area) and the limbic regions (the anterior and posterior cingulate cortices and thalamus) in the patients continued to be lower than that in the normal controls, although the successive recovery of decreased rCBF in the frontal region was observed during 1 month after ECT. (Fig. 1; B, C).

2. Time course of changes in the rCBF in the patients

Table 3 represents the mean counts per pixel in each region as obtained by the SEE method; these counts would reflect the relative rCBF values in the cerebral regions. Repeated measures of ANOVA revealed significant changes in the rCBF (mean counts) in the right medial frontal gyrus ($p = 0.012$), right cuneus ($p = 0.015$), and right parahippocampal gyrus ($p = 0.048$).

Post-hoc multiple comparisons using Bonferroni correction demonstrated a significant increase in the rCBF in the right medial frontal region at Post 2 compared to that at Pre ($p = 0.045$). It also showed a tendency for increase in the rCBF in the right medial frontal region at Post 2 compared to that at Post 1 ($p = 0.061$). Post hoc analysis also showed a trend of increase in the rCBF in the right parahippocampal gyrus at Post 1 compared to that at Pre ($p = 0.076$), whereas significant decreases were observed in rCBF in the right cuneus at Post 1 compared to that at Pre ($p = 0.025$).

Furthermore, due to the wide age range of our patients and the gender differences, we performed 2-way factori-

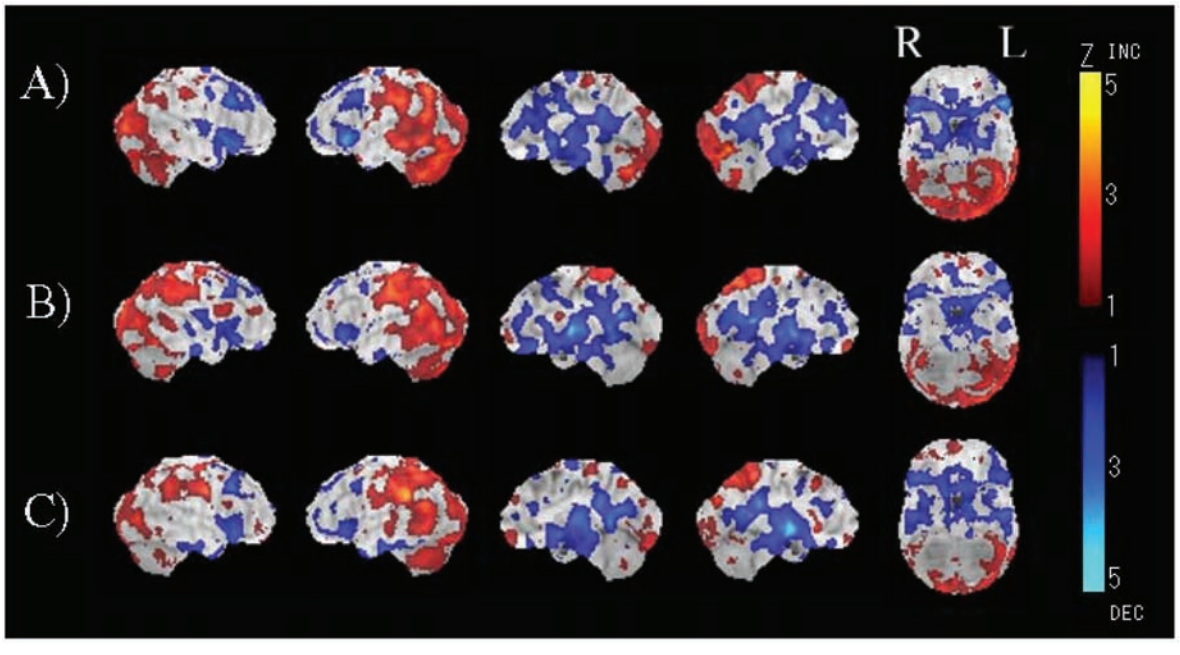

Fig. 1 Areas showing relative increases (red) and relative decreases (blue) in the regional cerebral blood flow (rCBF) in the patients compared to those in the normal controls. From left to right: right lateral view, left lateral view, right midline view, left midline view, and inferior view. L indicates left and R indicates right.
Color bars on the right side represent the Z scores. INC indicates relative increases in the rCBF in the patients in comparison with the normal controls, and DEC indicates relative decreases in the rCBF in the patients in comparison with the normal controls.
A) Observations at Pre (several days before electroconvulsive therapy (ECT)) in patients vs normal controls
B) Observations at Post 1 (approximately 5 days after the last ECT session) in patients vs normal controls
C) Observations at Post 2 (1 month after the last ECT session) in patients vs normal controls

Table 3 Relative Rates of the Mean Counts per Pixel in Each Brain Region\

			Pre			Post 1			Post 2		
Superior frontal gyrus		L	47.9	±	1.8	48.3	±	1.2	48.6	±	1.7
		R	48.3	±	1.8	48.6	±	1.4	48.9	±	1.6
Middle frontal gyrus		L	48.9	±	1.5	49.3	±	1.0	49.4	±	1.8
		R	49.3	±	1.2	50.1	±	1.0	49.9	±	1.5
Inferior frontal gyrus		L	46.8	±	0.8	47.3	±	1.5	47.7	±	1.7
		R	48.1	±	1.3	48.8	±	0.9	48.4	±	1.7
Medial frontal gyrus		L	48.7	±	1.2	48.8	±	1.3	49.1	±	2.2
	*	R	48.3	±	1.3	48.6	±	1.4	49.6	±	1.6
Orbital gyrus		L	50.6	±	2.1	49.9	±	2.8	48.7	±	2.9
		R	48.3	±	3.5	47.6	±	3.0	49.6	±	2.7
Rectal gyrus		L	46.8	±	2.9	47.4	±	2.2	46.0	±	2.7
		R	46.3	±	1.9	46.5	±	3.7	46.3	±	2.0
Paracentral lobule		L	49.2	±	2.4	48.7	±	2.9	49.2	±	3.4
		R	48.7	±	2.8	49.1	±	2.6	48.3	±	4.0
Precentral gyrus		L	49.1	±	1.9	49.0	±	1.6	49.1	±	1.4
		R	48.8	±	1.5	49.5	±	1.8	49.8	±	1.6
Subcallosal gyrus		L	43.0	±	2.9	42.9	±	2.3	42.9	±	1.7
		R	42.3	±	2.2	41.1	±	4.1	41.6	±	2.8
Superior parietal lobule		L	49.1	±	2.3	50.2	±	1.9	50.7	±	2.3
		R	49.7	±	2.4	50.5	±	2.0	50.2	±	2.4
Inferior parietal lobule		L	51.0	±	1.7	51.7	±	2.3	52.1	±	1.9
		R	51.1	±	2.2	52.4	±	2.1	51.6	±	2.4
Angular gyrus		L	52.2	±	2.3	50.9	±	3.2	50.9	±	2.1
		R	52.4	±	2.3	52.3	±	2.4	51.6	±	3.1
Postcentral gyrus		L	49.5	±	1.7	50.1	±	1.7	50.0	±	1.9
		R	49.6	±	1.9	50.4	±	2.6	49.6	±	2.2
Precuneus		L	53.2	±	0.9	53.4	±	2.0	53.8	±	2.2
		R	53.5	±	2.0	53.1	±	2.1	53.2	±	2.3
Supramarginal gyrus		L	54.1	±	2.8	54.0	±	2.4	54.2	±	2.6
		R	51.5	±	1.5	52.8	±	2.0	51.9	±	1.4
Superior temporal gyrus		L	49.9	±	1.5	49.8	±	1.5	49.7	±	1.3
		R	49.6	±	1.3	50.0	±	1.8	50.1	±	1.0
Middle temporal gyrus		L	52.2	±	1.5	52.1	±	1.9	51.8	±	1.6
		R	49.3	±	1.2	50.1	±	1.0	49.9	±	1.5
Inferior temporal gyrus		L	49.1	±	1.3	49.1	±	1.9	47.7	±	0.9
		R	49.6	±	0.9	49.3	±	1.3	48.5	±	1.4
Transverse temporal gyrus		L	53.4	±	3.2	52.8	±	3.3	53.8	±	3.6
		R	51.8	±	2.4	51.7	±	4.0	52.7	±	2.8
Superior occipital gyrus		L	52.6	±	3.9	52.9	±	3.3	52.3	±	4.4
		R	53.8	±	4.3	53.6	±	4.4	52.6	±	3.6
Middle occipital gyrus		L	52.8	±	3.4	52.9	±	3.1	52.4	±	2.7
		R	54.0	±	3.2	53.9	±	3.0	53.0	±	2.7
Inferior occipital gyrus		L	51.2	±	3.1	52.0	±	2.7	51.0	±	1.7
		R	51.5	±	3.5	51.7	±	2.5	51.8	±	3.4
Cuneus		L	55.2	±	3.4	54.5	±	3.3	54.6	±	2.5
	*	R	56.1	±	3.3	54.7	±	3.1	54.6	±	2.9
Fusiform gyrus		L	50.1	±	1.3	50.2	±	1.8	48.9	±	0.9
		R	50.1	±	1.5	50.3	±	1.4	49.6	±	1.8
Lingual gyrus		L	56.8	±	3.0	55.6	±	4.2	55.3	±	2.5
		R	55.8	±	3.9	54.6	±	3.5	55.4	±	2.6
Thalamus		L	54.7	±	5.1	55.3	±	4.6	54.1	±	3.6
		R	56.9	±	5.2	52.9	±	4.2	54.2	±	3.2
Cingulate gyrus		L	47.4	±	1.5	47.1	±	2.2	47.7	±	1.6
		R	47.5	±	0.9	47.2	±	2.6	47.9	±	1.6
Parahippocampal gyrus		L	44.7	±	2.5	45.1	±	2.0	45.8	±	2.2
	*	R	45.0	±	2.9	47.6	±	2.5	46.8	±	3.1
Anterior cingulate cortex		L	44.3	±	2.4	44.4	±	2.4	45.0	±	3.2
		R	44.0	±	2.1	44.2	±	3.1	44.6	±	3.5
Posterior cingulate		L	48.6	±	2.6	48.5	±	1.9	48.5	±	2.4
		R	50.4	±	2.3	49.5	±	1.4	49.1	±	2.5
Uncus		L	43.6	±	2.4	45.2	±	2.3	44.7	±	2.5
		R	44.4	±	1.6	46.3	±	3.0	44.8	±	1.8

*Represents statistical significance at $p < 0.05$ by repeated measures of analysis of variance.
Abbreviations: R: right, L: left, Pre: at few days before electroconvulsive therapy, Post 1: at approximately 5 days after the last electroconvulsive therapy session, Post 2: at 1 month after the last electroconvulsive therapy session

al ANOVA for comparing young (patients 1-4: age 35.3 ± 6.6 years) and old (patients 5-8: age 62.5 ± 8.4 years) patients as well as male and female patients (5 and 3, respectively). However, no significant change in the rCBF was observed in each region between young and old patients as well as between male and female patients.

Discussion

In the present study, the depressive symptoms of our patients improved after a course of ECT treatment, and this improvement was observed even at 1-month follow-up. In contrast, MMSE showed neither abnormality nor evident exacerbation; this suggests the safety of the treatment.

Compared to the normal controls, the depressive patients showed a reduction in the rCBF in the frontal part of the brain and limbic regions, particularly the medial frontal areas that include the anterior cingulate cortex before ECT treatment. These findings are in agreement with that of previous studies,[6,7] and these regions of the brain have been known to play a crucial role in mood regulation.

Regarding the changes in the rCBF before and after the ECT course, in the present study, the rCBF in the right medial frontal area showed no significant change at Post 1; however, it remarkably increased at Post 2, that is, 1 month after ECT. On the other hand, the rCBF remained lower in some frontal regions in the patients than in the normal controls at Post 1 and 2. To date, several studies have reported the changes in the CBF and cerebral metabolic rate for glucose (CMRglc) before and after an ECT course; however, the results of these studies were contradictory.[8] Although most studies indicated the involvement of the frontal lobe and anterior cingulate cortex, some studies reported an increased brain activity in these areas,[9–11] others reported a reduction,[12–14] whereas a few reports showed no change.[15,16] For example, Bonne *et al* reported increases in the rCBF in the anterior cingulate cortex only in patients responding to ECT 5-8 days after the last session.[9] This study was similar to our study in that the rCBF increased in the frontal area after recovery from depression and it was measured using ^{99m}Tc-HMPAO SPECT; however, in our study, the scanning was performed twice after the ECT course. In sharp contrast, by using fluorodeoxy-glucose (FDG) PET, Nobler *et al* demonstrated that the post-ECT reductions in CMRglc, particularly in the frontal and parietal cortices and the anterior and posterior cingulate gyri, were identified approximately 5 days after the ECT course.[13] Further, by using ^{133}Xe inhalation technique, they also showed the post-ECT reductions in the frontal areas of the brain 10 years before the abovementioned study was conducted.[12] The discrepancy between these results could be due to several factors.

One possible explanation for the difference would be the diverse modalities used to measure the brain function, such as CBF measurement by ^{133}Xe inhalation[12] and ^{99m}Tc-HMPAO SPECT[9–11] and the measurement of metabolism by FDG-PET.[13,14] The ^{133}Xe inhalation technique has a relatively low resolution; therefore, in earlier studies that used this technique, it was difficult to examine specific brain regions.

The second possible reason for the differences in the results could be the various methods of image analysis used. Recent advances in 3D brain image analysis methods, such as the introduction of statistical parametric mapping (SPM)[24] and 3D-SSP, enable us to conduct accurate investigations. Earlier studies were performed using manually drawn regions of interest (ROI) and cerebellar uptake normalization;[9–11,16] they may not be objective or reproducible. In particular, it could affect the results if the cerebellar uptake differs between scans. The 3D-SSP and SEE methods used in this study are automated, user independent with regard to data extraction; therefore, they are objective and reliable. These methods are also considered appropriate for use in cases of brain atrophy;[25] thus, using them in our study was advantageous because some of our elderly patients had mild cerebral atrophy.

Another possible reason for the difference would be the time lapsed after the final treatment because the effects of ECT change dramatically with time. Pevious reports, which were conducted at post-ECT subacute state, that is, within hours to several days post-ECT, consistently indicated that the rCBF in the anterior region of the brain was reduced post-ECT, while the present study revealed the increased rCBF in the frontal lobes at 1 month after ECT.

In subacute phase after ECT, Scott *et al* detected a post-ECT reduction in the rCBF only in the inferior anterior cingulate cortex 45 minutes after the ECT treatment.[26] Volkow *et al* performed FDG-PET 24 hours after the ECT session and observed a decreased uptake in the frontal cortex bilaterally.[27] These results in subacute period were in agreement with the hypothesis proposed by Sackeim *et al* that ECT caused postictal suppression of brain activity, and that the degree of suppression is correlated with the clinical outcome; the hypothesis further stated that one of the mechanisms of action of ECT was due to this anticonvulsant effect (ECT triggers an endogenous process that terminates the seizure and results in enhanced suppression of the postictal functional brain activity).[28]

However, only a few studies have reported mid-term or long-term follow-up observations of CBF or CMRglc after an ECT course. Awata *et al* reported that the mean rCBF reduction with cerebellar normalization in late-life depression before ECT was increased (normalized) 2 and 12 weeks after ECT.[29] However, persistent anterior

paralimbic hypoperfusion was observed even 12 weeks after ECT. Another study that used FDG-PET reported that hypometabolism in various frontal regions did not resolve at 1-month follow-up.[30] Although these studies were not controlled with regard to the patients' medication status, the results were similar to those of our study. Recently, Navarro *et al* demonstrated that in both the medication-treatment and ECT-treatment groups who showed remission for more than 12 months, the frontal hypoperfusion on SPECT at baseline was observed to normalize on follow-up SPECT that was conducted in a drug-free state (medications had been washed out 2 weeks before the examination).[31]

To summarize the results mentioned above, it may be suggested that the rCBF in the frontal region decreases immediately after a successful ECT treatment course (within hours to several days post-ECT), and then increases and tends to recover gradually. In other words, brain changes after ECT continue even after an improvement in the depressive symptoms.

One feature that requires further discussion is that a significant change in the rCBF in the cuneus of patients was also found in the study. It is difficult to explain its precise mechanism, because we did not quantify the absolute values of the rCBF, i.e., we only observed the relative changes (distribution) in the rCBF; however, from this way of measurement, it might be possible that the rCBF change in the cuneus might be secondary and induced by the primary change in the right medial frontal area. Additionally, we observed significant rCBF changes only in the right side of the brain. There has been no clear consensus on the laterality in the rCBF with regard to depression[7] as well as the change induced by ECT[8]; however, Drevets *et al*[6] demonstrated that right, but not left subgenual prefrontal cortex activity was associated with the severity of depression, and this observation appears to be consistent with our results.

The present study has several limitations, including the small sample size and variations in terms of patients' age and gender. However, no significant difference was observed in the rCBF changes in any region between the young and old patients as well as the gender difference. Moreover, our depression patients voluntarily participated in this study after giving informed consent; therefore, we cannot completely exclude the possibility of a selection bias in sampling subjects. In addition, although we maintained an almost uniform medication status during the entire study period, the patients concomitantly received some psychotropics. This was because it is extremely difficult to maintain a drug-free state after ECT for a long period due to ethical reasons, and after ECT treatment, almost all patients require antidepressant medications to prevent a relapse. Further follow-up studies with larger sample size are required to serially observe the post-ECT state or trait abnormalities in the brain.

Finally, it is important that ECT should be recognized as a scientific treatment. Its efficacy and safety should be assessed by performing objective measurements such as clinical evaluation scales and CBF changes, and be confirmed by evaluating both the effect of ECT on brain itself and the degree of recovery from depression. Thus, elucidating the mechanisms of action of ECT would help us to obtain a better understanding of the neurobiology of depression.

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