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Longitudinal rCBF Changes Measured with SPECT in Patients with Depression Undergoing Treatment

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Abstract

Regional cerebral blood flow (rCBF) studies of major depression have yielded variable results. The present study employed a longitudinal observation method to measure rCBF every 3 months during treatment. Thirteen patients with major depressive disorder underwent single-photon emission computed tomography (SPECT) with ^{99m}Tc-HMPAO three times over a 6-month period. rCBF was analyzed with the Statistical Parametric Mapping. The findings were compared to scans from 14 normal control subjects. Depression symptoms were rated using the Hamilton Rating Scale for Depression. At baseline, the main regions with lower rCBF compared to controls were the middle and inferior frontal gyri, superior temporal gyrus, and cingulate cortex. Three months later, despite significant improvement of depressive symptoms, decreased rCBF was observed in the same regions, but to lesser extent. At 6 months, depressive symptoms showed continued improvement, and rCBF in the superior temporal gyrus increased up to control levels, but rCBF in the temporal pole, cingulate, and inferior frontal gyrus remained low. The results of the present study suggest that there might be time- and state-dependent differences in rCBF recovery in patients with major depression.

Keywords

Depression, Regional Cerebral Blood Flow, SPECT, Dorsolateral Prefrontal Cortex, Cingulate Cortex

1. Introduction

Altered brain activity in patients with mood disorders can be reflected in changes in regional cerebral blood flow (rCBF). Many studies have reported rCBF measured by single-photon emission computed tomography (SPECT) in patients with major depression, but comparisons of rCBF with healthy controls and during the course of treatment are inconsistent [1]-[6]. Recovery from depressive symptoms can be obtained in approximately 3 months with antidepressants, but recovery from major depression reportedly requires almost 6 months before the risk of recurrence falls and patient condition stabilizes [7]. The inconsistent results of previous studies may partly be owing to the heterogeneous etiology of depression and personal and treatment conditions. They could also be owing to measurements being taken too early in the course of treatment.

The present study was conducted to solve the problem of inconsistent results in imaging studies. We prospectively followed patients during their treatment course for 6 months and measured rCBF (as a ratio to blood flow in the cerebellum) using SPECT every 3 months. To our knowledge, there have been no reports of serial rCBF measurements performed over 6 months. Our goal was to delineate altered brain function in patients with major depression during exacerbation periods and the alleviation of depressive symptoms following pharmacological treatment.

2. Subjects and Methods

2.1. Subjects

Subjects were patients with depression who fulfilled the diagnostic criteria for a major depressive episode in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [8] and whose symptoms were evaluated using the Hamilton Rating Scale of Depression (HRSD, 24-item) [9]. Thirty-two subjects participated in this study. They received pharmaceutical therapy with psychotropic agents, but the types of drugs and their doses were not controlled. Patients suspected of having a serious physical disorder or who had clear abnormalities on magnetic resonance imaging (MRI), X-ray computed tomography (X-CT), electroencephalography (EEG), or an intelligence test (WAIS-R) were excluded. Patients whose HRSD scores did not drop by 30% or more 3 months after study initiation were also excluded. Thirteen of the 32 (40.6%) subjects had a positive response and participated in the remainder of the study. After 6 months, their HRSD score was less than 10 points. Thirteen patients who met the above criteria were enrolled (9 female, 4 male) to complete the study. We also invited healthy control subjects to the present study who had no physical or mental disorders or history of treatment for mental disorders; individuals in this group were not taking any medications. They had no abnormalities on MRI, X-CT, EEG, or intelligence tests. The control group consisted of 14 subjects (7 female, 7 male). This study was conducted with the consent of the Fukushima Medical University Ethics Committee (No. 133). Written consent for participation in the

study was obtained from all subjects.

2.2. SPECT Imaging

SPECT was used in rCBF distribution measurements, with ^{99m}Tc-HMPAO (hexamethylpropyleneamineoxime) 1110 MBq as a radioactive agent given in an intravenous bolus injection via a line secured in the median antebrachial vein. Before and after the injection, the subjects rested in a quiet room with the lights dimmed while wearing an eye mask and ear plugs. Imaging was performed 40 min after injection. Because depressive symptoms such as psychomotor retardation in major depression patients show considerable diurnal variation, ^{99m}Tc-HMPAO injection was given between 10 and 11 a.m. SPECT imaging was performed three times, during the depressive phase before treatment (baseline) and 3 and 6 months later. Depressive symptoms were evaluated with the 24-item HRSD within 4 days of each SPECT study.

A Shimadzu Headtome 030 (ring type, HR collimator) was used in SPECT imaging, and image slices were parallel to the orbitomeatal base line (OM line). The obtained images were 64 × 64 pixels, and slice thickness was approximately 13 mm.

^{123}I and ^{99m}Tc are the most commonly used isotopes for imaging cerebral blood flow with SPECT. Absolute cerebral blood flow can be calculated by collecting arterial blood when using ^{123}I; however, this is not possible when using ^{99m}Tc. We calculated rCBF as a relative value based on the cerebellum as the reference region because cerebellar blood flow is not considered to be affected by factors such as age [10]-[15]. Using the whole brain as the reference region produces inherent contradiction because the target regions are within the reference region.

As a reference site for each imaging, the mean count for the entire cerebellum including the vermis on slices that contained the lower-central pons was calculated, and the value obtained through each pixel count divided by this value was defined as the ratio to the cerebellum used in the analysis.

2.3. Analysis

Nine slices were imaged, but the data were rearranged to form 20 slices with resampling (3-dimensional linear method) and expanded (normalized) to a standard brain. They were then compared voxel by voxel using SPM-99 (Statistical Parametric Mapping 99). The significance levels for the intra- and intergroup comparisons were set as $p < 0.005$ and $p < 0.001$, respectively.

Measurements at baseline, 3 months, and 6 months were compared in the subject group using paired *t*-tests ($p < 0.005$), and between-group comparisons with the healthy control group were performed with two-sample *t*-tests ($p < 0.001$). The cluster size threshold was set to greater than 40 voxels for the intra- and intergroup comparisons. Image processing was performed with Medex 3.3 (Sensor Systems, Inc.). From this analysis with SPM-99, the anatomical positions of each cluster and Brodmann area were identified using the Talairach atlas [16]

for locations in which differences or changes were seen. As an indicator of differences between groups on SPM, the Z score ([mean of control group-mean of subject group]/standard deviation of control group) was calculated.

The analyses of other variables such as age, education, and HRSD were conducted using *t*-tests.

3. Results

3.1. Symptoms and Medications

A total of 13 patients (9 female, 4 male) who met the criteria were enrolled. They had a mean age of 46 ± 13 (22 - 62) years and 11.5 ± 1.7 years of education. The control group consisted of 14 subjects (7 female, 7 male) with a mean age of 31.5 ± 12.8 years and had 15.4 ± 3.0 years of education. The control group was thus significantly younger ($t(24.31) = 2.952$, $p = 0.007$) and had significantly more years of education ($t(20.48) = 4.099$, $p < 0.01$). Depressive symptoms in terms of HRSD scores were 31.5 ± 12.0 at baseline, 11.0 ± 4.3 at 3 months, and 6.2 ± 2.7 at 6 months. The mean score had decreased by 65% or more at second and third measurements, and these differences were significant (baseline vs. 3 months, $t(12) = 6.187$, $p < 0.01$; baseline vs. 6 months, $t(12) = 8.415$, $p < 0.01$). Table 1

Table 1. Daily doses of antidepressant, antipsychotic, and antianxiety medications for each subject at 0, 3, and 6 months.

Case no.	Imipramine equivalent (mg)			Chlorpromazine equivalent (mg)			Diazepam equivalent (mg)		
	0 m	3 m	6 m	0 m	3 m	6 m	0 m	3 m	6 m
1	50	50	50	0	0	0	25	14	14
2	50	75	75	0	0	0	5	5	5
3	250	245	150	0	0	0	30	16	8
4	30	30	30	0	0	0	10	15	15
5	90	33	33	110	70	70	5	13	8
6	125	225	225	50	60	138	11	11	7
7	10	10	10	15	30	50	6	6	6
8	10	15	15	0	26	300	5	17	2
9	40	150	125	0	130	160	4	4	4
10	50	100	75	0	0	0	18	10	10
11	45	65	45	0	0	0	0	0	0
12	0	0	0	50	0	0	3	2	2
13	13	125	125	0	0	0	5	5	5
Avg	59.4	89.4	75.7	18.7	26.3	59.8	8.5	8.7	6
Std	69.9	82.6	68.3	34.5	41.2	94.9	8.2	5.8	4

a. The doses (mg/day) of antidepressants, antipsychotics, and antianxiety medications are expressed in imipramine, chlorpromazine, and diazepam equivalents, respectively. Equivalents were calculated based on the conversion table formulated by the clinical psycho-pharmacology study group of Keio University [17]. Avg, average; Std, standard deviation.

shows the antidepressant, antipsychotic, and antianxiety drug amounts in equivalent dosages of imipramine, chlorpromazine, and diazepam, respectively, that were taken by patients at each time point. The conversion in equivalent dosages of imipramine, chlorpromazine, and diazepam was calculated based upon the conversion table formulated by clinical psycho-pharmacology study group of Keio University [17]. The mean medication doses per day, in imipramine, chlorpromazine, and diazepam equivalents, were not significantly different between the three time points.

3.2. rCBF Distribution

3.2.1. Comparison of Patients with Healthy Controls

The regions where rCBF differences were seen in patients compared to the control group are listed in **Table 2**. At baseline, areas with lower rCBF ratios to the cerebellar blood flow as compared to the control subjects were the bilateral superior temporal gyri (temporal pole including amygdala), bilateral cingulate (frontal portion), right inferior frontal gyrus, bilateral middle frontal gyri, left anterior cingulate (antero-inferior), and left middle and superior frontal gyri.

The lower rCBF areas improved at 3 and 6 months, particularly in the lateral prefrontal cortices and cingulate gyrus. After 3 months, there were no longer differences in rCBF between the two groups in the right inferior frontal gyrus (orbitofrontal area), left middle frontal gyrus, left anterior cingulate (antero-inferior), or left middle and superior frontal gyri (**Table 2**).

After 6 months, the lower rCBF areas of patients with depression were no longer significant compared to controls in the right inferior frontal gyrus (orbitofrontal area), right superior temporal gyrus (temporal pole), bilateral middle frontal gyri, anterior cingulate (antero-inferior), and middle and superior frontal gyri (**Table 2**, **Figure 1**). There were no areas with higher rCBF in the patient group compared to the control group at baseline. After 3 months, patients had higher rCBF than controls in the bilateral superior temporal gyrus, bilateral inferior temporal gyri, left middle temporal gyrus, left middle occipital gyrus, right lingual gyrus, bilateral fusiform gyri, and right parahippocampal gyrus. These higher rCBF areas were also recognized at 6 months (except the right parahippocampal gyrus). Instead, the middle temporal gyrus of the patients showed higher rCBF than the controls de novo (**Figure 2**).

As there was a significant difference in mean age between the patient and control groups, we attempted to recruit an additional control group whose age corresponded to those of the patients; however, the Headtome γ-camera used in this study was unavailable during new data collection due to unforeseen circumstances. Therefore, we were unable to gather data from this older control group. To compensate the failed attempt to add control subjects, we examined the effect of age on rCBF in five representative regions of interest (ROIs: cingulate, caudate, putamen, thalamus, and dorsolateral prefrontal cortex [DLPFC]) in patients at baseline by assessing the correlation between age and bilateral rCBF. The Pearson correlation coefficient was 0.068 ($p = 0.442$), indicating no correlation between age and rCBF in our patient group.

Table 2. Comparison between the depression and control groups.

Comparison	Brain region	Left or right	Brodmann area	Z score
0 months < control	Middle & superior frontal gyri	Left	10	4.68
	Middle frontal gyrus	Right	10, 46	4.57
	Middle frontal gyrus	Left	11	5.02
	Inferior frontal gyrus (orbitofrontal area)	Right	47	5.02
	Inferior frontal gyrus	Right	44	4.70
	Cingulate (frontal portion)	Both	32	5.10
	Cingulate (antero-inferior)	Left	32	4.99
	Superior temporal gyrus (temporal pole)	Left	38	5.79
	Superior temporal gyrus (temporal pole)	Right	38	4.42
3 months < control	Middle frontal gyrus	Right	10, 9	4.21
	Inferior frontal gyrus	Right	47	4.6
	Cingulate (frontal portion)	Both	32	4.14
	Superior temporal gyrus (temporal pole)	Left	38	5.31
	Superior temporal gyrus (temporal pole)	Right	38	4.25
6 months < control	Inferior frontal gyrus	Right	47	4.22
	Cingulate (frontal portion)	Both	32	4.33
	Superior temporal gyrus (temporal pole)	Left	38	5.48
0 months > control	n. d.			
3 months > control	Parahippocampal gyrus	Right	27	3.95
	Middle temporal gyrus	Left	21	4.46
	Superior temporal gyrus	Both	22,	5.04
	Inferior temporal gyrus	Right	37	3.92
	Fusiform gyrus	Both	37	4.37
	Middle occipital gyrus	Left	19, 37	4.44
	Lingual gyrus	Right	18	4.37
	Cuneus	Right	17, 18	3.75
6 months > control	Middle temporal gyrus	Right	21	4.92
	Superior temporal gyrus	Left	22	4.14
	Fusiform gyrus	Both	37	4.12
	Middle occipital gyrus	Both	19	5.18
	Lingual gyrus	Both	18	4.60
	Cuneus	Both	17, 18	4.60

a. The regions with significant differences in blood flow between the depression and control groups for 0 (baseline), 3, and 6 months after treatment initiation are listed. Z scores represent the biggest differences in blood flow across voxels within the region. n.d.: not detected.

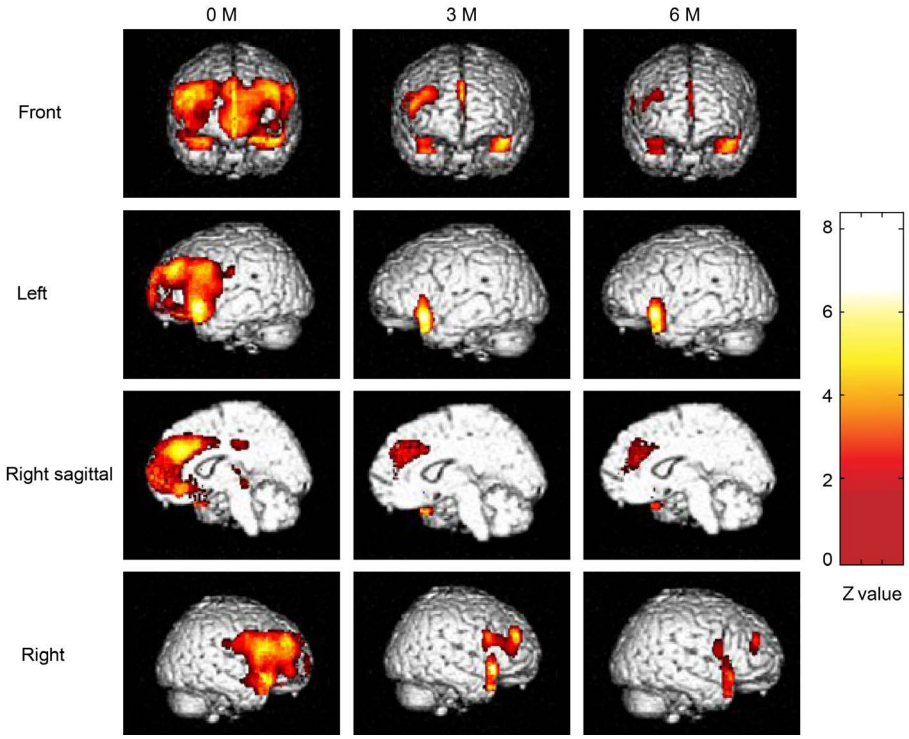

Figure 1. Brain regions in which patients' blood flow was lower than that of controls. The colored areas represent regions with significantly lower blood flow ($t \geq 3.725$ with 25 degrees of freedom, $p \leq 0.0001$).

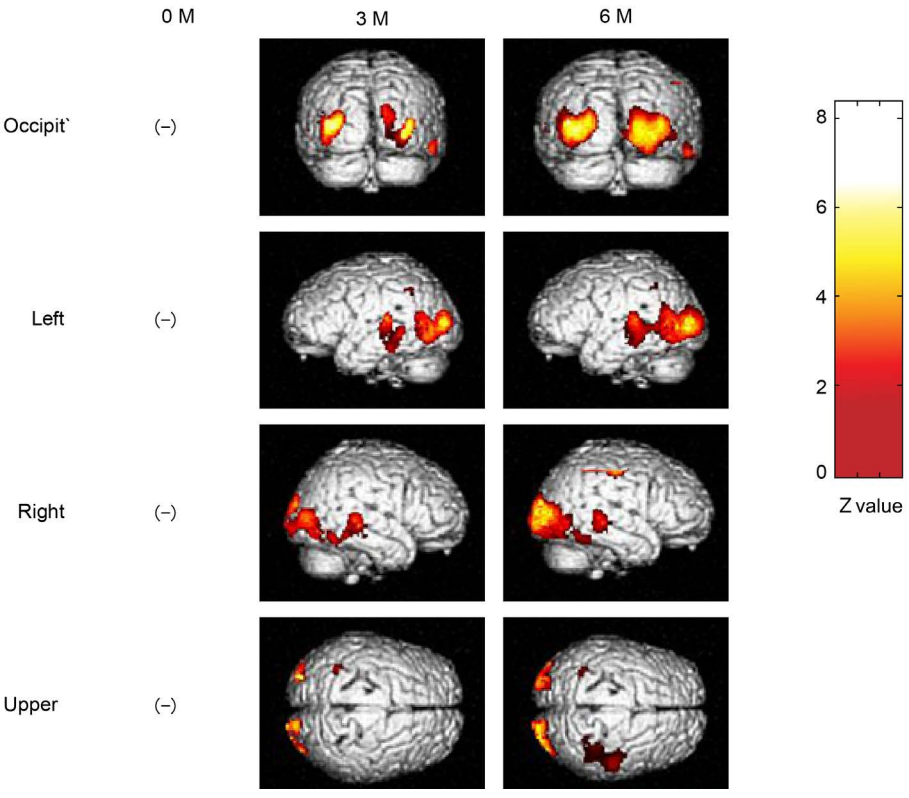

Figure 2. Brain regions in which patients' blood flow was higher than that of controls. The colored areas represent regions with significantly higher blood flow ($t \geq 3.725$ with 25 degrees of freedom, $p \leq 0.0001$).

3.2.2. Comparison within the Subject Group

Anatomical locations and Brodmann areas that changed over time among the subjects in the depression group are shown in Table 3. The areas in which rCBF increased from baseline to 3 months were the left superior frontal gyrus, left middle frontal gyrus, and left precentral gyrus, and middle temporal gyrus, and those in which rCBF decreased over that time were the right orbitofrontal gyrus, right superior temporal gyrus, right precentral gyrus, right sub-lobar insula, and left superior temporal gyrus. The areas in which rCBF increased from months 3 to 6 were the left anterior cingulate gyrus, left precuneus, left cuneus, left lingual and fusiform gyri, right superior frontal gyrus, and right middle frontal gyrus. Those in which rCBF decreased from months 3 to 6 were the left inferior frontal gyrus, left temporal tip, left middle temporal gyrus, and right superior temporal gyrus (Table 3).

Table 3. Comparison within the depression group.

Comparison	Brain region	Left or right	Brodmann area	Z score
3 months > 0 months	Middle frontal gyrus	Left	10	3.30
	Superior frontal gyrus	Left	9	2.75
	Middle temporal gyrus	Left	21	3.21
	Precentral gyrus	Left	4	3.82
	Orbitofrontal gyrus	Right	11	3.16
	Sub-lobar insula	Right	13	3.46
3 months < 0 months	Superior temporal gyrus (mid portion)	Right	22	3.89
	Superior temporal gyrus (posterior)	Left	22	3.40
	Superior temporal gyrus (anterior)	Right	22	3.26
	Precentral gyrus	Right	4	3.19
	Superior frontal gyrus	Right	10	3.34
	Middle frontal gyrus	Right	46	3.15
6 months > 3 months	Cingulate (frontal portion)	Left	32	2.95
	Precuneus	Left	7	3.41
	Fusiform gyrus	Left	37	3.20
	Lingual gyrus	Left	18, 19	3.20
	Cuneus	Left	17, 18	3.30
6 months < 3 months	Inferior frontal gyrus,	Left	47,	3.60
	Superior temporal gyrus (temporal pole)	Left	38	3.60
	Middle temporal gyrus	Left	21	3.10
	Superior temporal gyrus (posterior)	Right	22	3.38

a. The regions with significant changes in blood flow between 0 (baseline) and 3 months and 3 and 6 months after treatment initiation are listed. Z scores represent the biggest changes in blood flow across voxels within the region.

4. Discussion

4.1. Summary of Results

We found that rCBF values in the superior temporal gyrus (temporal pole), cingulate (frontal portion), and inferior frontal gyrus were consistently lower in patients with major depression compared to controls throughout the 6-month treatment period (**Table 2**). In terms of symptoms, at least 6 months of treatment is considered necessary for full recovery from depression [7]. During the 6-month period, rCBF of the patients consistently increased in the superior and middle frontal gyri (**Table 3**). At 6 months, patients showed higher rCBF ratios than the controls in the middle temporal gyrus, superior temporal gyrus, fusiform gyrus, middle occipital gyrus, lingual gyrus, and cuneus (**Table 2**).

Baseline rCBF in our patients was lower than that in controls in a wide range of the frontal regions. While depressive symptoms were significantly improved at 3 months, rCBF ratios in the superior and middle frontal gyri increased. However, rCBF ratios in the middle and inferior frontal regions remained low. At 6 months, depressive symptoms continued to improve, and rCBF ratios increased in the superior frontal gyrus, middle frontal gyrus, cingulate (frontal portion), precuneus, fusiform gyrus, lingual gyrus, and cuneus. Conversely, rCBF ratios decreased in the inferior frontal gyrus, superior temporal gyrus (temporal pole), middle temporal gyrus, and superior temporal gyrus.

4.2. Advantages of Our Study

In the present study, rCBF increased in the left middle and superior frontal gyri after 3 months, and those on the right side increased more after 6 months. rCBF decreased in the superior temporal gyrus (temporal pole) including the amygdala after 6 months. It remained unchanged in the cingulate gyrus after 3 months but increased after 6 months. Thus, there were temporal differences in brain activity changes represented by rCBF over the course of treatment.

A period of at least 6 months is thought to be required to recover from a major depressive episode [7]. Previous studies on rCBF in depression compared patients with healthy controls at a single time point or assessed rCBF changes before and after treatment. There have been some observations performed at three or more time points in the course of treatment, but all of these were case reports. The present study investigated changes in symptoms and rCBF at baseline and 3 and 6 months after treatment, which allows us to provide more accurate information regarding rCBF changes following treatment.

4.3. rCBF in Depression

There have many previous studies on rCBF using SPECT in patients with major depression [1]-[6]. To our knowledge, three have compared patients with healthy controls [1] [3] [18]. Oda *et al.* used ^{99m}Tc-ECD and reported lower rCBF in the frontal and temporal lobes and anterior cingulate gyrus in patients [3]. In line with this, Bonne and colleagues used ^{99m}Tc-HMPAO and reported

that rCBF was lower in the right parietal, occipital, and left temporal lobes in patients compared with controls [1]. Interestingly, Pagani *et al.* also used ^{99m}Tc-HMPAO and found relatively higher rCBF in the right temporo-parietal cortex, bilateral prefrontal and frontal cortices, and anterior temporal cortex [18].

Both Arthur *et al.* and Mayberg *et al.* conducted comparative studies with healthy controls and patients with major depression using positron emission tomography (PET) [10] [19]. Mayberg *et al.* reported higher CBF in the subgenual cingulate and lower CBF in the prefrontal, premotor, dorsal anterior cingulate, and anterior insular regions in patients with major depression compared with controls using ^{15}O as a tracer [19]. Arthur and colleagues used fludeoxyglucose (FDG) and found higher glucose metabolism in the prefrontal cortex, caudate, and thalamus and lower glucose metabolism in the temporal lobe of patients compared to controls [4]. Drevets observed high blood flow in the amygdala before treatment [5].

In summary, the previous reports are inconsistent regarding some areas including the prefrontal, frontal, temporal, and parietal cortices. Among them, the temporal cortex is consistently reported to show reduced rCBF in depression, with three studies reporting lower rCBF in patients [1] [3] [4], but discrepant results were reported by Pagani *et al.* In contrast, the anterior cingulate is consistently reported to have lower rCBF in patients than in controls [3] [19]. The premotor, anterior insula, and occipital cortex are reported to show lower rCBF, while the subgenual cingulate, caudate, thalamus, and amygdala display higher rCBF in depression than controls [4] [5] [19].

4.4. rCBF Changes Following Treatment for Major Depression

Davies at al. conducted a SPECT study with ^{99m}Tc-HMPAO that assessed the effect of treatment on rCBF in patients with major depression [2]. They reported increased rCBF in the bilateral thalamus and decreased rCBF in the right posterior temporal, left occipital lobe, and cerebellum following venlafaxine treatment. Three groups show changes in PET tracer levels following treatment [4] [19] [20]. Arthur *et al.* reported normalization of FDG in the prefrontal cortex, caudate, and thalamus to levels comparable with healthy control group following various treatments [4], and Mayberg *et al* [19]. reported normalization of rCBF to levels comparable with controls in the subgenual cingulate and prefrontal cortex of treated patients. Mayberg [20] also reported that treatment elevated blood flow in the anterior cingulate gyrus. Kennedy *et al.* investigated brain metabolism using PET before and after 16-week treatment for major depression [21]. They found reduced brain metabolism in the ventrolateral prefrontal cortex.

At the start of treatment, the left and right superior temporal gyrus (temporal pole) had low rCBF in the patient group (**Table 2**). The amygdala is thought to be included in the temporal pole. A further decrease in rCBF of the left superior temporal gyrus (temporal pole) was seen after treatment (**Table 3**). Our observation of treatment-related decrease in rCBF in the left temporal pole including

the amygdala has not been reported in previous SPECT studies of patients with depression. However, fMRI [22] and PET [20] [23] studies have described reduced activity in the left amygdala of patients with depression after treatment. This suggests a relationship between strong negative feelings and high amygdalar activity. Consequently, the treatment-related decrease in rCBF of the left amygdala is an intriguing result and may hint at the amygdala's pathophysiologic role in depression.

In the present study, the different brain areas of depressed patients demonstrated two different patterns of blood flow change during recovery from depression. In the superior and middle frontal gyri and cingulate, blood flow increased, while it decreased in the superior temporal gyrus and temporal pole including the amygdala (**Table 3**). Interestingly, these areas are all associated with emotion. This suggests that different brain areas related to emotions would are differentially involved in the pathogenesis of depression.

Previous brain imaging studies on depression can be summarized in that there were two common findings after successful treatment: 1) increased metabolism in the DLPFC and 2) decreased metabolism in the amygdala [5] [19] [21]. However, a major problem with these previous studies is that none found both increased and decreased blood flow changes in the same subject group. The present study is unique in that we found opposite changes in blood flow in a single group of patients during the course of treatment. To our knowledge, the findings of 1) a relatively early increase in blood flow in the superior and middle frontal gyri corresponding to the DLPFC and 2) a relatively late decrease in the amygdala have not been previously reported.

4.5. Time Difference of Treatment Response in Different Areas of the Social Cognitive Neural Network

In the present study, areas in which higher rCBF was observed in patients compared to controls at 3 months included the superior temporal gyrus, inferior temporal gyrus, middle temporal gyrus, middle occipital gyrus, and fusiform gyrus. At 6 months, rCBF increased more in these areas (**Figure 2**). The fusiform and superior temporal and middle temporal gyri are part of the social cognitive neural network [24] [25]. Therefore, it is speculated that multiple brain regions related with social cognition are differentially activated during recovery from a depressive state. Social cognition is thought to be involved in deficits associated with depression, which are expected to recover with clinical improvement. The recovery process from disordered social cognition is speculated to be gradual because the recovery processes of the neural substrates of social cognition are gradual, as shown in the above-cited results.

4.6. Possible Effect of Age on rCBF

The mean ages of the control and patient groups were 31.5 ± 12.8 and 46.3 ± 13.2 years, respectively, which were significantly different. Therefore, the effect of age is considered a potential problem. The literature contains several reports

on the influence of age on CBF flow in healthy adults. Ances *et al.* [26] reported that the mean elevation rate of CBF and cerebral metabolic rate of O_2 in response to visual stimuli was the same in 10 subjects with a mean age of 28 years and 10 with a mean age of 53 years; thus, age did not seem to affect the response to stimuli [26]. Giovacchini *et al.* reported no differences in whole gray-matter CBF among eight people with a mean age of 27 years and seven subjects with a mean age of 65 years after partial volume correction [27]. Similarly, Meltzer *et al.* [28] reported no difference in cortical CBF between groups aged 19 - 46 and 60 - 76 years after partial volume correction. These reports suggest that there is no significant age-dependent difference in rCBF in healthy adults.

Nagafusa *et al.* assessed the effect of age on rCBF in patients with depression using SPECT imaging [29]. They did not find an effect of age on rCBF decreases in the depression group; rather, the reductions were common to all ages, specifically in subjects from 30 to 79 years old. Based on the above-cited studies, we tentatively conclude that the age difference between the two groups in the present study did not critically distort a real difference between depressive patients and healthy control subjects.

Actually, Terada *et al* [30] compared rCBF in old patients with depression, very old patients with depression, and healthy controls. They found differences in the frontal lobe, thalamus, and entire cerebrum, but the differences in the cerebellum were not statistically significant. If an age difference of rCBF exists at all, its effect should be cancelled, because rCBF is expressed was the standardized ratio of cerebrum/cerebellum in the present study.

4.7. Study Limitations

The following points should be considered when interpreting the present results. The number of patients was limited, and the control group was significantly more educated than the patient group. Frontal lobe function is reported to have a general correlation with years of education [31], but there are also reports of negative correlation between frontal lobe activity and years of education in some young people and a positive correlation in elderly subjects [32]. Thus, we cannot rule out an effect of education on frontal lobe function between the patient and control groups.

5. Conclusions

Our results showed increased blood flow in the superior and middle frontal gyri and middle temporal gyrus and decreased blood flow in the superior temporal gyrus at 3 months, as well as decreased blood flow in the temporal pole including the amygdala at 6 months after initiation of treatment for major depressive disorder. This is the first study to report these three findings in a single group of subjects.

Our results confirm that rCBF is lower in the frontal lobe and temporal pole of patients with major depression as compared to the controls prior to treatment. After treatment initiation, rCBF of the posterior temporal lobe in patients

increased to a higher level than that observed in control, while rCBF of the temporal pole was further decreased in patients. The patients' rCBF changes are thought to reflect functional improvement in cognition involving the frontal lobe and social cognition mediated by the temporal lobe. The decrease in patients' temporal lobe rCBF may be due to less anxiety or discomfort in the course of treatment; thus, rCBF of the temporal pole including the amygdala, which plays a major role in controlling emotion, is lowered. By taking serial rCBF measurements at fixed times following the initiation of treatment for major depressive disorder, we provide the first evidence that there are temporal and regional differences in rCBF recovery in major depression. Thus, the extent of recovery from depression can be objectively monitored, and it may be possible to obtain objective data for antidepressant dose reduction and discontinuation.

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