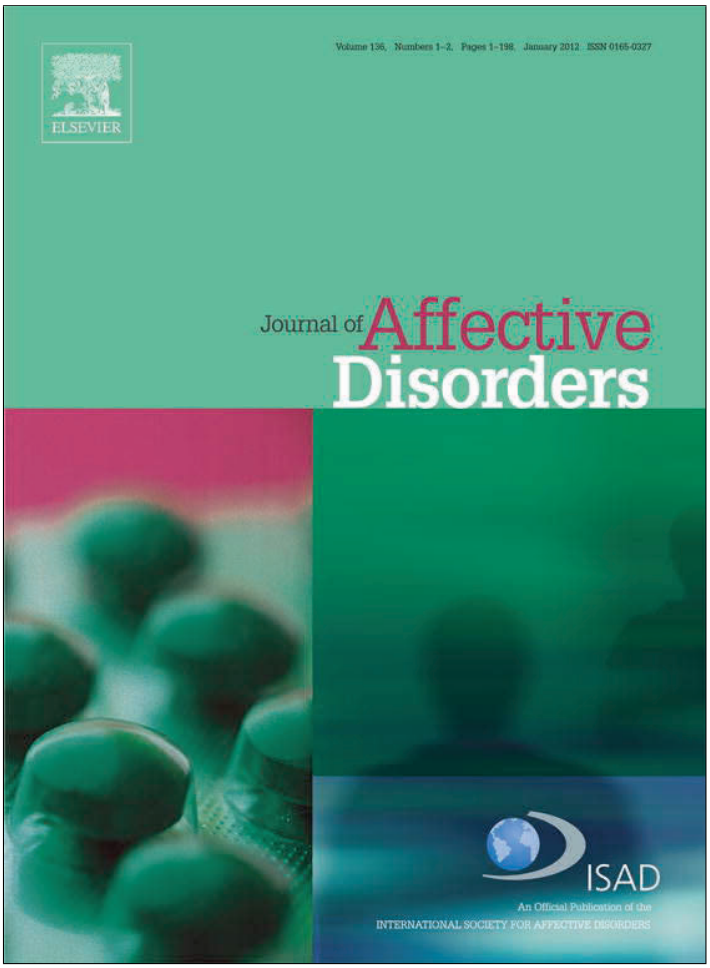

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Research paper

Changes in the regional cerebral blood flow detected by arterial spin labeling after 6-week escitalopram treatment for major depressive disorder

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ABSTRACT

Background: A few studies have used pseudo-continuous arterial spin labeling (pCASL) to assess the regional cerebral blood flow (rCBF) in patients with major depressive disorder (MDD). However, rCBF changes during treatment with escitalopram have not been studied in detail. We used pCASL to investigate the effect of 6-week escitalopram treatment on the rCBF in MDD patients.
Methods: We subjected 53 MDD patients and 36 controls to pCASL (T1, baseline). The patients then received treatment with escitalopram for 6 weeks and 27 were scanned again (T2). We used selected regions of interest that exhibited differences between the controls and patients at T1 and compared the T2 rCBF in the patients with the T1 rCBF of the controls. We also compared the T1 and T2 rCBF in the patients to assess their response to escitalopram.
Results: After 6-week treatment with escitalopram, the rCBF in the patients' left inferior temporal gyri, the middle- and inferior frontal gyri, and the subgenual anterior cingulate, which had been higher at T1 than in the controls, was decreased. Their rCBF in the right lingual gyrus remained significantly lower at T2.
Limitation: We did not have a placebo-control group and the number of patients available at T2 was small.
Conclusion: In MDD patients, 6-week escitalopram treatment elicited significant rCBF changes toward normalization in most of the areas that had shown significant differences between the patients and the controls at T1. The persistence of rCBF anomalies in the right lingual gyrus may be a trait marker of MDD.

1. Introduction

Major depressive disorder (MDD) is common and devastating, however, despite extensive research its pathophysiology remains unclear and in the absence of reliable objective diagnostic methods, MDD continues to be diagnosed on the basis of clinical symptoms. Findings in functional neuroimaging studies [positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI)] in patients with MDD have been inconsistent with respect to the precise region or direction of change (Bench et al., 1992; Biver et al., 1994; Brockmann et al., 2009; de Asis et al., 2001; Ebmeier et al., 1997; Ho et al., 2013; Järnum et al., 2011; Joe et al., 2006; Lui et al., 2009; Mayberg et al., 2000; Ota et al., 2014; Rose et al., 2006; Saxena et al., 2001; Siegle et al., 2007; Wise et al., 2014).

PET studies showed glucose metabolism abnormalities in the pre-frontal and limbic areas (Bench et al., 1992) and the parietal and frontal lobes (Biver et al., 1994) of patients with MDD, and in the hippocampal and dorsal anterior cingulate in geriatric patients with depression (de Asis et al., 2001). Ebmeier et al. (1997) who used SPECT, reported rCBF changes in the cingulate gyrus and other paralimbic areas in MDD and fMRI revealed an increase in the activation of the medial prefrontal cortex (PFC), the amygdala,

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and the hippocampus in depressed subjects (Rose et al., 2006; Siegle et al., 2007; Wise et al., 2014). As PET and SPECT involve radioactive tracers their repetition is limited. While fMRI using the blood-oxygen-level-dependent (BOLD) effect overcomes the limitation, it is inadequate for the study of brain perfusion. Arterial spin labeling (ASL) (Detre and Alsop, 1999) magnetically labels arterial blood water as an endogenous perfusion tracer and the resting-state rCBF can be determined without the use of contrast media. As the reliability and reproducibility of three-dimensional (3D) pseudo-continuous ASL (pCASL) perfusion imaging are sufficiently high for the assessment of the rCBF (Wu et al., 2007, 2014; Ye et al., 2000), it renders the interpretation of quantitative measurements of the rCBF, a physiological parameter, easier than assessment of the BOLD effect.

Earlier studies used pCASL to determine the rCBF in MDD. Ota et al. (2014) and Ho et al. (2013) compared the rCBF in MDD patients and controls. The rCBF in the right inferior PFC and the anterior cingulate cortices was significantly lower in MDD patients than in healthy controls (Ota et al., 2014). According to Ho et al. (2013) the rCBF was significantly decreased in the frontal-, the limbic-, and the paralimbic areas, and in the cingulate gyrus of MDD patients while it was increased in the subcallosal cingulate area, the putamen, and the fusiform gyrus. Lui et al. (2009) and Järnum et al. (2011) reported differences between responders and non-responders to pharmacological treatment; compared to the controls, responders showed hypoperfusion mainly in the limbic-striatal areas while non-responders manifested hypoperfusion in the left occipital lobe, the bilateral frontal and bilateral thalamic regions (Lui et al., 2009), the frontal lobes, and the anterior cingulate cortex (Järnum et al., 2011). Weiduschat and Dubin (2013) looked for predictors of a treatment response to repeated transcranial magnetic stimulation. They showed that pre-treatment, the rCBF in the left dorsolateral PFC was greater in responders than non-responders, whereas the latter exhibited greater baseline activity in the left medial frontal cortex than responders. Walther et al. (2012) who investigated the association between objective motor activity and the rCBF found positive associations between the CBF and the activity level in the right orbitofrontal cortex of MDD patients; the associations were inverse in the left supplemental motor area. However, to date, no studies used pCASL to examine rCBF changes in depressed individuals treated with antidepressants.

Escitalopram, the most selective of the selective serotonin reuptake inhibitors (SSRIs), is the S-enantiomer of citalopram (Owens et al., 2001). As its enhanced efficacy is not associated with an exacerbation of side effects, it yields a favorable benefit-risk ratio (Bielski et al., 2004; Burke et al., 2002; Montgomery et al., 2004). In healthy volunteers, Chen et al. (2011) detected a significant citalopram-induced reduction in the rCBF of the amygdala, fusiform gyrus, insula, and the orbitofrontal cortex. Klomp et al. (2012) reported small but significant effects of a citalopram challenge on the rCBF in the frontal gyrus and thalamus. An fMRI study of Wang et al. (2014) showed that in MDD patients, 8-week escitalopram therapy induced decreased regional homogeneity (ReHo) in the left dorsal medial prefrontal gyrus, the right insula, and the bilateral thalamus; it increased ReHo in the right superior frontal gyrus. How escitalopram affects the rCBF measured by ASL in MDD patients remained to be determined.

Prediction of the treatment response is an important goal of research on MDD but it remains unknown whether the baseline rCBF measured by ASL is predictive of the outcome of SSRI treatment. Using pCASL, Lui et al. (2009) reported that compared to healthy controls, patients with depressive disorders who responded to pharmacological treatment showed hypoperfusion in the left PFC and hyperperfusion mainly in the limbic-striatal areas and the bilateral occipital lobes. Non-responders manifested hypoperfusion in the left occipital lobe and the bilateral frontal- and thalamic regions. Järnum et al. (2011) detected significant hypoperfusion in the frontal lobes and the anterior cingulate cortex of unresponsive MDD patients compared with their controls. In the former study tricyclic, typical serotonin-nonepinephrine reuptake inhibitors and typical SSRIs were administered while in the latter, most patients received unidentified antidepressants.

The pattern of rCBF changes in MDD has not been characterized by pCASL studies. Furthermore, rCBF changes during SSRI treatment and reliable predictors of a SSRI response have not been identified. Under the hypothesis that 6-week treatment with escitalopram mitigates rCBF abnormalities in MDD patients and that the pre-treatment pattern of rCBF changes is predictive of a response to the drug, we performed pCASL studies. We compared the baseline (T1) rCBF in MDD patients and in healthy controls. Our patients were scanned again after 6-week escitalopram treatment and we compared the T1 and post-treatment (T2) rCBF in our patients. We also investigated whether rCBF abnormalities identified by comparing the baseline rCBF in MDD patients and healthy controls persisted after escitalopram treatment by comparing the rCBF of the controls with the T2 patients. In addition, the association between their baseline rCBF and subsequent symptom improvements was examined.

2. Materials and methods

2.1. Subjects

This prospective study was approved by the Ethics Committee of Hiroshima University, Japan; prior written informed consent was obtained from all participants.

Patients were recruited between February 2012 and August 2013. All were between 25 and 75 years of age and in the acute phase of the illness. They had either taken no antidepressants for at least one month preceding their entry into the study or the duration of their antidepressant treatment was less than 5 days. They were screened using DSM-IV criteria for a unipolar MDD diagnosis and the MINI-International Psychiatric Structural Interview (Otsubo et al., 2005; Sheehan et al., 1998). None had a current or past history of bipolar disorder or schizophrenic episodes. We excluded patients with a diagnosis of neurological illness, current or previous psychotic disorders, a current high risk of suicide, current or previous substance abuse, and serious physical disease. Also excluded were left-handed patients, pregnant or breastfeeding women, and patients who used mood stabilizers, antipsychotics, or central nervous system stimulants, or had undergone electroconvulsive therapy within the preceding 3 months.

We initially recruited 62 patients. On the day of brain MRI studies performed in the acute phase of the illness (T1) the severity of depression was recorded using the 17-item Hamilton Rating Scale for Depression (HRSD) where higher scores indicate more severe depressive symptoms.

We excluded 9 patients because the image quality was inadequate due to susceptibility artifacts induced by air in the frontal sinuses ($n=3$), machine trouble ($n=2$), venous malformation ($n=1$), brain atrophy ($n=1$), brain infarcts ($n=1$), and study discontinuation due to the patient's physical condition ($n=1$). Consequently, the final study population consisted of 53 patients.

Follow-up (T2) data were obtained in 49 patients after about 6-week treatment with escitalopram (10–20 mg/day, maximum total dose 13.4 mg/day during therapy; mean 5.6 weeks, standard deviation 1.2 weeks). Of these, 22 patients concomitantly received other drugs (anxiolytics, $n=17$; antipsychotics, $n=4$; anxiolytics and antipsychotics, $n=1$). All 49 patients underwent follow-up brain MRI studies and their HRSD scores were recorded on the

same day. In 27 of the 49 patients available for follow-up, brain MRI scans were performed on the same scanner as was employed at T1.

The controls were 36 healthy subjects from the local community. They were between 20 and 75 years of age, gave their prior written informed consent, had not experienced a major depressive episode within the past year as determined by a structured clinical interview, and had not received psychopharmacological or psychological treatment. Excluded were individuals with a lifetime history of bipolar disorder, an acute suicide attempt, difficulty understanding the purpose of the study or completing the self-report form for serious mental or physical disease. The controls underwent brain MRI only at T1.

2.2. MRI

All studies were performed on a 3T MR system (Signa HDxt, GE Healthcare, Milwaukee, WI) using an eight-channel phased-array head coil (USA Instruments, Aurora, OH). During the examination, all subjects were instructed to relax with their eyes closed but without falling asleep. All subjects underwent 3D pCASL perfusion imaging covering the whole brain using a 3D background-suppressed fast-spin-echo stack-of-spiral readout module with 8 in-plane spiral interleaves [repetition time (TR)/echo time (TE)= 4463/10.2 ms, labeling duration=1500 ms, post-labeling delay=1525 ms, no flow-crushing gradients, in-plane matrix=128 × 128, flip angle=155°, number of excitations=4, slice thickness=4 mm, field of view (FOV)=240 mm, voxel size=1.8 × 1.8 × 4 mm]. The echo train length was 1 to obtain 30 consecutive axial slices. A 10-mm-thick labeling plane was placed 20 mm inferior to the lower edge of the cerebellum. The total scan time was 335 s. For each of the 30 volumes, unlabeled-were subtracted from labeled images; M0 map correction was with vendor-supplied software. For voxel-based analysis, axial 3D fast spoiled gradient-recalled echo images covering the whole brain were acquired for image registration and normalization (TR/TE=6.8 ms/1.9 ms, inversion time=450 ms, matrix=256 × 256, flip angle=20°, slice thickness=1 mm, spacing=0 mm, acquisition time=359 s, FOV=256 × 256 mm).

2.3. Image analysis

For each subject we converted the image files from the proprietary format to Analyze. The rest of the analysis was conducted using both the FMRIB Software Library (FSL, v5.0.2.2, http://fsl.fmrib.ox.ac.uk) and Statistical Parametric Mapping 8 software (SPM8, Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk). We combined both geometric transformations (normalization and co-registration with removal of non-brain tissue) to express all ASL images of all subjects in the Montreal Neurological Institute (MNI) T1 template in SPM8 using the ASL toolbox (Institute of Psychiatry at King's College London, Reina Sofia Foundation and Rey Juan Carlos University, http://www.fundacioncien.es). Then the parameters were applied to the corresponding perfusion maps and each voxel was resampled to 2 × 2 × 2 mm. Finally, the images were spatially smoothed using an isotropic Gaussian filter (8-mm full-width at half-maximum).

2.4. Statistical analysis

Group analysis was performed using SPM8. First, for voxel-based comparisons of the perfusion maps of the MDD patients at T1 ($n=53$) and of the healthy controls ($n=36$) we applied the two-sample t-test that uses the age and sex as covariates to detect hyper- and hypoperfusion. To remove the potential confound created by inter-individual variability in the global CBF, the rCBF values at each voxel were divided by the subject's mean whole-brain blood flow. In this analysis we used a voxel threshold of p (uncorrected) < 0.005 and the cluster extent correction procedure implemented in SPM8 that computes the number of expected voxels per cluster (69 voxels) according to random field theory (Hayasaka and Nichols, 2004; Keator et al., 2006; Niedtfeld et al., 2013). In this initial analysis we identified the areas affected by MDD to delineate the region of interest (ROI) relevant for subsequent analyses.

To assess whether differences between MDD patients at T1 and the controls were decreased at T2 we performed ROI-based paired-sample t-tests by comparing the rCBF at T1 and T2 in 27 MDD patients. We also examined whether rCBF abnormalities identified by voxel-based comparisons of the perfusion maps of MDD patients at T1 and of the healthy controls persisted at T2. To this end we performed the two-sample t-test to compare the rCBF of patients at T2 with the rCBF of the controls with inclusive mask generated by the comparison of the rCBF in MDD patients at T1 and controls. We used a voxel threshold of p (uncorrected) < 0.005 and an extent threshold of 60 voxels (expected voxels per cluster on SPM). To examine the role of the subjects′ age on the rCBF at T1 and on treatment-induced rCBF changes, we analyzed the correlation between their age and their rCBF at T1 and between the age of MDD patients and the treatment-induced rCBF changes (i.e. T2 minus T1) using the Pearson correlation coefficient test. To determine whether the rCBF at T1 was predictive of the treatment outcome, in 49 patients available for follow-up we assessed the correlation between the T1 rCBF and improvement on the HRSD score [(score at T1 minus score at follow-up)/score at T1] using the Pearson correlation coefficient test.

The ROIs for the analyses were identified by comparing findings made at T1 in the patients and in the controls. Although we report all results meeting the threshold of $p < 0.05$ in the tables, we limit our discussion and conclusion to findings that exceeded the threshold of $p < 0.05/11 = 0.0045$ to deal with the problem of multiple comparisons as 11 different ROIs were used.

3. Results

As shown in Table 1, there was no significant difference in the age of the 53 patients and the 36 controls ($p=0.36$, two-sample t-test) nor in their gender ($p=0.87$, chi-square test). In the 49 patients available for follow-up there was a significant difference in the HRSD scores recorded at T1 and at follow-up ($p < 0.001$, paired-sample t-test); 26 patients (53.1%) showed a clinical response (≧50% reduction in the HRSD score) and 16 (32.7%) reported depression remission (T2 HRSD score ≦7).

3.1. Difference in the T1 rCBF between MDD patients and the controls

At T1 the rCBF in the left inferior parietal gyrus [Brodmann's area (BA) 40], the left middle- and inferior temporal gyri (BA 21 and 20), the left superior-, middle-, and inferior frontal gyri (BA 6 and 45), the left insula (BA 13), and the left anterior cingulate [BA 25, i.e. the subgenual anterior cingulate cortex (sgACC)] was significantly higher in the MDD patients than the controls; in the right lingual gyrus (BA 17 and 19) and the right superior temporal gyrus (BA 38) it was significantly lower (Fig. 1). All clusters exceeding the statistical threshold (uncorrected $p < 0.005$, extent threshold $k=69$ voxels) provided by the SPM8 software are listed in Table 2. Correlation analysis showed a significant correlation between the age of MDD patients and their rCBF in the right superior temporal gyrus at T1 ($r = -0.41$, $p < 0.0045$) and between the age of the controls and their rCBF in the left middle temporal

Table 1
Demographic and clinical characteristics of the patients and the healthy controls.

	Patients with MDD				Controls		*p*-Value	
	T1		*T2*				MDD vs HC	*T1* vs *T2*
Characteristics								
Gender (male/female)	27/26				17/19		0.87	–
Age (years)	42.2 ± 10.9	(28–73)	–	–	39.8 ± 11.6	(25–66)	0.36	–
HRSD score	20.4 ± 5.5		10.4 ± 6.3		–	–	–	< 0.001*

All variables except gender are presented as the mean ± standard deviation. Numbers in parentheses are ranges. The *p*-value for gender was obtained with the chi-square test (two-sided); for the age it was obtained with the two-sample *t*-test (two-sided). The HRSD score was obtained with the paired-sample *t*-test (two-sided).
MDD = Major depressive disorder.
HC = Healthy controls.
T1 = acute phase of MDD.
T2 = after 6-week treatment with escitalopram.
HRSD = 17-item Hamilton Rating Scale for Depression.
* $p < 0.05$.

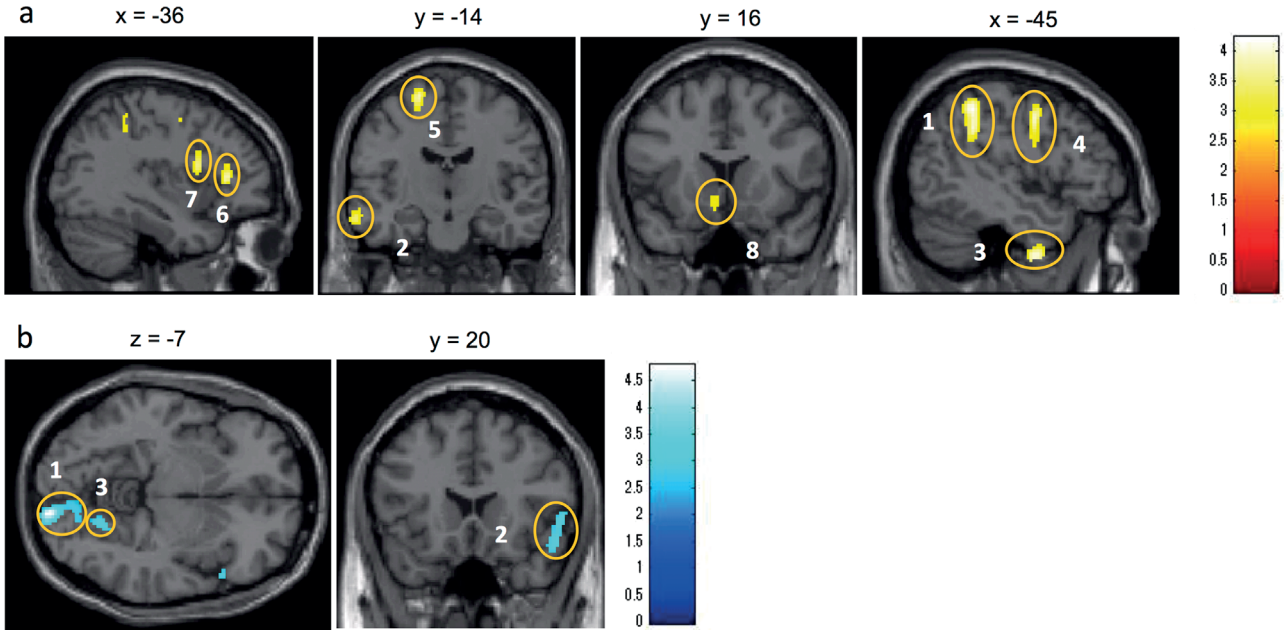

Fig. 1. Regional cerebral blood flow (rCBF) anomalies in patients in the acute phase of major depressive disorder (MDD) (T1). Color bars show the *t*-value of the rCBF changes. Regions where the rCBF was significantly higher in MDD patients than the controls (uncorrected $p < 0.005$ and an extent threshold of 69 voxels), see Table 1 for details. (1) left inferior parietal gyrus [Brodmann's area (BA) 40], (2) left middle temporal gyrus (BA 21), (3) left inferior temporal gyrus (BA 20), (4) left middle frontal gyrus (BA 6), (5) left superior frontal gyrus (BA 6), (6) left inferior frontal gyrus (BA 45), (7) left insula (BA 13), (8) left anterior cingulate (BA 25). Regions where the rCBF was significantly lower in MDD patients than the controls ($p < 0.005$ and an extent threshold of 69 voxels), see Table 1 for details. (1) right lingual gyrus (BA 17), (2) right superior temporal gyrus (BA 38), (3) right lingual gyrus (BA 19).

gyrus ($r = 0.64$, $p < 0.0045$) (Supplementary Table 1).

3.2. Difference in the rCBF of MDD patients at T1 and T2, and in the rCBF of the controls and the MDD patients at T2

We restricted our assessment of treatment-related rCBF changes to 11 ROIs that showed a difference in the controls and the patients at T1 (Table 3, Supplementary Fig. 1S). After 6-week escitalopram treatment, the rCBF was decreased (i.e., T1 > T2) in the left middle- and inferior temporal gyri (BA 21 and 20), the left middle- and inferior frontal gyri (BA 6 and 45), and the left sgACC (BA 25) ($p < 0.0045$). The data of whole brain analyses was presented in Supplementary Fig. 2S. At T2, rCBF anomalies persisted in the right lingual gyrus of MDD patients (Fig. 2).

Correlation analysis revealed a significant positive correlation between the age of MDD patients and the treatment-induced rCBF change only in the left superior frontal gyrus ($r = 0.58$, $p < 0.0045$), indicating that in that area, the older the patient, the smaller was the degree of rCBF mitigation by escitalopram (Supplementary Table 2).

3.3. Predictors of a treatment response

Our assessment was again restricted to ROIs that at T1 showed an rCBF difference between the MDD patients and the controls. Assessment of the correlation between the rCBF in the acute stage of MDD (T1) and improvement in the HRSD score showed that no ROIs exceeded the threshold of $p < 0.0045$ (Table 4). There was a weak negative correlation between the T1 rCBF in the left inferior parietal gyrus (BA 40), the left middle temporal gyrus (BA 21), and the left superior frontal gyrus (BA 6) and improvement on the HRSD score ($r = -0.330$ to 0.244, $p < 0.05$). However, based on multiple comparisons the correlation was not statistically significant.

Table 2
Cross-sectional analysis of statistical parametric mapping of patients in the acute phase of MDD (T1) and of the healthy controls.

Significant differencein the rCBF	Region of interest	Voxel size	Maximal *t*-score	MNI coordinates of the maximal *t*-score		
				x	*y*	*z*
Increased rCBF in MDD patients	Left inferior parietal gyrus (BA 40)	779	4.23	−44	−42	48
	Left middle temporal gyrus (BA 21)	421	3.97	−62	−4	−22
	Left inferior temporal gyrus (BA 20)	100	3.92	−46	−2	−48
	Left middle frontal gyrus (BA 6)	253	3.86	−46	−2	42
	Left superior frontal gyrus (BA 6)	113	3.78	−20	−14	68
	Left inferior frontal gyrus (BA 45)	76	3.73	−36	30	10
	Left insula (BA 13)	74	3.51	−36	10	18
	Left anterior cingulate (BA 25)	73	3.23	−6	−14	−10
Decreased rCBF in MDD patients	Right lingual gyrus (BA 17)	867	4.79	14	−96	−8
	Right superior temporal gyrus (BA 38)	85	3.40	54	20	−14
	Right lingual gyrus (BA 19)	93	3.16	20	−62	−6

All maximal *t*-scores are reported by using MNI coordinates. The *t*-scores were obtained with two-sample *t*-tests (two-sided).
The cluster of voxels exceeding the statistical threshold (p [uncorrected] < 0.005, expected voxels per cluster ≧69) encompasses the listed regions.
MDD=Major depressive disorder.
MNI=Montreal Neurological Institute.
BA=Brodmann's area.

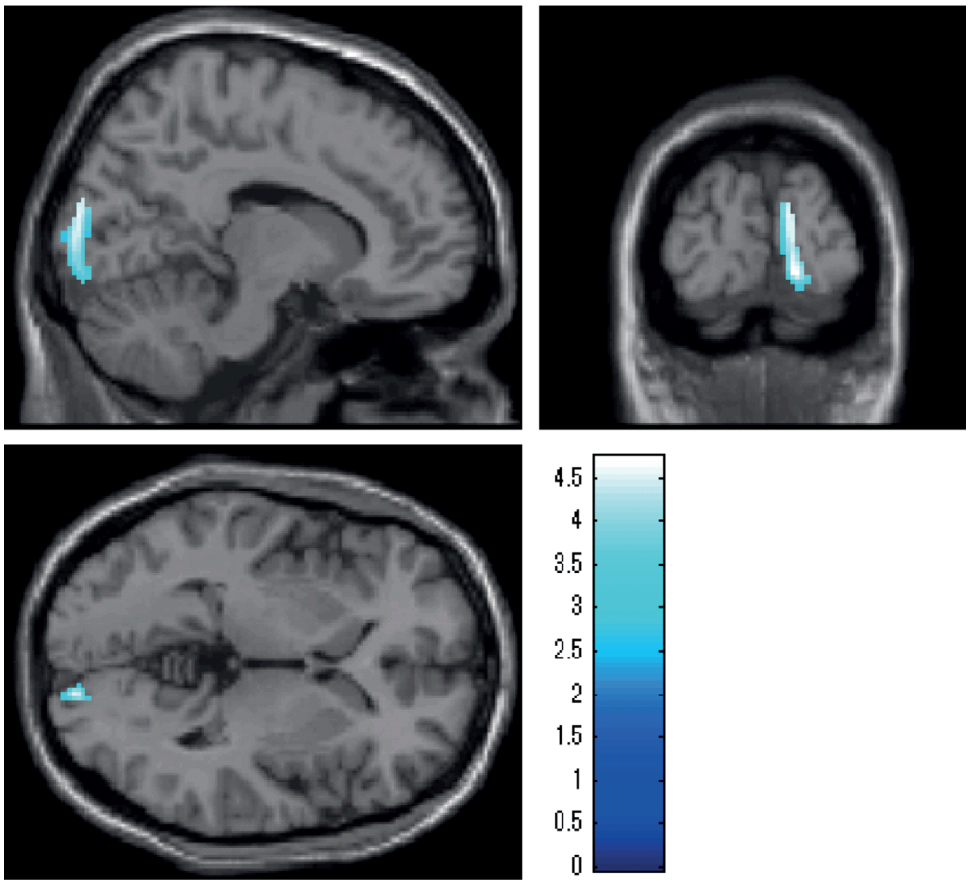

Fig. 2. Post-treatment (T2) rCBF anomalies in MDD patients. A region (the right lingual gyrus) where the rCBF was significantly lower in MDD patients at T2 than the controls (uncorrected $p < 0.005$ and an extent threshold of 60 voxels).

4. Discussion

To the best of our knowledge, this is the first pCASL study to report the rCBF changes elicited in MDD patients by 6-week escitalopram treatment. At T1 we observed rCBF differences in several regions between the controls and the MDD patients. At that point, the rCBF of MDD patients was increased in the left frontal-, temporal-, and parietal cortices, and in the left sgACC; it was decreased in the right occipital- and temporal cortices. Escitalopram elicited significant rCBF changes toward normalization in the left middle- and inferior temporal gyri, the left middle- and inferior frontal gyri, and the left sgACC. However, at T2, their rCBF abnormality remained significant in the right lingual gyrus. We document that in some regions, T1 rCBF differences between the MDD patients and the controls were reduced by 6-week treatment with escitalopram and we identify the regions in which the rCBF

Table 3
Longitudinal changes in the rCBF in ROIs exhibiting a difference between the rCBF of patients in the acute phase of MDD (T1) and the healthy controls.

Significant difference in the rCBF at T1	Region of interest	rCBF		T1 vs T2	
		T1	T2	*p*	*t*
Increased rCBF in MDD patients	Left inferior parietal gyrus (BA 40)	1.38 (0.02)	1.33 (0.02)	0.043*	2.13
	Left middle temporal gyrus (BA 21)	1.37 (0.02)	1.22 (0.01)	< 0.001**	7.94
	Left inferior temporal gyrus (BA 20)	1.15 (0.02)	0.98 (0.02)	< 0.001**	5.65
	Left middle frontal gyrus (BA 6)	1.43 (0.02)	1.27 (0.02)	< 0.001**	6.86
	Left superior frontal gyrus (BA 6)	1.06 (0.03)	0.97 (0.02)	0.005*	3.05
	Left inferior frontal gyrus (BA 45)	1.29 (0.02)	1.12 (0.02)	< 0.001**	6.28
	Left insula (BA 13)	1.44 (0.03)	1.37 (0.03)	0.060	1.97
	Left anterior cingulate (BA 25)	1.50 (0.02)	1.40 (0.01)	< 0.001**	4.15
Decreased rCBF in MDD patients	Right lingual gyrus (BA 17)	1.48 (0.03)	1.53 (0.02)	0.045*	−2.06
	Right superior temporal gyrus (BA 38)	0.98 (0.01)	0.99 (0.02)	0.364	−0.92
	Right lingual gyrus (BA 19)	1.37 (0.03)	1.45 (0.02)	0.005*	−3.09

Follow-up values (T2) were recorded after 6-week treatment with escitalopram.
All variables are presented as the mean (standard deviation). The *p*-values were obtained with the paired-sample *t*-tests (two-sided).
MDD = Major depressive disorder.
T1 = acute phase of MDD.
T2 = after 6-week treatment with escitalopram.
BA = Brodmann's area.
* $p < 0.05$.
** $p < 0.0045$.

Table 4
Pearson correlation between the rCBF in patients in the acute phase of MDD (T1, $n = 49$) and the improvement rate in the HRSD score after 6-week treatment with escitalopram. The ROIs are those in which there was a difference in the rCBF of patients at T1 and the controls.

Significant difference in the rCBF at T1	Region of interest	*r*	*p*
Increased rCBF in MDD patients	Left inferior parietal gyrus (BA 40)	−0.330	0.021*
	Left middle temporal gyrus (BA 21)	−0.294	0.041*
	Left inferior temporal gyrus (BA 20)	−0.131	0.370
	Left middle frontal gyrus (BA 6)	−0.113	0.440
	Left superior frontal gyrus (BA 6)	−0.284	0.048*
	Left inferior frontal gyrus (BA 45)	0.192	0.185
	Left insula (BA 13)	−0.176	0.225
	Left anterior cingulate (BA 25)	0.052	0.722
Decreased rCBF in MDD patients	Right lingual gyrus (BA 17)	0.244	0.091
	Right superior temporal gyrus (BA 38)	0.090	0.540
	Right lingual gyrus (BA 19)	0.123	0.398

The *r*-(correlation coefficient) and *p*-values were obtained with the Pearson correlation coefficient test (two-sided).
MDD = Major depressive disorder.
T1 = acute phase of MDD.
HRSD = 17-item Hamilton Rating Scale for Depression.
Improvement rate on the HRSD score = (score at T2 − score at T1)/score at T1.
BA = Brodmann's area.
* $p < 0.05$.

was normalized or non-responsive.

Our documentation of rCBF differences between the controls and the patients further strengthens the hypothesis that MDD is a multi-dimensional, systems-level mental disorder that affects discrete but functionally integrated circuits, rather than a dysfunction in one or more discrete brain regions (Mayberg, 1997). Most of the regions with abnormal rCBF are included in the limbic-cortical-striatal-pallidal-thalamic circuit (Drevets et al., 2008), the prefrontal-limbic-(Bennett, 2011), the default-mode-(Greicius et al., 2007; Zeng et al., 2012), and the cortical-limbic networks (Fang et al., 2012) that manifest functional connectivity that can produce pathological emotional symptoms (Drevets et al., 2008). Two earlier pCASL studies (Ho et al., 2013; Ota et al., 2014) that compared the rCBF of MDD patients and controls returned findings different from ours, possibly because the characteristics of the study populations were different. Ota et al. (2014) selected MDD patients who were already on medication and whose HRSD scores were 8 or higher and Ho et al. (2013) studied adolescents with MDD. Fang et al. (2012) who used diffusion tensor imaging reported an increase in cortical-limbic network connectivity in MDD and an fMRI study reported by Crowther et al. (2015) revealed relative hyperconnectivity of multiple brain regions in MDD. Thus, the increase in the rCBF we detected in some regions of MDD patients may reflect increased functional network connectivity. This issue requires further investigation.

We found that escitalopram affected the rCBF in brain regions that at T1 exhibited different rCBF values in our controls and patients. Notably, comparisons between the T2 rCBF of our patients and the baseline rCBF in the healthy controls showed that post-treatment, the rCBF differences disappeared in most of the investigated regions. Others also reported the treatment-induced normalization of brain activity in MDD patients. According to Kohn et al. (2007) the response to antidepressant medication was associated with a normalization of rCBF anomalies and Davies et al. (2003) reported that venlafaxine improved rCBF anomalies. In MDD patients responding to SSRIs such as paroxetine and

fluoxetine, Kennedy et al. (2007) and Mayberg et al. (1999) observed restitution of the metabolism in the prefrontal regions. Kocmur et al. (1998) found that in MDD, perfusion of the left frontal and temporal regions was significantly lower than on the contralateral side; the highly significant perfusion asymmetry between the left and right frontal and temporal lobes almost disappeared during pharmacotherapy. In a meta-analysis of reports addressing SSRI treatment, Fitzgerald et al. (2008) identified 9 reports that documented areas of decreased activation following treatment; another 9 reported increased treatment-induced activation in the bilateral middle frontal gyri, cingulate cortex (dorsal and posterior), the putamen, and in other cortical regions. Activation was decreased in deeper structures, e.g. the insula, putamen, parahippocampal gyrus, and hippocampus, and in the pre- and subgenual anterior cingulate, the inferior medial PFC, and the left superior frontal gyrus.

Although escitalopram involves mechanisms of action different from those of other treatments, it also helped to normalize rCBF changes in patients with MDD. The brain regions with post-treatment rCBF normalization included the sgACC, considered one of the key components in the pathophysiology of MDD. The meta-analysis of Fitzgerald et al. (2008) showed decreased post-treatment sgACC activation. Mayberg et al. (2000) documented changes in the brain glucose metabolism in MDD patients receiving fluoxetine. In responders, the metabolism in the sgACC was decreased while in non-responders it remained unchanged. Our findings are consistent with their responder patterns. We found that the rCBF in the left inferior temporal gyrus was also normalized after treatment. van Heeringen et al. (2010) reported that perfusion in this region was relatively increased in patients with high- rather than low levels of mental pain. Increased perfusion in the left inferior temporal gyrus in depressed patients might be associated with an increased risk of suicide because levels of mental pain were significantly and positively associated with suicidal ideation (Shneidman, 1993). Kalisch (2009) who performed a meta-analysis of the induction of negative emotions upon reappraisal reported that activation within the pre-supplementary motor area, the middle temporal gyrus, and the inferior frontal gyrus was a consistent finding across studies. All of these regions are located within the cortical-limbic-, especially the frontal-limbic network involved in emotion processing. In MDD, an increase in the rCBF in the supplemental motor area was linked to decreased motor activity (Walther et al., 2012); hyperactivity of the lateral PFC including the middle- and inferior frontal gyri has been linked to cognitive functions (Braver et al., 1997; Harvey et al., 2005). Together with findings from these studies, our results suggest that in patients with MDD, escitalopram mitigates their symptoms associated with those areas and improves the rCBF in most affected areas.

However, escitalopram failed to normalize the rCBF in all affected regions. In their study on late-life depression, Ishizaki et al. (2008) found that rCBF abnormalities in some regions and residual anomalies in the anterior ventral/dorsal medial PFC were improved by treatment with antidepressants. They hypothesized that neural circuits, including regions with persistent post-treatment rCBF changes, reflect the underlying tenacious pathognomonic brain dysfunction of depression. In their fMRI study of MDD patients, Wang et al. (2014) found that most of the pre-treatment changes in ReHo were no longer apparent after 8-week escitalopram therapy. However, anomalies persisted in the right precuneus and the left cerebellum. They suggested that 8 to 12 weeks of antidepressant treatment are required to reach maximal clinical effects and that longer therapy may correct residual anomalies. Alternatively, the changes may represent trait markers of MDD. We found that rCBF differences remained significant in the right lingual gyrus after 6-week treatment with escitalopram. We posit that the residual rCBF anomalies we observed may respond to longer treatment; alternatively, they may reflect the trait of brain dysfunction in MDD. The decreased rCBF in the right lingual gyrus of our patients is consistent with findings reported by Bonte et al. (2001) and Song et al. (2008). On the other hand, the meta-analysis of Fitzgerald et al. (2008) with respect to changes in brain activation in depressed individuals documented increased activation in the lingual gyrus. These contradictory findings are suggestive of a complex neuropathophysiology in depressive disorder.

Our hypothesis that in MDD, the pattern of pre-treatment rCBF changes is predictive of a response to escitalopram was denied by our findings although earlier pCASL studies had identified predictors of a response to pharmacological treatment (Lui et al., 2009; Järnum et al., 2011). However, those studies involved different treatments and Järnum et al. (2011) selected MDD patients with an HRSD score of 18 or above and Lui et al. (2009) studied MDD patients aged between 18 and 60 years, none of whom had received antidepressants before their enrollment. Thus, the difference in the reported results may reflect not only the complex neuropathophysiology of MDD but also differences in the study populations. Further studies are needed to identify reliable predictors of a response to treatment with SSRIs because correct response predictors help to develop individualized treatment plans, save time, and decrease suffering (Kemp et al., 2008).

Although functional imaging studies on normal subjects had shown age-related rCBF impairment (Krausz et al., 1998), few investigations of the rCBF in MDD patients considered the effects of age (Nagafusa et al., 2012; Ohgami et al., 2005). Because there was a wide age distribution in our patients (from 28 to 73 years) and a significant correlation between their age and the rCBF in some regions, we used age as one of the covariates in our comparison of the T1 rCBF in MDD patients and the controls. We did not consider the influence of age in our investigation of treatment-induced rCBF changes because we performed an inter-patient analysis. In supplementary tables we present our findings based on a correlation analysis between the age and the rCBF. Studies focusing on the correlation between their age and rCBF in MDD patients are needed to address this issue.

Our study has some limitations. First, because the voxel-based comparisons of the rCBF in healthy controls and MDD patients at T1 used SPM8 at a significance threshold of $p < 0.005$ uncorrected for multiple testing, type I errors were unavoidable. The control- was smaller than the patient group (53 vs 36) and this may have reduced the sensitivity for detecting inter-group differences. Therefore, we did not correct for multiple testing to avoid type II errors (Lieberman and Cunningham, 2009). Second, the lack of a placebo-control treatment arm limits our attribution of the observed effects to escitalopram and we did not account for possible time-confounds. Third, 22 of the 49 patients available for follow-up concomitantly received other drugs and this may have affected our observations on the rCBF-relieving as well as the symptom-relieving effect of escitalopram. Lastly, the number of patients available for follow-up pCASL study was relatively small ($n=27$); this may have reduced the sensitivity for the detection of rCBF changes that occurred between T1 and T2. Despite a tendency toward rCBF normalization, in some ROIs there was no significant difference at T1 and T2, suggesting that the lack of power elicited type II errors. Consequently we addressed only the ROIs that met the threshold of not only $p < 0.0045$ but also of $p < 0.05$ in our ROI analyses.

In conclusion, in MDD patients experiencing an acute depressive episode, our pCASL findings indicated increased rCBF of a variety of brain regions involved in emotion processing including the left middle- and inferior temporal gyri, the left middle- and inferior frontal gyri, and the left sgACC. We found that 6-week treatment with escitalopram elicited a significant change in these

anomalies toward normalization. We also found that escitalopram did not help to normalize the rCBF in all affected regions. This raises the possibility that they may reflect the trait of brain dysfunction in MDD. Our pCASL study sheds new light on the nature of pre- and post-treatment differences in the rCBF of MDD patients and may contribute to a better understanding of the pathophysiology of MDD.

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Conflict of interest

We have no conflict of interest to declare.

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None.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2015.12.062.

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