Table 1
Demographic and clinical characteristics of the study participants.

	Healthy volunteers	Schizophrenia patients	*p* value
Male/female	21/21	17/19	0.81
Age (year)	37.9 ± 13.0	39.8 ± 12.6	0.52
Education (year)	14.7 ± 2.5	13.9 ± 3.2	0.27
Inpatient/outpatient		21/15	
First-episode/second and later		2/34	
Duration of illness (year)		16.8 ± 11.3	
Antipsychotic medication (mg/day)*		604.8 ± 459.2	
PANSS total		61.8 ± 19.3	
Positive		15.3 ± 5.6	
Negative		14.9 ± 6.2	
General		31.7 ± 10.4	

PANSS; positive and negative syndrome scale.
*: Chlorpromazine equivalent.

2.6. Statistical analysis

Statistical analyses were performed by using SPM5 software. Differences in gray matter volume and rCBF between the patients and controls were assessed by using the subjects' age, gender, and education years as nuisance variables. We evaluated the gray matter volume, controlling for the whole brain volume. When the rCBF differences were analyzed, we added the regional gray matter volume derived from the individual segmented gray matter volume image as a covariate using Biological Parametric Mapping (BPM) (Casanova et al., 2007). Since the gray matter volume values are different in various brain regions, each voxel of the rCBF image was adjusted by gray matter volume in the BPM analysis. Only differences that met the following criteria were deemed significant. In this case, a seed level of $p < 0.001$ (uncorrected) and a cluster level of $p < 0.05$ (uncorrected) were adopted. We next examined the possible correlation between rCBF and PANSS subscales of the subjects controlling for age, gender and regional gray matter volume by multiple regression model. The same p values shown above were regarded as significant. Skeletonized FA data were analyzed to identify differences between the two groups, controlling for age, gender and education years using the FSL "Threshold-Free Cluster Enhancement (TFCE)" option in "randomize" with 10 000 permutations (Nichols and Holmes, 2002; Smith and Nichols, 2009). The significance level was set at the p-value of less than 0.05 with the family-wise error (FWE) rate correction for multiple comparisons.

3. Results

The demographic and clinical characteristics of the participants are shown in Table 1. There was no significant difference in age, gender, or education years between the patients with schizophrenia and controls.

We evaluated the gray matter volume differences by performing a DARTEL analysis. A significant gray matter volume reduction was found in the left inferior prefrontal cortex in the patients compared to the controls (Fig. 1). No significant increase was detected in the patients.

We then examined the possible differences in rCBF between the two groups by using SPM5 with regional gray matter volume, age, gender, and education years as nuisance variables. There was a significant rCBF reduction in the left inferior prefrontal cortex and bilateral occipital cortices in the patients compared to the controls (Fig. 2). No significant increase in rCBF was detected in any region in the patients. Using the Wake Forest University (WFU) PickAtlas (Maldjian et al., 2003), we then performed small volume corrections (SVCs) for inferior frontal gyri defined by the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). For this SVC analysis, FWE-corrected voxel level threshold of $p < 0.05$ was applied to account for multiple comparisons of the results (Table 2).

As for the relationships between the clinical variables and rCBF, we could not detect any significant correlations, however we found a nominal negative correlation between PANSS negative scale and rCBF in bilateral superior temporal gyri, left inferior prefrontal cortex, and left thalamus at trend level (Fig. 3).

When we examined the DTI results, we observed significant reductions of FA values in the left superior temporal region, left external capsule, and left inferior frontal region in the schizophrenia patients compared to the controls (Fig. 4). No significant increase in FA was detected in any region in the patients.

4. Discussion

To our knowledge, this is the first study of ASL-based rCBF changes in schizophrenic patients that took the regional gray matter volume into

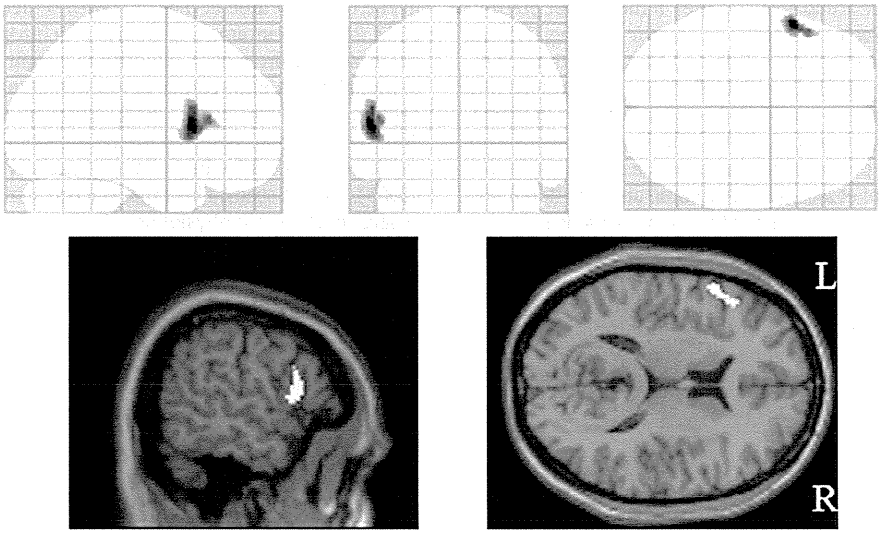

Fig. 1. Regional gray matter volume changes in schizophrenia. There were significant reductions of gray matter volume in the left prefrontal cortex of the patients with schizophrenia ($p < 0.001$, uncorrected). L: left, R: right.

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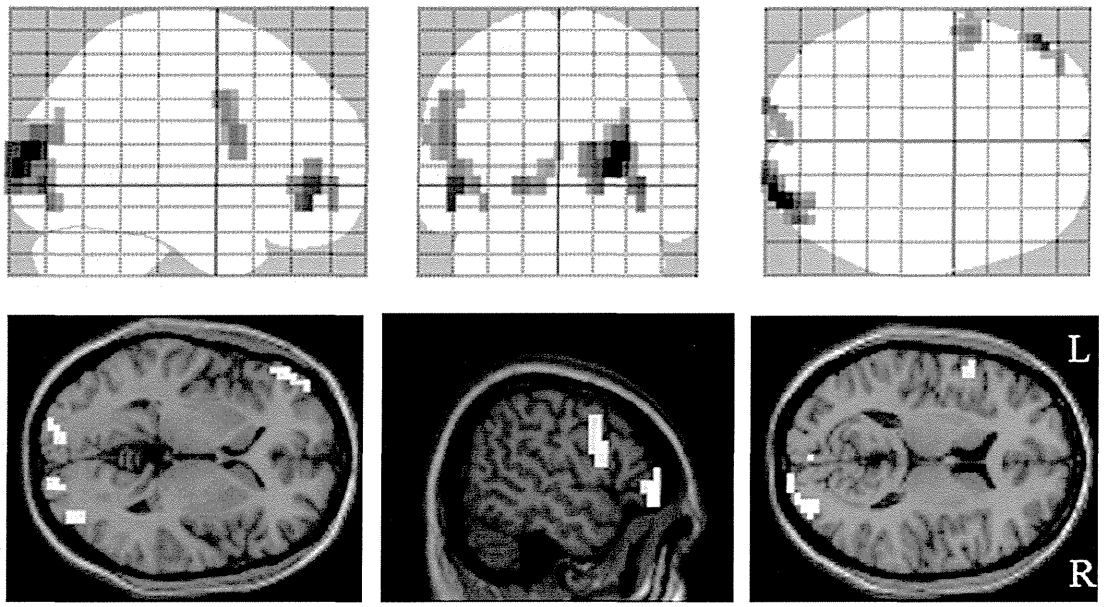

Fig. 2. Regional cerebral blood flow (rCBF) changes in schizophrenia. There were significant reductions of rCBF in the left prefrontal cortex and bilateral occipital cortices of the patients with schizophrenia ($p < 0.001$, uncorrected). L: left, R: right.

account. Using the pCASL method, we found that there were significant rCBF reductions in the left inferior prefrontal cortex and bilateral occipital cortices in patients with schizophrenia compared to the healthy subjects. In particular, the reduced rCBF in the left inferior prefrontal cortex accords with the structural changes observed in volumetric and DTI analyses in schizophrenic patients.

Structural abnormalities of the frontal cortex in schizophrenic patients have been suggested by many studies of MR volumetric images (reviewed in Honea et al., 2005; Glahn et al., 2008) and DTI (reviewed in Ellison-Wright and Bullmore, 2009). Altered function in the frontal cortex in schizophrenia has also been reported by functional MR imaging (fMRI) studies (e.g., Cannon et al., 2005; Ragland et al., 2005) and ASL studies (Scheef et al., 2010; Pinkham et al., 2011; Walther et al., 2011). In addition, other studies using SPECT found that patients with schizophrenia have decreased rCBF, particularly in the frontal lobes and/or left hemisphere (Weinberger et al., 1988; Andreasen et al., 1992; Vita et al., 1995; Kanahara et al., 2009).

In the present study, we found abnormalities in the inferior prefrontal region of the schizophrenic patients by volumetric imaging, DTI, and pCASL with partial volume effect correction, and these results are compatible with the above-mentioned previous findings. Longitudinal MRI studies suggested a progressive loss of prefrontal gray matter in schizophrenia (Sporn et al., 2003; Ota et al., 2009). Inferior prefrontal cortex was associated with the performance in cognitive switching by the MRI volume study (Ohtani et al., 2014). A volume and functional MRI study also supported that deficits in default mode network deactivation explained by the left inferior frontal gyrus thinning are related to impaired executive function in schizophrenia (Pujol et al., 2013). It is also known that the severity of schizophrenic negative symptoms is well correlated with the hypoactivity of the inferior prefrontal region and bilateral superior temporal regions (Pinkham et al., 2011), and these detections were compatible with our results that showed a nominal correlation between PANSS negative scale and rCBF in bilateral superior temporal gyri and left inferior prefrontal region. Since the majority of our patients were chronic cases, the observed brain change in the inferior prefrontal region may have arisen due, in part, to the progressive change and symptomatological change.

ASL studies of schizophrenia revealed several rCBF changes (Horn et al., 2009; Scheef et al., 2010; Pinkham et al., 2011; Walther et al., 2011). As shown in Table 3, the results of these studies differ substantially. For the frontal cortex, however, three of these four studies reported reduced rCBF, which is compatible with our results. We found rCBF reduction in bilateral occipital cortices of the individuals with schizophrenia, which is consistent with the study by Pinkham et al. (2011) in medicated schizophrenic patients and the study by Scheef et al. (2010) in drug-free subjects. Several studies obtained evidence of deficits of schizophrenia in visual processing, using electroencephalography (EEG) (Butler et al., 2001, 2005; Doniger et al., 2002), and other studies documented the abnormal EEG activities in the occipital lobe of patients with schizophrenia (Spencer et al., 2003, 2004). Neuroimaging studies of schizophrenia also revealed the decrease of white matter integrity in occipital white matter adjacent to the splenium of the corpus callosum that may originate in visual perception area (Agartz et al., 2001; Ardekani et al., 2003; Butler et al., 2005). Butler et al., detected the relationship between the evoked potential deficits and white matter intensity in the optic radiations (2005). Thus, it seems likely that the occipital lobe is involved in some aspects of the pathophysiology of schizophrenia. For other brain regions, previous studies pointed to reduced rCBF in temporal and parietal regions (Vita et al., 1995; Kanahara et al., 2009). The discrepancy between the previous results and ours may be attributable, at least in part, to the different methodology used for the ASL, particularly our study's consideration of the partial volume effect. Since this is the first ASL study that took this effect into account, further studies are necessary to draw any conclusion regarding rCBF changes in schizophrenia beyond structural brain changes.

In conclusion, our pCASL study with partial volume effect correction together with the volumetry and DTI data demonstrated hypoactivity in the left prefrontal area beyond structural abnormalities in schizophrenia patients. There were also hypofunction areas in bilateral occipital cortices, although the accompanying structural abnormalities were not apparent. Further studies are warranted to delineate the rCBF

Table 2
Differences of cerebral blood flow between schizophrenia patients and healthy volunteers in the inferior frontal gyri.

	x	y	z	Cluster size	FWE *p*	Z score
Inferior frontal gyri	−52	44	−8	10	0.022	3.98

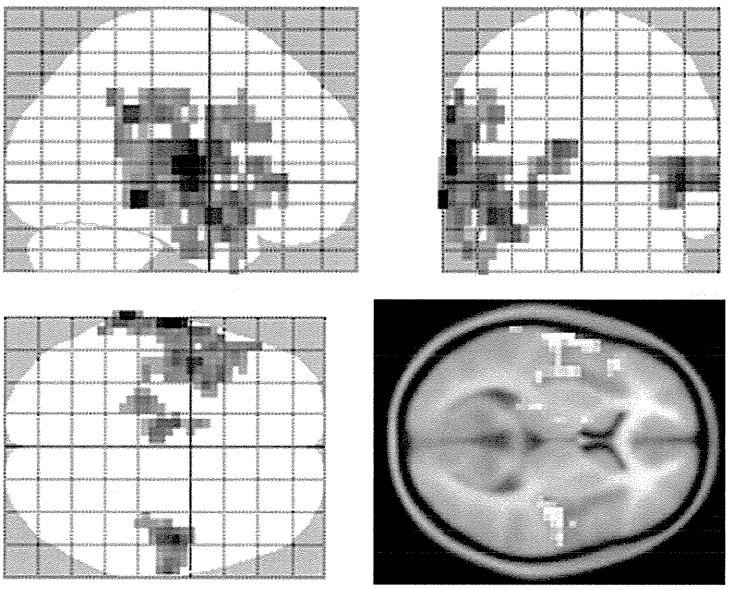

Fig. 3. Correlations between rCBF and symptomatology. There were no significant correlations between rCBF and PANSS subscales, however we found a nominal negative correlation between PANSS negative scale and rCBF in bilateral superior temporal gyri, left inferior prefrontal cortex, and left thalamus at trend level ($p = 0.006$).

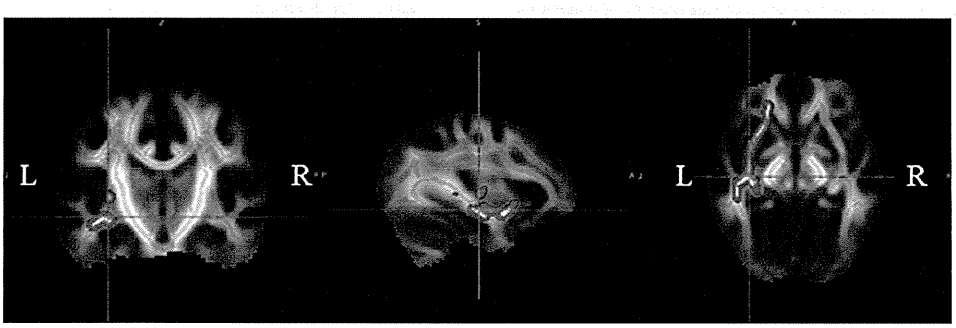

Fig. 4. Anisotropic changes in schizophrenia. There were significant reductions of fractional anisotropy (FA) in the left superior temporal region, left external capsule, and left inferior frontal region of the patients with schizophrenia (threshold-free cluster enhancement [TFCE], $p < 0.05$ family-wise error [FWE]). The background image is the standard MNI152 brain template. Green voxels represent the FA white matter skeleton.

changes in schizophrenia based on ASL. Consideration of the partial volume effect might be an important factor in evaluations of rCBF using ASL.

Role of the funding source

The funding source had no involvement.

Contributors

Miho Ota designed the study and wrote the first draft of the manuscript.
Masanori Ishikawa collected data.
Noriko Sato managed the analyses.
Mitsutoshi Okazaki collected data.
Norihide Maikusa brushed up the method of processing MRI data.
Hiroaki Hori collected data.
Kotaro Hattori collected data.
Toshiya Teraishi collected data.
Kimiteru Ito collected data.
Hiroshi Kunugi managed the analyses.
All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

Table 3
Overview of regional cerebral blood flow changes in patients with schizophrenia using arterial spin labeling.

Study	Subjects	Findings patients < control	Findings patients > control
Horn et al. (2009)	13 Patients with schizophrenia and 13 healthy controls	None	None
Pinkham et al. (2011)	30 Patients with schizophrenia and 24 healthy controls	Left frontal lobe, bilateral occipital lobes, and bilateral parietal lobes	Left putamen/superior corona radiata and right middle temporal lobes
Scheef et al. (2010)	11 Nonmedicated patients with schizophrenia and 25 healthy controls	Bilateral frontal lobes, bilateral parietal lobes, bilateral temporal lobes, and left cuneus	Cerebellum, brainstem, and thalamus
Walther et al. (2011)	11 Patients with schizophrenia and 14 healthy controls	Right prefrontal lobe, left temporal lobe, left parahippocampal gyrus, and right thalamus.	None

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