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# Altered resting-state cerebral blood flow and its connectivity in schizophrenia

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ABSTRACT

Small sample sizes and large inter-subject variations result in inconsistent findings in resting-state cerebral blood flow (CBF) in schizophrenia. The CBF connectivity alterations in schizophrenia remain unclear. Recently, three-dimensional pseudo-continuous arterial spin labeling (pcASL) imaging was performed to measure the resting-state CBF in 100 schizophrenia patients and 94 healthy comparison subjects. The normalized CBF was used to reduce the inter-subject variations. Both group comparisons in the CBF and correlations between the CBF alterations and clinical parameters were assessed. The CBF connectivity of the brain regions with regional CBF differences was also compared between the groups. Compared with the healthy controls, the schizophrenia patients exhibited increased CBF in the bilateral inferior temporal gyri, thalami and putamen and decreased CBF in the left insula and middle frontal gyrus and the bilateral anterior cingulate cortices and middle occipital gyri. In the schizophrenia patients, significant correlations were identified between the CBF and clinical parameters. Importantly, the schizophrenia patients exhibited CBF disconnections between the left thalamus and right medial superior frontal gyrus and between the left insula and left postcentral gyrus. Our results suggest that schizophrenia patients may exhibit both regional CBF abnormalities and deficits in CBF connectivity, which may underlie the clinical symptoms of schizophrenia.



## 1. Introduction

Schizophrenia is a common and severe brain disorder characterized by abnormal mental activities and disturbed behaviors (Lewis and Lieberman, 2000). It has been associated with alterations in resting-state cerebral blood flow (CBF). Positron emission tomography (PET) and single photon emission computerized tomography (SPECT) have traditionally been used to measure CBF changes in schizophrenia. Patients have exhibited increased or decreased resting-state CBF in multiple brain regions, especially the prefrontal cortex (Andreasen et al., 1997; Catafau et al., 1994; Kanahara et al., 2013, 2009; Kawasaki et al., 1993; Malaspina et al., 2004; Mathew et al., 1988; Rubin et al., 1994; Weinberger et al., 1986). Moreover, several resting-state CBF alterations have been associated with the core clinical symptoms of schizophrenia (Lahti et al., 2006; Yuasa et al., 1995). However, PET and SPECT techniques require the use of invasive radioactive tracers, which limits repeated examinations. The other limitations of the two techniques include the time-consuming, expensive image acquisition and low spatial resolution.

With the advantages of a noninvasive nature and short acquisition time, arterial spin labeling (ASL) magnetic resonance imaging (MRI) provides an alternative approach to the measurement of resting-state CBF using magnetically labeled arterial blood water as an endogenous tracer (Detre et al., 1992). Using this technique, several studies have demonstrated resting-state CBF changes in schizophrenia (Liu et al., 2012; Pinkham et al., 2011; Scheef et al., 2010; Walther et al., 2011), although one study failed to identify significant group differences (Horn et al., 2009). Furthermore, associations between the altered resting-state ASL-CBF and clinical

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symptoms have also been identified in schizophrenia (Pinkham et al., 2011). Although the decreased CBF in the frontal cortex has been repeatedly discerned in schizophrenia, the CBF changes in other brain regions differ largely across studies (Liu et al., 2012; Pinkham et al., 2011; Scheef et al., 2010; Walther et al., 2011). The small sample size and large inter-subject variations may account for the inconsistent findings across investigations. Thus, studies that investigate normalized CBF to reduce inter-subject variations in a larger sample size are needed.

As a reflection of neuronal activity, the regional CBFs of different brain regions are not independent. Instead, the CBFs of brain regions from the same functional network may change synchronously to fulfill the function of the network. In support of the hypothesis, the highest concurrent fluctuations in CBF have been identified between homologous cortical regions, and the functional network constructed by CBF connectivity exhibits similar network properties to the networks constructed by anatomical or functional connectivity (Melie-Garcia et al., 2013). Recently, using a group-level independent component analysis on ASL-CBF data, Kindler and colleagues have found increased CBF connectivity within the default-mode network (DMN) (Kindler et al., 2015). However, the CBF connectivity alterations outside the DMN in schizophrenia remain largely unknown.

The first aim of this current study was to clarify the CBF alteration patterns in schizophrenia. We adopted a 3D pseudo-continuous arterial spin labeling (pcASL) technique that used fast spin echo acquisition and background suppression to provide robustness to motion and susceptibility artifacts and to improve the signal to noise ratio (SNR). We used normalized CBF to reduce the inter-subject difference and a large sample size (100 patients with schizophrenia and 94 healthy comparison subjects) to improve the statistical power. To exclude the effect of cortical atrophy on the CBF results, we also repeated the CBF comparisons after controlling for the regional gray matter volume (GMV). The second aim was to investigate the associations between CBF alterations and clinical parameters. The final aim was to test whether the brain regions with altered CBF also exhibited CBF connectivity changes in schizophrenia.

## 2. Materials and methods

### 2.1. Subjects

A total of 106 patients with schizophrenia and 94 healthy comparison subjects were included in our study. The individual patient diagnoses were confirmed using the Structured Clinical Interview for DSM-IV by trained psychiatrists. The inclusion criteria were age (16–60 years) and right-handedness. The exclusion criteria were MRI contraindications, a poor quality of the imaging data, the presence of a systemic medical illness (i.e., cardiovascular disease, diabetes mellitus) or central nervous system disorder (i.e., epilepsy) that would affect the study results, a history of head trauma (i.e., hematencephalon), or substance (i.e., hypnotics, alcohol) abuse within the previous 3 months or a lifetime history of substance abuse or dependence. Additional exclusion criteria for the comparison subjects included a history of any Axis I or II disorders and a psychotic disorder and first-degree relative with a psychotic disorder. Six patients were excluded because of a poor quality of the imaging data. The final sample included 100 schizophrenia patients and 94 comparison subjects (Table 1). There were no significant group differences in sex ($\chi^2 = 2.017$, $P = 0.156$) or age ($t = 0.198$, $P = 0.844$). Ninety-one patients were receiving atypical antipsychotic medications when the MRI examinations were performed, and the other 9 patients have never received any medications. The clinical symptoms of psychosis were quantified with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The investigation was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Tianjin Medical University General Hospital. The participants provided informed written consent to participate in the study.

**Table 1**
Demographic and clinical characteristics of the schizophrenia patients and comparison subjects.

| Characteristics | Schizophrenia patients | Comparison subjects | *P* value |
|---|---|---|---|
| Number of subjects | 100 | 94 | |
| Age (years) | 33.6 ± 8.6 | 33.3 ± 10.4 | 0.844 |
| Sex (female/male) | 43/57 | 50/44 | 0.156 |
| Antipsychotic dosage (mg/d) (chlorpromazine equivalents) | 453.2 ± 342.9 | – | |
| Duration of illness (months) | 122.9 ± 98.7 | – | |
| PANSS | | | |
| Positive score | 17.0 ± 7.8 | – | |
| Negative score | 20.1 ± 9.0 | – | |
| Total score | 71.3 ± 22.7 | – | |

The data are shown as the mean ± SD. PANSS, The Positive and Negative Syndrome Scale.

### 2.2. MRI data acquisition

MRI was performed using a 3.0-T MR system (Discovery MR750, General Electric, Milwaukee, WI, USA). Tight but comfortable foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. Sagittal 3D T1-weighted images were acquired using a brain volume (BRAVO) sequence (repetition time = 8.2 ms; echo time = 3.2 ms; inversion time = 450 ms; flip angle = 12°; field of view = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm, no gap; and 188 sagittal slices). The resting-state perfusion imaging was performed using a pcASL sequence with a 3D fast spin-echo acquisition and background suppression (repetition time = 4886 ms, echo time = 10.5 ms, post-label delay = 2025 ms, spiral in readout of eight arms with 512 sample points; flip angle = 111°; field of view = 240 mm × 240 mm; reconstruction matrix = 128 × 128; slice thickness = 4 mm, no gap; 40 axial slices; number of excitation = 3; and 1.9 mm × 1.9 mm in-plane resolution). The total acquisition time for the resting state ASL scan was 4 min and 44 s. During the ASL scans, all subjects were instructed to keep their eyes closed, relax and move as little as possible, think of nothing in particular, and not fall asleep.

### 2.3. CBF calculation

The pcASL difference images were calculated after the subtraction of the label images from the control images. The CBF maps were subsequently derived from the ASL difference images. The detailed calculation procedures have been described in a previous study (Xu et al., 2010). SPM8 software was used to coregister the CBF images of the 94 comparison subjects to a PET-perfusion template in the MNI space using non-linear transformation. The MNI-standard CBF template was defined as the mean coregistered CBF image of the 94 healthy comparison subjects. The CBF images of all participants, including the patients and controls, were subsequently coregistered to the MNI-standard CBF template. Each coregistered CBF map was removed of non-brain tissue and spatially smoothed with a Gaussian kernel of 8 mm × 8 mm × 8 mm FWHM. The CBF of each voxel was normalized by dividing the mean CBF of the whole brain (Aslan and Lu, 2010).