Resting Regional Cerebral Perfusion in Drug-Free First-Episode Schizophrenia with Arterial Spin Labeling Magnetic Resonance Imaging

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Abstract: **Objective** This study aimed to explore the regional cerebral blood flow (rCBF) of first-episode schizophrenia (FES) by Arterial Spin Labeling (ASL) Magnetic Resonance Imaging (MRI) technique under resting condition. **Method** The rCBF was measured in 28 patients with FES and 28 healthy controls (HC). **Result** Patients with the FES showed significantly decreased rCBF. **Conclusion** Alteration of rCBF in FES patients observed in the current study suggested that the functional abnormalities of those areas were the features of early stage of the disease.

Keywords: Arterial Spin Labeling; Magnetic Resonance Imaging; Regional Cerebral Blood Flow.

1. Introduction

Schizophrenia is a mental disorder characterized with a breakdown of thinking process, poor emotional responsiveness, delusion, hallucination and other mental disorders. Therefore, studying cerebral function in the antipsychotic-naïve state of the schizophrenia patients is necessary for better understanding the mechanisms of the disease [1, 2].

Some studies demonstrated that the symptoms of schizophrenia are associated with reduced cerebral blood flow (CBF) [3, 4]. Previous studies of CBF in schizophrenia were mostly supported with the nuclear medicine techniques such as PET and SPECT [5]. Different brain areas with decreased CBF have been highlighted including temporal, thalamus, frontal and limbic-paralimbic regions. However, these techniques require the injection of invasive radioactive tracers, which to some extend limits repeated applications.

The ASL technology enables to measure CBF using magnetically labeled water as an endogenous tracer . In this study, we used pulse arterial spin labeling (PASL) to determine whether the rCBF has changed in FES patients under resting state.

2. Methods and Materials

2.1 Subjects

Twenty-eight patients with FES were diagnosed according to the DSM-IV criteria for schizophrenia . All patients were in their first episode and drug naive. All patients were enrolled from the Department of Psychiatry, the Shaanxi Provincial People's Hospital in China. The symptom severity of all patients was assessed by a trained and experienced psychiatrist using the the Positive and Negative Syndrome Scale (PANSS) within one week of MR scanning. In addition, 28 age-and-sex-matched controls were also enrolled. Patients with neurological diseases, a history of psychotropic drugs or substance (alcohol, smoking or drug) abuse, head injury or any severe physical diseases were excluded from the study. This study was approved by the Ethics Committee of the Shaanxi Provincial People's Hospital. All participants provided written informed consent before entering the study.

2.2 Imaging Data Acquisition

2.2.1 Structural MRI Data

All the images were obtained using a 3.0 T Philips Ingenia scanner with a 16-channel phased-array head coil. A 3D-T1 magnetization-prepared rapid-acquisition gradient echo T1-weighted sequence covering the whole brain (332 sagittal slices) was collected. The acquisition parameters were: TR = 1,900 ms; TE = 2.26 ms; TI = 900 ms; FA = 9°; matrix = 256 × 256; FOV = 220 × 220 mm; and 1.00 mm slice thickness with no interslice gap.

2.2.2 Perfusion data

The ASL images were acquired using a pulsed arterial spin labeling sequence with a single-shot EPI part to map the perfusion signal. The sequence consisted of 20 slices, each with 5 mm thick with 1.2 mm inter-slice gap and 3.75 × 3.75 mm^2 in-plane resolution. ASL was accomplished with 2- second labeling pulses and a 1-second long labeling delay before the signal was mapped by EPI with TR/TE =2500/15 ms timing.

2.3 Image Processing

2.3.1 Structural MRI data

The MRI data were analyzed using VBM in SPM5, as described in detail elsewhere .

2.3.2 Perfusion data

The perfusion data were first corrected for cerebrospinal fluid (CSF) and WM partial volume effects, using the voxel-by-voxel "modified Mu¨ller-Gartner" method , described in detail elsewhere.

2.4 Smoothing

For comparing the between-group comparison, blurring individual variations in gyral anatomy and increasing the signal-to-noise ratio, the corrected and spatially normalized rCBF datasets were smoothed (14mm) before quantitative normalization. To this end, we used a Gaussian kernel of 14.6mm for the MRI GM data, resulting in an effective smoothness identical to rCBF maps smoothed at 14mm.

2.5 Masking

The resulting MRI (GM and WM) and rCBF images were masked so as to include only GM voxels of interest and prevent contamination by misclassified voxels as much as possible. Briefly, mean images for the GM partitions of the whole sample (n=56) were created as the mask. The mask was applied twice (before and after smoothing) to the rCBF data sets, to avoid contamination of misclassified voxels by smoothing in the first case and big edge effects in the second case.

2.6 Statistical analyses

Group differences in demographic variables were examined with independent t-tests ANOVA by SPSS17.0. The rCBF were performed using analysis of two sample t-test in SPM5 with the diagnostic group as age and gender as covariates. The results were thresholded using an FDR-corrected p-value of <0.05, with a minimum cluster size set at 80 voxels.

In the regression analysis, covariates of interest included the sum of global scores on the PANSS. Age and gender were treated as a controlling covariate. FDR-corrected p-value of <0.05.

3. Result

4. 3.1 Subject demographics

There were no significant differences in age, sex and the level of education between the two groups (P >0.05; Table 1). Demographics and clinical information of the two groups were summarized in Table 1.

3.2 The rCBF analysis

FES patients showed decreased rCBF in the right superior medial frontal gyrus, the right frontal orbital gyrus, the right anterior cingulate gyrus, the right paracentral lobule, the left anterior cingulate gyrus, the left inferior frontal gyrus and, the bilateral precentral gyrus compared with the healthy controls group (Table 2, Fig 1). No significant correlation was observed between rCBF and clinical characteristics in patients with FES.

5. Discussion

In the current study, in comparing the rCBF between FES patients and controls, hypoperfusions in the multiple brain regions were observed., which suggested the rCBF in those areas were the features of early stage of the disease

Several studies have utilized ASL for examining CBF in schizophrenia patients. They were taking second generation antipsychotics and antipsychotic medications at the time of study. Therefore, it could not be distinguished whether the cerebral blood flow abnormalities were initial brain abnormalities or drug treatment-caused. Our study enrolled drug naïve patients without current or past alcohol and substance abuse. Therefore, the rCBF distributions could indicate a progression of brain cerebral perfusion changes after early disease.

We observed reduced perfusion in the right frontal superior medial gyrus, frontal orbital gyrus and the left frontal inferior gyrus in FES, which is consistent with previous studies . Previous brain structural studies FES found that reduce volume in frontal lobe region . These studies suggest that frontal lobe dysfunction, especially the abnormalities in the prefrontal and frontal orbital regions of the brain, might be closely related to cognitive impairment in schizophrenia patients.

In summary, using ASL-MRI technique, we detected rCBF changes in FES patients. Our results might reveal certain initial brain abnormalities present at the onset of the illness, excluding progressive changes over time and effects by antipsychotic medications.

6. Conflict of Interests

The authors declare that they have no conflict of interests.

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Figure Legends

Table 1 Demographicandclinicalcharacteristicsofpatients.

	Patients (n=28)	Controls (n=28)	*P*

	Gender			1.000
	Male	14	14	
	Female	14	14	
	Age	26.93±2.74	26.71±6.66	0.876
	Sum of SAPS global scores	22.68±3.67		
	Sum of SANS global scores	24.00±6.87		

Table 2 Brain regions showing significant group differences in rCBF.

	Brain regions	Peak MNI			Cluster voxels	*T*	*P*
R	frontal superior medial gyrus	16	50	0	598	4.17	0.000
	frontal orbital gyrus	12	44	-8	267	5.01	0.000
	anterior cingulate gyrus	14	50	14	717	4.38	0.000
	paracentral lobule	14	-38	54	160	4.23	0.000
	precentral gyrus	42	-6	52	128	3.95	0.000
L	precentral gyrus	−52	8	36	205	3.75	0.000
	frontal inferior gyrus	−52	14	26	205	4.10	0.000
	anterior cingulate gyrus	-3	38	26	269	5.01	0.000

Figure 1. Group differences in rCBF.