Assessment of cerebral perfusional and functional connectivity in schizophrenia using magnetic resonance imaging

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Abstract

Schizophrenia is a significant mental disorder that compromises structural and functional aspects of the brain, with an extreme effect on the patient's thoughts, feelings, and behavior. Physiologically, changes in neuronal activity are reported besides functional and structural abnormalities. Since the cerebral blood flow (CBF) is directly related to neuronal activity, the magnetic resonance imaging (MRI) technique called arterial spin labeling (ASL), which allows the quantification of CBF, is a useful tool in brain perfusional evaluation. In addition, ASL can be used to assess functional connectivity, which is efficient in investigating functional impairment between regions of the brain. Pseudo-continuous arterial spin labeling (pCASL) images were acquired from 28 schizophrenia patients in treatment and 28 age-matched healthy controls. Static CBF and connectivity patterns were assessed in both groups. Decreased CBF and functional connectivity were observed in regions that form two resting brain networks, default mode (DMN) and salience (SN), for schizophrenia patients. Previous studies related the features of this pathology with altered resting CBF and functional disconnections. Therefore, using a noninvasive technique, it was possible to find CBF deficits and altered functional organization of the brain in schizophrenia patients that are associated with the symptoms and characteristics of the disorder.

Keywords*: magnetic resonance imaging; arterial spin labeling; cerebral blood flow; functional connectivity schizophrenia.*

1. Introduction

Schizophrenia is a disabling psychiatric disorder, and in its most common form, patients present themselves with paranoid delusions and auditory hallucinations late in adolescence. A relevant issue on schizophrenia is the high rate of morbidity and mortality; moreover, life expectancy for those with the severe mental illness can be reduced by 20 years [1]. Therefore, there is a scientific interest and clinical relevance to investigate this disorder and add more information that may help its diagnosis and treatment.

Schizophrenic patients show altered level of neuronal activity, and due to the direct relationship between the neuronal activity and the cerebral blood flow (CBF), brain function and CBF have been extensively investigated and their alterations during resting state have been reported when compared with healthy age-matched individuals [2].

Thereby, the CBF synchronous fluctuations in brain regions that form functional networks have allowed the investigation of resting brain networks (RBNs) and functional connectivity (FC) [3]. In this context, the arterial spin labeling (ASL) has emerged as an important tool, since it is a noninvasive magnetic resonance imaging (MRI) technique that can provide CBF maps. ASL uses the water present in the arterial blood as a diffusible endogenous contrast. Besides that, ASL can provide a quantitative measure of CBF, the opposite of most perfusion techniques that provide relative changes [4].

Previous studies related the features of the schizophrenia with disconnection or a dysfunction in functional connectivity [5], so we chose to study two RBNs that have high relevance to the symptoms of this psychopathology: default mode network (DMN) and salience network (SN).

Therefore, we assessed static CBF maps and FC at rest in schizophrenia patients using a single acquisition of pseudo-continuous ASL (pCASL) approach.

2. Materials and Methods

2.1. Subjects

Twenty-eight schizophrenia patients recruited at the Clinical Hospital of Ribeirao Preto, and twenty-eight healthy controls with no history of psychoses episode participated in the study. Patients with diagnosed schizophrenia (PANSS score ≥ 4 per item; PANSS, *Positive and Negative Syndrome Scale*) and in treatment for the presence of positive or negative symptoms were evaluated by a trained psychiatrist.

This study was approved by the ethics committee in research of the institution where the experiments were performed (number: 773.290), and all

participants gave their written consent to participate after being informed about the experimental procedures.

2.2. Data acquisition

Imaging was performed on a 3T system (Philips Achieva, The Netherlands) using a 32-channel head coil for reception. pCASL images were obtained using a 2D single-shot EPI sequence with the following parameters: TR/TE = 4000/14 ms, FA = 90°, FOV = 240 x 240 mm^2, matrix = 160 x 160, 20 5-mm slices, label duration/post-labeling delay = 1650/1525 ms, 50 control/label pairs, total scan duration = 6 min and 48 s. Anatomical 3D T1-weighted images were acquired with the following parameters: TR/TE = 7/3.2 ms, FA = 8°, matrix = 240 x 240, FOV = 240 x 240 mm^2, 160 1-mm slices. In addition, all subjects were instructed to stay awake, to think of nothing, and move as little as possible during the scan. For CBF quantification, a proton density (M0) image was acquired separately with the same geometry and parameters of the pCASL sequence, but without labeling pulses.

2.3. Data processing

Data processing was performed using Statistical Parametric Mapping (SPM12) and a toolbox for ASL (ASLtbx) [6] in conjunction with in-house routines developed in MATLAB. The processing pipeline included motion correction, co-registration of anatomical and ASL images, temporal filtering, spatial smoothing with an isotropic Gaussian kernel (FWHM = 4 mm for static CBF, and FWHM = 6 mm for CBF-FC analysis), CBF quantification, and normalization to MNI standard space. Residual motion and global signals were regressed out from the control/label ASL images before CBF calculations [7]. For average static CBF maps, outlier CBF images were removed using the SCORE algorithm [8]. For CBF quantification we used a General Kinect Model propose by Buxton [9].

Then, we measured the average CBF of each region of interest (ROI) that forms DMN and SN, and compared between groups using a two-sample t-test (Welch's) with p < 0.05 corrected for multiple comparisons (FDR).

2.4. Functional connectivity with ASL images

Functional connectivity study was performed using FC toolbox [10]. In the FC toolbox, CBF images were detrended and filtered with a low-pass filter (f < 0.07 Hz)[11]. In addition, white matter (WM) and cerebrospinal fluid (CSF) signals were removed by principal component analysis (PCA) using the Compcor algorithm [12,13]. We have chosen to study FC from three different perspectives, using independent component analysis (ICA), seed-based approach and graph theory.

First, we obtained the RBNs (DMN and SN) from CBF maps using group-level ICA with an *a priori* selection of 20 components. The spatial similarity of RBNs between groups was calculated using the Dice similarity coefficient (DSC) [14,15].

In addition, we assessed the correlations within each RBN, calculating Pearson's correlation between the following ROIs: DMN – medial prefrontal cortex (mPFC), bilateral inferior parietal lobule (IPL) and posterior cingulate cortex (PCC); SN – anterior cingulate cortex (ACC), bilateral anterior insula (AI), bilateral rostral prefrontal cortex (rPFC), and bilateral supramarginal gyrus (SMG).

For graph theory analysis, we used the functional connectivity strength (FCS), which is defined for each region as the sum of the correlations between this region and all others within the RBN.

3. Results

All 56 subjects were included in final analysis. There was no difference between groups regarding age (p = 0.178) and gender (p = 0.0192) (Table 1).

Table 1. Demographic characteristics of both groups

Variables	Schizophrenia	Healthy controls	p-value
Gender (female/male)	4/24	8/20	0.192[a]
Age (Mean ± SD years)	32.8 ± 7.8	31.1 ± 5.8	0.178[b]

[a] The p-value was obtained by chi-square test
[b] The p-value was obtained by two sample t-test

With ICA analysis, it was possible to visually recognize the two RBNs proposed (DMN and SN). Comparing with healthy controls, patients showed both RBNs with reduced extension (Figure 1). DSC between groups were 0.59 and 0.64, for DMN and SN respectively.

Within DMN, we found significantly increased connectivity between left LP and PCC in schizophrenia patients (p < 0.05, uncorrected for multiple comparisons). Regarding the FCS, no significant differences were found between groups.

For SN, we observed significantly reduced connectivity in schizophrenia patients for the connections between ACC and right AI, ACC and right rPFC, left AI and bilateral SMG, right AI and bilateral rPFC, right AI and left SMG (p < 0.05, uncorrected for multiple comparisons; Figure 2a). Moreover, each ROI of SN showed significant reduced FCS in the schizophrenia group (p < 0.05, Sidak-corrected for multiple comparisons; Figure 2b).
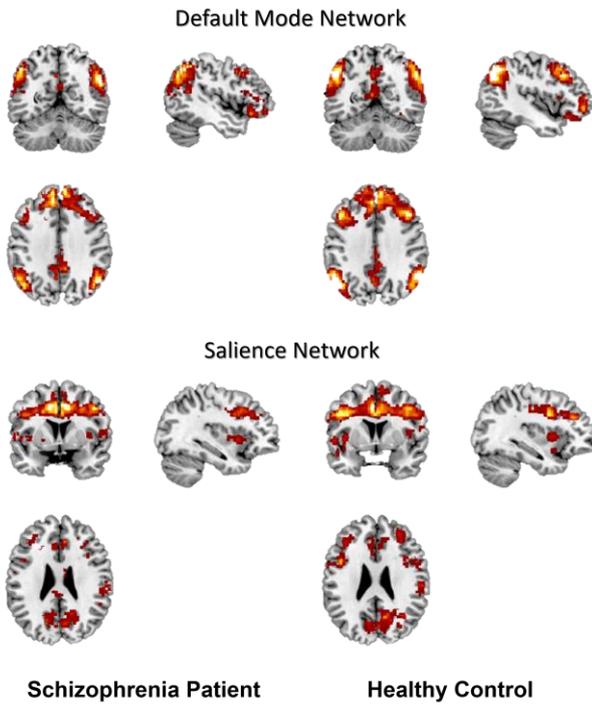
Figure 1. Default mode and salience networks for both groups.
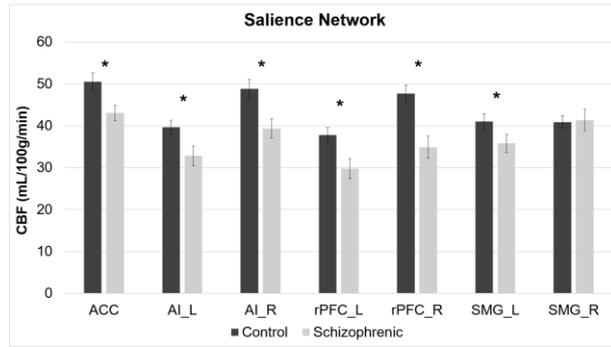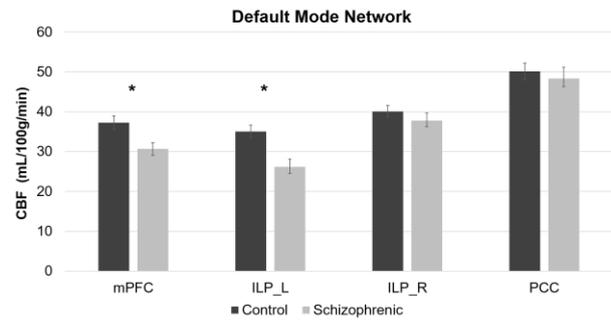
Figure 3. Static CBF results for DMN and SN (*p < 0.05, FDR-corrected).
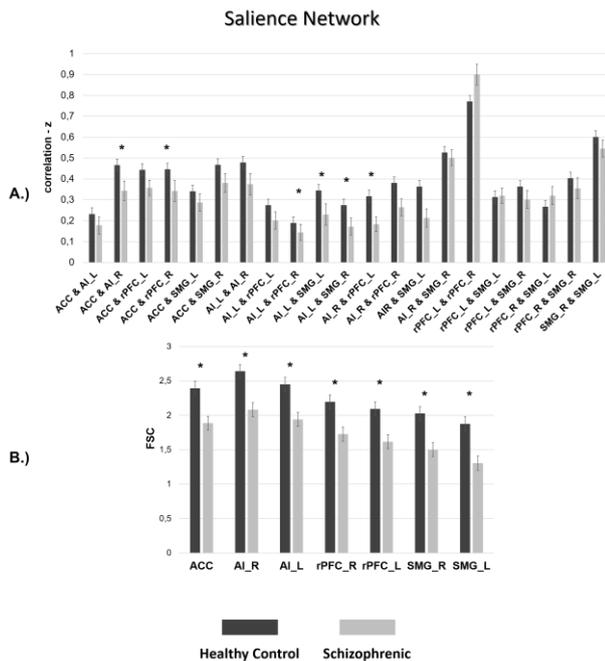
Figure 2. Connectivity results for salience network. (A.) Pearson's correlation between each region of SN (*p < 0.05, uncorrected for multiple comparisons). (B.) Functional connectivity strength (FCS) of each SN region (*p < 0.05, Sidak-corrected for multiple comparisons).

Finally, compared with the healthy control group, schizophrenia patients showed decreased CBF in regions of the DMN and SN (Figure 3). More specifically, in mPFC (p = 0.04), left IPL (p = 0.002), ACC (p = 0.005), left AI (p = 0.01), right AI (p = 0.003), left rPFC (p = 0.004), right rPFC (p = 0.0002) and left SMG (p = 0.03).

4. Discussion

Both DMN and SN showed reduced extension and different spatial distribution in patients, which may explain the decreased ability of schizophrenic patients to engage in self-processing during non-goal directed activities [16]. Our results are consistent with previews studies using BOLD-fMRI, which showed presence of disconnections within SN [17].

In addition, other studies also observed reduced functional connectivity strength in the insula of schizophrenia patients [18], which may be associated with the diminished capacity of individuals to discriminate between self-generated and external information. Moreover, ACC, AI, and SMG connections are necessary for mental life, since they are involved in cognitive, affective and behavioral displays, and in controlling empathy towards people [19].

Regarding the decreased CBF in regions that constitute the DMN, frontal areas with decreased perfusion in patients at rest were previously related to the regulation and processing of behavior and emotion and with mentalization [20]. These findings are also consistent with previous studies in schizophrenia using ASL [21–23].

5. Conclusion

Using the proposed methodology with a 2D pCASL sequence, it was possible to quantify regional CBF and assess functional connectivity, highlighting abnormalities present in schizophrenia. Using ICA approach, we identified the DMN and SN with different spatial distribution and reduced extent in schizophrenia compared with the healthy group. Moreover, it was possible to evaluate the

FC impairments associating connectivity alterations with the symptoms of the disorder. Further information about cerebral perfusion was successfully evaluated through static CBF maps and decreased CBF values were observed in relevant regions for schizophrenia patients.

Acknowledgments

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