The association of cerebral deficits with the symptoms in drug-naïve first episode schizophrenia: an optimized VBM and resting functional connectivity study on 3T

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Introduction

Although gray matter deficits were reported in patients with schizophrenia [1], the inhomogeneous findings were confounded by various factors such as progressive grey matter atrophy and prolonged exposure to anti-psychiatry medication [2]. To date, no study yet identify whether the symptoms of schizophrenia were associated only with the regional structural deficits or/and with the impaired functional connectivity among brain regions [3]. The present study aims to apply the optimized voxel based morphometry (VBM) in conjunction with the analysis of the resting state functional brain connectivity to determine the relationship of the cerebral deficits and the symptoms in drug-naïve first episode schizophrenia (FSE).

Method

The study was approved by the local ethical committee, and written informed consent was obtained from all subjects. 21 drug-naïve FSE and 21 age, sex, height, weight, handedness and years of education matched controls were recruited, and were scanned using a volumetric 3D Spoiled Gradient Recall (SPGR) sequence and a gradient-echo echo-planar imaging (EPI) sequence on a 3T MR imaging system (EXCITE, General Electric, Milwaukee, USA). The severity of FSE was assessed using the Positive and Negative Symptom Scale (PANSS) including total score, positive score, negative score and general score. The symptoms of FSE were evaluated using six-factor structure of PANSS including thought disturbance, activation, paranoid, depression, anergia and complementary. Optimized VBM was used to characterize the gray matter volume (GMV) reduction areas in FSE. The corresponding GMV were subsequently extracted from all FSE and input into SPSS11.5 along with PANSS scores. A multiple correlation analysis between the GMV alterations and PANSS scores was carried out using Pearson coefficient. A $P < 0.05$ (two tailed) was deemed significant. Subsequently, using the areas with GMV reduction as seeds, a method based on the seed-voxel correlation approach was used to examine the relationship of the symptoms and the functional connectivity. This approach included following steps: (1) Obtaining seed reference by averaging the fMRI time series of all voxels within the areas with GMV reduction; (2) Temporally bandpass filtering (0.01–0.08 Hz) for each time series; (3) Correlation analysis of the seed reference with the rest of the brain in a voxel-wise manner using the realigned images, and subsequently individual relativity value (r-value) map was produced, and (4) Performing a multiple correlation analysis between individual r-value maps and corresponding PANSS scores. A $P < 0.05$ corrected after multiple comparisons was deemed significant.

Results

Significantly reduction in gray matter volume (GMV) was observed in two regions, i.e., the right superior temporal gyrus (STG, Talairach: 51, -25, 14; 1541mm^3) and the left posterior cerebella lobe (Talairach:-27, -44, -39; 4010mm^3) (Figure 1). Meanwhile, a negative correlation was found between the GMV of right STG and PANSS positive ($r = -0.45$, $p = 0.04$), general ($r = -0.43$, $p = 0.05$), thought disturbance ($r = -0.56$, $p = 0.008$), activation ($r = -0.48$, $p = 0.027$) and paranoid ($r = -0.44$, $p = 0.047$) score. However, no significant correlations were found between the GMV of left cerebellum and PANSS scores ($P > 0.05$). In addition, a significantly negative correlation was observed between PANSS depression score the right temporo-frontal connection when the seed was placed in right STG. When the seed was in left cerebellum, correlations between PANSS scores and functional connectivity were observed (Figure 2), including: (1) positive correlation between PANSS activation score and left cerebelo-frontal connection (left cerebellum to left middle frontal gyrus); (2) positive correlation between PANSS anergia score and cerebelo-frontal connection (left cerebellum to bilateral middle frontal gyrus and left inferior frontal gyrus), and (3) negative correlation between PANSS negative score and cerebelo-frontal connection (left cerebellum to right superior frontal gyrus and left middle frontal gyrus).

Discussion

Current study applied the analysis of morphometry and resting-state functional connectivity to examine the relationship of the regional GMV deficits and its functional connection with the symptoms in patients with FSE, and for the first time, we reported that symptoms in patients with FSE associate with both structural deficits and its relational functional networks. Thus, future study should take into account of not only the brain structural changes but also the functional connectivity so to provide fuller insight into the underlying pathophysiology of the schizophrenia.

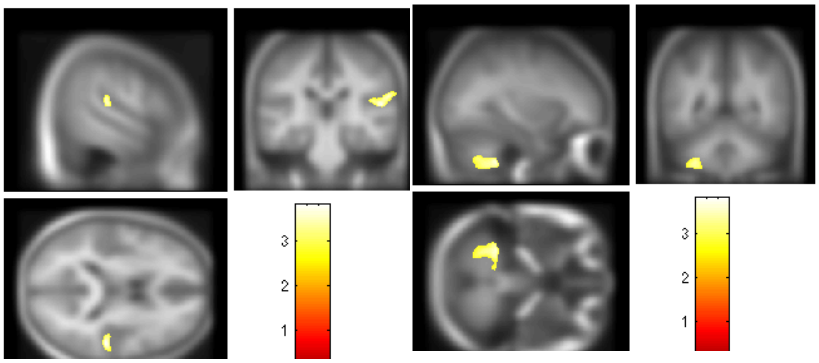

Figure 1. Statistical parameter images show results of VBM analysis of patients. Comparing with normal controls, patients have significant reduced gray matter volume in right superior temporal gyrus (left panel) and left cerebellum (right panel).

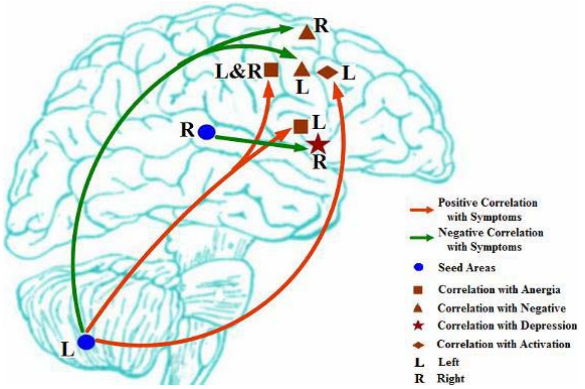

Figure 2 Sketch map shows the associations between the symptoms of FSE and the functional connectivity. Red arrows indicated positive correlation between functional connectivity and symptoms, while green arrows indicated negative correlation between connectivity and symptoms. When the seed was in right STG, only the right temporo-frontal connection was negatively associated with PANSS depression score. However, when the seed was in left cerebellum, correlations between PANSS score and functional connectivity were observed including positive correlation between PANSS activation score and left cerebelo-frontal connection; positive correlation between PANSS anergia score and cerebelo-frontal connection, and negative correlation between PANSS negative score and cerebelo-frontal connection.

References

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