Short-term effects of antipsychotic treatment on cerebral function in drug-naive first-episode schizophrenia revealed by rfMRI

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Introduction

Most of what we know about antipsychotic drug effects is at the receptor level, distal from the neural system effects that mediate beneficial psychological changes associated with antipsychotic treatment [1]. Studying cerebral function in drug-naive schizophrenia patients before and after pharmacotherapy can significantly enhance understanding of how clinically effective treatments alter functional brain systems. Thus, present study aims to examine alterations of regional and neural network function in antipsychotic-naive patients with first-episode schizophrenia before and after treatment with second generation antipsychotic medication.

Method

Thirty-four antipsychotic-naive first-episode schizophrenia patients were scanned using gradient-echo echo-planar imaging while in a resting state on a 3T MR imaging system (EXCITE, General Electric, Milwaukee, USA). After six weeks of antipsychotic treatment, patients were re-scanned. All patients were evaluated at baseline and six weeks after treatment, using the Positive and Negative Syndrome Scale (PANSS); as expected, significant reductions in psychopathology ratings were observed after treatment. Thirty-four matched healthy control subjects were studied at baseline for comparison purposes. The amplitude of low frequency fluctuations of BOLD signals, believed to reflect spontaneous neural activity, was used to characterize regional cerebral function [2]. Functional connectivity across brain regions was evaluated using a seed voxel correlation approach and an independent component analysis. Seed voxel correlation approach included following steps: (1) Obtaining seed reference by averaging the fMRI time series of all voxels within the areas with ALFF alteration; (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) the correlation coefficients were transformed to z-values using the Fisher r-to-z transformation to improve normality prior to averaging data across subjects. The ICA algorithm evaluates the degree to which synchronous activity occurs across spatially-independent widely-distributed brain regions. This was evaluated by computing a constrained maximal lagged correlation using the FNC toolbox (http://icatb.sourceforge.net/, version 1h). Changes in these measures after treatment were examined to characterize effects of antipsychotic drugs on regional function and functional integration respectively. These analyses were performed across the whole brain using two sample t-tests as implemented in SPM2 software. Inferences were made with a statistical threshold of $P < 0.05$ (corrected with FWE). Two correlation analyses were used: 1) ALFF values in regions where changes were observed after treatment were correlated with psychopathology ratings before and after treatment. 2) ALFF values in these regions were also correlated with connectivity z-scores in areas with connectivity alterations. The statistical threshold for these exploratory analyses was set at $P < 0.05$ (two tailed)

Results

After short term treatment with second generation antipsychotic medications, patients showed increased ALFF, particularly in bilateral prefrontal and parietal cortex, left superior temporal cortex, and right caudate nucleus (Figure 1). Increased regional ALFF was associated with reduction of clinical symptoms. A widespread attenuation in the functional integration of brain activity was observed (Figure 2). Further, decreased functional connectivity was correlated with increased regional ALFF.

Discussion

We demonstrate for the first time that widespread increased regional synchronous neural activity occurs after antipsychotic therapy, accompanied with decreased integration of function across widely distributed neural networks. These findings contribute to the understanding of complex beneficial and adverse effects of antipsychotic drugs.

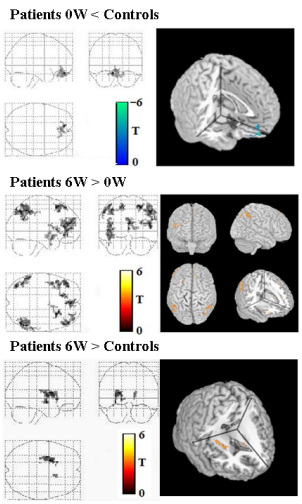

Figure 1. Glass brain images (left panel) and rendered images (right panel) showing results of the ALFF analysis. Upper: compared with normal controls, patients at baseline showed significantly decreased (blue) ALFF only in bilateral ventral medial frontal cortex ($P < 0.05$ corrected). Middle: compared with baseline, patients after six weeks showed significantly increased (red) ALFF mainly in bilateral prefrontal and parietal lobes ($P < 0.05$ corrected). Lower: compared with controls, patients after six weeks showed significantly increased (red) ALFF in right caudate and left putamen ($P < 0.05$ corrected).

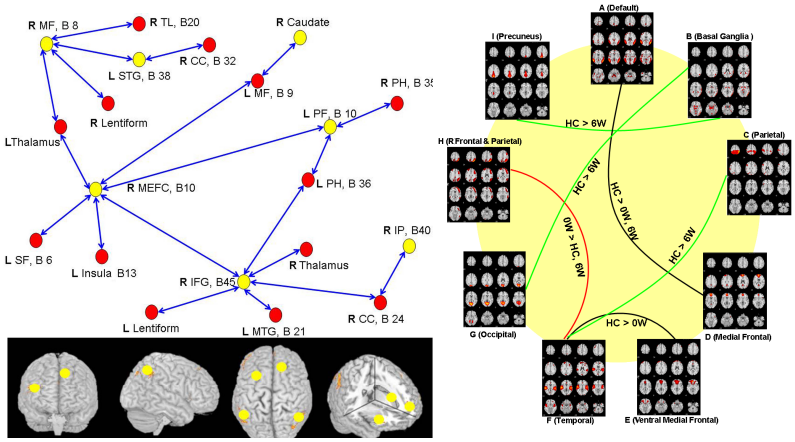

Figure 2 Left: Illustration of widespread decreased functional connectivity (blue arrows) in patients after six weeks of treatment compared to baseline involving areas with functional alterations (yellow circles) with other cortical and subcortical areas (red circles) ($p < 0.05$, corrected for multiple comparisons). Right: Significant differences of functional network connectivity between groups by ICA. R: right, L: left, B: Brodmann, MF: middle frontal gyrus, TL: temporal lobe, CC: anterior cingulate cortex, STG: superior temporal gyrus, SF: superior frontal gyrus, MEFC: medial frontal cortex, PF: prefrontal cortex, PH: parahippocampus, IFG: inferior frontal gyrus, MTG: middle temporal gyrus, IP: inferior parietal lobule.

References

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