Long-term effects of antipsychotic treatment on cerebral function in drug-naive first-episode schizophrenia: a two years longitudinal study by rfMRI

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Introduction:

How does the antipsychotic treatment affect the cerebral function? Most of what we know about antipsychotic drug effects is at the receptor level, distal from the neural system effects that mediate their clinical efficacy. Studying cerebral function in antipsychotic-naive schizophrenia patients before and after pharmacotherapy can enhance understanding of the therapeutic mechanisms of these clinically effective treatments (1). Our previous study has reflected short term (6 weeks) effect of second-generation antipsychotic drugs on cerebral function (1) using the amplitude of low-frequency fluctuations (ALFF) of blood oxygen level-dependent (BOLD) resting-state functional magnetic resonance imaging (rfMRI) signal (2). In this study, changes in ALFF after two-year pharmacotherapy were examined to characterize the long term effects of antipsychotic drugs on regional function of schizophrenia patients.

Subjects and Methods:

The study was approved by the local ethical committee and written informed consent was obtained from all subjects. The diagnoses of schizophrenia patients were determined using the structured clinical interview for DSM-IV patient edition and all patients were evaluated at baseline and 12 and 24 months after second-generation antipsychotic drugs treatment using the Global Assessment of Functioning Scale (GAF) and Positive and Negative Syndrome Scale (PANSS). Finally twenty antipsychotic-naive first-episode schizophrenia patients were recruited and scanned at baseline, and 12 and 24 months after antipsychotic treatment for three times. Thirty healthy control subjects were studied at baseline for comparison purposes. The MRI examinations were performed via a 3-Telsa GE MRI system with an 8 channel phase array head coil. The resting-state fMRI sensitized to changes in BOLD signal levels were obtained via a GE-EPI sequence (TR/TE=2000/30msec, flip angle=90°, slice thickness=5mm with no gap, 30 axial slices, 200 volumes in each run). During MR examination, subjects were instructed to relax with their eyes closed without falling asleep. The fMRI data processing was then conducted by DPARSF software (http://www.restfmri.net) to calculate the parametric maps of ALFF. Head translation movement of all participants was <1.5 mm and rotation was < 1.5°. Voxel-based analysis of the ALFF maps between the three-time points of schizophrenia patients was performed using a full factorial model with one-way ANOVA analysis in SPM8 (http://www.fil.ion.ucl.ac.uk/spm), and the voxel-based analyses of ALFF maps between control and patients at baseline and 12 and 24 months after pharmacotherapy respectively were performed with two-sample t-test. The corrected *P* value of less than 0.05 was deemed to be significant for all analyses.

Results:

After pharmacotherapy, schizophrenia patients showed significantly increased ALFF in the right orbitofrontal cortex (OFC), bilateral inferior parietal lobule (IPL) relative to baseline (P=0.04, FDR corrected) (Figure 1). However, no significant difference of ALFF was found between 12 and 24 months after pharmacotherapy, though an increasing trend of ALFF was observed (Table 1). The alterations of ALFF within the three regions mentioned above had significant interaction with the changes of all the clinical symptoms (P<0.001), i.e., the increased ALFF paralleling the increased GAF and decreased PASS scores after 12 and 24 months treatment (Figure 2). Relative to controls, patients showed increased ALFF in left occipital lobe and right cuneus and decreased ALFF in the bilateral orbitofrontal cortex and right inferior parietal lobule at baseline, and after 12 months treatment patients showed increased ALFF in bilateral putamen and decreased ALFF in bilateral orbitofrontal cortex, and after 24 months treatment patients showed increased ALFF in bilateral putamen (P<0.05, SVC corrected) (Figure 3).

Figure 1. The main effect results of the ANOVA analysis of the schizophrenia patients between the baseline and 12 and 24 months after treatment.

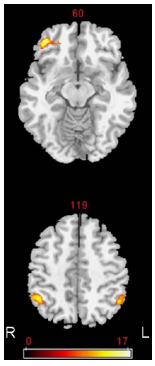

Figure 2. The interaction and trend line between the ALFF values (magnified 100 times) and scores of the clinical measures.

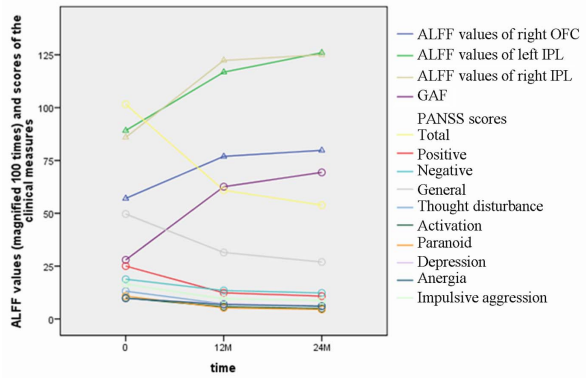

Figure 3. Two-sample t-test analyses of ALFF between schizophrenia patients and normal control for three-time points.

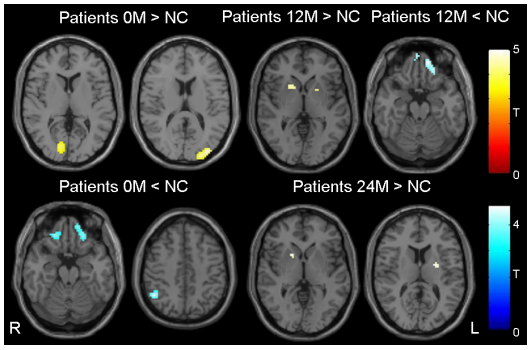

Table 1. The ALFF changes within the three main effect regions in schizophrenia patients

Region	Baseline	After 12M	Change%*	*P* *	After 24M	Change%#	*P* #
1.R OFC	0.57(0.14)	0.77(0.14)	42(46)↑	<0.001	0.8(0.15)	8(34)↑	=0.565
2.L IPL	0.89(0.23)	1.17(0.27)	61(78)↑	=0.001	1.26(0.25)	10(38)↑	=0.263
3.R IPL	0.86(0.27)	1.22(0.32)	47(84)↑	<0.001	1.25(0.29)	16(48)↑	=0.773

OFC, orbitofrontal corex; IPL, inferior parietal lobule; R, right; L, left; ↑, increased;
* Change (%) and *P* value for baseline versus 12M
# Change (%) and *P* value for 12M versus 24M

Conclusion:

To our knowledge, this is the first two-year longitudinal study evaluating regional function by rfMRI in antipsychotic-naive schizophrenia patients. After 24 months of treatment with second-generation antipsychotic drugs, schizophrenia patients showed significantly increased synchronous regional brain function in the resting state relative to pretreatment in regions within the fronto-striato-parietal networks. Furthermore, such alterations paralleled the clinical recovery. In accord with previous researches reported the hypofrontality in drug-naive schizophrenia patients and hyperactivity of subcortical dopaminergic systems after pharmacotherapy (3), our results demonstrated the fronto-striato-parietal networks in schizophrenia patients with enhanced responsiveness to pharmacotherapy may be pathophysiologically significant in schizophrenia. Our current study also offered promise that rfMRI has the potential to track long-term effects of antipsychiatric drug on brain function of schizophrenia patients.

Reference: 1. Lui S, et al. Arch Gen Psychiatry 2010; 2. Fox MD, et al.Nat Rev Neurosci 2007; 3. Kegeles LS, et al. Neuropsychopharmacology 2008