Aberrant Default Mode Functional Connectivity in Early Onset Schizophrenia

Jinsong Tang1,2, Yanhui Liao1,2, Ming Song3, Jia-Hong Gao4, Bing Zhou5, Changlian Tan5, Tieqiao Liu1,2, Yanqing Tang6, Jindong Chen1,2, Xiaogang Chen1,2,7*

1 Institute of Mental Health, the Second Xiangya Hospital, Central South University, Changsha, Hunan, PR China, 2 Hunan Province Technology Institute of Psychiatry, Changsha, Hunan, PR China, 3 National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing, PR China, 4 Department of Radiology, University of Chicago, Chicago, Illinois, United States of America, 5 Department of Radiology, Second Xiangya Hospital, Central South University, Changsha, Hunan, PR China, 6 Department of Psychiatry, First Affiliated Hospital, China Medical University, Shenyang, Liaoning, PR China, 7 The State Key Laboratory of Medical Genetics, Central South University, Changsha, Hunan, PR China

Abstract

**Background:** The default mode network (DMN) has been linked to a number of mental disorders including schizophrenia. However, the abnormal connectivity of DMN in early onset schizophrenia (EOS) has been rarely reported.

**Methods:** Independent component analysis (ICA) was used to investigate functional connectivity (FC) of the DMN in 32 first-episode adolescents with EOS and 32 age and gender-matched healthy controls.

**Results:** Compared to healthy controls, patients with EOS showed increased FC between the medial frontal gyrus and other areas of the DMN. Partial correlation analyses showed that the FC of medial frontal gyrus significantly correlated with PANSS-positive symptoms (partial correlation coefficient = 0.538, Bonferroni corrected P = 0.018).

**Limitations:** Although the sample size of participants was comparable with most fMRI studies to date, it was still relatively small. Pediatric brains were registered to the MNI adult brain template. However, possible age-specific differences in spatial normalization that arise from registering pediatric brains to the MNI adult brain template may have little effect on fMRI results.

**Conclusion:** This study provides evidence for functional abnormalities of DMN in first-episode EOS. These abnormalities could be a source of abnormal introspectively-oriented mental actives.

Citation: Tang J, Liao Y, Song M, Gao J-H, Zhou B, et al. (2013) Aberrant Default Mode Functional Connectivity in Early Onset Schizophrenia. PLoS ONE 8(7): e71061. doi:10.1371/journal.pone.0071061

Editor: Wang Zhan, University of Maryland, College Park, United States of America

Received March 9, 2013; Accepted June 24, 2013; Published July 29, 2013

Copyright: © 2013 Tang et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This study was supported by the National Science Foundation of China (Grant No. 30900486 to JT, 81100996 to Y.L, 81271484 to X.C, 81271499 to Y.T), the National Key Basic Research and Development Program (973) (Grant No. 2012CB517904 to X.C), Central Colleges basic scientific research operating expenses (2011QNZT170 to Y.T), and Specialized Research Fund for the Doctoral Program of Higher Education (20110162120013 to Y.L). However, the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: chenxghn@gmail.com (XC); chenjd269@163.com (JC)

Introduction

Some brain regions, such as the precuneus, anterior and posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), parahippocampal, and inferior parietal cortices, are particularly active during “rest” and are deactivated during a variety of cognitive tasks [1,2]. These brain regions form the “default mode network” (DMN). This concept first emerged in literature in 2001 [3] and has rapidly become a central theme in contemporary cognitive and clinical neuroscience [4]. The DMN is involved in many aspects of brain function, and healthy functional connectivity of the DMN is imperative for normal mental functions. For example, early stage studies suggested that the brain’s DMN supports “self-referential” or “introspective” mental activity [5]. Particularly, the mPFC has been linked to internal “narrative” [6], the “autobiographical” self [7], “stimulus independent thought” [8] “mentalizing” [9], and “self-projection” [7].

Recently, impairment in the connectivity or activation of the DMN has been linked to many mental disorders. In autism, reduced self-referential, affective, and introspective thought have been revealed to be associated with weak activation of the DMN in the resting state [4]. Reduced deactivation of mPFC and increased deactivation of the PCC are believed to be associated with anxiety disorders [10]. The subgenal cingulate cortex is a prominent region within the DMN and was found to be associated with the length of a depressive episode [11]. Recent studies have demonstrated that functional connectivity of the DMN is disrupted in schizophrenia [12–14]. In schizophrenia, positive symptom severity correlated with increased deactivation of the middle frontal regions, precuneus, and the left middle temporal gyrus in an oddball task [1]. Impaired self-monitoring processes and stimulus-independent thought have been associated with abnormally low frequency resting state connectivity [15]. However, all of
these studies in schizophrenia are focused on adult onset or mixed onset schizophrenia.

Schizophrenia is characterized by hallucinations or disorganized thinking, loss of goal-directed behaviors, social withdrawal and cognitive deficits [16]. Early-onset schizophrenia (EOS) is defined herein as schizophrenia with onset by 18 years of age [17]. In comparison to patients with adult onset schizophrenia, adolescents with EOS might represent a more homogeneous subgroup associated with greater familial diathesis for the disorder [18]. Therefore, we investigated the functional connectivity of DMN in EOS patients compared with age-matched healthy controls.

Materials and Methods

Subjects

42 patients were recruited from the inpatient unit at the Institute of Mental Health at the Second Xiangya Hospital of Central South University. The patients were selected to participate in this study based on the following inclusion criteria: 1) fulfilled the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, American Psychiatric Association, 2000) criteria for schizophrenia, 2) aged 12 to 19, 3) onset of schizophrenia before the 18th birthday, 4) no comorbid Axis I diagnosis, and 5) no mental retardation. Confirmation of the schizophrenia was made by clinical psychiatrists for all patients, using the Structured Clinical Interview for DSM-IV-TR, Patient version (SCID-I/P) [19]. These patients were interviewed six months after the study to review the diagnosis, and all patients received a final diagnosis of schizophrenia. Patients were free of neurological or physical disorders that could lead to an altered mental state. Ten first-episode adolescents with EOS were included in data analysis. All patients were free of any known psychiatric condition and had no family history of psychosis in their first-degree relatives. None of the subjects have a past history of major physical or neurological illness. Patients and healthy controls with a current or history of drug use or abuse were excluded from this study. 6 healthy controls were excluded due to excessive head motion, so only 32 healthy controls were finally included in data analysis. All patients and control subjects were right-handed. Patients and control subjects were statistically similar in terms of gender composition, age, educational level, and head motion (see Table 1).

The study protocol was approved by the university ethics committee (The Review Board of Second Xiangya Hospital of Central South University), and the studies were carried out in accordance with the Declaration of Helsinki. Written informed consent was received from all participants and their parents or guardians after the risks and benefits were discussed in detail. If the patient failed to fill out the consent form correctly for more than two times, the parents or guardians were asked to fill out the consent form.

Imaging data acquisition

Scans were performed on a 1.5 T GE MRI scanner. Foam pads were used to limit head motion and reduce scanner noise. The functional scanning was carried out in the dark, and the participants were explicitly instructed to keep their eyes closed, relax, and to not move during the scan. Functional images were acquired with gradient-echo echo-planar imaging with the following parameters: TR = 2.0 s, TE = 40 ms, field of view = 24 cm, acquisition matrix = 64×64, flip angle = 90°, in-plane resolution = 3.75×3.75 mm, slice thickness = 5 mm, gap = 1 mm, 20 slices, axial acquisition, Time point = 180, scan time = 6 min. T1 structural image was only acquired from some of the subjects because several subjects could not remain motionless for the duration of the fMRI scan.

Imaging data preprocessing

Functional MRI data were preprocessed using Statistical Parametric Mapping (SPM5, http://www.fil.ion.ucl.ac.uk/spm/). The first 10 time points from each functional image were discarded to allow for equilibration of the magnetic field. The remaining data were realigned using INRIalign, a motion-correction algorithm unbiased by local signal changes [21]. The participants included in the analysis should have less than 1 mm maximum displacement in the x, y or z direction and less than 1° of angular rotation about each axis. Six healthy controls and 10 EOS patients were excluded from data analysis because they did not achieve the above criteria. Data were then spatially normalized into standard Montreal Neurological Institute space [22], spatially smoothed with a 8×8×8 mm³ full width at half-maximum Gaussian kernel. The data (originally acquired at 3.75×3.75×5 mm³) were slightly subsampled to 3×3×3 mm³, resulting in 61×73×61 voxels.

Independent component analyses

Independent Component Analyses were preprocessed in 32 first-episode adolescents with EOS and 32 healthy controls. We

Table 1. Characteristics of EOS and control groups in fMRI analysis.

|                          | Control (n = 32) | EOS (n = 32) | P value |
|--------------------------|-----------------|-------------|---------|
| Age(year)                | 16.4±0.9        | 16.2±1.2    | 0.39 a  |
| Gender (male/female)     | 15 M/17 F       | 16 M/16 F   | 0.8 b   |
| Education(year)          | 9.7±0.7         | 9.4±1.5     | 0.29 a  |
| Onset age(year)          | –               | 15.4±1.2    | –       |
| Head motion (translation, mm) | 0.46±0.22      | 0.48±0.25   | 0.75 a  |
| Head motion (rotation, degree) | 0.45±0.26      | 0.43±0.28   | 0.75 a  |
| PANSS Positive Symptoms  | –               | 22.4±3.2    | –       |
| PANSS Negative Symptoms  | –               | 20.8±3.3    | –       |
| PANSS General psychopathology | –             | 34.4±3.5    | –       |
| CPZ equivalent (mg)      | –               | 229.3±188.7 | –       |

* T-test; a Chi-square tests; EOS: Early-onset schizophrenia.

doi:10.1371/journal.pone.0071061.t001
used the Group ICA fMRI Toolbox (GIFT) to analyze the fMRI data with spatial ICA [23]. We first used a minimum description length algorithm to find the optimal number of spatially independent components [24]. The mean dimension estimation was 28.14 (SD = 4.07). Therefore, 28 brain components were decomposed from images by GIFT. The data were then further

Figure 1. Default Mode Network Map for Patients with Early onset Schizophrenia and Healthy Comparison Subjects. doi:10.1371/journal.pone.0071061.g001

Figure 2. Brain regions with significantly increased strength of connectivity in patients with EOS compared with healthy controls. doi:10.1371/journal.pone.0071061.g002
We compared each component’s spatial map with methods [1,26] to select components of the default mode network. The components that were related to artifacts, we used published applied to this reduced data-set and performed on all of the regions in these components closely resembled regions in the included brain areas previously reported to be part of the DMN [26] (Fig. 1): (A) anterior component of DMN; (B) posterior component of DMN; Spatial correlation with the DMN a priori mask revealed that these components were the two highest ranked components (r = 0.28 and 0.27, respectively), indicating that regions in these components closely resembled regions in the DMN mask. Although the DMN maps of patients and controls were similar overall, voxelwise two-sample t-test revealed significant differences in connectivity for component A in the medial frontal gyrus (x = 6, y = 24, z = 36; t = 4.38, FDR corrected P < 0.05). EOS patients showed increased strength of connectivity compared to healthy controls (Fig. 2). There were no significant differences in connectivity for component B.

Relationship between clinical factors and connectivity of medial frontal gyrus
Partial correlation analyses showed that the connectivity of medial frontal gyrus significantly correlated with PANSS-positive symptoms (partial correlation coefficient = 0.538, Bonferroni corrected P = 0.018) controlled for age, gender, years of education and antipsychotic treatment.

Discussion
Functional and structural abnormalities in both white and gray matters of EOS patients have been widely reported [27]. For instance, Alexander-Bloch investigated the topology of networks derived from resting-state fMRI and revealed that modularity of brain functional networks was significantly reduced in childhood-onset schizophrenia [28,29]. On the other hand, impairments in connectivity or activation in the DMN have also been observed in adult onset or mixed onset schizophrenic [4]. In this study, we observed that EOS patients showed a significant increase in strength of connectivity in the medial frontal gyrus (MFG) compared to age-matched healthy controls. The DMN maps identified in this study are consistent with previous findings in non-EOS patients [30–32]. Moreover, the connectivity of MFG significantly correlated with PANSS-positive symptoms. Our findings suggest that functional abnormalities in the DMN may be associated with abnormal mental activation in schizophrenia.

Aberrant DMN in EOS
schizophrenia [1]. Mingoia et al study reported an inverse correlation of negative symptoms with activity in the right anterior PPC of schizophrenic patients at rest [35]. Importantly, we found that the increased resting state functional connectivity in the MFG significantly correlated with PANSS-positive symptoms in EOS. The DMN is thought to reflect internal, self-referential, and stimulus-independent thought. Therefore, it is not surprising that there are anomalies in this network in patients with EOS. The enhanced connectivity within the DMN may blur the normal boundary between internal thoughts and external perceptions. The failure to recognize internally generated thought is believed to be a fundamental aspect of schizophrenia [37]. Also, hallucination is thought to be the result of a blurring of internal reflection and external perception. In addition, many symptoms of schizophrenia involve an exaggerated sense of self-relevance in the world, such as paranoid ideation. Our and others’ studies suggest that altered connectivity within the DMN may have implications for the pathogenesis of schizophrenia.

In this study, pediatric brains were registered to the MNI adult brain template. We acknowledge that registering pediatric brains to the MNI adult brain template could result in some age-specific differences in spatial normalization. However, these differences are unlikely to affect fMRI results because fMRI has a relatively low spatial resolution [29,38,39] and functional activity is represented by regional mean time series averaged over multiple voxels comprised of regions of the parcellation template image. In conclusion, the investigation of resting brain function provides novel access into the pathophysiology of schizophrenia. Aberrant functional connectivity of the DMN may explain abnormalities in the coordination of information processing in the brain of EOS patients at rest. The findings in this study suggest the involvement of DMN in schizophrenia.

Author Contributions
Conceived and designed the experiments: JT JC XC. Performed the experiments: JT YL MS JHG BZ. Analyzed the data: CT TL YT. Contributed reagents/materials/analysis tools: CT TL YT. Wrote the paper: JT JC XC.

References
1. Garrity AG, Pearlson GD, McKiernan K, Lloyd D, Kiehl KA, et al. (2007) Aberrant "default mode" functional connectivity in schizophrenia. Am J Psychiatry 164: 450–457.
2. Hafnermeier A, van der Grond J, Rombouts SA (2012) Imaging the default mode network in aging and dementia. Biochim Biophys Acta 1822: 431–441.
3. Raichle ME, MacLeod AM, Snyder AZ, Pfeffer WJ, Gusnard DA, et al. (2001) A default mode of brain function. Proc Natl Acad Sci U S A 98: 676–682.
4. Broyd SJ, Demanuele C, Debener S, Helsp SK, James CJ, et al. (2009) Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci Biobehav Rev 33: 279–296.
5. Raichle ME, Snyder AZ. (2007) A default mode of brain function: a brief history of an evolving idea. Neuroimage 37: 1083–1090.
6. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc Natl Acad Sci USA 98: 4259–4264.
7. Buckner RL, Carroll DC (2007) Self-projection and the brain. Trends Cogn Sci 11: 49–57.
8. Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, et al. (2007) Wandering minds: the default network and stimulus-independent thought. Science 315: 393–395.
9. Frith U, Frith CD (2003) Development and neurophysiology of mentalizing. Philos Trans R Soc Lond B Biol Sci 358: 459–473.
10. Zhao XH, Wang PJ, Li CB, Hu ZH, Xi Q, et al. (2007) Altered default mode network activity in patient with anxiety disorders: an fMRI study. Eur J Radiol 63: 373–378.
11. Whitfield-Gabrieli S, Ford JM (2012) Default mode network activity and connectivity in psychopathology. Am J Psychiatry 169: 1191–1201.
12. Karbasforoushan H, Woodward ND (2012) Resting-state networks in schizophrenia: a developmental perspective. Curr Top Med Chem 12: 2404–2414.
13. Liemburg EJ, van der Meer L, Swart M, Curcic-Blake B, Bruggeman R, et al. (2012) Reduced connectivity in the self-processing network of schizophrenia patients with poor insight. PLoS One 7: e42707.
14. Woodward ND, Rogers B, Heckers S. (2011) Functional resting-state networks are differentially affected in schizophrenia. Schizophr Res 130: 86–93.
15. Bluhm RL, Miller J, Janius RA, Osuch EA, Boksan K, et al. (2007) Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenic patients: anomalies in the default network. Schizophr Bull 33: 1004–1012.
16. Schultz SK, Andreasen NC (1999) Schizophrenia. Lancet 353: 1425–1430.
17. Rapoport JL, Addington AM, Frangou S, Psych MR (2005) The neurodevelopmental model of schizophrenia: update 2005. Mol Psychiatry 10: 434–449.
18. Anderson RF, Norderhein K, Fangholt D, Subotnik KL, Payne DA, et al. (2001) Schizophrenia and schizophrenia-spectrum personality disorders in the first-degree relatives of children with schizophrenia: the UCLA family study. Arch Gen Psychiatry 58: 581–588.
19. Frith C (1995) Functional imaging and cognitive abnormalities. Lancet 346: 615–620.
20. Burgund ED, Kang HC, Kelly JE, Buckner RL, Snyder AZ, et al. (2002) Aberrant functional connectivity in schizophrenia studied at resting state using probabilistic ICA. Schizophr Res 53: 143–149.
21. Jafri MJ, Pearlson GD, Stevens M, Calhoun VD (2008) A method for functional connectivity analysis of fMRI time-series revisited. Neuroimage 2: 45–53.
22. Jafri MJ, Pearlson GD, Stevens M, Calhoun VD (2008) A method for functional connectivity analysis of fMRI time-series revisited. Neuroimage 2: 45–53.
23. Calhoun VD, Adali T, Pearlson GD, Pekar JJ (2001) A method for making group inferences from functional MR data using independent component analysis. Hum Brain Mapp 14: 140–151.
24. Li YQ, Adali T, Calhoun VD (2007) Estimating the number of independent components for functional magnetic resonance imaging data. Hum Brain Mapp 28: 1231–1266.
25. Bell AJ, Sejnowski TJ (1990) An information-maximization approach to blind separation and blind deconvolution. Neural Comput 7: 1129–1159.
26. Assaf M, Jagannathan K, Calhoun VD, Miller L, Stevens MC, et al. (2010) Abnormal functional connectivity of default mode sub-networks in autism spectrum disorder patients. Neuroimage 53: 247–256.
27. Pailhère-Martinet M, Caclin A, Artiges E, Poline JB, Jailon M, et al. (2001) Cerebral gray and white matter reductions and clinical correlates in patients with early onset schizophrenia. Schizophr Res 50: 19–26.
28. Alexander-Bloch A, Lambiote R, Roberts B, Giedd J, Gogtay N, et al. (2012) The discovery of population differences in network community structure: new methods and applications to brain functional networks in schizophrenia. Neuroimage 59: 3889–3900.
29. Alexander-bloch AF, Gogtay N, Murray D, Biren R, Clasen L, et al. (2010) Disrupted modularity and local connectivity of brain functional networks in childhood-onset schizophrenia. Front Syst Neurosci 4: 147.
30. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, et al. (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 102: 9673–9678.
31. Fransson P (2005) Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp 26: 15–29.
32. Zhou Y, Liang M, Tian L, Wang K, Hao Y, et al. (2007) Functional disintegration in paranoid schizophrenia using resting-state fMRI. Schizophr Res 97: 194–205.
33. Woodward ND, Rogers B, Heckers S (2011) Functional resting-state networks are differentially affected in schizophrenia. Schizophr Res 130: 86–93.
34. Onur D, Lundy M, Greenhouse I, Shin AK, Meeusen V, et al. (2010) Default mode network abnormalities in bipolar disorder and schizophrenia. Psychiatry Res 183: 59–68.
35. Mingoia G, Wagner G, Langhein K, Maira R, Smeyns S, et al. (2012) Default mode network activity in schizophrenia studied at resting state using probabilistic ICA. Schizophr Res 130: 145–149.
36. Jafri MJ, Pearlson GD, Stevens M, Calhoun VD (2008) A method for functional network connectivity among spatially independent resting-state components in schizophrenia. Neuroimage 39: 1666–1681.
37. Frith C (1995) Functional imaging and cognitive abnormalities. Lancet 346: 615–620.
38. Burgund ED, Kang HC, Kelly JE, Buckner RL, Snyder AZ, et al. (2002) The feasibility of a common stereotactic space for children and adults in fMRI studies of development. Neuroimage 17: 108–200.
39. Kang HC, Burgund ED, Luag HM, Petersen SE, Schlaggar BL (2003) Comparison of functional activation foci in children and adults using a common stereotactic space. Neuroimage 19: 16–28.