Schizophrenia Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Attenuated resting-state functional connectivity in patients with childhood- and adult-onset schizophrenia

Rebecca E. Watsky [a], Stephen J. Gotts [b], Rebecca A. Berman [a], Harrison M. McAdams [a], Xueping Zhou [a], Dede Greenstein [a], Francois M. Lalonde [a], Peter Gochman [a], Liv S. Clasen [a], Lorie Shora [a], Anna E. Ordóñez [a], Nitin Gogtay [a], Alex Martin [b], Deanna M. Barch [c], Judith L. Rapoport [a], Siyuan Liu [a,*]

[a] Child Psychiatry Branch, National Institute of Mental Health, National Institutes of Health, 10 Center Drive, Building 10, Bethesda, MD 20892, USA
[b] Laboratory of Brain and Cognition, National Institute of Mental Health, National Institutes of Health, 10 Center Drive, Building 10, Bethesda, MD 20892, USA
[c] Departments of Psychology, Psychiatry and Radiology, Washington University in St. Louis, One Brookings Drive, St. Louis, MO 63130, USA

ARTICLE INFO

Article history:
Received 10 March 2017
Received in revised form 24 December 2017
Accepted 1 January 2018
Available online xxxx

Keywords:
Neurodevelopment
Childhood psychosis
Network connectivity

ABSTRACT

Background: Childhood-onset schizophrenia (COS) is a rare, severe form of the adult-onset disorder (AOS). Our previous resting-state fMRI study identified attenuated functional connectivity in COS compared with controls. Here, we ask whether COS and AOS patients and their siblings exhibit similar abnormalities of functional connectivity.
Methods: A whole-brain, data-driven approach was used to assess resting-state functional connectivity differences in COS (patients/siblings/controls, n: 26/28/33) and AOS (n: 19/28/30). There were no significant differences in age, sex, or head motion across groups in each dataset and as designed, the COS dataset has a significantly lower age than the AOS.
Results: Both COS and AOS patients showed decreased functional connectivity relative to controls among a wide set of brain regions ($P < 0.05$, corrected), but their siblings did not. Decreased connectivity in COS and AOS patients showed no amplitude differences and was not modulated by age-at-onset or medication doses. Cluster analysis revealed that these regions fell into two large-scale networks: one sensorimotor network and one centered on default-mode network regions, but including higher-order cognitive areas only in COS. Decreased connectivity between these two networks was notable ($P < 0.05$, corrected) for both patient groups.
Conclusions: A shared pattern of attenuated functional connectivity was found in COS and AOS, supporting the continuity of childhood-onset and adult-onset schizophrenia. Connections were altered between sensorimotor areas and default-mode areas in both COS and AOS, suggesting potential abnormalities in processes of self-monitoring and sensory prediction. The absence of substantial dysconnectivity in siblings indicates that attenuation is state-related.

Published by Elsevier B.V.

1. Introduction

Schizophrenia is increasingly understood as a disease involving disordered brain connectivity (Andreasen et al., 1998; Friston and Frith, 1995; Satterthwaite and Baker, 2015). Childhood-onset schizophrenia (COS), defined as onset of psychosis before age 13, is a rare, severe form of the illness that is continuous with the adult-onset disorder (AOS) (Nicolson and Rapoport, 1999). Patients with COS display symptomatology similar to that of poor-outcome adult patients (David et al., 2011; Gordon et al., 1994) as well as high rates of disease-related genetic anomalies (Ahn et al., 2014) and pronounced gray matter loss (Gogate et al., 2001).

Our group has previously assessed resting-state neural connectivity in COS (Alexander-Bloch et al., 2010; Berman et al., 2016). We recently took an agnostic, global approach to resting-state functional analysis, measuring "connectedness" (the average Pearson correlation of each voxel with all others), which revealed brain regions of decreased connectivity in our patient cohort. These regions clustered into two functional networks, one primarily related to social and cognitive processing, and one to somatosensory and motor processing (Berman et al., 2016).

In AOS, researchers have identified altered, generally decreased, functional network connectivity relative to controls (Baker et al., 2014; Cocchi et al., 2014; Fornito et al., 2013; Repovs et al., 2011). While work with both adult- and childhood-onset populations has demonstrated abnormal network connectivity, comparisons between these two populations are scarce. To our knowledge, only one study by Jiang et al. (2015) explored connectivity differences between early- and later-onset patients. However, in this study, no quantitative

* Corresponding author at: Child Psychiatry Branch, National Institute of Mental Health, National Institutes of Health, 10 Center Drive, Building 10, 4N242A, Bethesda, MD 20892, USA.
E-mail address: siyuan.liu@nih.gov (S. Liu).

https://doi.org/10.1016/j.schres.2018.01.003
0920-9964/Published by Elsevier B.V.

comparisons were conducted between the two groups, results were mainly based on local connectivity measures, and remote comparisons were restrained to selected regions.

The adult-onset literature suggests that a widespread set of networks are altered in schizophrenia, and thus a whole-brain analysis is needed for a comprehensive comparison between these two patient populations. Here, we evaluate global brain connectivity (GBC) (Cole et al., 2010) as connectedness among all voxels in the brain. GBC affords an agnostic way to examine the averaged connectivity in the whole brain, which we supplement with a second search to identify the regions most responsible for driving the changes in GBC (Gotts et al., 2012). AOS data are those used in a separate, earlier resting-state study that focused on a preselected set of networks (Repovs et al., 2011). The COS data include those from our previous paper, with the addition of 30% more recently recruited subjects (Berman et al., 2016).

Phenotypic comparisons, including structural brain changes, have shown that AOS and COS groups exhibit similar abnormalities relative to controls. COS has sometimes been shown to represent a more severe phenotype than AOS, with some studies showing similar effect sizes for COS and AOS (Bertolino et al., 1998; Jacobsen et al., 1997) and others showing a trend towards greater severity in COS (Frazier et al., 1996; Jacobsen et al., 1996; Olabi et al., 2011). We hypothesize that COS and AOS groups will exhibit qualitatively similar patterns of decreased connectivity in the same regions identified in our prior study.

In addition to comparing COS and AOS patients to controls, we test whether unaffected siblings show a similar pattern of reduced connectivity to those with manifest illness to determine if these abnormalities are familial traits or disease-related. Studies of siblings in adult populations are mixed, with some showing siblings to have functional abnormalities that are similar to, though less severe than, those seen in patients (Khadka et al., 2013; Liu et al., 2012; Repovs et al., 2011; Yu et al., 2013), while other work indicates no difference between AOS patients and siblings (Meda et al., 2012). COS siblings have yet to be investigated for resting-state connectivity. We hypothesize that siblings will show diminished neural connectivity in similar regions to patients.

2. Methods

2.1. Participants

Twenty-six individuals with childhood-onset schizophrenia (COS), 28 nonpsychotic siblings of individuals with COS (COS_SIB), and 33 typically developing controls (COS_CON) participated in the COS study (Table 1).

Table 1
Participant demographics. The schizophrenia, sibling, and control groups did not differ significantly by age or sex within childhood-onset (COS) and adult-onset (AOS) schizophrenia data (all $P > 0.22$; F or Fisher's exact tests). Age-at-onset was set as the age when diagnosis was made and illness duration was calculated by the difference between age at scan and age-at-onset. As designed, COS patients had significantly lower age and age-at-onset than AOS patients ($P < 0.0015$; two-sample t-tests). Medication doses were recorded and converted to chlorpromazine equivalents (Woods, 2003). COS patients were on higher doses of antipsychotic medication than AOS but the difference was not significant ($P = 0.15$, two-sample t-tests). COS/AOS_CON/SIB: respective control participants/siblings for each patient group.

	COS	COS_CON	COS_SIB	AOS	AOS_CON	AOS_SIB
n	26	33	28	19	30	28
Age (years, mean [SD])	19.89 [5.55]	17.73 [4.96]	17.47 [6.20]	24.69 [3.04]	23.22 [2.66]	24.32 [3.90]
Sex (male:female)	15:11	16:17	14:14	14:05	18:12	15:13
Age-at-onset (years, mean [SD])	12.68 [2.14]			19.24 [3.01]		
Illness duration (years, mean [SD])	7.21 [5.99]			5.45 [3.20]		
Medication (chlorpromazine equivalents, mg, mean [SD])	1043 [698]			738 [591]		

Some of the included COS patients and siblings were related. Informed assent and consent were obtained from all participants and their parent/guardian as applicable in accordance with a National Institutes of Health Institutional Review Board approved protocol. COS participants were recruited nationwide and diagnosed after inpatient observation that included medication washout when clinically appropriate. Exclusionary criteria included medical or neurological illness, substance abuse, or full-scale IQ below 70 prior to onset of psychotic symptoms (for further details, see McKenna et al., 1994). Control participants were free of lifetime medical or psychiatric disorders as determined by clinical examination and standardized interview, and none had psychiatric illness in a first-degree relative. All COS patients were rated by staff clinicians using the Scale for the Assessment of Positive Symptoms (SAPS (Andreasen, 1984)) and Scale for the Assessment of Negative Symptoms (SANS (Andreasen, 1983)) for quantification of symptom severity. All COS patients were receiving treatment with antipsychotic medication at the time of the study, typically clozapine, and had been stabilized for at least 2 weeks.

The participants for the AOS study (Table 1) were the same set as reported in Repovs et al. (2011) but 12 participants were excluded to match groups for motion and age; see Supplemental Image Preprocessing for details. Sex and other demographic variables were still matched across groups. These participants were recruited through the Conte Center for the Neuroscience of Mental Disorders at Washington University School of Medicine in St. Louis and included: 1) 19 individuals with DSM-IV schizophrenia (AOS); 2) 28 nonpsychotic siblings of individuals with schizophrenia (AOS_SIB); 3) 30 healthy control subjects (AOS_CON). Some of the AOS patients and siblings were related. All participants gave written informed consent for participation. Subjects were diagnosed using a semi-structured interview and the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 2001). Participants were excluded for substance dependence/abuse within the last 6 months; medical illness; history of head injury; or mental retardation (diagnostic and exclusion details elsewhere (Repovs et al., 2011)). The AOS patients were all outpatients and had been stabilized on antipsychotic medication for at least 2 weeks. Control subjects had no lifetime history of Axis I psychotic or mood disorders and no first-degree relatives with a psychotic disorder. All patients were assessed using the SAPS and SANS (Andreasen et al., 1995) by a master's-level research assistant who regularly participated in training and reliability sessions.

2.2. Image acquisition

For each participant, resting state EPI (echo-planar-imaging) images were acquired; parameters varied between COS and AOS data, including make of scanner (see Table S1 for details). T_1-weighted anatomical images (MPRAGE) were obtained (voxel size = $0.86 \times 0.86 \times 1.3$ mm for COS data, $1 \times 1 \times 1$ mm for AOS).

2.3. Image analyses

Both COS and AOS fMRI images were analyzed as previously described by our group (Berman et al., 2016) and as further detailed in Supplemental methods. Briefly, preprocessing was done within AFNI (Cox, 1996) using the basic ANATICOR approach (Jo et al., 2013; Jo et al., 2010) and the cleaned, smoothed residual time series were spatially normalized to the Talairach and Tournoux anatomical template (Talairach and Tournoux, 1988). Quality of these two datasets was compared using two measures, motion and global signal amplitude, which did not differ across groups (Table S2).

After preprocessing, for both COS and AOS data, first we conducted a whole-brain, data-driven search as previously described (Berman et al., 2016; Gotts et al., 2012) to identify regions of interest showing connectivity differences, measured by "connectedness" (the average Pearson correlation of each voxel with all others (Cole et al., 2010; Salomon et al., 2011)) of schizophrenia vs. controls and siblings vs. controls (see details in Supplemental methods). Second, these regions showing reduced

Please cite this article as: Watsky, R.E., et al., Attenuated resting-state functional connectivity in patients with childhood- and adult-onset schizophrenia, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.01.003