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

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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.

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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

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	17.73	17.47	24.69	23.22	24.32
	[5.55]	[4.96]	[6.20]	[3.04]	[2.66]	[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			19.24		
	[2.14]			[3.01]		
Illness duration (years, mean [SD])	7.21			5.45		
	[5.99]			[3.20]		
Medication (chlorpromazine equivalents, mg, mean [SD])	1043			738		
	[698]			[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

connectedness were used as seeds to find the locations driving connectedness differences. Combining these two sets of regions resulted in one set of all regions that showed differences in functional connectivity between groups. Using K-Means cluster analysis on all pairwise correlations, these regions were organized into two clusters, the optimal number as determined by elbow plots and confirmed by silhouette values (Berman et al., 2016; Gotts et al., 2013; Meoded et al., 2015). We examined group differences of region-by-region correlations within- and across-clusters as well as their correlations with clinical measures (SAPS and SANS). ANCOVA models were used to compare groups and examine modulation effects of age-at-onset, medication doses, and clinical measures. Age and transient Motion were co-varied as nuisance variables in all models and results were corrected using cluster size (AFNI's 3dClustSim, family-wise Type I error (FWE) < 0.05, employing AFNI's updated spatial auto-correlation function) for whole-brain comparisons and Bonferroni correction for the number of seeds tested. More details of data analyses are in Supplemental methods.

3. Results

3.1. Group comparisons of functional connectivity

Using resting-state fMRI, we investigated whole-brain network alterations in COS and AOS patients and their siblings. Groups were matched for age and sex in both COS and AOS data (Table 1). As designed, COS patients had significantly lower age and age-at-onset than AOS. Although COS and AOS fMRI data were collected using different protocols and on different MRI scanners, the motion magnitude and global signal amplitude of the preprocessed fMRI data were not significantly different either across groups within each dataset or between the two datasets, indicating that data quality was comparable among all groups (Table S2). In each dataset, a whole-brain, data-driven approach was applied separately to compare the average correlation of each voxel's time series with all brain voxels, termed "connectedness," between groups.

Compared to controls, both COS and AOS patients showed decreased connectedness in a set of widely distributed brain regions; no regions with increased connectedness were found (Fig. 1). Some of these

regions with reduced functional connectivity in COS (Table S3) and AOS (Table S4) were overlapping, including superior temporal, occipito-temporal and post-central gyri, supplementary motor area, and cerebellum (overlaps indicated by red outlines in Fig. 1 and stars in Tables S3 and S4).

To quantify the differences between COS and AOS patients, we compared the magnitude of connectedness using an interaction analysis (COS-COS_CON vs. AOS-AOS_CON), and found no differences in overall extent or severity of dysconnectivity between childhood and adult-onset patients at the corrected significance level. This lack of significant magnitude difference was confirmed by a secondary analysis in which we examined modulation effects of age-at-onset on connectedness in the merged group of COS and AOS patients. These findings imply that COS and AOS share a similar pattern of reduced connectivity without significant overall differences in amplitudes of dysconnectivity between the two patient groups.

We considered two further issues that could potentially influence our central dysconnectivity results. First, both AOS and COS patient groups were on antipsychotic medication (Table 1); as controls were medication-free, medication effects cannot be examined directly in group comparisons. We did a modulation analysis to examine whether medication doses were correlated with connectedness amplitudes in the merged group of COS and AOS patients (see Supplemental methods). We found no regions showing significant modulation effects of medication, consistent with our previous findings that medication is unlikely to be the primary factor driving group differences (Berman et al., 2016). Second, we conducted an analysis to determine whether the inclusion or exclusion of physiological regressors (heartrate and respiration) in preprocessing confounds the results of group comparisons. This control analysis was of interest because the physiological data were available and regressed only in the COS dataset. Our results, which were unchanged, ruled out the possibility that this methodological difference contributed to the observed group differences (Fig. S1).

As in patients, we compared connectedness between siblings of COS and AOS patients and controls. Interestingly, no significant differences were found in either sibling group except in the thalamus, where COS siblings showed higher connectedness than their controls ($P < 0.05$, corrected; Fig. S2A, B). A further interaction analysis of (COS_SIB-COS_CON vs. AOS_SIB-AOS_CON) found no significant differences in
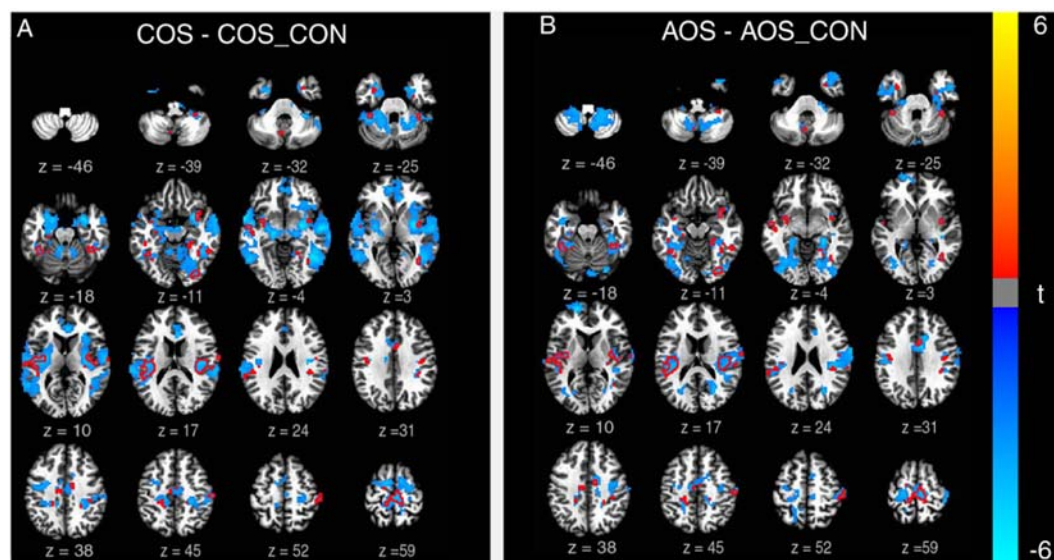

Fig. 1. Decreased connectedness in both childhood- and adult-onset schizophrenia patients compared to their respective controls. T-values shown in blue indicate that both COS (A) and AOS (B) patients showed significantly decreased connectedness (i.e., lower average correlation of each voxel's time series with all other brain voxels) in a broad set of brain regions compared to their controls. 21% of AOS regions with reduced connectedness were spatially overlapped with COS (in red outline). Results were corrected for multiple comparisons, with degrees of freedom of 56 (A) and 46 (B). Talairach coordinates of these regions are listed in Table S3 for COS and Table S4 for AOS, with shared regions starred. No regions with increased connectedness were found in either COS or AOS patients compared to controls. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the whole brain including the thalamus between childhood and adult-onset siblings. In addition, when we lowered the threshold, AOS_SIB also showed higher, though nonsignificant, connectivity in the thalamus compared to their controls. Therefore, this thalamic hyperconnectivity may not be specific to childhood-onset siblings. Next, patients showed decreased connectivity compared to siblings in a similar set of brain regions to those found when comparing to controls ($P < 0.05$, corrected; Fig. S2C, D). This pattern of hypoconnectivity in patients relative to siblings remained unchanged when their family relationship was modeled to account for the possible confounding effects of some patients and siblings being related (Fig. S3). This suggests that the decreases in functional connectivity that we identified in patients were disease-related.

The regions with reduced connectedness in patients (seed regions: 12 in COS, 10 in AOS) were used as seeds in more typical seed-based t-tests to identify the entire set of locations with different connectivity in schizophrenia relative to controls, correcting for whole-brain comparisons and the number of seeds tested. We identified 11 non-seed regions in COS and 5 in AOS, resulting in a total of 23 regions in COS (Table S3) and 15 in AOS (Table S4) with 8 regions overlapping (indicated by stars in these tables).

3.2. Organization of inter-regional relationships

We further investigated the relationships between these regions (23 in COS, 15 in AOS). We created a region-by-region correlation matrix for each participant and did t-tests on this correlation matrix between patients and controls with Age and Motion as covariates (Fig. 2). Using K-Means analyses, we categorized these regions into two clusters, the optimal number determined by Silhouette values and 'elbow' plots in both COS (Fig. S4B, C) and AOS data (Fig. S4E, F).

A demarcation of functions is associated with these two clusters. In COS and AOS, Cluster 1 (the red cluster in Fig. 3A, B; regions listed in the top parts of Tables S3, S4) was comprised predominantly of areas of the default-mode network (DMN) (Frith and Frith, 2007; Raichle et al., 2001). Cluster 1 in COS also included other higher-order cognition-related areas of the perisylvian or language-related network (Catani et al., 2005; Turken and Dronkers, 2011) and the dorsal attention network (Corbetta and Shulman, 2002). Cluster 2 (the green cluster in Fig. 3A, B; regions listed in the bottom parts of Tables S3, S4) in COS and AOS was comprised predominantly of somatosensory, motor, and auditory regions, many shared by COS and AOS, including the pre- and post-central gyri, supplementary motor area (SMA), cerebellum, and auditory cortices (Buckner et al., 2011; Di Martino et al., 2008; Hall, 2006; Picard and Strick, 1996; Zhang et al., 2012).

Correlations between most regions in Clusters 1 and 2 were altered for both COS (Fig. 2C) and AOS (Fig. 2F) relative to controls. In Fig. 2, the bottom left quadrant of each matrix shows interregional correlations within Cluster 1 (red), and the top right within Cluster 2 (green). The upper left and lower right quadrants (mirror images above and below the diagonal) show that most of the across-cluster region pairs exhibited greater correlation values in controls than patients (Bonferroni-corrected differences shown in dark red in C and F).

3.3. Relationship of altered functional connectivity to clinical symptoms

Finally, we investigated the relationship between these functional connectivity alterations and clinical symptoms, SAPS and SANS, in schizophrenia. In COS, consistent with our previous report, positive symptoms were associated with reduced correlation strength of region-by-region pairs across clusters (Fig. S5A) and negative symptoms appeared to be more strongly associated with decreased region-by-
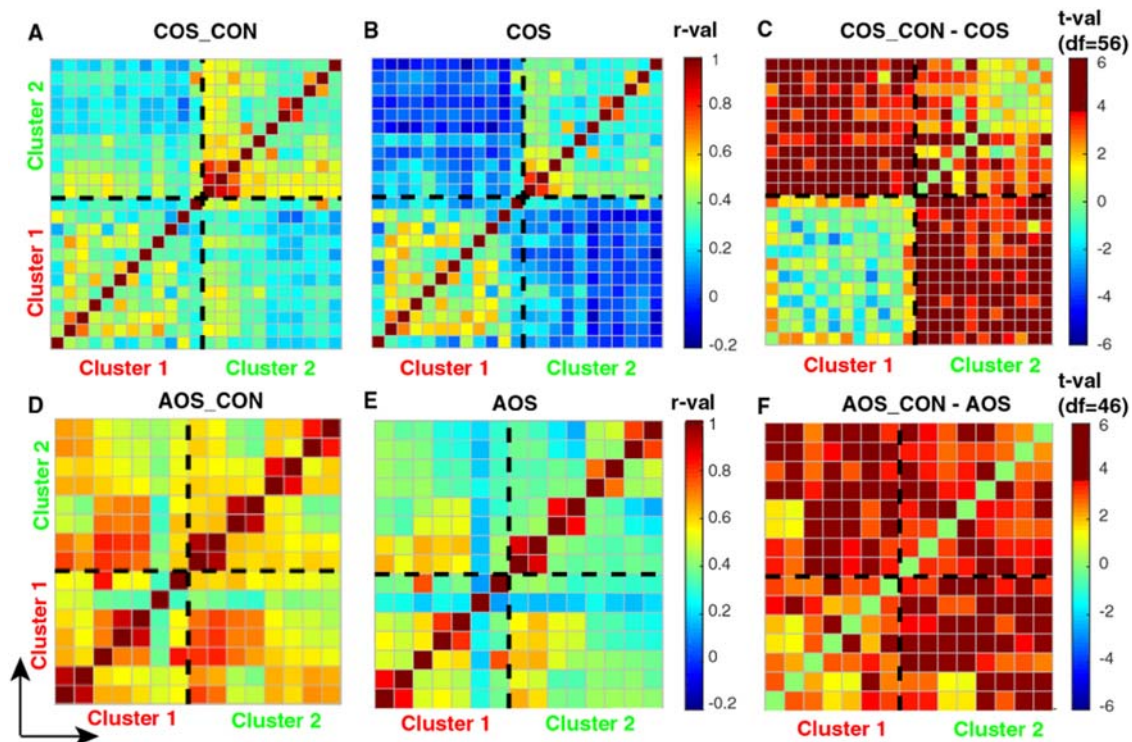

Fig. 2. Two clusters of regions with decreased across-cluster correlation in childhood- and adult-onset schizophrenia. Using K-Means analysis, ROIs were categorized into two clusters (number determined as shown in Fig. S4) for both COS and AOS. Region-by-region correlation matrices, pooled across groups (A COS controls, B COS patients; D AOS controls, E AOS patients), and corresponding t-tests (covarying Motion and Age; C Control-COS, F Control-AOS) were sorted by cluster membership (red and green, matching Clusters 1 and 2 in Fig. 3). The order of ROIs in the matrices is identical to the order in Tables S3 and S4 (ROI number increases as arrows indicate, from bottom to top row and leftmost to rightmost column). Significantly decreased correlations between the two clusters (in the upper left and lower right quadrants of each matrix) were found in patients compared to controls (most t values, shown in dark red, were higher than Bonferroni corrected t threshold of 3.77 for COS in C, 3.53 for AOS in F), and in COS some of these across-cluster correlations were negative (B). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
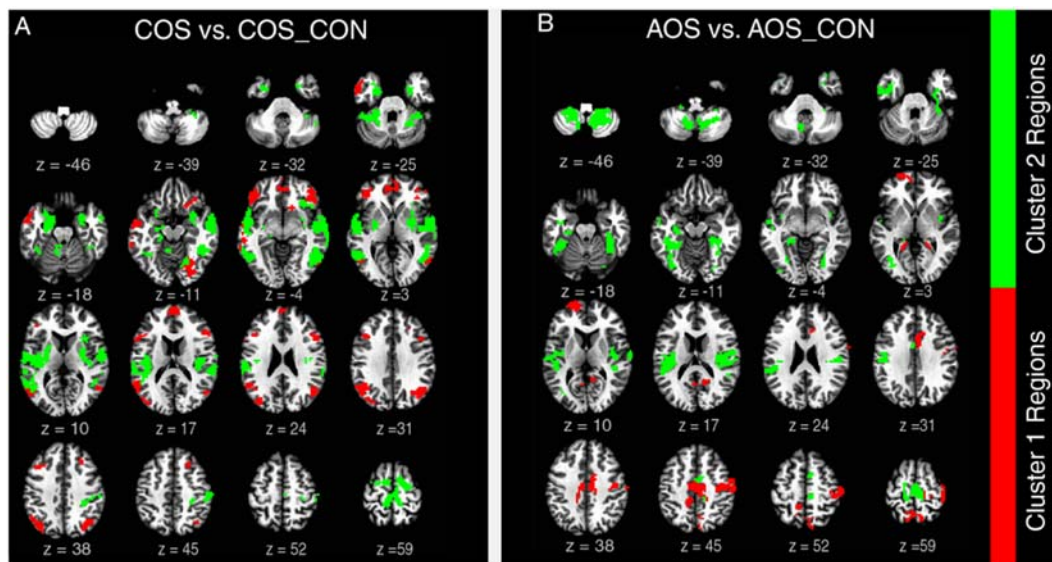
Fig. 3. Clusters of regions with reduced functional connectivity in childhood- and adult-onset schizophrenia patients compared to their controls. Voxels are colored by membership in the two major clusters defined in Fig. S4: a 'red' cluster including different components of the default-mode network in AOS and COS, and additional language and attention related areas only in COS (Cluster 1), and a 'green' cluster including somatosensory, motor and auditory regions in both AOS and COS (Cluster 2). Results were corrected for multiple comparisons (see Methods for details). Talairach coordinates of each region are shown in Tables S3 (COS) and S4 (AOS). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

region correlations within Cluster 1 (Fig. S5B). However, correlations were not prominent; few region-by-region pairs survived correction for multiple comparisons (indicated by white circles), suggesting that these results require further examination with a larger sample size. On the other hand, in AOS, no clear patterns at the corrected level were found in association with either positive (Fig. S5C) or negative symptoms (Fig. S5D). This lack of positive results in AOS could be due to the relatively large variance across regional functional connectivity in AOS patients compared to COS patients, which may not be fully accounted for by these two clusters.

4. Discussion

We found diminished resting-state functional connectivity in patients with childhood- and adult-onset schizophrenia. There were no significant amplitude differences between these two patient groups, and age-at-onset showed no modulation effect. In siblings of the patients in both groups, we found few or no differences compared with controls. The regions of decreased connectivity in patients relative to controls fell into two clusters, or large-scale networks, one relating to sensory and motor activity and one involving components of the default-mode network in both COS and AOS, though also with a number of higher-order prefrontal and parietal areas in COS.

COS and AOS are characterized by similar disrupted neural connections relative to healthy controls, suggesting the continuity of COS and AOS. Consistent with the main trends in adult literature, we found that schizophrenia is associated with connectivity reductions, as opposed to increases (Baker et al., 2014; Fornito et al., 2013; Garrity et al., 2007; Pettersson-Yeo et al., 2011; Schilbach et al., 2016), aligning with the hypothesis that schizophrenia is a disorder of dysconnectivity (Andreasen et al., 1998; Friston and Frith, 1995). Structural covariance evidence corroborates findings of dysconnectivity, showing delayed development of corticocortical connections in COS (Zalesky et al., 2015). In an earlier study, Jiang et al. (2015) also found that local functional connectivity was altered in both early- and adult-onset schizophrenia patients compared with controls. While they reported qualitative differences in a few regions between early- and adult-onset patients without statistical tests, these differences may not survive a more stringent quantitative and direct comparison as we did here.

In both COS and AOS groups, brain regions with reduced connectivity were best grouped into two clusters. The "green" cluster, made up of somatosensory and motor regions, was largely shared between COS and AOS. In AOS, the "red" cluster mainly comprised areas of the previously-defined default-mode network (DMN) (Fransson, 2005; Greicius et al., 2003; Raichle et al., 2001). In COS, the corresponding cluster included different areas of the DMN as well as regions related to higher order cognitive functions. The DMN may be involved in attention to internal emotional states (Gusnard et al., 2001) and self-referential processing (McGuire et al., 1996). Both the COS and AOS groups showed significantly reduced connectivity between the two clusters. Impaired connectivity between somatomotor regions and regions involved in self-reference is congruous with previous reports that schizophrenia patients exhibit deficits in self-monitoring mechanisms. Impairment in distinguishing between sensory events produced by their own actions and those caused by external agents has been proposed to underlie positive symptoms such as hallucinations and delusions (Blakemore et al., 1998; Blakemore et al., 2000; Ford et al., 2013; Mathalon and Ford, 2008; Shergill et al., 2005; Shergill et al., 2014; Simons et al., 2010; Spering et al., 2013).

Previous resting-state research has sometimes identified abnormalities in siblings of schizophrenia patients which seem to be less extreme forms of the alterations found in the patients themselves (Wang et al., 2015). We detected only weak differences in functional connectivity between COS siblings and controls, and no significant differences between AOS siblings and controls. Compared with siblings, both patient groups showed reduced functional connectivity in similar patterns as when controls were used as baselines. This absence of abnormalities in siblings suggests that aberrant functional connectivity is state-related. However, it is possible that siblings show abnormality in functional connectivity only at an early age and do not differ from controls later, as appears to be true for structural connectivity (Zalesky et al., 2015).

In our previous resting-state analysis of COS, our group found evidence of correlations between behavior and network connectivity (Berman et al., 2016). Positive and negative symptoms in patients correlated, respectively, with reductions in across-cluster connectivity and within-"social-cognitive" cluster functional connectivity. After increasing the number of subjects for the present study, we found a similar pattern of results in COS but with fewer findings surviving correction for

multiple comparisons, and we observed almost no significant symptom correlations in AOS. The lack of correlations in AOS may relate to the larger variance across regional functional connectivity in AOS patients compared to COS patients, as reflected by elbow plots showing greater percent variance unexplained by two clusters in AOS (Fig. S4C, F). Further studies with larger sample sizes and additional, objective behavioral measures will be critical to more definitively establish the most stable relationships between symptoms and connectivity, particularly in AOS.

Limitations to our methodology include the bluntness of a global brain connectivity (GBC) approach, in which GBC may fail to detect voxels with a perfect balance of increases and decreases by averaging connectedness. While we complemented the GBC analysis with a ROI-to-ROI correlation/cluster analysis, and in previous applications of GBC (Berman et al., 2016; Meoded et al., 2015; Song et al., 2015; Steel et al., 2016; Stoddard et al., 2016) have not identified a failure to detect mixtures of increases/decreases that were successfully identified by another method, the risk of Type II errors still exists and interpretation of these results have to be cautious. In addition, although the robustness of the current region-level cluster method has been previously tested by identifying a similar cluster resolution with a completely different voxel-level method [Supplemental Fig. 6 in (Berman et al., 2016)], we cannot completely rule out the possibility that our cluster solution could have been affected by the selection of methods. Another limitation stems from the different sources of imaging data for the COS and AOS cohorts. Acquisition parameters for resting-state functional MRI differed for the two datasets, such as eyes-open versus eyes-closed conditions and make of scanner, which could cause variations in results (Patriat et al., 2013). To mitigate such confounds, we measured the data quality in terms of motion and global signal amplitude and found they were not significantly different, and we always compared COS and AOS to their own controls. The cross-sectional design increased the difficulty in clearly separating age-at-onset from age modulation effects and the correlation between them (Pearson r = 0.396) was moderate. In addition, although this study included almost 200 participants, our patient sample size was relatively modest. Future longitudinal studies with more patients would increase the statistical power.

Other common confounding factors in neuroimaging studies of schizophrenia include motion artifacts and medication doses. As described above, we excluded subjects with severe motion and implemented multiple de-noising strategies in preprocessing (for a recent review of motion treatment methods, see Power et al., 2015). Neither groups nor datasets differed significantly in transient head motion and we further accounted for residual motion in the group-level analyses through the use of nuisance covariates, arguing against an interpretation of the group differences as an artifact of motion differences. Nevertheless, careful interpretation of our results and future replication studies are needed. There is a lack of agreement in previous findings on whether or not medication use alters fMRI connectivity (Baker et al., 2014; Sarpal et al., 2015). A direct analysis showed no significant modulation effect of medication doses in the current dataset, which is consistent with our previous findings (Berman et al., 2016). Therefore, we believe that our results of group differences are unlikely to have been driven by medication.

In summary, COS and AOS patients exhibited similar disease-related patterns of resting-state functional connectivity disruption that may result from aberrant neurodevelopment. Disruption was mainly characterized by reduced connectivity between sensory/motor related regions and regions associated with self-referential processing, suggesting potential impairment in differentiating perception of external stimuli from internal prediction. Whether these dysconnectivity symptoms emerge even earlier than childhood-onset warrants further investigations based on prospective community-based studies.

Author contributions

REW and SL wrote the manuscript. DMB and JLR designed the study and made major edits to the manuscript. SL performed the data analyses with SJG's help; REW, RAB, HMM, DG, AM, and XZ also contributed. REW, NG, AEO, FML, PG, LSC, and LS contributed to data collection and management. All authors edited and have approved the final manuscript.

Conflicts of interest

All authors report no financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.01.003.

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