

Brain Network Connectivity in Individuals with Schizophrenia and Their Siblings

Grega Repovs, John G. Csernansky, and Deanna M. Barch

Background: Research on brain activity in schizophrenia has shown that changes in the function of any single region cannot explain the range of cognitive and affective impairments in this illness. Rather, neural circuits that support sensory, cognitive, and emotional processes are now being investigated as substrates for cognitive and affective impairments in schizophrenia, a shift in focus consistent with long-standing hypotheses about schizophrenia as a disconnection syndrome. Our goal was to further examine alterations in functional connectivity within and between the default mode network and three cognitive control networks (frontal-parietal, cingulo-opercular, and cerebellar) as a basis for such impairments.

Methods: Resting state functional magnetic resonance imaging was collected from 40 individuals with DSM-IV-TR schizophrenia, 31 siblings of individuals with schizophrenia, 15 healthy control subjects, and 18 siblings of healthy control subjects while they rested quietly with their eyes closed. Connectivity metrics were compared between patients and control subjects for both within- and between-network connections and were used to predict clinical symptoms and cognitive function.

Results: Individuals with schizophrenia showed reduced distal and somewhat enhanced local connectivity between the cognitive control networks compared with control subjects. Additionally, greater connectivity between the frontal-parietal and cerebellar regions was robustly predictive of better cognitive performance across groups and predictive of fewer disorganization symptoms among patients.

Conclusions: These results are consistent with the hypothesis that impairments of executive function and cognitive control result from disruption in the coordination of activity across brain networks and additionally suggest that these might reflect impairments in normal pattern of brain connectivity development.

Key Words: Cerebellum, cognitive control, functional connectivity, risk, schizophrenia

Research focused on elucidating the neural systems that contribute to cognitive impairments among individuals with schizophrenia (1–4) suggests that changes in the function of a single region cannot explain the range of impairments seen in this illness. As such, research has increasingly focused on understanding the integrity of neural circuits that work together to support sensory, cognitive, and emotional processes (5). This shift in focus is consistent with long-standing hypotheses about schizophrenia as a disconnection syndrome (6,7).

The efforts to understand altered brain connectivity in schizophrenia have been aided by recent work identifying core networks in the brains of healthy individuals. For example, a default mode network (DMN) has been identified (8,9), which consists of a set of brain regions that reliably reduce their activity during active cognitive demands (10) and that may be involved in processes such as attention to internal emotional states (11), self-referential processing (12), or task-independent thought (13). Other work has identified networks that are activated by a variety of cognitive tasks, including a dorsal frontal-parietal network (FP), a cingulo-opercular network (CO), and a cerebellar network (CER) (14–16). The FP network is engaged by a wide range of higher level cognitive tasks and is thought to be involved in adaptive task control (14–16). The CO network is also en-

gaged in a variety of tasks but is thought to be involved in stable task-set maintenance and error processing (14–16). The CER network also shows error-related activity in a range of tasks, and its activity often covaries with the activity of the dorsal frontal-parietal and cingulo-opercular networks (14–17). Some of the work identifying these networks has focused on examining connectivity among and between networks during resting state. This work complements research on task-related activation of networks by examining the functional correlations between regions that may not be simply a result of deterministic task demands and that may help shape the ability of networks to respond to task demands.

A number of studies have identified abnormalities in the function of the DMN in schizophrenia, with the interpretation that impaired connectivity in this network may contribute to difficulties in disengaging attention to internal states (18). However, the nature of these abnormalities has been variable across studies. For example, work by Whitfield-Gabrieli *et al.* (18) identified abnormally enhanced connectivity within the DMN among individuals with schizophrenia and their first-degree relatives compared with control subjects, as well as reduced task-related deactivation. Somewhat consistent with this finding, Salvador *et al.* (19) found that a medial prefrontal region of the DMN showed hyperconnectivity among individuals with schizophrenia in an overall brain connectivity analysis. In contrast, a number of other studies have found either reduced connectivity in the DMN in schizophrenia (20–23) or a mixed pattern of increased and decreased connections within the DMN (24).

Other studies have identified abnormalities in the connectivity of regions that play a part in the FP and CO networks. For example, Welsh *et al.* (25) found reduced functional connectivity between the medial dorsal nucleus of the thalamus and the anterior cingulate and caudate. Zhou *et al.* (26) found reduced functional connectivity between bilateral dorsolateral prefrontal cortex and regions of the parietal cortex, thalamus, and striatum in first-episode patients with schizophrenia.

From the Department of Psychology (GR), University of Ljubljana, Ljubljana, Slovenia; Department of Psychiatry and Behavioral Sciences (JGC), Feinberg School of Medicine, Northwestern University, Chicago, Illinois; and Departments of Psychology, Psychiatry, and Radiology (DMB), Washington University in Saint Louis, Saint Louis, Missouri.

Address correspondence to Deanna M. Barch, Ph.D., Washington University, Departments of Psychology, Psychiatry, and Radiology, Box 1125, One Brookings Drive, St. Louis, MO 63130; E-mail: dbarch@artsci.wustl.edu.

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Table 1. Demographic and Clinical Characteristics of Study Participants

Measure	Group							
	Healthy Control Subjects (CON)		Siblings of Control Subjects (CON-SIB)		Individuals with Schizophrenia (SCZ)		Siblings of Schizophrenia (SCZ-SIB)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	23.4	2.9	22.2	2.9	24.4	3.1	24.3	3.7
Gender (% male)	60%		61%		72%		58%	
Education	14.2	1.9	13.7	1.8	12.2	1.8	13.5	2.5
Parental Education	13.9	1.8	14.5	1.5	14.3	2.2	15.0	2.4
History of Substance Dependence	0%		6%		24%		16%	
History of Substance Abuse	0%		22%		44%		23%	
Negative Symptoms ^a	-.39	.21	-.31	.41	1.17 ^b	.76	-.11	.54
Positive Symptoms ^a	-.48	.13	-.31	.40	1.02 ^b	1.07	-.28	.28
Disorganization Symptoms ^a	-.27	.38	-.24	.26	.88 ^b	1.08	-.16	-.34
IQ ^c	-.12	.80	-.49	.78	-1.05 ^d	.79	-.37	.78
Working Memory ^c	.67	.64	.43	.70	.28 ^d	.74	-.63	.75
Episodic Memory ^c	.53	.79	.30	.78	.07 ^d	.56	-.85 ^e	.51
Executive Function ^c	.61	.44	.50	.44	.16 ^d	.47	-.47 ^f	.90

Note: The four groups did not differ significantly in age [$F(3,85) = 2.0, p > .10$], parental education [$F(3,85) = .66, p > .50$], gender ($\chi^2 = 1.3, p > .5$) or race ($\chi^2 = 3.05, p > .55$). The groups did differ in personal education [$F(3,85) = 3.68, p < .05$], with the individuals with schizophrenia having significantly fewer years of education than control subjects.

The *N*s for individuals with schizophrenia and their siblings, and control subjects and their siblings are not identical, given that some participants were excluded for failure to complete the entire protocol or due to excessive movement during the functional connectivity runs. Of the 101 participants aged 18 or older from whom we collected resting state data, there were 11 who had to be excluded for poor quality imaging data (3 SCZ, 4 SCZ-SIB, 1 CON, and 3 SCN).

ANOVA, analysis of variance; CON, healthy control subjects; CON-SIB, siblings of healthy control subjects; HSD, honestly significant difference; IQ, intelligence quotient; SCZ, individuals with schizophrenia; SCZ-SIB, siblings of individuals with schizophrenia.

^aSymptom scores are reported in Z scores relative to the mean of the entire sample. See Methods and Materials for details. One-way ANOVAs comparing the four groups on each of these three symptom domains indicated significant group differences for positive [$F(3,85) = 29.16, p < .001$], negative [$F(3,85) = 39.77, p < .001$], and disorganization [$F(3,85) = 17.68, p < .001$] symptoms.

^bPost hoc contrasts using Tukey's HSD indicated that the SCZ participants had higher scores on all three symptom domains, with no significant differences among the remaining groups.

^cCognitive scores are reported in Z scores relative to the mean of the entire sample. See Methods and Materials for details. One-way ANOVAs comparing the four groups on each of these four cognitive domains indicated significant group differences for IQ [$F(3,85) = 5.47, p < .001$], working memory [$F(3,85) = 13.57, p < .001$], episodic memory [$F(3,85) = 18.57, p < .001$], and executive function [$F(3,85) = 13.24, p < .001$].

^dPost hoc contrasts using Tukey's HSD indicated that the SCZ participants had worse performance in all four cognitive domains than CON and CON-SIB.

^eSCZ-SIB showed a trend for reduced performance on episodic memory ($p < .10$).

^fSCZ-SIB performed worse than CON and CON-SIB on executive function.

Although functional connectivity within a given network is clearly important to understanding how network impairments may contribute to disease states, relationships among these networks may be equally important. Changes in how networks integrate and segregate from one another are an important feature of cognitive development (16,27,28). For example, impaired neurodevelopmental processes in schizophrenia (e.g., impaired synaptic plasticity, white matter development, or neural migration [6]) could lead to disruptions in the interactions across as well as within brain networks. However, to date, only a few studies have provided data relevant to this hypothesis.

Shen *et al.* (29) found that reduced connectivity between a range of frontal/cingulate regions and the cerebellum contributed most strongly to discriminating individuals with schizophrenia from control subjects in an unsupervised learning classifier. Zhou *et al.* (26) found a reduced negative correlation between dorsolateral prefrontal cortex and the precuneus (part of the DMN) among the individuals with schizophrenia compared with control subjects. Similarly, Zhou *et al.* (30) found altered connectivity between a task-negative network (overlapping with the DMN) and a task-positive network (both FP and CO regions) in schizophrenia. Jafri *et al.* (31) used independent component analysis to identify seven networks in resting state data. One of these networks corresponded to the DMN, and several of the other networks engaged regions involved in the FP and CO networks, as well as additional temporal and subcortical regions. Examination of the

relationships between these networks revealed altered connectivity between the default network and two of the additional networks that strongly overlapped with the FP and CO networks in individuals with schizophrenia.

The goal of the current study was to examine alterations in functional connectivity within and between the DMN, FP, CO, and CER networks to provide further evidence that schizophrenia reflects—at least in part—a disconnection syndrome. We hypothesized that individuals with schizophrenia and their siblings would show evidence of impaired connectivity between networks involved in cognitive control, as well as potentially between cognitive control networks and either or both the DMN and CER networks. We studied both individuals with schizophrenia and their currently nonaffected siblings. We included nonaffected siblings both to address potential confounds associated with medication status (because siblings have never been exposed to antipsychotic medications) and to determine the degree to which changes in connectivity may reflect an endophenotypic marker of risk for psychosis versus a marker of manifest illness.

Methods and Materials

Participants

The participants (Table 1) for this study were recruited through the Conte Center for the Neuroscience of Mental Disorders at Wash-

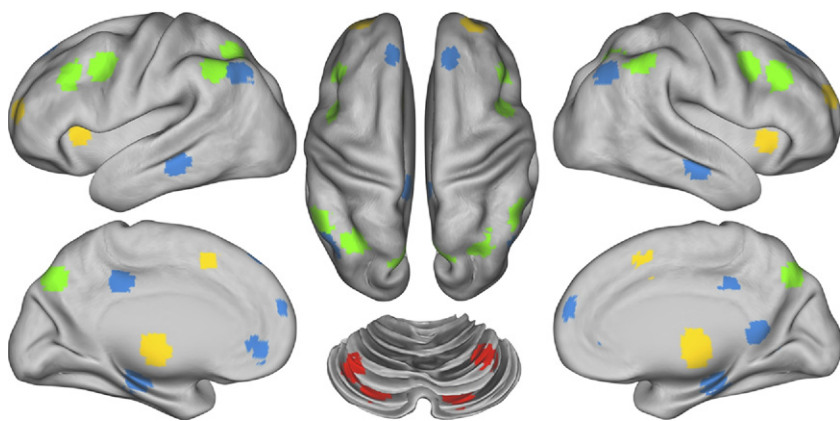


Figure 1. Figure illustrating the location of regions within each of the four networks. Regions of the frontal-parietal network are marked in green, the cingulo-opercular network in yellow, the default mode network in blue, and the cerebellar network in red.

ington University School of Medicine in St. Louis and included: 1) probands who were individuals with DSM-IV schizophrenia (SCZ; $n = 25$); 2) the nonpsychotic siblings of individuals with schizophrenia (SCZ-SIB; $n = 31$); 3) healthy control subjects (CON; $n = 15$); and 4) the siblings of healthy control subjects (CON-SIB; $n = 18$). Siblings were full siblings, based on self-report. All participants gave written informed consent for participation.

All subjects were diagnosed on the basis of a consensus between a research psychiatrist who conducted a semistructured interview and a trained research assistant who used the Structured Clinical Interview for DSM-IV Axis I Disorders (32). Participants were excluded if they: 1) met DSM-IV criteria for substance dependence or severe/moderate abuse during the prior 6 months; 2) had a clinically unstable or severe medical disorder; 3) had a history of head injury with documented neurological sequelae or loss of consciousness; or 4) met DSM-IV criteria for mental retardation.

The individuals with schizophrenia were all outpatients and had been stabilized on antipsychotic medication for at least 2 weeks. Control subjects were required to have no lifetime history of Axis I psychotic or mood disorders and no first-degree relatives with a psychotic disorder. Potential SCZ-SIB subjects were excluded if they had a lifetime history of any DSM-IV Axis I psychotic disorder but not other DSM-IV Axis I disorders. The CON-SIB subjects were enrolled in an identical manner to SCZ-SIB subjects and met the same general and specific inclusion and exclusion criteria.

Clinical and Cognitive Assessments

Psychopathology and cognitive function were assessed as previously described (33,34) and as described in Supplement 1. Scores for each symptom domain and each cognitive domain are shown in Table 1.

Functional Magnetic Resonance Imaging Scanning

All scanning occurred on a 3T TimTrio Scanner (Siemens, Erlangen, Germany) at Washington University Medical School. Functional images (blood oxygenation level-dependent [BOLD]) were acquired using an asymmetrical spin-echo, echo-planar sequence (T2*) (repetition time = 2500 msec, echo time = 27 msec, field of view = 256 mm, flip = 90°, voxel size = $4 \times 4 \times 4$ mm). Data were acquired from each participant for two BOLD runs in which participants rested quietly with their eyes closed. Each run contained 164 images, for a total of 328 images, and 13.7 minutes of resting state activity. In addition, a T1 structural image was acquired using a sagittal magnetization prepared rapid gradient echo three-dimensional (3-D) sequence (repetition time = 2400 msec, echo time = 3.16 msec, flip = 8°; voxel size = $1 \times 1 \times 1$ mm).

Functional Connectivity Magnetic Resonance Imaging Data Preprocessing

Data preprocessing included: 1) compensation for slice-dependent time shifts; 2) removal of first five images from each run during which BOLD signal was allowed to reach steady state; 3) elimination of odd/even slice intensity differences because of interpolated acquisition; 4) realignment of data within and across runs to compensate for rigid body motion (35); 5) intensity normalization to a whole brain mode value of 1000; 6) registration of the 3-D structural volume (T1) to the atlas representative template in the Talairach coordinate system (36) using a 12-parameter affine transform; and 7) co-registration of the 3-D functional magnetic resonance imaging volume to the structural image and transformation to atlas space using a single affine 12-parameter transform that included a resampling to a 3-mm cubic representation. In addition, before performing functional connectivity magnetic resonance imaging (fcMRI) analyses, all raw time series BOLD images were further preprocessed to remove baseline and possible sources of spurious correlations, as outlined in Supplement 1. Each of the two BOLD runs was preprocessed independently; the two runs were then concatenated into a single time series before fcMRI analyses. The initial BOLD preprocessing was accomplished using inhouse software; fcMRI preprocessing and analyses described below were performed using custom MATLAB (The Mathworks, Natick, Massachusetts) code. See Supplement 1 for signal-to-noise ratio analyses.

Network Region Definition

We examined regions included in the DMN as defined by Fox *et al.* (9) and regions included in the FP, CO, and CER networks as defined by Dosenbach *et al.* (14). To control for individual anatomical variability, regions of interest (ROIs) were defined for each individual in two steps. First, we created spherical ROIs in standard Talairach space centered on the reported coordinates for each region (Figure 1; Table S1 in Supplement 1) and 15 mm in diameter. Second, we masked the resulting group ROIs with the individual FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>; version 4.1) segmentation of high-resolution structural image that was previously registered to standard Talairach space, excluding any voxels within the group-defined ROIs that did not represent the relevant gray matter in the specific individual. We extracted the time series for each of these ROIs and computed the ROI-ROI correlation matrix for all ROIs for each participant. We estimated group-level statistical significance by converting individual correlations to Fisher z values using Fisher r -to- z transformation and used these as the dependent measure.

Data Analysis

We computed the average connectivity (mean Fisher z value) across all ROI-ROI connections within each of the four networks and computed the average connectivity across all ROI-ROI connections between each network. We denoted within-network averages as wDMN, wFP, wCO, and wCER and between-network connectivity averages as bDMN-FP, bDMN-CO, bDMN-CER, bFP-CO, bFP-CER, and bCO-CER. We used separate repeated measures analyses of variance (ANOVAs) to compare the groups on within- and between-network connectivity using these overall measures. We then conducted secondary analyses, using false discovery rate (FDR) to control for multiple comparisons, examining connectivity of each region within a network to its own network and to the other three networks. For the sake of brevity, we do not report main effects or interactions that do not include group. We also conducted analyses that included hemisphere as a factor. This did not change the results reported below and are presented in Supplement 1.

Results

Within-Network Connectivity

The within-network ANOVA included diagnostic group and sibling type as between-subject factors and network as a within-subject factor. This ANOVA revealed a trend level main effect of diagnostic group [$F(1,85) = 3.34, p = .07$], which reflected slightly lower within-network connectivity among SCZ and SCZ-SIB compared with CON and CON-SIB (Figure 2). We next examined whether specific regions within any of the networks showed reduced connectivity with its own network. To do so, we computed, for each region in a network, the average connectivity between it and all other regions in the network. We then used an FDR correction for multiple comparisons within each network. None of the individual regions within any of the networks showed significantly reduced connectivity among SCZ and/or SCZ-SIB.

Between-Network Connectivity

Next, we examined between-network connectivity using the same analysis approach. This ANOVA revealed a highly significant main effect of diagnostic group [$F(1,85) = 14.58, p < .001$] and network [$F(5,425) = 32.23, p < .001$], as well as a significant interaction between diagnostic group and network [$F(5,425) = 5.76, p < .001$], but no significant three-way interaction between network, diagnostic group, and sibling type [$F(5,425) = .57, p > .70$]. As shown in Figure 3, the interaction was driven by the fact that the SCZ and SCZ-SIB showed significantly reduced connectivity between the CO and FP, the CO and CER, and the FP and CER networks

but did not show reduced connectivity between the DMN and any other network.

We were interested in examining whether the reduced connectivity between the CO, FP, and CER networks was a general property of all regions within these networks or specific to some regions. To address this question, we computed the average connectivity of each region within a network with all the regions in another network (e.g., the average connectivity of the right dorsolateral prefrontal cortex within the FP with all regions of the CO or with all regions of the CER). We again used FDR to correct for multiple comparisons.

Frontal-Parietal Network. Within the FP network (Figures S1A and S1B in Supplement 1), the right intraparietal sulcus region showed significantly reduced connectivity with the CO network among SCZ and SCZ-SIB ($p = .001$). In addition, bilateral intraparietal sulcus and inferior parietal lobe regions, as well as the left dorsolateral prefrontal cortex, all showed reduced connectivity with the CER network (all p 's $< .008$). No FP regions showed significantly reduced connectivity with the DMN network among SCZ and SCZ-SIB (Figure S2A in Supplement 1).

Cingulo-Opercular Network. Several regions (Figures S1A and S1B in Supplement 1) within the CO network showed reduced connectivity with the FP network in SCZ and SCZ-SIB, including bilateral frontal operculum ($p = .003$) and left anterior thalamus ($p = .008$). In addition, several regions showed reduced connectivity with the CER network among SCZ and SCZ-SIB, including dorsal anterior cingulate cortex ($p = .009$), bilateral anterior thalamus (both $p < .001$), and left anterior prefrontal cortex ($p = .002$). Again, no regions within the CO network showed altered connectivity with the DMN network among SCZ or SCZ-SIB (Figure S2B in Supplement 1).

Cerebellar Network. All but one CER region (right inferior colliculus, Figure S3 in Supplement 1) showed reduced connectivity with the FP network in SCZ and SCZ-SIB (all $p < .007$), and all four CER regions showed reduced connectivity with the CO network in SCZ and SCZ-SIB (all $p < .002$). In contrast, none of the CER regions showed reduced connectivity with the DMN among SCZ or SCZ-SIB.

Default Mode Network. Only two DMN regions (cerebellar tonsils and posterior cingulate) showed reduced connectivity with the CO network among SCZ and SCZ-SIB ($p < .003$; Figure S4 in Supplement 1). No DMN regions showed reduced connectivity with either the FP or the CER networks among SCZ or SCZ-SIB.

Local versus Distal Connections

The analyses presented above focused on within- and between-network connectivity. However, one might argue that this distinc-

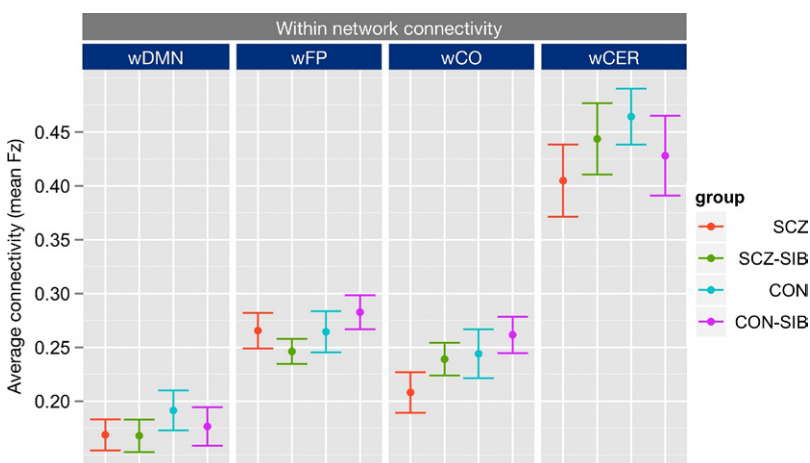


Figure 2. Graph illustrating within-network connectivity in each of the four groups. Segments marked in blue indicate networks for which group differences did not reach statistical significance. CER, cerebellar network; CO, cingulo-opercular network; CON, healthy control subjects; CON-SIB, siblings of healthy control subjects; DMN, default mode network; FP, frontal-parietal network; SCZ, individuals with schizophrenia; SCZ-SIB, siblings of individuals with schizophrenia; w, within.

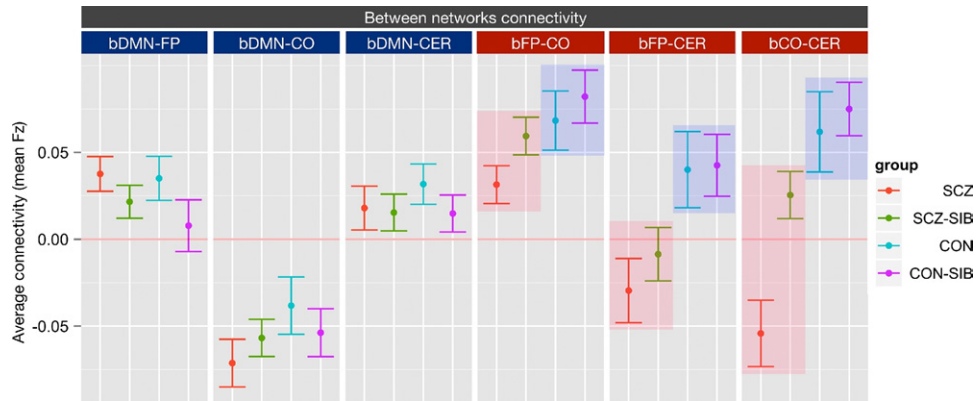


Figure 3. Graph illustrating between-network connectivity in each of the four groups. Segments marked in red indicate networks for which connectivity measures showed significant diagnostic group differences. For those networks, the shaded boxes delineate the diagnostic groups (pink = individuals with schizophrenia and their siblings; purple = healthy control subjects and their siblings). Segments marked in blue indicate networks for which group differences did not reach statistical significance. b, between; CER, cerebellar network; CO, cingulo-opercular network; CON, healthy control subjects; CON-SIB, siblings of healthy control subjects; DMN, default mode network; FP, frontal-parietal network; SCZ, individuals with schizophrenia; SCZ-SIB, siblings of individuals with schizophrenia.

tion could be biased by the distance between regions within networks versus between networks. Thus, we divided connections between all the regions in all four networks into five categories: 1) between homologous regions; 2) within the same network and within the same lobule (within-local); 3) between different networks but within the same lobule (between-local); 4) within the same network but between different lobules (within-distal); and 5) between different networks and different lobules (between-distal).

We analyzed these data using diagnostic group and sibling type as between-subject factors and network type (between, within) and lobule (local, distal) as within-subject factors, ignoring the homologous connections. This analysis revealed a significant three-way interaction between diagnostic group, network type, and lobule [$F(1,85) = 12.92, p < .001$]. To parse this interaction, we conducted ANOVAs with diagnostic group and sibling type as factors for each of the four connection types. These analyses indicated a significant main effect of diagnostic group for both between-local [$F(1,85) = 4.18, p < .05$] and between-distal [$F(1,85) = 13.75, p < .001$] connections but no significant effects of diagnostic group for either within-local [$F(1,85) = .74, p > .35$] or within-distal [$F(1,85) = 2.28, p > .10$] connections. Interestingly, the source of these main effects of diagnostic group differed for between-local versus between-distal connections. The SCZ and SCZ-SIB (Figure S5 in Supplement 1) showed reduced connectivity for between-distal connections but increased connectivity for between-local connections.

Relationship to Clinical and Cognitive Variables

We conducted hierarchical regressions for the three network connectivity metrics that differed between groups (bFP-CO, bFP-CER, bCO-CER), predicting our cognitive and clinical measures (Table 1). In step 1, we entered categorical variables for group status. In step 2, we entered the connectivity measures. In step 3, we entered interaction terms between group status and the connectivity measures to determine if there were group differences in the relationship between that connectivity measure and the dependent variable. To protect against false-positives, we used $p < .01$. For bFP-CO and bCO-CER connectivity, there were no significant increases in variance accounted for by adding the connectivity measures in step 2 (Table 2). However, for bFP-CER, the increase in variance accounted for in step 2 was significant for all four cognitive measures, with greater connectivity predicting better performance (Table 2).

Step 3 was not significant for any of the cognitive measures, with the scatter plots visually confirming a similar relationship between bFP-CER and cognitive performance in all groups (Figure S6 in Supplement 1). In addition, bFP-CER connectivity accounted for a significant increase in explained variance in disorganization symptoms in step 2, with greater connectivity associated with less disorganization (Table 2). However, step 3 was also significant ($p < .01$), indicating a significant group difference in the relationship between bFP-CER connectivity and disorganization symptoms. Follow-up correlations conducted for each group revealed a significant negative correlation in the SCZ ($r = -.48, p < .05$) but not in SCZ-SIB ($r = -.07, p > .2$), CON ($r = -.35, p > .2$), or CON-SIB ($r = -.32, p > .19$). See Supplement 1 for additional mediation analyses.

Discussion

The goal of the current study was to examine differences in functional connectivity within and between known brain networks in patients with schizophrenia and their unaffected siblings to test the hypothesis that schizophrenia involves disruptions in the coordinated activity of brain regions. Our results suggest that both individuals with schizophrenia and their siblings have impaired brain connectivity and

Table 2. Beta Coefficients Describing the Relationship Between Connectivity Measures and Clinical and Cognitive Variables

	Connectivity Type		
	FP to CO Connectivity	FP to CER Connectivity	CO to CER Connectivity
Cognitive Domains			
IQ	β -.07	β .28 ^a	β .14
Working memory	-.10	.35 ^b	.16
Episodic memory	-.11	.25 ^a	.11
Executive function	-.04	.32 ^b	.24
Clinical Domains			
Positive symptoms	-.01	-.04	-.07
Negative Symptoms	.03	-.09	-.05
Disorganization	-.01	-.26 ^a	-.21

CER, cerebellar network; CO, cingulo-opercular network; FP, frontal-parietal network; IQ, intelligence quotient.

^a $p < .01$.

^b $p < .001$.

that these impairments are most prominent between networks compared with within networks. The presence of these abnormalities in the siblings of individuals suggests that they are not due to treatment and other secondary environmental factors. Importantly, the strength of connectivity between the FP and CER networks was associated with better cognitive function across all domains in all groups and was associated with fewer disorganization symptoms among the patients with schizophrenia. These findings suggest that the observed differences in connectivity have important functional implications for patients with schizophrenia.

The FP, CO, and CER network are thought to be key networks involved in cognitive control, task set maintenance, and error processing (14,15,17). We did not find that individuals with schizophrenia and their siblings showed impaired connectivity within these networks but did show impairments in the connectivity across networks. These results are consistent with a number of prior studies that also found reduced connectivity between regions in CO, FP, and CER networks (26,29), though they differ from those studies that also found reduced connectivity between DMN and regions in CO or FP networks (30,31). The fact that impairments in the connectivity between the FP and CER networks consistently predicted cognitive performance across domains and across groups further speaks to the importance of these networks for a range of cognitive processes and the need to evaluate the functionality of the networks as whole and not just individual regions. Further, the finding that the CER network was involved in these disruptions is consistent with previous suggestions that cognitive impairments in schizophrenia reflect deficits in cortical-subcortical-cerebellar circuits (7). Although the precise contribution of the CER to higher level cognition is not yet clear, it has been speculated that the CER may play a key role in learning from errors and in the timing and sequencing of a range of cognitive functions (37–42). Thus, disruptions in the coordination of CER activity with other networks may have major implications for impairments in cognitive adaptation and coordination in schizophrenia.

Interestingly, although we found evidence for decreases in average between-network connectivity for some of the networks, these decreases were primarily driven by reductions in between-network connectivity for more distal (across lobule) connections, with contrasting evidence of increased connectivity for more local connections. This combination resulted in decreased average between-network connectivity because of the higher number of distal versus local connections in these analyses. These results are intriguing from the perspective of hypotheses about the cellular mechanisms that may underlie disrupted connectivity in schizophrenia. For example, Stephan *et al.* (6) argued that such disconnection in schizophrenia could arise from disruptions in the wiring of association fibers during the course of brain development (43–46) and/or impaired synaptic plasticity. There is now a growing body of research on the normative development of the FP, CO, and CER networks, which suggests that development proceeds from what has been described as a local to distributed fashion (16,27). In other words, normative development is characterized by a decrease in correlation strength among spatially close brain regions (local) and an increase in correlation strength between spatially distant brain regions (distal). As such, the patterns of altered connectivity in schizophrenia could reflect—at least in part—alterations in the normative development of connectivity among these networks that results in stronger local, but reduced distal, connectivity. However, we should note that these patterns of altered local and distal connectivity in schizophrenia were only present for between-network connections. In the developmental literature, the progression of local to distributed changes occurred both within and between networks. This suggests that additional processes or mechanisms that specifically influence the coordination of activity across networks may be altered in schizophre-

nia. For example, one speculative hypothesis is that the interactions among networks may develop later than connectivity within networks, potentially occurring during the pubertal period. If so, connectivity between networks could potentially be susceptible to greater disruption by the processes or mechanisms that may be contributing to the increased risk for schizophrenia that seems to arise through the course of puberty.

Surprisingly, we did not find evidence for disrupted connectivity within or with the DMN. While there is evidence for altered DMN connectivity in schizophrenia, prior findings have been mixed (18–24). It is possible that factors such as stage of illness may influence these variable results. Our patients were relatively young and early in the course of illness compared with patients in a number of the studies that did find altered DMN connectivity (18,20,21,31). This raises the possibility that altered DMN connectivity may evolve as a function of extended experience with altered internal experiences. However, we should note that the findings of Whitfield-Gabrieli *et al.* (18) (enhanced DMN connectivity in schizophrenia) are not consistent with this suggestion, given the young age of their sample.

The current study had several limitations. First, the individuals with schizophrenia were medicated, and there is some evidence that antipsychotic medications might reduce resting state functional connectivity across neural networks (47). However, the fact that the majority of our results were also present in the siblings of the individuals with schizophrenia—who were not taking any antipsychotic medications—argues against this interpretation. Second, while we suggest that our results may reflect the outcome of disrupted developmental processes, our data are cross-sectional and cannot directly address developmental issues. Third, we could not control for the arousal level of our participants during the resting state scans, and it is possible that arousal levels differed across groups. However, given our focal pattern of connectivity differences across groups, global changes in arousal as a factor contributing to group differences is less likely to be a confounding factor.

In summary, the current study contributes important new information to the body of the literature on the functional significance of brain network connectivity and its impairment in schizophrenia. We found that connections among brain networks thought to be critical for cognitive control were reduced among individuals with schizophrenia and their unaffected siblings and that these reductions were associated with both cognitive impairments and clinical symptoms. These alterations may reflect impairments in the neurodevelopment of these key brain circuits, a hypothesis that remains to be directly tested in longitudinal studies of brain maturation in individuals at risk for the development of the illness.

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Supplementary material cited in this article is available online.

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