General and Specific Functional Connectivity Disturbances in First-Episode Schizophrenia During Cognitive Control Performance

Alex Fornito, Jong Yoon, Andrew Zalesky, Edward T. Bullmore, and Cameron S. Carter

Background: Cognitive control impairments in schizophrenia are thought to arise from dysfunction of interconnected networks of brain regions, but interrogating the functional dynamics of large-scale brain networks during cognitive task performance has proved difficult. We used functional magnetic resonance imaging to generate event-related whole-brain functional connectivity networks in participants with first-episode schizophrenia and healthy control subjects performing a cognitive control task.

Methods: Functional connectivity during cognitive control performance was assessed between each pair of 78 brain regions in 23 patients and 25 control subjects. Network properties examined were region-wise connectivity, edge-wise connectivity, global path length, clustering, small-worldness, local efficiency, and global efficiency.

Results: Patients showed widespread functional connectivity deficits in a large-scale network of brain regions, which primarily affected the frontoparietal systems related to cognitive control processes. These connectivity deficits occur in the context of relatively preserved global network organization.

Conclusions: The first episode of schizophrenia is associated with a generalized connectivity impairment affecting most brain regions but that is particularly pronounced for frontal cortex. Superimposed on this generalized deficit, patients show more specific cognitive-control-related functional connectivity reductions in frontoparietal systems. These connectivity deficits occur in the context of relatively preserved global network organization.

Key Words: Complex, executive function, fMRI, graph, psychosis, small world

Cognitive deficits are a core characteristic of schizophrenia (1–3). Although patients typically perform poorly across a range of cognitive domains (4), impairments of cognitive control—the coordination of cognitive resources in support of goal directed behavior—feature prominently (5). These impairments are stable (6,7), present before illness onset (8), and manifest in patients' unaffected relatives (9). Characterizing their neural basis is therefore critical for understanding the pathogenesis of the disorder.

Cognitive control deficits in schizophrenia are associated with abnormal activation of frontal, temporal, parietal, and subcortical regions (10–12). The widespread spatial distribution of these abnormalities suggests that a network-based understanding will provide a useful model of neural dysfunction in schizophrenia. Indeed, most contemporary pathophysiological theories characterize the illness as emerging from disturbed interregional brain connectivity, rather than isolated dysfunction in specific loci (13–16). Several studies have reported disturbances of functional connectivity, defined as the temporal correlation between spatially distributed neurophysiologic signals (17), in schizophrenia across a range of experimental paradigms, with frontotemporal and frontoparietal systems being the most affected (18–24). However, it is often unclear whether such disturbances are task-specific or reflect a generalized, context-independent dysfunction. Some studies provided evidence for both (23,24,25,26), but these analyses have only been tractable for networks comprising a select few brain regions. To our knowledge, no distinction between general and specific connectivity deficits in schizophrenia has been made at the level of whole-brain networks.

In this study, we adapted a beta series correlation technique (27,28) to construct whole-brain, event-related functional connectivity networks in people with first-episode schizophrenia and healthy volunteers performing a cognitive control task (29–31). We characterized general and cognitive control-specific effects of schizophrenia on functional brain connectivity, as well as global properties of network organization quantified using graph analysis (32–34). Following evidence that cognitive control impairments occur against a background of generalized cognitive deficit in schizophrenia (4,5), we hypothesized that patients would show a widespread reduction of functional connectivity, particularly in frontotemporal regions, regardless of task demands, in addition to more circumscribed connectivity reductions specific to cognitive control processes.

Methods and Materials

Participants

Twenty-three patients with schizophrenia (two schizotypal-form) and 25 healthy subjects were recruited from the community (demographic and clinical data are shown in Table 1). Volunteers with schizophrenia were outpatients within the first year of psychosis onset. Participants were evaluated with the Structured Clinical Interview for DSM-IV-TR to confirm diagnosis and exclude illness in control subjects. Patients aged under 16 years underwent the
Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version. Board certified PhD and MD-level clinicians conducted diagnostic evaluations. Diagnoses were confirmed by consensus conference. Psychosis onset was determined by establishing the time at which DSM-IV criteria A and B for schizophrenia were met.

Control subjects were excluded if they had a lifetime Axis I diagnosis or a first-degree relative with a psychotic disorder. Exclusion criteria for all subjects were IQ < 70, drug/alcohol dependence history or abuse in the previous 3 months, positive urine drug screen before testing, significant head trauma, or any known magnetic resonance imaging contraindication. The study was approved by the internal review board at the University of California—Davis.

Cognitive Task
Subjects performed the AX-Continuous Performance Task (35–37). A cue letter was presented for 500 msec, followed by a 3500-msec delay period, and a 500-msec probe letter. Subjects made a target response (right index finger button press) to the probe letter “X” only when it followed the cue letter “A.” All other stimuli required a nontarget response (right middle finger button press), including trials in which X was preceded by any letter other than a (collectively referred to as “B”). Trials with target (AX) cue–probe pairings occurred with 75% frequency, establishing a tendency to make a target response to the probe letter X. BX trials placed the highest demand on cognitive control because subjects had to overcome the tendency to make a target response to X. Trials in which either the A or B cue was followed by a non-X letter (collectively referred to as Y) were also included.

Neuroimaging Methods

Acquisition. Functional scans (T2*-weighted echo-planar imaging, repetition time 2000 msec, echo time = 40 msec, flip angle = 90°, field of view = 22 cm) were acquired using a 1.5-T GE (Waukesha, Wisconsin) scanner. Twenty-four contiguous 4.0-mm axial slices with 3.4 mm² in-plane resolution from 80.0 mm above to 16 mm below the anterior commissure–posterior commissure line were obtained.

fMRI Processing. Initial preprocessing steps, implemented in Automated Image Registration software (http://bishopw.loni.ucla.edu/AIR), were slice-time and motion correction, and removal of linear trends and significant time series outliers. The images were then spatially normalized using a nonlinear algorithm and spatially smoothed (8-mm full-width at half-maximum Gaussian kernel) using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software).

To generate measures of event-related functional connectivity (27,28), we modeled every cue and probe event with a unique delta function, convolved with a canonical hemodynamic response function, using SPM5. All events were modeled, but only cue events for correct trials were included in the analysis, because these represented trial periods in which cognitive control demands were maximized. Subjects who committed no errors had 160 trials (128 A cue; 32 B cue). Separate regressors modeling each event were defined in a general linear model to yield 128 unique A cue and 32 unique B cue beta values for every voxel. Each beta value reflected the magnitude of the hemodynamic response evoked by each event. The beta values were then sorted by condition (i.e., A cue or B cue) and concatenated to generate a beta series for each condition. We then parcellated each participant’s brain into discrete regions of interest to represent network nodes (19,38,39) using an anatomic atlas (40). Regions with less than 25% brain coverage were excluded, yielding 78 anatomic regions (Table S1 in Supplement 1). Pairwise Pearson correlations between regional mean beta series were computed to generate a (78 × 78) functional connectivity matrix for each participant and each task condition (A or B cue). These correlations between regional beta series reflected correlated variations in hemodynamic responses evoked by each task condition. An overview of our method is provided in Figure 1 (see Section S1 in Supplement 1 for further details).

Table 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 25)</th>
<th>Schizophrenia (n = 23)</th>
<th>χ²/t, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female (n)</td>
<td>13/12</td>
<td>14/9</td>
<td>.38, .54</td>
</tr>
<tr>
<td>Age (years)</td>
<td>22.12 (3.92)</td>
<td>20.45 (4.36)</td>
<td>1.40, .17</td>
</tr>
<tr>
<td>Wechsler Abbreviated Scale of Intelligence—Intelligence Quotient</td>
<td>113.43 (9.25)</td>
<td>100.91 (12.07)</td>
<td>3.92, &lt;.001</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.94 (3.19)</td>
<td>12.09 (2.59)</td>
<td>3.33, .002</td>
</tr>
<tr>
<td>Parent Education (years)</td>
<td>14.68 (2.31)</td>
<td>15.02 (2.02)</td>
<td>−.53, .60</td>
</tr>
<tr>
<td>Scale for the Assessment of Negative Symptoms Total</td>
<td>7.59 (3.96)</td>
<td>7.05 (3.40)</td>
<td></td>
</tr>
<tr>
<td>Scale for the Assessment of Positive Symptoms Total</td>
<td>7.05 (3.40)</td>
<td>44.36 (10.54)</td>
<td></td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale Total</td>
<td>10.33 (2.57)</td>
<td>10.33 (2.57)</td>
<td></td>
</tr>
<tr>
<td>Strauss Carpenter Outcome Scale Total</td>
<td>51.14 (10.30)</td>
<td>51.14 (10.30)</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical</td>
<td>13</td>
<td>14/9</td>
<td>.38, .54</td>
</tr>
<tr>
<td>Typical</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Antidepressant</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unmedicated</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Age range for control subjects was 16 to 32 years; for patients, it was 14 to 30 years.
 Figure 1. Schematic overview of the analysis strategy. The analysis could be divided into four broad steps. First, a unique regressor was generated for every event, and event-specific evoked responses were estimated using a general linear model. The result was a map of $\beta$ coefficients for each event, representing the degree to which each voxel’s activity was modulated by that event. Second, these event-specific $\beta$ maps were sorted into different task conditions (cue A shown in blue, cue B shown in red) and concatenated to generate a condition-specific pseudo–time series of $\beta$ coefficients (i.e., a $\beta$ series) at each voxel. Third, an anatomic template was used to parcellate the brain in 78 regions. The mean $\beta$ series of each region was extracted, and correlations between every possible pair of regional beta series were computed to generate a $(78 \times 78)$ functional connectivity matrix for each participant and each task condition. Fourth, network connectivity and topology were analyzed using graph-based representations of network structure. Network connectivity was analyzed using the values in the correlation matrix. Edge-wise connectivity ($E_{ij}$) reflected the strength of the correlation for each value in the functional connectivity matrix. For example, in the connectivity matrix shown, $S_{12}$ for the connection between region of interest (ROI) 1 and ROI 2 would be .33. Region-wise connectivity ($S_{R}$) was computed as the sum of each region’s correlation values. For example, $S_{R}$ for ROI 1 is computed as the sum of its correlation values with all other regions. Topologic measures were computed using graph-based representations of network structure as detailed in the main text and Section S.2 in Supplement 1. In the graph-based representation shown, each region is represented as a blue circle plotted according to the stereotactic coordinates of its centroid. Each connection, or edge, is represented as a red line and represents a suprathreshold correlation between regional beta series. The graph has been overlaid on a cortical surface rendering to provide an orientation with respect to approximate anatomical location.

Statistical Analyses

Behavioral data were analyzed in PASW Statistics v. 18 (IBM, Somers, New York) using multivariate analysis of variance with diagnosis and trial type (i.e., AX, AY, BX, BY) as factors. For the neuroimaging data, for each network property analyzed ($S_{Ri}$, $S_{R}$, $\lambda$, $\gamma$, $\sigma$, and $\sigma$), main effects of cue (A or B cue), diagnosis, and their interaction, were modeled using analysis of variance. Empiric $p$ values were estimated using permutation methods suitable for factorial designs (42,43). We performed 5000 permutations for each analysis.

Regional connectivity effects were corrected for multiple comparisons using a false-positive adjustment, $1/N = .013$, where $N$ = the number of comparisons, which implies that, on average, there was $\leq 1$ false positive per analysis (19,44). Edge-wise connectivity effects were characterized using the network-based statistic (45). To compute the network-based statistic, an analysis of variance was fitted to each of the $(N^2 - N)/2 = 3003$ edges (correlation values) in the $(78 \times 78)$ functional connectivity matrix, yielding a $p$ value matrix representing the probability of rejecting the null hypothesis for each effect at each edge. A component-forming threshold, $K$, was applied to each $p$ value matrix, and the size of each connected component in these thresholded matrices was computed. A connected component represents a subnetwork of edges that can be linked to each other via suprathreshold connections. The size of the observed components was compared with a null distribution of maximal component sizes obtained through permutation testing to obtain component-wise $p$ values corrected for multiple comparisons (46). The method identifies connected subnetworks of edges showing a particular effect of a size larger than would be expected by chance (see Zalesky et al. for details and validation) (45). Here, we report results for $k = .005$ (i.e., retaining only edges with $p < .005$). Results obtained at higher ($k = .01$) and lower ($k = .001$) values are provided in Figure S2 in Supplement 1 to illustrate sensitivity to parameter settings.

Results

Behavioral Analysis

Analysis of performance accuracy revealed significant main effects of diagnosis [$F(1,46) = 8220.41, p < .001$] and trial type [$F(3,44) = 19.30, p < .001$], as well as a diagnosis $\times$ trial type interaction [$F(3,44) = 2.41, p = .01$; Figure 2]. Bonferroni-adjusted post hoc testing revealed that patients were significantly less accurate for BX trials ($t(28.44) = 3.60, p = .004$, corrected) but not for other conditions ($p > .10$), suggesting a specific deficit for trials requiring cognitive control. For averaged reaction time (RT), we found significant effects of diagnosis [$F(1,46) = 612.55, p < .001$] and trial type [$F(3,44) = 108.75, p < .001$]. The diagnosis $\times$ trial type interaction [$F(3,44) = 5.00, p = .004$], while significant, was smaller than the diagnosis effect [$F(1,46) = 612.55, p < .001$] and did not reach significance in post hoc comparisons. These results support the hypothesis of an interaction between cognitive control and diagnosis.
interaction trended towards significance \(F(1,44) = 2.75, p = .054; \) Figure 2].

**Functional Connectivity Analysis**

**Region-Wise Connectivity.** Regional main effects of cue surviving false-positive correction were found in 14 regions, localized to bilateral hippocampi, subgenual cingulate cortices, lingual and angular gyri; temporal poles; left amygdala, angular and posterior cingulate gyri; and right middle frontal gyrus (Figure 3, top row; Table S1 in Supplement 1). At uncorrected levels, there was more extensive involvement of left posteromedial and midcingulate cortices, right lateral parietal cortex, and bilateral orbitofrontal regions. For all regions, functional connectivity was increased during B cue trials. These findings reflected significant effects of cognitive control on regional functional connectivity that were common to patients and control subjects.

Regional main effects of diagnosis were widespread and in each case reflected reduced functional connectivity in patients (Figure 3, bottom row). At uncorrected levels, the reductions were significant in 50% of regions \(n = 39\). These effects survived false-positive correction in \(\sim 20\%\) of regions \(n = 16; \) Table S1 in Supplement 1).

Significant effects were distributed bilaterally, primarily localizing to frontal, temporal, and parietal areas, with an additional reduction in left visual cortex. These findings reflected generalized, context-independent connectivity reductions in patients that were apparent in both task conditions. No cue-by-diagnosis interaction effects survived false-positive correction.

**Edge-Wise Functional Connectivity.** For the main effect of cue, one connected component, comprising 56 edges connecting 42 regions, was statistically significant \(p < .001, \) corrected; Figure 4, top left). For all but one edge in this subnetwork, connectivity increased in the more difficult B cue condition. Functional connectivity of right medial temporal regions showed particularly pronounced effects (29 hippocampal and 14 amygdala connections).

To better understand the regional distribution of these connections, we classified each region as belonging to one of five broad lobar subgroupings: frontal, temporal, parietal, occipital, or subcortical. We then categorized each edge in the affected subnetwork on the basis of the lobes they connected (e.g., frontotemporal, temporoparietal, etc.) and counted the proportion of edges falling into each category. Most connections showing a significant effect of cue

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**Figure 2.** Mean accuracy (left) and reaction time (right) of patients and control subjects in each task condition. Error bars represent standard deviations. *\(p < .05\), corrected.

**Figure 3.** Brain regions showing significant main effects of cue (top row) and diagnosis (bottom row). Main effects of cue reflected increased functional connectivity in the more difficult B cue condition; main effects of diagnosis reflected reduced functional connectivity in patients compared with control subjects. Effects surviving false-positive correction for multiple comparisons are shown in yellow; those significant at \(p < .05\), uncorrected are shown in red.

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were frontotemporal (36%) or temporosubcortical (25%; Figure 4, bottom left). Similar findings were obtained across different values of K (Figure S2 in Supplement 1).

For the main effect of diagnosis, one component comprising 200 edges connecting 54 regions was significant (p < .001, corrected; Figure 4, top middle). For all edges, functional connectivity was reduced in schizophrenia patients. The most affected regions included bilateral hippocampi, middle temporal, and lateral prefrontal cortex. Most of these connections linked frontal cortex to posterior regions: 34% were frontotemporal, and 20% were fronto-parietal (Figure 4, bottom middle). Most of the remaining connections were either temporoparietal (18%) or occipitotemporal (10%). Similar findings were obtained across different values of K (Figure S2 in Supplement 1).

One connected component, comprising seven edges connecting eight regions, demonstrated a significant main effect of cue-by-diagnosis interaction (p = .042, corrected; Figure 4, top right). Approximately two thirds of these involved frontal regions: 29% were frontofrontal and 29% were frontoparietal. For each edge, control subjects showed a B cue > A cue task effect on connectivity, whereas patients showed the reverse pattern (Figure S3 in Supplement 1). These findings were not significant for k = .01 or k = .001.

To examine medication effects, we compared S values between patients on or off antipsychotics for each of the 200 edges implicated in the subnetwork showing a diagnosis main effect. Only 26 edges (13%) showed significant effects at p < .05 uncorrected, and no differences survived multiple comparison correction. None of these edges were part of the subnetwork showing a significant diagnosis × cue interaction.

Correlations Between Brain Connectivity and Behavior

To assess the relationship between functional connectivity and patients’ cognitive control performance deficits, we focused on the subnetwork showing a significant cue-by-diagnosis interaction. Because these seven edges specifically showed a cognitive-control-related functional connectivity deficit in schizophrenia patients, we reasoned that they were the most relevant for understanding patients’ cognitive control impairments. For each edge, we defined a cognitive-control-related connectivity index as the normalized difference between B cue and A cue connectivity:

$$\frac{[S_{E,i}(B) - S_{E,i}(A)]}{[S_{E,i}(B) + S_{E,i}(A)]},$$

where $S_{E,i}$ refers to the edge-wise connectivity values for edge i during A cue and B cue trials, respectively. Positive values on this scale reflect greater connectivity during trials requiring cognitive control (i.e., B > A cue). Similarly, we derived a behavioral measure of cognitive control as the normalized difference between BX and AX trial accuracy and RT [i.e., (BX - AX)/(BX + AX)]. For the accuracy scale, higher values reflect better cognitive control performance (i.e., relatively more accurate responses); for the RT scale, higher values reflect poorer cognitive control performance (i.e., relatively slower responding).
The RT cognitive control measure was significantly and specifically correlated with cognitive-control-related functional connectivity in one edge, linking right midcingulate and superior frontal regions (i.e., R Mid Cing and R Fron Sup in Figure 4) in control subjects (p = .026) but not patients (p = .689; Figure 5). This effect did not survive Bonferroni correction for seven comparisons (p = .007). There were no significant correlations between functional connectivity and cognitive control accuracy. There were no significant associations between connectivity measures and symptom ratings or IQ.

Network Topology Analysis

Group means and key statistical findings for each topological measure studied are presented in Table 2. The only significant effects on network topology were main effects of cue for F, E, reflecting a reduction in both during B cue trials.

Discussion

Schizophrenia is often characterized as a disorder of aberrant brain connectivity, although mapping putative connectivity disturbances at the level of whole-brain circuits, and their relation to cognitive impairments, has proved challenging. We analyzed whole-brain maps of task-related functional connectivity measured during cognitive control performance and found evidence for a widespread disturbance of functional connectivity in people with first-episode schizophrenia, which occurred regardless of task context and which was most pronounced in frontoposterior systems. In addition, we identified a more specific deficit in functional connectivity of frontoparietal regions that was associated with the implementation of cognitive control. Together these findings suggest that schizophrenia is associated with a generalized and widespread functional connectivity deficit upon which are superimposed more specific, context-dependent alterations of interregional functional coupling.

Generalized Functional Connectivity Deficits in Schizophrenia

Our analysis of region-wise functional connectivity revealed widespread and generalized (context-independent) patient deficits localized predominantly to frontotemporal and medial posterior cortices. In addition, our analysis of edge-wise connectivity identified a subnetwork of 200 connections linking nearly 70% of the regions studied in which patients showed a context-independent functional connectivity reduction. More than half of these connections linked frontal cortex with posterior regions. Together these results point to a generalized and pervasive reduction in functional connectivity between frontal and other brain regions in schizophrenia. Our findings are consistent with a wide range of evidence implicating frontal dysfunction as a core feature of schizophrenia pathophysiology (5,10,47–51), and other connectivity studies implicating frontotemporal disturbances in particular (21–23,26,52–56).

Alterations in functional connectivity between frontal cortex and other brain regions has been demonstrated in schizophrenia patients using a variety of techniques, some of which specifically isolated task-dependent connectivity changes (57–59), and others which did not (22,54,56,60). Of these, the only studies that attempted to distinguish between generalized and task-dependent connectivity changes have been those using dynamic causal modeling, which allows assessment of group differences in task-related causal interactions (effective connectivity), as well as so-called endogenous, or context-independent, connectivity, between specific regions of interest (61,62) (Section S1 in Supplement 1). This work has identified altered effective connectivity between frontal and other brain regions at different illness stages of schizophrenia and

Table 2. Summary Statistics for Network Topological Properties as a Function of Cue and Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>Patients</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A Cue</td>
<td>B Cue</td>
<td>A Cue</td>
<td>B Cue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>λ</td>
<td>1.154 (.047)</td>
<td>1.138 (.051)</td>
<td>1.165 (.052)</td>
<td>1.148 (.076)</td>
<td>4.06, .042</td>
<td>.55, .470</td>
<td>&lt;.001, .953</td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>1.773 (338)</td>
<td>1.730 (417)</td>
<td>1.883 (395)</td>
<td>1.798 (322)</td>
<td>1.22, .263</td>
<td>.96, .335</td>
<td>.13, .711</td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>1.488 (299)</td>
<td>1.480 (344)</td>
<td>1.559 (361)</td>
<td>1.534 (312)</td>
<td>.10, .752</td>
<td>.62, .443</td>
<td>.03, .867</td>
<td></td>
</tr>
<tr>
<td>Eσ</td>
<td>.513 (032)</td>
<td>.511 (036)</td>
<td>.519 (032)</td>
<td>.525 (034)</td>
<td>.19, .664</td>
<td>1.27, .259</td>
<td>.69, .405</td>
<td></td>
</tr>
<tr>
<td>E£</td>
<td>.739 (034)</td>
<td>.721 (035)</td>
<td>.743 (030)</td>
<td>.726 (027)</td>
<td>12.57, &lt;.001</td>
<td>.41, .527</td>
<td>&lt;.001, .999</td>
<td></td>
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</tbody>
</table>

Data represent means. Standard deviations are presented in parentheses.

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across a range of paradigms, including those assessing perceptual discrimination (23), memory (25), and cognitive control (26,63), but the most replicated differences have been for the context-independent endogenous connectivity parameters. These results concur with our finding of a widespread and generalized connectivity deficit in schizophrenia, which particularly affects functional integration between frontal cortex and other regions. Measuring connectivity differences across a range of tasks in the same sample will help to clarify precisely how generalized these effects are. Another important question concerns whether these generalized connectivity deficits reflect alterations in underlying anatomical connectivity (64–66). Studies combining fMRI with diffusion-based imaging are necessary to address this question.

Specific, Cognitive-Control-Related Functional Connectivity Deficits in Schizophrenia
Superimposed against a pervasive and generalized functional connectivity deficit, patients showed a specific cognitive-control related connectivity impairment in a subnetwork of seven connections linking eight regions located in frontal and parietal cortex. For each connection in this network, control subjects generally showed increased connectivity in the B cue condition, whereas patients showed the reverse pattern (i.e., A > B cue connectivity). These findings complement and extend prior activation- and connectivity-based studies of the A×C Continuous Performance Task in schizophrenia (27,29,67,68) by characterizing network abnormalities at a whole-brain level and mapping the specific dysfunctional subnetwork associated with cognitive control performance in patients. The importance of frontoparietal dysfunction for understanding cognitive control deficits in schizophrenia is underscored by the convergence of findings between this past work and our own.

Patients’ apparent failure to increase frontoparietal connectivity appropriately in response to the B cue may reflect difficulty recruiting key elements of the neural network required to implement cognitive control. This is consistent with the observed correlations between connectivity and task performance. In control subjects, greater connectivity between dorsal cingulate and prefrontal cortex in the B cue condition was associated with slower B cue RTs. It is thought that dorsal cingulate activity signals the need for engagement of cognitive control processes mediated by lateral prefrontal regions (69–71). This signal typically initiates when task performance elicits conflict. Higher conflict is associated with greater task difficulty and a greater need for strategic control (72,73). One prediction of this view is that cingulofrontal connectivity should be highest when task difficulty is high, indexed by increased conflict and an increased need for cognitive control. Our results accord with this prediction, because healthy individuals who found B trials more difficult, as reflected by relatively slower RTs, showed greater cingulofrontal connectivity during these trials. This association between connectivity and behavior was not present in the patient group, suggesting a breakdown of conflict monitoring and a relative failure to implement cognitive control, evidenced by patients’ significantly lower accuracy rates for BX trials. Together these data suggest that patients did not appropriately alter frontoparietal functional connectivity in response to increased cognitive control demands, resulting in a decoupling of network dynamics from task performance and a relative failure to implement control processes.

We found a significant main effect of task on both region- and edge-wise connectivity in a distributed network of regions incorporating primarily frontal and temporal cortices. These findings are consistent with activation-based studies showing greater prefrontal activation for B relative to A cue trials (27,29,67). In addition, we found strong task effects on connectivity of medial temporal regions, areas that have not been identified as key task-related regions in prior work. This likely reflects the differing sensitivities of beta series connectivity- and activation-based methods. The former are sensitive to task effects on interregional correlations in trial-to-trial variations of task-evoked responses, whereas the latter characterize mean differences in the strength of these responses. Consequently, the two do not always yield convergent findings (28) (Section S1 in Supplement 1).

Topologic Properties
Both patients and control subjects showed increased global integration (i.e., lower normalized path length, L) and reduced local information processing (i.e., lower local efficiency, E_L) in the more difficult B cue condition, suggesting that global properties of brain network organization are responsive to changing task contexts (74). These findings are consistent with evidence that increased global integration of functional brain networks is a marker of adaptive behavior (75,76). The findings were not uniform across other measures of similar topological properties (e.g., we found no effects for E_E or γ), however, and should be interpreted with respect to differences in how these measures are computed (Section S2 in Supplement 1).

We found no group differences in network topology. In contrast, studies of chronic patients have reported differences in a variety of network parameters, during both rest and working memory performance (18,19,77,78). One hypothesis explaining this discrepancy is that, despite showing widespread functional connectivity impairment, patients’ global network topology is relatively intact during a first psychotic episode but subsequently deteriorates with ongoing illness. Longitudinal studies are required to test this postulate.

Limitations
We used an a priori anatomic template to define the network nodes used in our analyses. This approach is widely used in the literature (19,38,39), but the node definitions remain arbitrary. Further work examining the effects of template selection on reported findings will be important to determine their generalizability (79–81). In addition, our analyses suggested that antipsychotics could not account for our case–control differences, although more systematic investigation of medication effects on functional connectivity is required given emerging evidence that connectivity can be modulated by antipsychotic use (82,83).

The main effects on functional connectivity observed in our analyses were robust to different analysis parameter settings. The interaction effect was more sensitive to such variations, suggesting that it may have been present across a more restricted range of network component sizes. In addition, the correlation between connectivity and task performance in control subjects did not survive multiple comparison correction. Replication of these effects in a larger sample is warranted. However, the consistency of our results with past findings, as well as the strength of the connectivity–behavior association (~20% shared variance), suggest that our findings are indeed robust and relevant for understanding the neural basis of cognitive control deficits in schizophrenia.

Conclusions
Cognitive control impairments are regarded as a core feature of schizophrenia, but relatively little is known about the large-scale connectivity abnormalities that give rise to such deficits. Our results suggest that the first episode of schizophrenia is associated with specific cognitive-control-related functional connectivity deficits in a circumscribed network of frontoparietal regions, which occur.
against a background of a more pervasive and generalized impairment affecting the connectivity of frontal regions with the rest of the brain. These connectivity impairments parallel, and may therefore underlie, the profile of general and specific cognitive deficits known to characterize the disorder.

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