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The Anatomical Distance of Functional Connections Predicts Brain Network Topology in Health and Schizophrenia

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The human brain is a topologically complex network embedded in anatomical space. Here, we systematically explored relationships between functional connectivity, complex network topology, and anatomical (Euclidean) distance between connected brain regions, in the resting-state functional magnetic resonance imaging brain networks of 20 healthy volunteers and 19 patients with childhood-onset schizophrenia (COS). Normal between-subject differences in average distance of connected edges in brain graphs were strongly associated with variation in topological properties of functional networks. In addition, a club or subset of connector hubs was identified, in lateral temporal, parietal, dorsal prefrontal, and medial prefrontal/cingulate cortical regions. In COS, there was reduced strength of functional connectivity over short distances especially, and therefore, global mean connection distance of thresholded graphs was significantly greater than normal. As predicted from relationships between spatial and topological properties of normal networks, this disorder-related proportional increase in connection distance was associated with reduced clustering and modularity and increased global efficiency of COS networks. Between-group differences in connection distance were localized specifically to connector hubs of multimodal association cortex. In relation to the neurodevelopmental pathogenesis of schizophrenia, we argue that the data are consistent with the interpretation that spatial and topological disturbances of functional network organization could arise from excessive "pruning" of short-distance functional connections in schizophrenia.

Keywords: brain network, functional connectivity, graph theory, normal development, schizophrenia

Introduction

The human brain is a nonrandom topologically complex network, physically embedded in anatomical space. From a purely "topological" perspective, the brain network is characterized by the pattern of interactions between nodes, without reference to spatial properties such as the physical distances spanned by these interactions. Methods such as graph theory have recently been used to show that brain functional networks have a complex topology, characterized by the existence of both highly connected hubs and densely intraconnected subnetworks (modules) (Bullmore and Sporns 2009; He and Evans 2010). The "anatomical" perspective on network organization, in contrast, focuses on the physical distance between connected brain regions. Dating back to the seminal work of Ramón y Cajal (1899), anatomical studies have suggested that the minimization of connection distance, sometimes called wiring cost, is an important economical principle constraining the brain's organization (Sporns 2010). More generally, it is appreciated that complex networks embedded in physical space will have topological properties that are influenced to varying degrees by the spatial constraints and physical costs entailed in their formation (Barthélemy 2011). However, anatomical and topological perspectives on normal human brain network architecture have not yet been fully reconciled. The interplay between topologically and spatially abnormal aspects of human brain network organization in neurological and psychiatric disorders also remains to be clearly defined. For neurodevelopmental disorders, such as schizophrenia, disturbances of spatial and topological aspects of brain networks in patients should ultimately be related to perturbations of key neurodevelopmental processes such as synaptic pruning (Feinberg 1982, 1983; Gogtay et al. 2004).

Many aspects of brain anatomy have been explained by an economical principle that seeks to minimize connection distance or wiring cost between neurons. Such a principle has been invoked to account for phenomena as diverse as cortical folding (Van Essen 1997), the layout of functional regions within mammalian cortex (Cherniak et al. 2004), and the cellular morphology of neurons (Chklovskii 2004). A model that minimizes the cost of neuronal connections approximates the actual layout of the *Caenorhabditis elegans* nervous system, which currently remains the only nervous system that has been completely mapped at the cellular level of neurons and synapses (Chen et al. 2006). At the coarser spatial scale of human functional magnetic resonance imaging (fMRI), there is evidence that the strength of functional connectivity between regions is greatest for pairs of regions separated by short physical distance and that connectivity strength decays rapidly as the Euclidean distance between brain regions increases (Salvador et al. 2005; Bellec et al. 2006). Likewise, the extent of white matter tract connectivity as measured with diffusion spectrum imaging (DSI) also decays with distance, but the inverse relationship between fMRI and distance is significant even after controlling for the strong association between anatomical connectivity (measured with DSI) and functional connectivity (measured with fMRI) (Honey et al. 2009).

These preliminary observations from neuroimaging suggest that shorter range connections may be preferred in the large scale organization of human brain networks. However, returning to the case of *C. elegans*, recent work has shown that although wiring cost is evidently submaximal, it is not strictly minimized (Kaiser and Hilgetag 2006). Using the computational

technique of component placement optimization, it was possible to rewire the *C. elegans* connectome in silico so that its total wiring length was substantially reduced compared with the natural nervous system. However, the minimally rewired network had longer average path length (or lower global efficiency of information transfer) than the natural system, suggesting that nervous systems may have been selected not simply to minimize wiring cost but rather to optimize some trade-off between cost minimization and the emergence of "expensive" but behaviorally advantageous topological properties (Bassett et al., 2010; Kaiser, 2011; Fornito et al., 2011; Varier and Kaiser 2011).

The wave of topological studies of human brain networks over the last 5 years or so has produced fairly convergent results. Brain networks are typically clustered, modular, robust, highly efficient for information transfer, and have a fat-tailed degree distribution comprising a number of highly connected nodes or hubs (Bullmore and Sporns 2009). The combination of high clustering—meaning that a node's nearest neighbors are likely to be cliquishly connected to each other—and high efficiency—meaning that there is a short path between any pair of nodes—is often referred to as the "small world" property (Watts and Strogatz 1998). This topological profile is broadly conserved both for structural networks, such as those derived from DSI data, and for functional networks, such as those derived from fMRI data, although there is typically not exact correspondence between structural and functional networks (Honey et al., 2007, 2009; Hagmann et al. 2008).

Recent studies have begun to investigate the relationships between topological and spatial aspects of functional brain networks. fMRI studies of the brain's modular community structure have shown that regional nodes belonging to the same topological module are often anatomical neighbors; some modules can comprise nodes that are spatially distant from each other, such as contralaterally homologous regions of cortex in symmetrically distributed modules (Meunier et al. 2010). It has also been shown that different regional nodes may vary in their spatial and topological profile of connectivity to the rest of the network. On average in normal volunteers, it was shown that primary sensory and motor cortical areas have high clustering and predominantly short-distance connections; in contrast, heteromodal cortical areas have short average path length (high efficiency) and predominantly long-distance connections (Sepulcre et al. 2010). However, to our knowledge, no studies have explored normal individual differences in both spatial and topological aspects of fMRI brain network organization nor considered how between-subject variation in connection distance (a spatial property) could explain variation in efficiency, clustering, and other topological properties at global (whole brain) and nodal levels of network analysis.

Schizophrenia has increasingly been conceived as a disorder of brain network connectivity at both the micro scale of the synapse and the whole brain scale of neuroimaging (McGlashan and Hoffman 2000; Stephan et al. 2006). Evidence for abnormal connectivity and topology of functional and anatomical networks has emerged from several recent studies. Brain network organization in schizophrenia is typically less small world, less clustered, less cost efficient, less dominated by hubs, and less hierarchical (Liu et al. 2008; Bassett, Bullmore, Meyer-Lindenberg, et al. 2009; Bassett, Bullmore, Verchinski, et al. 2009; Alexander-Bloch et al. 2010; Lynall et al. 2010; Van den Heuvel et al. 2010). These findings have been summarized as indicating that there is "subtle randomization" of brain network topology in schizophrenia (Rubinov et al. 2009). The most replicated finding is that resting-state fMRI networks in patients with schizophrenia are less clustered (Liu et al. 2008; Alexander-Bloch et al. 2010; Lynall et al. 2010). Reduced network modularity or community structure has also previously been reported in childhood-onset schizophrenia (COS; Alexander-Bloch et al. 2010). Evidence for schizophrenia as a neurodevelopmental disorder (Rapoport et al. 2005), and for age-related changes in the anatomical distance of functional connections (Supekar et al. 2009; Fair et al. 2009), motivates the hypothesis that abnormal adolescent brain development in COS is associated with formation of anatomically, as well as topologically, abnormal brain functional networks. Abnormally increased connection distance between nodes in anatomical brain networks constructed from gray matter volume data on patients with schizophrenia has previously been reported Bassett, Bullmore, Verchinski, et al. (2009). However, anatomical aspects of brain functional networks have not previously been explored in relation to the topological abnormalities in schizophrenia.

Here, we used resting-state fMRI to measure functional connectivity (low-frequency correlation in endogenous brain oscillations) in networks comprising ~300 gray matter nodes in a group of healthy controls ($N = 20$) and an age-matched group of patients with COS ($N = 19$). We estimated the spatial distance of connection as the Euclidean distance between functionally connected nodes, and we explored how this spatial property of connection distance or "wiring cost" was related to global, modular, and nodal topological properties of the brain networks in health and disease. We also used a simple generative model of brain networks, which defined the probability of functional connection between regions as a function of the physical distance between them, to explore how variability in penalization of long-distance connections might account for variability in topological properties of brain networks.

Materials and Methods

Participants with COS ($N = 23$) and also healthy volunteers (HV, $N = 23$) were recruited for the NIH study of COS and normal brain development. Patients with COS were recruited through nationwide referral and extensive prescreening. The institutional review board of the National Institutes of Health approved the study, and written informed consent and assent were obtained from parents and children, respectively. Diagnoses were made using unmodified Diagnostic and Statistical Manual of Mental Disorders-IIIR/IV criteria for schizophrenia with the onset of psychosis before age 13. Any history of significant medical/neurological problems, substance abuse, or premorbid IQ below 70 was exclusionary. All of the patients were being treated with the antipsychotic medication Clozapine. Four COS patients and 3 healthy participants were excluded for excessive head motion during fMRI (see below) resulting in final samples of 19 participants with COS and 20 healthy participants (HP). There was no significant difference between groups in terms of maximum displacement due to motion (COS sample mean = 0.61 mm; HP sample mean = 0.52 mm; *t*-test, $P = 0.51$; 95% confidence interval = −3.6 to 1.9), gender (10 females, 9 males, COS; 9 females, 11 males, HP; chi-square test $P = 0.88$), or age (COS sample mean age = 18.7; standard deviation [SD] = 4.9; range = 12.2–30.4; HP sample mean age = 19.7; SD = 5.0; range = 13.2–33.7; *t*-test, $P = 0.52$; 95% confidence interval = −2.2 to 4.3). For additional demographic information, please see Table 1.

Image Acquisition and Analysis

All images were acquired using a 1.5 T General Electric Signa MRI scanner located at the National Institutes of Health Clinical Center

Table 1
Demographic information for healthy participants and patients with COS

	Patients with COS (N = 19)	Healthy participants (N = 20)	Statistic (df)	P value
Mean age of onset (SD)	10.0 (1.8)	—	—	—
Mean age (SD)	18.7 (4.9)	19.4 (4.9)	t = 0.49 (37)	0.62
Sex	10 F; 9 M	10 F; 10 M	χ^2 = 0.02 (1)	0.86
Race	0A; 5B; 0H; 2O; 12W	2A; 3B; 1H; 1O; 13W	χ^2 = 3.85 (4)	0.42
IQ, mean (SD)	76.1 (17.7)	111.0 (13.3)	t = 6.45 (31)	<0.01
Socioeconomic status, mean (SD)	62.1 (25.9)	43.9 (13.7)	t = 2.75 (37)	<0.01
Handedness (SD)	2 L; 17 R	3 L; 17 R	χ^2 = 0.17 (1)	0.67

Note: df, degrees of freedom; F, female; M, male; race: A, Asian; B, Black/African–American; H, Hispanic; O, other/mixed race; W, White; L, left handedness; R, right handedness.

(Bethesda, MD). One anatomical T_1-weighted fast spoiled gradient echo MRI volume was acquired: time to echo (TE) 5 ms; time to repetition (TR) 24 ms; flip angle 45°; matrix 256 × 256 × 124; field of view (FOV) 24 cm. Two sequential 3-min echo-planar imaging scans were acquired while subjects were lying quietly in the scanner with eyes closed: TR 2.3 s; TE 40 ms; voxel 3.75 × 3.75 × 5 mm; matrix size 64 × 64; FOV 240 × 240 mm; 27 interleaved slices.

Image preprocessing was accomplished with Analysis of Functional NeuroImages (Cox 1996) and the Oxford Centre for Functional MRI of the Brain Software Library (FSL) (Jenkinson and Smith 2001; Jenkinson et al. 2002). After discarding the first 4 volumes, the functional data was despiked (removing artifactual outliers in voxelwise time series), motion corrected, and skull stripped. Maximum displacement was defined as the maximum of the 6 motion parameters within any 10 s period, with an exclusion threshold of 2 mm (or degrees). Registration was performed from each functional scan to that subject's structural scan using a 6 degrees of freedom transformation, and from each structural scan to MNI stereotactic standard space using a 12 degrees of freedom transformation. All images were registered to the MNI adult brain template (Burgund et al. 2002; Kang et al. 2003). White matter and cerebrospinal fluid (CSF) were segmented with a probability threshold of 0.8. Each voxel's time series was regressed against the 6 parameters from motion correction, the average CSF signal, and the average white matter signal, with the residuals used for all further analysis.

Gray matter areas in the brain were initially defined using FSL's cortical and subcortical Harvard–Oxford probabilistic atlas and cerebellar probabilistic atlas (Diedrichsen et al. 2009) thresholded at 25%. This gray matter template was filtered to include only voxels with fMRI coverage in every subject, and downsampled or subparcellated to ~300 uniform regions (Fornito et al. 2010), maximizing compactness with the additional constraints that the largest brain region was less than twice the size of the smallest; also no regions spanned hemispheres or cortical lobes. This resulted in 293 regions whose average time series were extracted for each functional scan. The maximal overlap discrete wavelet transform with a Daubechies 4 wavelet was used to band-pass filter the time series to the scale 2 frequency interval, 0.05–0.111 Hz. Sequential scans were concatenated to form a single series of 144 wavelet coefficients. The absolute wavelet correlation, $0 \leqslant |r| \leqslant 1$, quantified the covariability or functional connectivity between all 42 778 pairs of anatomically defined regions, constituting an association or functional connectivity matrix.

Graph Theoretical Analysis of Network Connection Distance and Topology

Each association matrix was thresholded to make a graph model of the brain functional network. In such a brain graph (Bullmore and Bassett 2011), the nodes are defined as the brain regions included in the graph, the edges are the functional connections included, and the degree of each node is the number of edges that connects it to the rest of the network. Sparse networks, with relatively few edges representing relatively large wavelet correlations or relatively strong functional connections, were constructed using a minimum spanning tree followed by global thresholding (Alexander-Bloch et al. 2010). Graphs were constructed over the whole range of connection densities or costs, from 1% to 99% at 1% intervals; this measure of topological cost refers to the percentage of all possible edges included in the graph, such that at 100% there would be edges from each node to every other node. Summary statistics were averaged over the range of 1–10%, and sparse networks were analyzed in more detail at 2% cost (for further information, see Supplementary Material).

The physical distance of an edge in the resulting graphs was simply estimated as the Euclidean distance ("as the crow flies") between the centroids of the 2 graphically connected brain regions. The global mean connection distance or wiring cost was the average Euclidean distance over all pairs of connected regions in the graph. The nodal mean connection distance was the average Euclidean distance over all edges connecting a given node to the rest of the network. The distance strength of a node was defined as the nodal mean connection distance multiplied by the nodal degree: thus high-degree nodes with many long-distance connections will have high distance strength. Although Euclidean distance between nodal centroids is clearly an imperfect approximation of the anatomical distance between the regions, it has previously been shown to be comparable to more refined diffusion imaging-based measures of connection distance (Supekar et al. 2009).

All other topological properties considered, including global efficiency, clustering, small worldness, modularity and the participation coefficient, have been described previously and used in several prior graph theoretical studies of human brain networks (Meunier et al. 2009; Lynall et al. 2010). Formal definitions and references are provided in the Supplementary Materials. In brief, global efficiency is a measure of the integration of a network (Latora and Marchiori 2001). If many edges must be traversed to define a path between nodes, that is, if the characteristic path length is high, then a network has low global efficiency for parallel information transfer. In contrast, topologically random graphs (see below) have high global efficiency (Latora and Marchiori, 2001; Achard and Bullmore 2007). Clustering, sometimes also called transitivity, is a measure of cliquishness: in a highly clustered network, if node X is directly connected by a single edge to node Y and also with node Z, then Y and Z are likely also to be directly connected by a single edge. Modularity is a measure of community structure or the extent to which a network is nearly decomposable into densely intraconnected subnetworks or modules (Newman and Girvan 2004). The extent to which a node's edges mediate connections between these different modules or subnetworks, as opposed to all of its edges connecting to nodes within its own module, can be measured by its participation coefficient (Guimerà and Amaral 2005). Nodes with a high participation coefficient and high degree can be described as connector hubs, since they play a particularly important topological role in mediating connections between otherwise isolated modules.

In addition, to compare the spatial and topological properties of brain networks to the properties of more-or-less random networks, we estimated the same parameters in random graphs. We used 2 methods to construct random graphs. In one procedure, the new edges are chosen entirely by chance, with the only constraint being that the randomized graphs have the same number of nodes and edges as the brain graphs (Erdös and Rényi 1959). In the other procedure, random graphs were constructed in such a way as to preserve the degree distribution and number of connected nodes in the brain graphs (Viger and Latapy 2005). We also explored networks that were only partially randomized. In this case, a proportion of the edges in a normal brain graph were randomly rewired. All results from partially randomized graphs were averaged over 50 random realizations for each of the 20 healthy participants.

Graph analysis was conducted using in-house programs (http://sourceforge.net/projects/brainnetworks/files/) and the R package "igraph" (Csardi and Nepusz 2006), graphics made use of the R package "ggplot2" (Wickham 2009), and statistics were also calculated using R (http://www.r-project.org). This study utilized the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, MD (http://biowulf.nih.gov).

Computational Network Models

We analyzed the topological properties of an explicitly spatial network model, many varieties of which have been described previously (Kaiser and Hilgetag 2004; Kaiser and Hilgetag 2006; Barthélemy 2010). The model defined the probability of an edge between nodes as an exponential function $P(\text{edge}) \sim e^{-\eta x}$, where x is the Euclidean distance between the centroids of 2 brain regions. We explored a range of values for the parameter η that resulted in different topological properties and wiring costs for the simulated networks, comparing models that matched the different topological profiles of the healthy and the patient groups. The use of this model allowed us to investigate the extent to which between-group differences in distance of functional connections could explain differences in functional network topology.

Results

Anatomical Distance of Functional Connections

The global mean anatomical distance of functional connections increased as a function of network connection density, as weaker functional connections were included in denser networks (Fig. 1*A*). This indicates that most of the stronger functional connections, which comprise the more sparsely connected networks, are between regions separated by relatively short anatomical distances; see also Figure 2*B*.

Focusing on networks with a sparse connection density (2% of possible interactions included as connections), we estimated the distance between each pair of connected nodes and compiled these estimates as an empirical probability distribution of anatomical distance. All individual networks had asymmetric distance distributions skewed toward short-distance connections. An exponential probability distribution provided a reasonable fit to the cumulative distance distribution (Fig. 1*B*), although the data include fewer very short-range connections and also a fatter tail, with more long-range connections than predicted simply by an exponential decay.

These results confirm a strong selection bias in favor of short-distance functional connections in sparsely thresholded normal human brain networks.

Topological Correlates of Connection Distance

There was a fair degree of between-subject variability in the global mean distance of functional connectivity, which was strongly associated with individual differences in network topology (Fig. 2*A*). Among the healthy participants, the global mean anatomical distance of functional connections was significantly correlated with modularity (Pearson's $r = -0.59$; t-test, $P < 0.007$), clustering coefficient ($r = -0.50$; $P < 0.03$), and global efficiency ($r = 0.49$; $P < 0.04$). In other words, individual brain networks with greater mean distance of functional connections tend to be less clustered, less modular, and more globally efficient (have shorter path lengths) than networks that are configured more economically in terms of the average distance of functional connections. The small-worldness scalar, which is a ratio of path length and clustering, appears to be robust to variation in the length of connections ($r = -0.22$; $P = 0.4$), at least among the healthy participants.

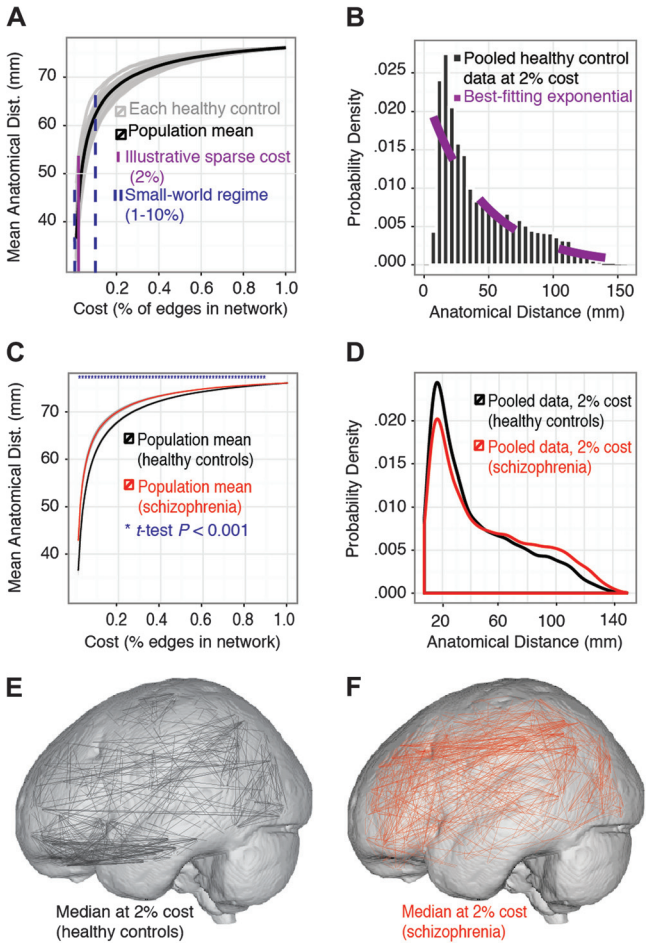

Figure 1. Anatomical distance of functional connectivity in fMRI brain networks of healthy participants and patients with COS. (*A*) The mean network connection distance increases as a function of connection density or cost, indicating that the sparsest networks formed from the most strongly correlated edges are dominated by short-distance connections. The longer distance, less strongly correlated connections are added as the networks become denser. We focus on sparsely connected networks (1–10% cost). (*B*) The empirical probability density of functional connection distance is highly skewed toward short-distance connections. An exponential probability distribution, $P(\text{edge}) \sim e^{-\eta x}$, where x is the anatomical distance of the edge, provides a reasonable (though imperfect) fit to the data. (*C*) Across the whole range of connection densities, the healthy volunteers have a lower mean network connection distance than the patients. (*D*) The empirical probability densities reveal proportionally more short-distance connections and proportionally less long-distance connections in the healthy volunteers compared with the patients with schizophrenia. (*E*,*F*) More long-distance and fewer short-distance connections are evident in a representative network from the patient group, compared with a representative network from the healthy volunteer group.

There was also a high degree of within-subject variability in terms of the anatomical distance of functional connections to specific brain regions, which was related to the topological roles played by different nodes and edges in the functional network. Edges comprising triangular motifs, which are characteristic of highly clustered networks, tend to be shorter distance than edges comprising acyclic motifs (Fig. 2*C*); and intermodular edges, which connect nodes in different modules, tend to be longer distance than intramodular edges (Fig. 2*D*). Brain regional nodes associated with greater than average connection distance to the rest of the network tend also to have high degree and high participation coefficient, indicating that these are connector hubs that mediate integrative connections between different spatially distributed modules (Fig. 2*E*).

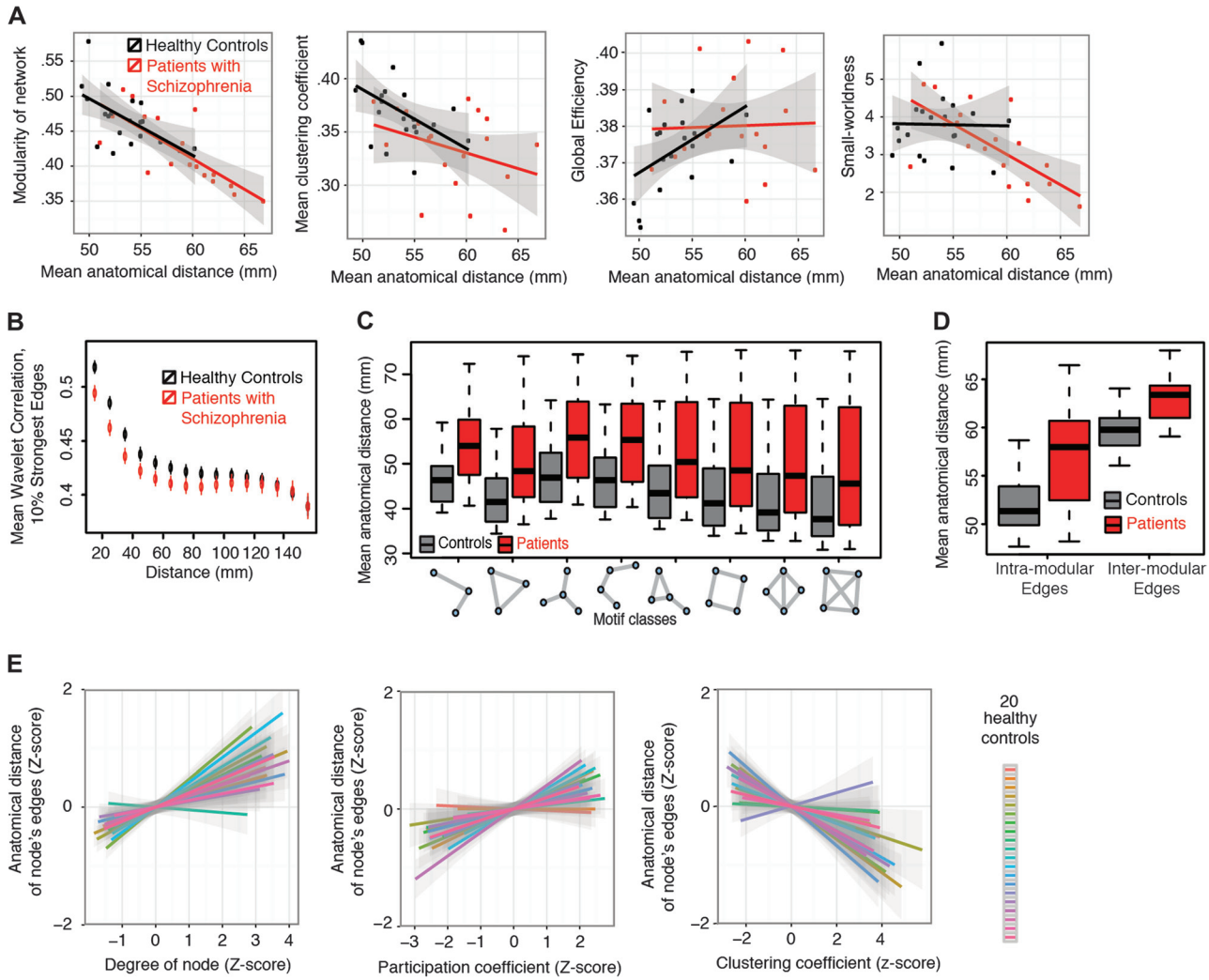

Figure 2. Interplay between the anatomical distance of functional connections and topological (nonspatial) attributes of brain networks in health and schizophrenia. (*A*) Across subjects, the mean anatomical distance of brain networks is related to complex network properties including modularity (a measure of decomposability of the network into component modules), clustering (the "cliquishness" of connections), global efficiency (the capacity for parallel information transfer), and small worldness (the normalized ratio of clustering to path length). (*B*) The average functional connectivity (absolute wavelet correlation at 0.05–0.11 Hz) is lower in the schizophrenia population than in the control population, most notably for short-distance anatomical connections <5 cm. (*C*) Triangular or triangle-containing network motifs tend to have shorter anatomical distances in both groups. (*D*) Intermodular edges are longer than intramodular edges in both groups. (*E*) As illustrated in the population of healthy participants, nodes with longer distance anatomical connections tend to have higher degree (more connections), higher participation coefficient (more connections between different modules or communities), and lower clustering.

For each node, the product of its degree and its mean connection distance (denoted distance strength) provides a simple summary of its importance as a long-distance hub. We found that distance strength was highest for connector hubs located bilaterally, predominantly in areas of multimodal association cortex: left and right lateral temporal lobe (anterior superior temporal gyrus/planum temporale); left and right inferior lateral parietal cortex (angular gyrus/supramarginal gyrus/superior lateral occipital cortex); right anterior medial frontal lobe (frontal pole/medial frontal cortex/paracingulate cortex); and right dorsolateral prefrontal cortex (middle frontal gyrus).

COS: Anatomical Distance and Functional Dysconnectivity

Like healthy participants, patients with COS had greater strength of functional connectivity between nodes separated by short distances. However, we found that the strength of functional connectivity was generally attenuated in schizophrenia and was significantly less than normal for shorter distance connections (separated by <5 cm Euclidean distance; Fig. 2*B*). Strength of functional connectivity of longer anatomical distances was relatively normal in the COS group. Therefore, the proportion of long-distance connections in brain networks was greater for patients with COS compared with healthy participants (Fig. 1*D–F*; Supplementary Fig. S2). As exemplified by networks with a sparse (2%) connection density, the mean connection distance of the individual COS networks was higher than the mean connection distance of the networks of healthy participants (COS population grand mean = 51 mm; SD across subjects = 6 mm; healthy participant grand mean = 44 mm; SD = 4 mm; $t = 3.93$; $P < 0.0005$). This group difference is also reflected in significant differences in the parameter, η, of the best-fitting exponential probability distribution for each subject (COS mean $\eta = 0.020$; SD = 0.002; healthy participant mean $\eta = 0.023$; SD = 0.002; $t = 4.0$; $P < 0.0004$). In addition, the group difference

is robust to replacing parametric statistical tests with non-parametric permutation tests of significance (difference in mean connection length, $P = 0.0007$; difference in η parameter, $P = 0.0005$; see Supplementary Fig. S2). The group difference in the mean connection distance remained strongly significant (t-test $P < 0.001$) for networks matched at any connection density between 1% and 90% at 1% intervals (Fig. 1*C*). We note that the selective attenuation of short-distance connectivity strength in COS patients is difficult to reconcile with the null hypothesis (discussed in greater detail below) that the observed differences between groups are attributable to "noisier" data in the patient group. Under this hypothesis, the strength of functional connectivity would be attenuated more consistently across all pairs of nodes, regardless of the distance between them.

The difference between patients and healthy participants in functional connection distance was related to differences in topological network measures (Fig. 2*A*). For networks with connection density in the range 1–10%, we tested key topological metrics for a main effect of distance, a main effect of diagnostic group, and a diagnosis-by-distance interaction effect. There were main effects for distance on modularity ($F = 33.2$; $P < 0.00001$), clustering ($F = 6.6$; $P < 0.02$), and small worldness ($F = 8.8$; $P < 0.006$); main effects for diagnostic group on modularity ($F = 17.9$; $P < 0.0002$), clustering ($F = 11.5$; $P < 0.002$), and small worldness ($F = 4.5$; $P < 0.05$); and there were no interaction effects. In other words, longer connection distances were generally associated with reduced modularity, clustering, and small worldness; there followed the predictable corollary that these topological metrics were significantly abnormal in the COS group.

In terms of the within-subject variability of nodal connection distances in relation to the topological roles of specific brain regions, the general framework established for the healthy brain networks holds true for the COS data, while reflecting the overall increase in global mean connection distance (Fig. 2*C,D*). The patients with schizophrenia show broadly the same pattern as the healthy participants in terms of the anatomical distribution of connector hubs, but specific brain regions also have more long-distance connections in COS (Fig. 3*B,C*). Using a false positive correction for multiple t-tests of $P < 0.003$, the nodal distance strength was significantly lower in the healthy group in the left dorsolateral prefrontal cortex (superior frontal gyrus/middle frontal gyrus); right inferior parietal lobule (angular gyrus/supramarginal gyrus); right anterior medial (frontal pole/paracingulate cortex); and right dorsolateral prefrontal cortex (superior frontal gyrus/middle frontal gyrus). This anatomical pattern of disturbances is further supported by a supplementary analysis of each cortical lobe as its own independent network: Bilaterally the frontal and parietal lobes showed a similar pattern of alterations to the whole brain networks, whereas there was no difference in connection distance between controls and patients within the temporal or occipital lobes (see Supplementary Fig. S1*C,D*).

Network Randomization and Schizophrenia

One important caveat to consider in interpreting these results is that some of the differences observed between groups may not indicate real differences but could instead be attributable to contamination of the data on COS patients by greater contributions of statistical noise. This interpretation is allowed by the fact that the strength of functional connectivity is generally lower than normal in the COS group. Therefore, to

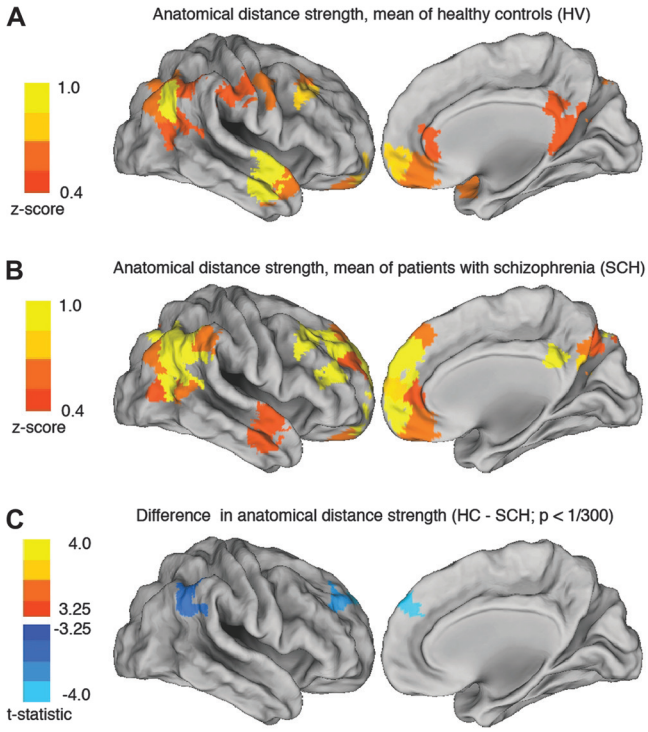

Figure 3. Anatomical locations of long-distance connector hubs, in health and schizophrenia. Cortical surface maps show the distance strength of each node, defined as the degree (number of connections) of each node multiplied by its average connection distance to the rest of the network, Z-scored for each participant relative to the mean and SD of their group. Connector hubs are shown as regions of multimodal association cortex with high distance strength in (*A*) the healthy volunteer group and (*B*) the patients with schizophrenia. (*C*) Distance strength was significantly reduced for some connector hubs in frontal and parietal cortex in the healthy participants compared with the patients with schizophrenia (false positive correction; t-test $P < 0.003$).

generate networks that are matched in terms of connection density, it has been necessary to apply thresholds for definition of an edge that are somewhat lower for the COS group than for the healthy participants. It follows that some of the edges included in the COS network may simply represent chance association between time series and any such "noise-generated" edges might be expected to result in randomization of the network topology. It is important to note that a global decrease in functional connectivity, as simulated for example by decreasing all of the interregional correlations to the same extent, would not alter the topology of networks thresholded at the same connection density. To account for the altered topology in sparsely thresholded networks, not only the absolute value but also the order of even the strongest interregional correlations would have to be affected.

To address this possible interpretation explicitly, we conducted a number of additional analyses. First, we compared the observed brain graphs (in both healthy and COS groups) with random or partly randomized graphs in terms of their connection distance and clustering over a range of connection densities (Fig. 4*A*). These analyses confirmed that the COS networks are clearly different from the random graphs in terms of connection distance and clustering. Random graphs, for example, have high global mean connection distance at all connection densities. Comparing the COS networks to the data obtained by randomly rewiring 10% of the edges in the healthy

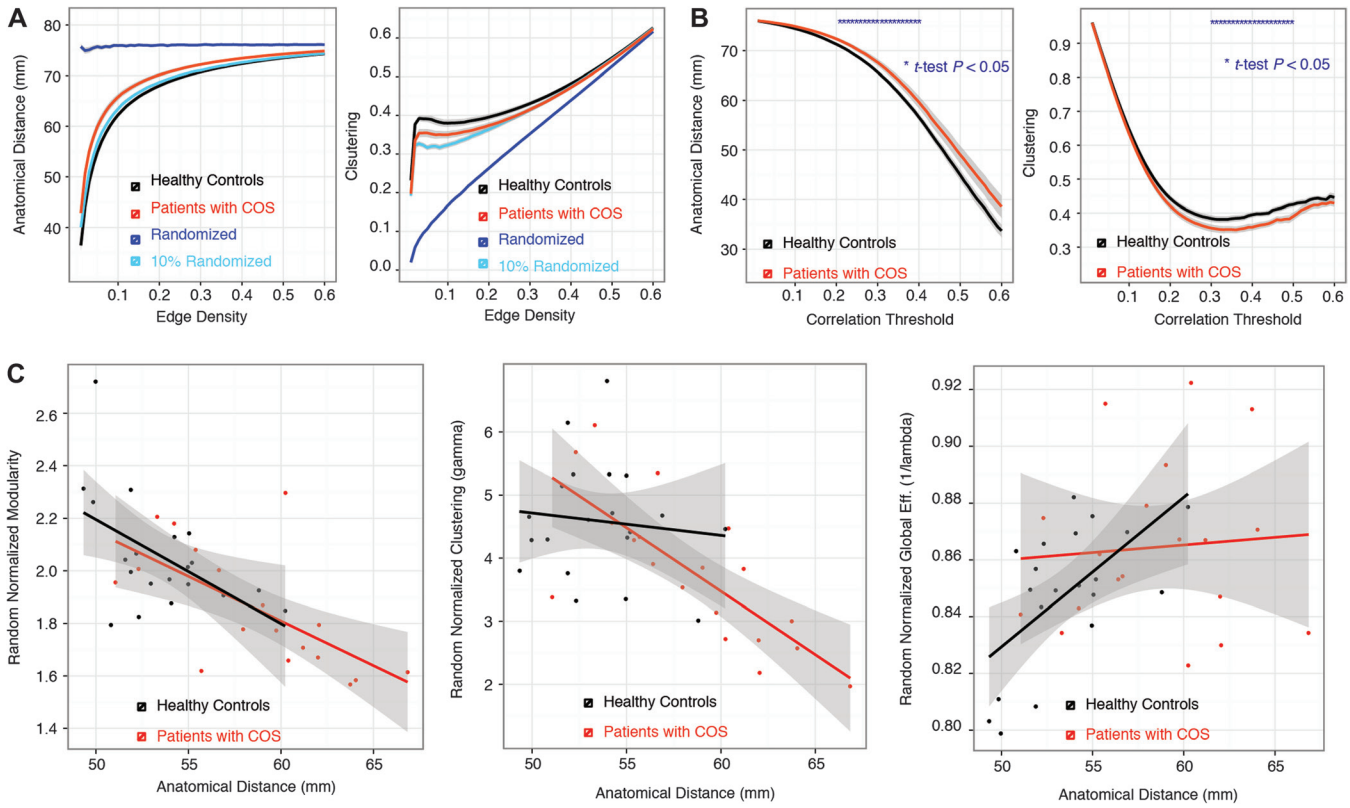

Figure 4. The topological and spatial abnormalities of functional networks in COS are not attributable simply to randomization of networks. (*A*) The schizophrenia networks are far from fully random networks, and they are also not consistent with a process of subtle randomization where 10% of normal network edges are randomized. Partial randomization of healthy brain networks causes excessive reduction in clustering and insufficient increase in connection distance compared with the results on COS networks. (*B*) Between-group differences in clustering and connection distance persist when networks are constructed over a range of identical threshold values, thus ensuring that all edges in all networks represent between-regional correlations greater than the same minimum value. (*C*) The relationships between connection distance, efficiency, modularity, and clustering persist when the topological metrics are normalized by their values in comparable random networks.

brain networks, we find that clustering is reduced to a greater degree in the partly randomized networks than in the COS networks; but connection distance is not increased by as much in the partly randomized networks as it is in the COS networks. In short, simple randomization of normal network topology cannot account simultaneously for both the spatial and the topological profiles of patients with COS. The data show subtler topological alterations and grosser spatial alterations than would be predicted by a randomization process.

Second, we recalculated clustering and connection distance in networks constructed for both groups of data by applying a range of identical thresholds to each individual's correlation matrix. In other words, we generated networks matched for strength of functional connectivity rather than being (as previously) matched for connection density. This analysis allows some differences between networks in terms of their connection density, but it ensures that the probability of adding an edge that represents chance correlation is matched between groups. We found that the key results previously reported when networks are controlled for connection density are also found when the networks are controlled for minimum strength of correlation. Clustering was reduced, and connection distance was increased, over a wide range of threshold values in the COS group compared with healthy volunteers (Fig. 4*B*). The fact that this control preserves the higher mean connection length in COS is particularly striking, because the COS networks have fewer edges than the control networks when they are matched at a minimum strength of correlation, which other things being equal would result in lower mean connection lengths (see Fig. 4*A*).

Third, we normalized the topological metrics of the brain graphs by dividing each observed metric by its value in a random graph of equivalent size and connection density. We found that the relationships between connection distance, efficiency, modularity, and clustering remained as previously reported (see Fig. 4*C*). Collectively, these results support the conclusion that the observed between-group differences in connection distance and topology are not explicable simply in terms of greater "noisiness" of the COS data contributing a disproportionate number of edges representing chance association between regions.

Distance Penalization Model of Brain Functional Network Formation

To further explore the interplay between anatomical and topological aspects of network organization, we used a simple model for the probability of a functional connection between nodes as an exponentially decaying function of the physical distance between them (Kaiser and Hilgetag 2004). The exponential parameter can be regarded as a distance penalty: Larger values of the parameter will make it less probable that 2 regions will form a functional connection unless the distance between them is short. We first found the value for the exponential parameter, which most closely approximated the key topological properties of the healthy brain networks

(Table 2). Then we reestimated the exponential parameter to optimally match the equivalent topological properties of the networks observed in the COS group. We found that the topological profile of the patients with COS, for example reduced clustering and modularity, could be reasonably well reproduced in the simulations simply by reducing the exponential parameter. In other words, a less severe penalization of connection probability as a function of physical distance allowed the formation of less clustered and modular networks.

This simple model of connection probability as an exponential function of distance is far from a perfect model of the data. For example, the connection distance distributions generated by the model are consistently different to those observed in the actual data. But the model provides proof-of-concept that topological abnormalities of the networks in COS could be determined by relaxation of normal "cost controls" that favor short-distance connections (see Table 2).

Discussion

We can think of the network organization of the brain topologically, yet it is also physically embedded and anatomically wired within the limited 3D space available. These results reveal the strong interplay between spatial and topological attributes of human brain networks. Healthy brain networks were formed by strong short-distance connections favoring clustered and modular network topologies, as well as a number of long-distance connections concentrated on intermodular or connector hubs in areas of multimodal association cortex. In contrast, COS networks showed a profile of topological and spatial abnormalities which, we will argue, is compatible with developmental formation by a process of "overpruning" of short-distance connections.

The (near) Minimization of Wiring Cost

As noted originally by Cajal in the late 19th century, and extensively corroborated by multiple experimental and modeling studies since then, many aspects of brain organization are compatible with minimization of connection distance or wiring cost (Ramón y Cajal 1899; Van Essen 1997; Chklovskii 2004; Chen et al. 2006; Kaiser 2011; Sporns 2011). Previous studies have revealed that functional connectivity decays with the distance between brain regions, anticipating our finding that healthy brain functional networks are composed predominantly of short-distance connections (Salvador et al. 2005; Bellec et al. 2006; Honey et al. 2009). We provide fresh evidence that key topological attributes of brain networks, such as clustering and modularity, are strongly negatively correlated with the distance between the most strongly correlated nodes in whole brain networks. However, we have also found that global efficiency of information transfer (a property inversely related to path length) is positively correlated with connection distance; intermodular connections are quantifiably longer than intramodular edges (~20% longer on average in sparse functional networks); and a subnetwork of highly connected nodes or network hubs with many long distance connections, with the appearance of a "rich club" (Van den Heuvel and Sporns 2011), is located in consistent regions of heteromodal association cortex.

These results on normal brain functional networks support the theory that cost minimization alone is an important principle in brain organization, but it cannot account for all aspects of brain network topology (Kaiser and Hilgetag 2006; Bassett et al. 2010; Kaiser et al. 2010; Fornito et al. 2011; Varier and Kaiser 2011). If that were the case, we would expect brain networks to be more regular or lattice-like in their organization with correspondingly low global efficiency of information transfer. Whereas, in fact, the parsimonious principle favoring formation of clustered intramodular connections appears to be somewhat offset by factors favoring a minority of relatively long-distance connections which can sustain communication between modules and confer greater global efficiency on the network. Recent studies (Li et al. 2009; Van den Heuvel et al. 2009; Zalesky et al. 2011) have shown that fluid intelligence (as measured by classical IQ tests) is negatively correlated with the global minimum path length of structural and functional networks, suggesting that the cognitive and behavioral advantages of more efficient networks might drive their selection despite the somewhat greater connection cost entailed.

Table 2
Computational modeling of network topology

	Average length of connections in network simulations, (mm) with the parameter η tuned to mach the following topological properties		
	Modularity	Efficiency	Clustering
Healthy participants	31.8 ± 0.3 (η = 0.08)	20.1 ± 0.1 (η = 0.2)	18.2 ± 0.1 (η = 0.23)
Patients with COS	40.0 ± 0.6 (η = 0.056)	21.7 ± 0.1 (η = 0.3)	19.2 ± 0.1 (η = 0.196)

Note: Using models of network growth to explicitly fit the topological (nonspatial) properties of the networks, we find that the simulations of the patients with COS also have longer connection lengths than the simulations of the healthy participants, in accordance with the actual increase in network connection lengths that we find in COS (Fig. 1*C*,*D*). The model includes edges with a probability $P(\text{edge}) \sim e^{-\eta x}$, where x is the anatomical (Euclidean) distance between 2 brain regions. The parameter η was tuned to match the modularity, global efficiency, and clustering of each clinical group, and 20 simulations were conducted to estimate the mean connection length (mm) (±SD) of the resulting networks. The simulated graphs and the data were identically thresholded at 2% edge density.

Brain Organization in Childhood-Onset Schizophrenia

Our study confirms topological disturbances in schizophrenia and relates them for the first time to anatomical abnormalities in connection distance. For thresholded networks that include the strongest functional connections as edges, the average wiring cost in COS is increased; COS networks contain proportionally fewer short-distance edges, about the same number of medium-distance edges, and proportionally more long-distance edges. Regionally, the increased wiring cost is highest in parts of the same subnetwork of highly connected heteromodal hubs that contain the most long-distance connections in the healthy participants. Given previous reports of a reduction in gamma band synchrony within this subnetwork in schizophrenia (Lee et al. 2003; Spencer et al. 2004; Symond et al. 2005), we note that we do not find an absolute increase in their interregional correlations. Rather, a disease-related deficit in connectivity at short distances appears to spare the long-distance connectivity of these hub regions, which accentuates their role in thresholded brain networks.

In addition to alterations in the profile of connection distances, the COS functional networks appear less clustered, less modular, and less small-world than normal, which is

consistent with reports from previous graph theoretical resting fMRI studies (Liu et al. 2008; Alexander-Bloch et al. 2010; Lynall et al. 2010). It is notable that these topological disruptions in schizophrenia are generally as predicted given the greater mean connection distance between the most strongly connected brain regions, although the relationship between wiring cost and some topological properties is nonlinear. Thus, while clustering and modularity decrease approximately linearly with greater connection distance across the whole population, global efficiency increases with connection distance in the healthy controls but less so in the COS patients. The patients thus have decreased clustering without a concomitant increase in global efficiency, resulting in networks that are less small world.

Although a statistical correlation between anatomical and topological properties does not imply causation, the difference in connection distance predicts the pattern of topological alterations in schizophrenia. This can be illustrated with reference to network growth models that simulate networks under variable spatial constraints (Barthélemy 2010; Kaiser and Hilgetag 2004; Kaiser et al. 2009). More severe distance penalties that encourage more short-range connectivity create graphs that are more modular and more clustered, consistent with the topological properties of healthy brain networks compared with those of patients with schizophrenia (Table 2). Thus it is possible that the topological abnormalities observed in the COS patients are determined by an aberrant neurodevelopmental process favoring proportionally fewer short-distance connections (we return to this hypothesis below).

It is also tenable a priori that the randomization of network topology in COS could be a statistical artifact caused by the method of graph construction. This involves applying a threshold to the functional connectivity (wavelet correlation) matrix for each individual. As this threshold is lowered toward zero, it is inevitable that some edges will be added to the graph due to chance association rather than functional connectivity between fMRI time series. Since the COS patients generally had lower strength of correlation than normal, especially at short distances, it is possible that for any given connection density there will be more edges attributable to chance association in the COS networks, and this would have the effect of rendering the network topology more random. However, we have shown that random or partly randomized graphs imperfectly simulate the spatial and topological characteristics of the COS networks; that the observed abnormalities in both clustering and connection distance persist when identical thresholds are used to ensure that weak correlations are equally likely to be included as edges in both normal and COS graphs; and that the relationships between connection distance and topological properties are conserved when the topological metrics are normalized by their values in comparable random graphs. Collectively, these results argue strongly against the null hypothesis that the COS networks contain more edges representing weak association by chance between fMRI time series.

A "Functional Overpruning" Hypothesis

More substantively, we suggest that our results are consistent with schizophrenia as a consequence of a neurodevelopmental process of synaptic overpruning. In resting-state fMRI network studies of normal development, it has been suggested that pruning, coupled with maturational processes of axonal myelination, could explain an apparent shift from short-distance functional connectivity in children toward long-distance connectivity during normal adolescence (Fair et al. 2009; Supekar et al. 2009). The attenuation of short-distance functional connectivity, and the increase in connection distance between the most strongly functionally connected brain regions, could thus be interpreted as the results of overpruning in patients with COS. Prior support for overpruning as a pathogenetic mechanism in schizophrenia is provided by evidence that several putative markers of synaptic density normally decline in adolescence after an early childhood increase, and the same markers may also be decreased in schizophrenia. Synaptic pruning markers that are also abnormally reduced in adolescent or adult patients with schizophrenia include slow wave (delta) sleep; the cortical metabolic rate; gray matter volume, as measured in structural MRI studies; and cortical synaptic density itself (Feinberg 1982, 1983; Harrison 1999; Keshavan et al. 1994; McGlashan and Hoffman 2000; Gogtay et al. 2004; Feinberg and Campbell 2010). To this list, we would potentially add short-distance functional connectivity, which is certainly reduced in this sample of patients with schizophrenia; but we note that we did not also find a reduction in short-range functional connectivity as a function of age, either in patients or controls, as would be expected if this was indeed a novel marker of normal pruning processes. However, this could be a false negative due to a lack of any children younger than age 12 in our study. Larger studies of network properties over a wider range of ages in childhood and adolescence will be helpful to inform neurodevelopmental interpretations of brain network abnormalities in patient groups.

Other pathogenetic explanations are also consistent with our pattern of results. The absolute decrease in short-distance functional connectivity, coupled with the lack of alteration in the functional connectivity between distant brain regions (Fig. 2*B*), suggests a primary deficit in formation or maintenance of short-distance connections in schizophrenia and therefore a proportionally greater contribution of long-range connections to the global network configuration. But this short-range connectivity deficit could be plausibly explained by other mechanisms than synaptic overpruning, such as a disturbance or loss of formation or demyelination of short-distance white matter tracts. A recent diffusion imaging study indeed demonstrates decreased interregional white matter network connectivity in patients with schizophrenia, although the topological alteration in these white matter networks was toward decreased efficiency and increased clustering (Zalesky et al. 2011). In spite of broad similarities between diffusion imaging and fMRI networks (Honey et al. 2007; Hagmann et al. 2008; Honey et al. 2009), this apparent discrepancy points to the nontriviality of predicting how specific alterations in white matter connectivity will impact functional networks, as well as the need for more multimodal imaging studies in larger samples of this clinically heterogeneous disorder.

Methodological Issues

The power to measure disorder-related differences in connection distance from fMRI measurements may be limited by the adoption of coarse-grained anatomical templates to parcellate the images and thus define the nodes of the networks. Previous

fMRI network studies of schizophrenia have not reported differences in connection distance, but they have typically used anatomical templates (e.g., FSL's Harvard-Oxford atlas; Alexander-Bloch et al. 2010 or the Anatomical Automatic Labeling atlas; Liu et al. 2008; Lynall et al. 2010) to define ~100 regional nodes that are highly variable in terms of shape and size. The use of such templates could mask the group difference that we report in several possible ways. It is known that large variation in the size of regions biases the strength of functional connections in favor of larger regions (Salvador et al. 2008). It is difficult to meaningfully assign physical distances to all of the connections between differently sized regions. For example, the Euclidean distance between the centroids of a large region and an adjacent small region could be the same as, or larger than, the distance between 2 nonadjacent regions that are both small in size. In addition, working with a smaller number of total regions will generally narrow the distance distribution and reduce the range of possible distances, which may reduce sensitivity to detect effects that are localized either to short- or long-distance connections. In fact, using anatomical templates with relatively few regions that vary significantly in size, we fail to replicate our finding of increased connection distance in COS networks. However, this key finding is robust to using ~4000 6-mm isotropic voxels as network nodes, to analyzing each cortical hemisphere or lobe separately, and to constructing graphs using alternative methods (see Supplementary Materials and Fig. S1).

Our case-control study is limited by the fact that IQ is significantly lower in the patient population. This discrepancy is difficult to avoid in studies of schizophrenia, because cognitive impairment is a clear part of the disease phenotype (Heinrichs and Zakzanis 1998). Ongoing sibling studies may provide the best opportunity to look at the fMRI phenotype of schizophrenia risk genes, in more exactly IQ-matched samples. However, it is unlikely that the network alterations that we report in schizophrenia are due to IQ differences alone. Several studies (Li et al. 2009; Van den Heuvel et al. 2009; Zalesky et al. 2011) have demonstrated a positive correlation between IQ and the global integration of brain networks (as measured by high network efficiency and low minimum path length), but the patients in our study do not show any evidence of decreased network integration, as might be predicted by their lower IQ score. Rather, the loss of short-distance connectivity in patients appears to manifest in topological deficits of clustering and modularity, segregative network properties that are inversely correlated with integrative properties. However, this pattern of results does raise the question of why low IQ in the schizophrenia patients is not associated with a significantly reduced efficiency, as might be expected from the normative studies mentioned above. Evidently, the relationship between efficiency and IQ that holds for healthy individuals may not be predictive of the relationships between cognition and brain network topology in the disease state. On the other hand, a previous magnetoencephalography study did find reduced cost efficiency in schizophrenia networks associated with reduced working memory performance (Bassett et al. 2009), and diffusion imaging studies have also suggested that there is decreased global integration of networks in schizophrenia (Van den Heuvel et al. 2010; Zalesky et al. 2011), so it is evident that these issues are in need of further study.

Since fMRI functional connectivity cannot be used to directly infer axonal projections, our data does not immediately address the question of whether dysconnectivity in schizophrenia is primarily synaptic, axonal, or both (Stephan et al. 2006; Ellison-Wright and Bullmore 2009). Our results do help to clarify the fMRI phenotype of alterations in connectivity. If disconnectivity denotes specifically a loss of connectivity, whereas dysconnectivity denotes a broader range of pathologically increased, decreased, or rearranged connections (Stephen et al. 2009), our results suggest that short-distance disconnection may underlie network-level dysconnection that is reflected in alterations of global topological properties. We do not find evidence of increased functional connectivity in patients in any brain regions, nor do we find evidence for decreased connectivity of long-distance connections; but the relative importance of interregional connections is rearranged in a way that decreases segregative properties of the brain network such as modularity and clustering, even when we control for any differences in global connectivity strength between networks.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/. Code to perform network analysis described in this paper is available online at http://sourceforge.net/projects/brainnetworks/files/.

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Notes

Conflict of Interest: E.T.B. is employed half-time at the University of Cambridge and half-time at GlaxoSmithKline.

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