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Review

Schizophrenia, neuroimaging and connectomics

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ABSTRACT

Schizophrenia is frequently characterized as a disorder of brain connectivity. Neuroimaging has played a central role in supporting this view, with nearly two decades of research providing abundant evidence of structural and functional connectivity abnormalities in the disorder. In recent years, our understanding of how schizophrenia affects brain networks has been greatly advanced by attempts to map the complete set of inter-regional interactions comprising the brain's intricate web of connectivity; i.e., the human connectome. Imaging connectomics refers to the use of neuroimaging techniques to generate these maps which, combined with the application of graph theoretic methods, has enabled relatively comprehensive mapping of brain network connectivity and topology in unprecedented detail. Here, we review the application of these techniques to the study of schizophrenia, focusing principally on magnetic resonance imaging (MRI) research, while drawing attention to key methodological issues in the field. The published findings suggest that schizophrenia is associated with a widespread and possibly context-independent functional connectivity deficit, upon which are superimposed more circumscribed, context-dependent alterations associated with transient states of hyper- and/or hypo-connectivity. In some cases, these changes in inter-regional functional coupling dynamics can be related to measures of intra-regional dysfunction. Topological disturbances of functional brain networks in schizophrenia point to reduced local network connectivity and modular structure, as well as increased global integration and network robustness. Some, but not all, of these functional abnormalities appear to have an anatomical basis, though the relationship between the two is complex. By comprehensively mapping connectomic disturbances in patients with schizophrenia across the entire brain, this work has provided important insights into the highly distributed character of neural abnormalities in the disorder, and the potential functional consequences that these disturbances entail.

Contents

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Introduction

Schizophrenia may be characterized as a prototypical disorder of brain connectivity. The very name implies a splitting (*schizen*) of the mind's (*phren*) normally integrated processes. This breakdown is evident in the disorder's clinical manifestations, including cognitive and affective deficits, positive symptoms such as delusions, hallucinations and thought disorder, and negative symptoms such as flattened affect and volitional disturbances. The link between these symptoms and brain connectivity was not lost on early writers; over a century ago, Wernicke first suggested that the disorder arose from pathology of the brain's association fibers (1906; Figs. 7C and D) and Bleuler, who coined the name schizophrenia, viewed a loosening of mental associations as a cardinal feature of the illness (1911/1950). The advent of modern neuroimaging techniques has provided an unprecedented capacity to test and extend these ideas via detailed mapping of brain network structure and dynamics. From the earliest *in vivo* demonstrations of brain abnormalities in people with schizophrenia (Ingvar and Franzen, 1974a, 1974b; Johnstone et al., 1976), to the first study of connectivity disturbances in the disorder (Volkow et al., 1988), it did not take long before connectivity-based hypotheses of schizophrenia re-emerged; first in the form of the disconnection hypothesis laid out by Friston and Frith (1995), followed by subsequent variants (Andreasen et al., 1998; Bullmore et al., 1997; Friston, 1998; McGuire and Frith, 1996; Tononi and Edelman, 2000) and recently in more general characterizations of schizophrenia as a dysconnection disorder[1] (Pettersson-Yeo et al., 2011; Stephan et al., 2006, 2009).

In recent years, the study of connectivity abnormalities in schizophrenia has benefited greatly from rapid advances in the field of connectomics. Connectomics is an umbrella term that refers to scientific attempts to accurately map the set of neural elements and connections comprising the brain, collectively referred to as the human connectome, at either mico-, meso- or macro-scopic resolutions (Sporns; Sporns et al., 2005). The term connectome was initially invoked in reference to a structural description of the brain's physical wiring, but the concept has since been extended to include maps of the brain's functional interactions (e.g., Biswal et al., 2010), which are, by nature, more transient and state-dependent.

Imaging connectomics refers to the use of neuroimaging methods to map various properties of structural and functional brain connectivity, principally at macroscopic resolution. In a general sense, imaging connectomics encompasses the full range of neuroimaging investigations into brain connectivity, including region-of-interest and voxel-wise mapping approaches. In a more specific sense however, it refers to studies that aim to comprehensively map the large-scale architecture of the connectome by quantifying pair-wise interactions between large numbers of brain regions distributed throughout the cerebrum. Methodological advances have enabled construction of these connectomic maps with increasing detail, and their application to schizophrenia has led to novel insights into how the disorder affects distributed neural circuits. In this article, we critically evaluate this literature, focusing principally on studies using magnetic resonance imaging (MRI). We consider how this work has informed our understandings of two key aspects of connectomic disturbance in schizophrenia—altered inter-regional connectivity and altered brain network topology—and discuss its implications for pathophysiological models while highlighting important methodological issues. As a general orientation, we begin with a brief primer on the main principles and methods of imaging connectomics applied thus far. (For reviews of other types of connectivity studies in schizophrenia, see Ellison-Wright and Bullmore, 2009; Konrad and Winterer, 2008; Pettersson-Yeo et al., 2011).

A brief primer on connectomics

A central tenet of the connectomic endeavor is that brain connectivity can be succinctly described as a connectivity matrix, C, whose rows and columns correspond to different brain regions. The elements c_{ij} of C therefore index the degree of (structural or functional) interaction between regional pairs (Fig. 1). This representation allows quantification of different aspects of network connectivity and topology, facilitated through the application of graph theory, a rich mathematical framework for the generic study of pair-wise relations between interacting elements (Bollobás, 1985). Graph theory has been applied to a wide range of technological (e.g., the world wide web), social (e.g., collaborative networks in science), and biological (e.g., protein–protein interactions) networks (Barabasi and Oltvai, 2004; Boccaletti et al., 2006; Newman, 2003). Such analyses have revealed a striking conservation of certain organizational principles across these diverse datasets, suggesting that the human connectome may be one example of a more general universality class of complex systems found in nature (Bullmore et al., 2009).

Node definition

The connectivity matrix, C, can be represented in graph form, termed a brain graph (Bullmore and Bassett, 2011), as a collection of nodes interconnected by edges (Fig. 1). The nodes should represent distinct, functionally homogeneous neural elements or brain regions. However, in the absence of any gold standard for large-scale parcellation of the brain on such grounds, the nodes are typically defined arbitrarily using various methods. The most common approach has involved the use of an *a priori* anatomical parcellation, typically comprising ~10^2 regions (e.g., Tzourio-Mazoyer et al., 2002; Fig. 1; Desikan et al., 2006). The boundaries of these parcellations are often subjective and may only marginally approximate true anatomical borders. Moreover, the size of the resulting regions can vary considerably, biasing subsequent analyses (Salvador et al., 2007). One alternative is to treat each voxel as a separate node, which results in very large, high-resolution networks ($>10^4$ nodes) (van den Heuvel et al., 2008; Fig. 1; Zalesky et al., 2011b) but may also yield noisy and/or underpowered estimation of brain network properties, given that voxels typically coalesce into functionally related clusters (though see Zalesky et al., 2011b for an approach that exploits this property). A middle ground involves using random parcellations, comprising 10^2 to 10^3 or more regions, constrained to minimize regional

[1] The distinction between the prefixes *dis* and *dys* was made by Stephan et al. (2006) on etymologic grounds. In Latin, *dis* implies apart, and suggests a disintegration or reduction in connection. In Greek, *dys* connotes 'bad' or 'ill' and is favored because it is agnostic with respect to the direction of the abnormalities (i.e., increased or decreased). In this article, we follow this distinction and use the term dysconnection in general reference to connectivity abnormalities in schizophrenia, and not in reference to the specific dysconnection hypothesis of the disorder proposed by Stephan and colleagues.

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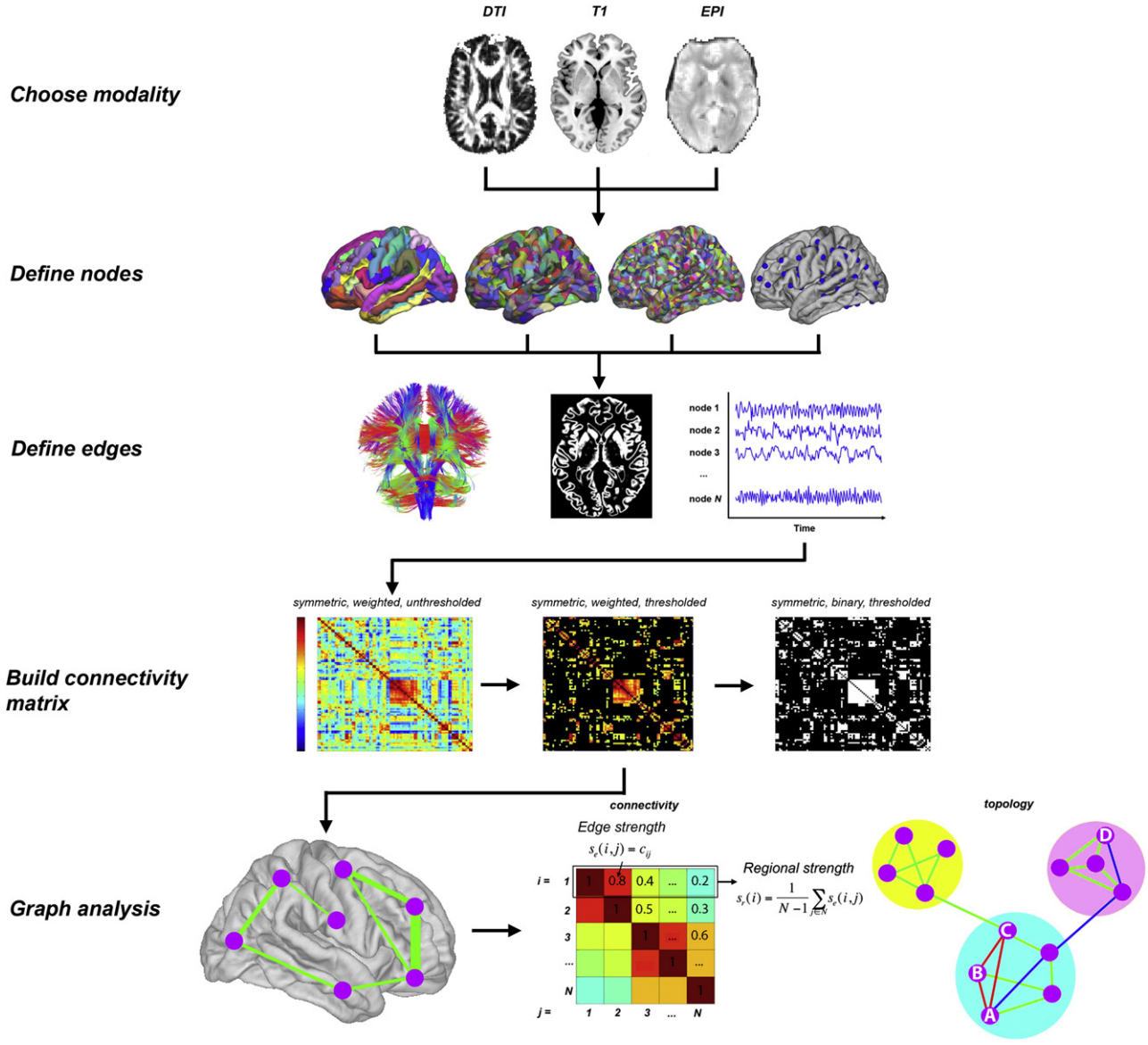

Fig. 1. Illustration of the main steps involved in graph analysis of human neuroimaging data. Top row: the most commonly used imaging modalities are diffusion-tensor imaging (DTI), T1-weighted imaging, and echo-planar imaging (EPI). Second row: the raw data are parcellated into distinct network nodes using various methods. Shown here are examples of an anatomic parcellation (left), random parcellations of 500 (middle left) and 2000 (middle right) regions, and a parcellation using functionally defined spherical regions-of-interest (right). Third row: once the network nodes have been delineated, the interconnecting edges must be defined. For DTI, this typically involves using some tractographic estimate of inter-regional connectivity (left); for T1-weighted imaging it involves computing cross-subject correlations in morphometric parameters, such as cortical thickness or gray matter density (middle); for EPI, it involves computing some estimate of functional dependence between regional activity time courses (right). Fourth row: once the edges have been defined, inter-regional connectivity is represented as a continuously weighted matrix, *C*. Shown here is an example of a symmetric matrix where each edge represents the Pearson's correlation between regional activity time courses obtained using resting-state fMRI (left). This matrix is then typically thresholded to create either a weighted (middle) or binary (right) adjacency matrix, *A*. Bottom row: the matrix *A* is used to construct a graph-based representation of brain network connectivity, termed a brain graph. Shown here is a simplified example of a weighted, undirected graph where nodes are represented as purple circles and their interconnecting edges as green lines sized in proportion to edge weight (left). Based on these matrix and graph representations, several measures of network connectivity and topology can be computed. Connectivity measures (middle) can be defined in terms of edge strength, s_e, reflecting the weight assigned to each element, c_{ij}, of the connectivity matrix, *C* (or *A*), or regional strength, s_r, defined as the mean of each region's s_e values. (Note that connectivity changes can also be examined at the level of inter-connected sub-networks using approaches such as the NBS (Zalesky et al., 2010a, 2010b; see Section 2)). Network topology (right) can be analyzed in many ways. We use a binary undirected graph for simplicity here. A simple topological measure of connectivity is the nodal degree, *k*, which is simply the number of supra-threshold connections possessed by a node (e.g., for node *A*, $k = 4$). The edges in red highlight computation of the clustering coefficient, *Cl*. Nodes *B* and *C* are connected to *A*, as well as being connected to each other. In graph theoretic terms they form a transitive triangle. The clustering coefficient of a node is essentially a ratio of the number of triangles present in the subgraph defined by that node's neighbors, relative to the total possible number of triangles in the subgraph. The clustering coefficient of the network, *Cl*, is the mean of these nodal values. The edges highlighted in blue illustrate calculation of the network's characteristic path length, *L*. These four edges represent the shortest path between nodes *A* and *D*; thus, $d_{AD} = 4$. Contrast this with the shortest path between nodes *A* and *B*, which involves a single, direct connection; i.e., $d_{AB} = 1$. The mean path length of a node is computed as the average path length between any index node and all other *N*-1 nodes. The characteristic path length of a network, *L*, is the mean nodal path length. Also note that the nodes are grouped into three distinct modules, defined by the large colored circles. Nodes within modules have higher connectivity with each other than with the rest of the network. See text for further details. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

variations in size (Fornito et al., 2010; Hagmann et al., 2008; Zalesky et al., 2010b) though again, the resulting regions may only partially capture true node boundaries (Wig et al., 2011). Spherical regions-of-interest (ROIs) centered on stereotaxic coordinates of relevance identified in functional imaging studies (Dosenbach et al., 2010; Fair et al., 2009) can more accurately define functionally homogeneous regions, but they are difficult to apply to structural imaging data. Thus, each of the available methods has associated strengths and

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limitations. Evidence that differences in node definitions can affect network properties (Fornito et al., 2010; Hayasaka and Laurienti, 2010; Wang et al., 2009a; Zalesky et al., 2010b), and that invalid node definitions can distort estimates of true network interactions (Smith et al., 2011), underscores the caution that should be exercised when defining nodes for graph analytic MRI (ga-MRI) studies.

Edge definition

Edges can also be defined in various ways. They can be either weighted according to the strength of measured connectivity between regions or unweighted and binary (i.e., a connection is either present or not) (Fig. 1). They can also be undirected, meaning that C is symmetric (i.e., $c_{ij} = c_{ji}$), or directed, to represent the causal structure of the network (i.e., C is asymmetric and $c_{ij} \neq c_{ji}$). In imaging connectomics, the edges describe the degree of either anatomical connectivity or functional interaction between network nodes. In MRI studies, anatomical connectivity is defined using either T1- or diffusion-weighted MRI. With the former approach, connectivity is indirectly estimated as the cross-subject correlation between regional morphometric parameters, such as gray matter volume or cortical thickness (e.g., Bassett et al., 2008). In diffusion-weighted MRI, connectivity is typically inferred from a tractographic estimate of anatomical connections between regional pairs, such as the number of intersecting reconstructed fiber trajectories (e.g., Zalesky et al., 2011a), or some index of fiber integrity averaged over the reconstructed tract (e.g., van den Heuvel et al., 2010). In both cases, the resulting edges will be undirected (it is currently not possible to resolve fiber tract direction using current imaging techniques) and are typically weighted.

MRI studies of functional brain network interactions generally use blood-oxygenation-level-dependent (BOLD) functional MRI (fMRI), and the network edges measure either functional or effective connectivity between regional pairs. Functional connectivity reflects the statistical dependence between neurophysiological signals recorded from each network node. The dependence can be estimated using numerous techniques (see Bullmore and Bassett, 2011). Most commonly however, it is computed using the simple Pearson correlation between regional activity time courses, resulting in edges that are weighted and undirected. Effective connectivity is defined as the influence that one brain region exerts over another and explicitly models the causal structure of inter-regional interactions, resulting in a weighted, directed connectivity matrix. Dynamic causal modeling (DCM) (Friston et al., 2003) and granger causality analysis (Goebel et al., 2003) are two examples of methods designed to model effective connectivity between regions, though inferring causal interactions from BOLD measurements is often computationally intensive and

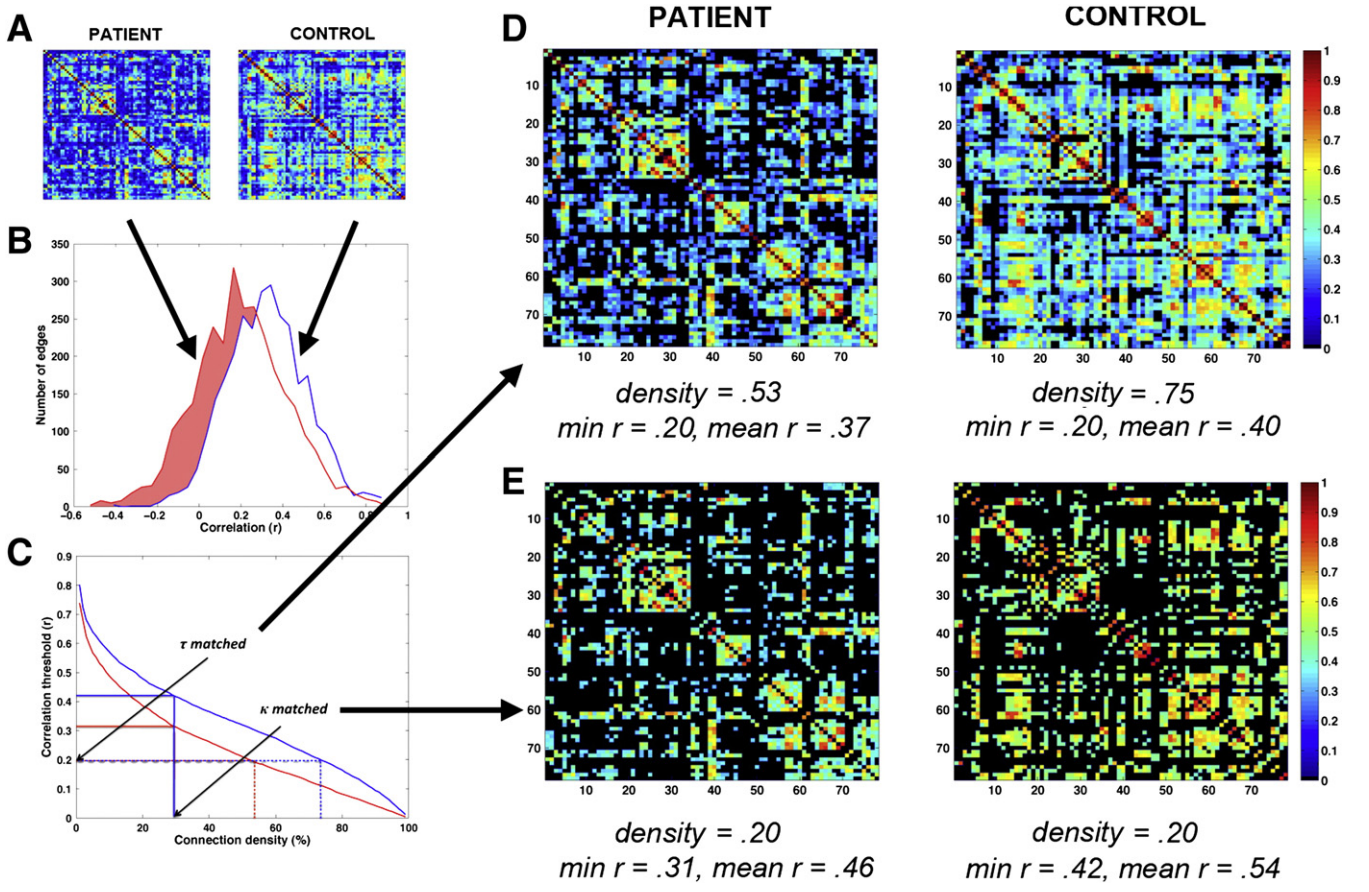

Fig. 2. Illustration of the relationship between thresholding and connectivity weight. A, A representative functional connectivity matrix taken from a single patient (left) and control (right) from the sample analyzed in Fornito et al. (2011c). The network comprised 78 anatomical nodes interconnected by 3003 edges, defined using a beta series correlation technique (see Fig. 5). B, The distribution of connectivity weights, c_{ij} is shifted towards lower values in the patient (red) relative to the control (blue); the area shaded in red highlights the excess number of low weighted values in the patient's connectivity matrix. C, The difference between using a weight-based threshold, τ, and a connection density-based threshold, κ; applying the same τ threshold (solid lines) to the patient and control (e.g., $\tau = .20$) results in different connection densities whereas applying the same κ threshold (e.g., κ; broken lines) results in a different minimum correlation weight threshold. D, The correlation matrices after τ matched thresholding. The minimum weight in the matrix for the patient and control is the same and the mean weight is approximately equal, but the connection density is very different. E, The connectivity matrices after κ matched thresholding. The connection densities are equivalent, but the minimum and mean weight for the patient is lower than for the control. Thus, the patient's connectivity matrix will contain more low-value weights. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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subject to controversy (David, 2011; Friston, 2009; Roebroeck et al., 2011a, 2011b). As such, most imaging connectomic studies of schizophrenia to date have been concerned with analysis of undirected edges; that is, *functional* connectivity between regional pairs.

Comparing brain graphs

Most graph theoretic measures are dependent on the number of network nodes and edges. Consequently, graphs should only be compared if they are matched for the number of nodes, N, and connection density, $0<\kappa<1$. The connection density is simply the total number of non-zero edges in the connectivity matrix relative to the total $N(N-1)/2$ possible number of edges. Connectivity matrices defined using ga-MRI are often continuously weighted, and so κ is typically defined by applying an arbitrary threshold to remove spurious associations and emphasize key topological properties. The result is a thresholded adjacency matrix, A, which is used to generate the brain graph (Fig. 1). Matching for κ in case–control comparisons poses a particular problem when there are group differences in mean connectivity levels (i.e., mean weight of C). If the weight distribution is shifted in one group relative to the other, applying the same threshold, τ, to both groups will result in graphs with unequal κ (Figs. 2A–D). A simple alternative is to fix κ in both groups and allow τ to vary (e.g., retain the highest 10% of weights for all subjects, regardless of what these values are). Such a method ensures that the networks will be matched for κ, but can result in the inclusion of more low-value and potentially noisy edges for the group with lower mean connectivity (Fig. 2E). This can have important implications for subsequent analyses (discussed below). Further development and application of methods for analyzing weighted, unthresholded graphs (e.g., Rubinov and Sporns, 2011; Zalesky et al., 2010a) will help to address these problems.

Once a brain graph has been generated for each subject, graph theory can be used to compute numerous measures characterizing various properties of connectome organization. Of relevance to studies of schizophrenia are those quantifying different aspects of network

Table 1
Summary of main findings in ga-fMRI studies of functional dysconnectivity in schizophrenia.

Study	Paradigm	Sample	Illness duration (years)	Network nodes	Node definition	Edge definition	Measures	Main findings
Liang et al. (2006)	Rest	15 SZ 15 HC	2.15	116 BW	A	TC	s_e	↓ s_e in 158 edges, involving connections with frontal, temporal, insular and striatal regions; ↑ in 19 edges involving cerebellar regions.
Zhou et al. (2007)	Rest	18 SZ 18 HC	2.08	10 DMN and 15 TPN	F	TC	s_e	↑ s_e within DMN; ↑ and ↓ s_e in edges linking DMN and TPN and within TPN.
Liu et al. (2008)	Rest	31 SZ 31 HC	2.25	90 C and SC	A	pTC	s_r, s_e and k	↓ s_r in most regions, particularly fronto-temporal cortex; ↑ s_r in occipital, frontal and striatal regions; ↓ s_e in 32 edges and ↑ s_e in 29 edges linking frontal, parietal temporal and occipital cortices; ↓ k in frontal, occipital and medial temporal regions.
Alexander-Bloch et al. (2010)	Rest	13 COS 19 HC	n/a	100 BW	A	WC	s_r	↓ mean s_r in all regions (significant in nearly all tested).
Liu et al. (2012)	Rest	25 SZ 25 HC	1.53	7 DMN and 10 and TPN	F	TC	s_e	↑ s_e within DMN; ≈ within TPN and between DMN and TPN.
Lynall et al. (2010)[a]	Rest	12 SZ 15 HC	n/a	72 BW	A	WC	s_r, k, s_d, I	↓ mean s_r in all regions (significant in frontal, temporal parietal and occipital regions) and k in medial parietal cortex; ↓ I ; ↑ s_d ; ↑ k in orbital PFC.
Repovs et al. (2011)	Rest	40 SZ 15 HC	n/a	13 DMN, 10 FPN, 7 CON and 4 CERN	F	TC	s_r	≈ mean s_r within-networks; ↓ mean s_r r between CON, FPN and CERN.
Salvador et al. (2010)	Rest	40 SZ 40 HC	20	Hybrid-VW	A/V	PC	s_r	↑ s_r in medial PFC cluster.
Skudlarski et al. (2010)	Rest	27 SZ 27 HC	n/a	Hybrid-VW	A/V	TC	s_e	↓ s_e in PFC; ↑ s_e in temporal, thalamic and DMN regions.
Wang et al. (2010)	Contextual memory	23 SZ 33 HC	8.1	43 C and CER	A	pSC	k	Qualitative evidence for a reduction in the number of PFC hub nodes.
Zalesky et al. (2010a, 2010b)[a]	Rest	12 SZ 15 HC	n/a	74 BW	A	TC	s_e	↓ s_e in a sub-network of frontal, temporal and occipital regions.
Becerril et al. (2011)	Error processing	37 SZ 32 HC	17.4	13 C and CER	F	TC	s_r and s_e	↓ s_r in cerebellum.
Fornito et al. (2011c)	Response inhibition	23 SZ 25 HC	FE	78 C and SC	A	BSC	s_r and s_e	Context-dependent ↓ s_e in a fronto-parietal sub-network; coupled Context independent ↓ s_e and s_r in frontal, temporal and parietal regions.
Zalesky et al. (2011b)[a]	Rest	12 SZ 15 HC	n/a	13, 668 voxels	VW	TC	s_r, s_e, H, P	↓ s_r and s_e of a subnetwork of frontal, temporal parietal and occipital regions, which correlated with measures of intra-nodal dysfunction (H and P).

↓= decreased in schizophrenia; ↑ = increased in schizophrenia; ≈ = no significant difference; A = Anatomical; A/V = combined anatomic and voxel-based parcellation; BSC = beta series correlation (see Fig. 5); BW = brain-wide; C = cortical; CON = cingulo-opercular network; COS = childhood-onset schizophrenia; CER = cerebellum; CERN = cerebellar network; DMN = default mode network; F = functional; FE = first episode; H = intra-regional signal homogeneity; HC = healthy control; I = global functional integration, defined as the ratio of variance accounted for by the first principal component of the connectivity matrix relative to the other components; k = nodal degree; P = signal power; PFC = prefrontal cortex; PC = partial coherence; pSC = partial cross-subject correlation in task activation contrast values; pTC = partial temporal correlation, computed using the partial correlation between regional time courses; SC = subcortical; ; s_e = edge connectivity strength; s_d = regional connectivity diversity, defined as the variance of each region's s_e values; s_r = regional connectivity strength; SZ = schizophrenia; TC = temporal correlation, computed as the Pearson correlation between regional time courses; TPN = task-positive network; VW = voxel-wise; WC = Pearson correlation between mean regional wavelet coefficients.

[a] These studies used the same sample.

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connectivity and topology. The following discussion is organized according to these two major themes.

Brain network connectivity in schizophrenia

Most imaging connectomic studies of schizophrenia have investigated functional brain networks so our discussion is anchored on this work. In particular, we focus on four key issues in the literature; namely whether functional dysconnectivity in the disorder (1) is localized or diffuse, (2) abnormally increased or decreased, (3) state-dependent, and (4) has a structural basis.

Is functional dysconnectivity in schizophrenia localized or diffuse?

ga-fMRI studies of functional brain networks in schizophrenia (see Table 1) have localized functional connectivity abnormalities at three different levels: (1) regionally, either in terms of regional connectivity strength, s_r, or (for binary graphs) nodal degree, k (Fig. 1, bottom row, middle); (2) at the level of single edges, using edge strength, s_e, (Fig. 1, bottom row, middle); and (3) at the level of interconnected subnetworks, using techniques such as the network-based statistic (NBS) (Zalesky et al., 2010a). The last provides substantially more power than will be afforded by testing large numbers of pairwise connections (e.g., mass bivariate hypothesis testing of each s_e value in C) when effects are distributed over multiple linked edges.

Of all brain regions, abnormalities of the prefrontal cortex (PFC) have perhaps been the most replicated finding in studies of schizophrenia, at either the regional (Fornito et al., 2011c; Liu et al., 2008; Lynall et al., 2010; Salvador et al., 2010b), edge (Liang et al., 2006; Liu et al., 2008; Skudlarski et al., 2010; Zhou et al., 2007) or subnetwork (Fornito et al., 2011c; Zalesky et al., 2010a) level (Table 1). Fronto-temporal dysconnectivity has featured prominently (Fornito et al., 2011c; Liu et al., 2008; Zalesky et al., 2010a), though alterations in PFC connectivity with other brain regions, including cerebellum, and parietal and occipital cortices, have been reported (Fornito et al., 2011c; Liu et al., 2008; Repovs et al., 2011; Zalesky et al., 2010a). Altered regional connectivity of parietal, temporal, and occipital cortex, as well as subcortical nuclei, has also been found (Fornito et al., 2011c; Liu et al., 2008; Lynall et al., 2010), indicating a somewhat diffuse functional dysconnection syndrome. Indeed, studies using relatively comprehensive regional sampling of the brain have found evidence for mean connectivity reductions across nearly all areas examined (e.g., Fig. 3), suggestive of a global connectivity deficit. It is as yet unclear whether these global changes are the product of a primary, localized abnormality exerting diffuse effects throughout the brain, or a truly whole-brain dysfunction in which some regions, such as PFC, are more affected than others. The latter notably parallels the neuropsychological profile of schizophrenia, which is characterized by domain-specific strengths and weakness superimposed on a generalized cognitive deficit (Heinrichs and Zakzanis, 1998), as well as cortical volumetric changes occurring in the earliest stages of the disorder (Sun et al., 2009).

One important question concerns whether altered functional connectivity between two regions results from a primary abnormality in inter-regional functional coupling dynamics or as a secondary consequence of intra-regional dysfunction in one or both regions. In schizophrenia, this distinction has been framed in terms of pathophysiological processes affecting either micro (intra-regional) or macro (inter-regional) connectivity (Konrad and Winterer, 2008; Stephan et al., 2006; Zalesky et al., 2010b). The former relates to alterations in synaptic plasticity and/or signaling that disrupt local function; the latter to a potential miswiring of inter-regional association fibers (Stephan et al., 2006).

Inter-regional miswiring is readily detectable using MRI (e.g., Zalesky et al., 2011a), though the putative microscopic mechanisms underlying intra-regional dysfunction make their investigation with current imaging technologies difficult. However, certain consequences of intra-regional dysfunction may be measurable with fMRI. Recently, we proposed that one such consequence is a change in the signal homogeneity of voxels comprising the dysfunctional region, which would result from an alteration of local synchronization dynamics (Zalesky et al., 2011b). This change in regional signal homogeneity could alter the phase, frequency and/or amplitude of that region's mean signal and secondarily affect functional connectivity with other regions (Fig. 4A). We investigated this possibility by generating fMRI brain graphs comprising 13,668 voxel-wise nodes in a sample of patients and healthy controls (Zalesky et al., 2011b). Group differences in inter-voxel connectivity at each of 93.4×10^7 possible edges were tested and subnetworks showing reduced connectivity in schizophrenia were identified using a spatial pairwise clustering procedure followed by the NBS (Fig. 4B). A subnetwork of eight nodes interconnected by eight edges linking frontal, parietal and occipital regions was identified as showing reduced functional connectivity in patients. For each node, we computed mean inter-regional connectivity, intra-regional homogeneity (mean correlation between each pair of its constituent voxels) and mean amplitude of signal fluctuations (power spectral density). (We did not examine phase or frequency effects due to the limited temporal resolution and bandwidth of fMRI.) Consistent with other findings (Hoptman et al., 2010; Liu et al., 2006), intra-regional homogeneity was reduced in patients in all but two of the eight nodes, while mean signal power was decreased in all but three nodes. In patients, inter-regional connectivity was correlated with intra-regional homogeneity in four regions and with mean signal power in two of these four (Fig. 4C),

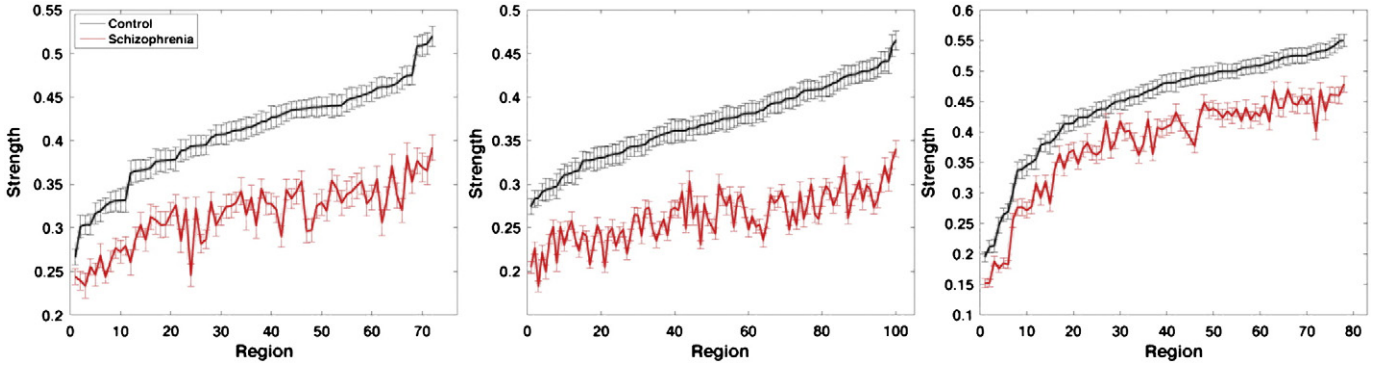

Fig. 3. Mean regional functional connectivity strength, s_r, for all network nodes examined in three different studies comparing healthy controls and people with schizophrenia. Left presents data from a resting-state fMRI study of patients with chronic schizophrenia (Lynall et al., 2010). Middle presents data from a resting-state fMRI study of childhood-onset schizophrenia (reproduced from Alexander-Bloch et al., 2010). Right presents data from a study of functional brain networks in first episode patients and controls performing a cognitive control task (Fornito et al., 2011c). Nodes have been ordered according to mean strength in the control sample of each study. Error bars represent the standard error.

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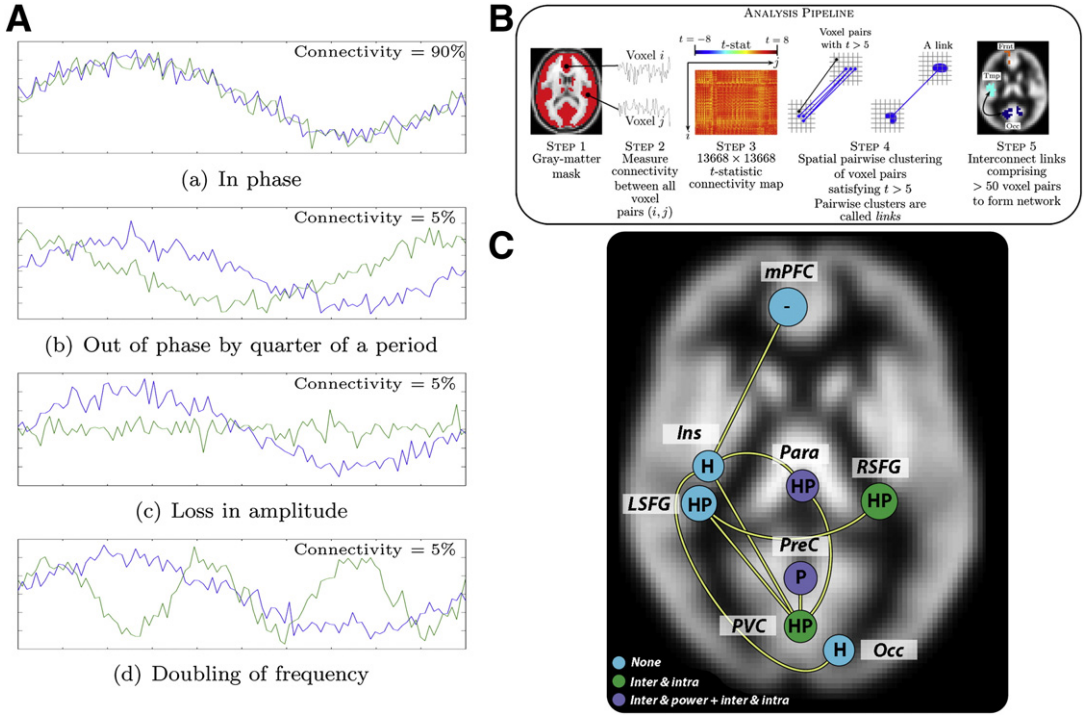

Fig. 4. Illustration of the relationship between intra-regional dysfunction and inter-regional functional connectivity. A, Some hypothetical scenarios demonstrating possible relationships between the two. Blue and green lines represent two synchronous sinusoidal oscillations corrupted by Gaussian noise (a). Altering the phase (b), reducing the amplitude (c) and doubling the frequency (c) of the green time course, each of which may result from intra-regional dysfunction, leads to a substantial reduction in inter-regional functional connectivity, as computed using the Pearson correlation coefficient (reproduced from Zalesky et al., 2011b). B, Overview of the method implemented by Zalesky et al. (2011b) to identify altered resting-state functional networks in patients with schizophrenia. A gray-matter mask was used to define 13,668 voxel-based nodes (step 1). Activity time courses from each voxel were extracted and functional connectivity estimated between each possible pair of voxels (step 2). A *t*-statistic was computed at each of the resulting 93.4×10^7 edges, comparing each edge strength s_e value between patients and controls to generate a difference matrix (step 3). Edges surviving a primary threshold of $t > 5$ were clustered according to the spatial proximity of their linked voxels to form merged links between multi-voxel nodes (step 4). Statistical inferences were then performed at the subnetwork level using the NBS (Zalesky et al., 2010a, 2010b). C, A single axial slice showing the sub-network of eight nodes and eight edges showing reduced functional connectivity in patients. Nodes are located according to their x and y coordinates (the z-plane has been collapsed to ease visualization). Nodes are colored according to whether a significant correlation was found between its intra-regional properties and inter-regional connectivity (blue: no significant relationship; green: inter-regional connectivity and intra-nodal homogeneity were significantly correlated; purple: inter-regional connectivity was significantly correlated with both intra-regional homogeneity and mean signal power). Letters within each node represent whether a significant group difference was found for intra-regional properties: *P* indicates a difference was found in regional mean fluctuation amplitude (power spectral density); *H* indicates a difference was found in intra-regional homogeneity; – indicates no difference was found. By definition, all nodes showed reduced inter-regional connectivity. Thus, for example, the insula node (Ins) showed reduced intra-regional homogeneity (*H*) and no correlation between intra-regional properties and inter-regional connectivity (blue color). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) …web version of this article.) mPFC = medial prefrontal cortex; Para = Parahippocampus; LSFG = left superior frontal gyrus; RSFG = right superior frontal gyrus; PreC = Precuneus; PVC = primary visual cortex; Occ = Occipital cortex.

indicating that alterations of inter-regional functional coupling in schizophrenia are related to intra-regional dysfunction in some, but not all, cases. This points to a potential heterogeneity of the mechanisms causing inter-regional functional dysconnectivity in the disorder. Unfortunately, our correlational design did not allow us to determine whether intra- or inter-regional dysfunction was the primary deficit. Mechanistically, it is unclear whether microscopic alterations of synaptic processes or macroscopic miswiring of association fibers caused the observed findings, though various lines of evidence point to a potential role for both (Glantz and Lewis, 2001; Harrison and Weinberger, 2005; Walterfang et al., 2006; Zalesky et al., 2011a).

Is functional connectivity in schizophrenia increased, decreased, or both?

Schizophrenia has variously been characterized as a disorder of hypo-connectivity (Alexander-Bloch et al., 2010; Fornito et al., 2011c; Lynall et al., 2010), hyper-connectivity (Salvador et al., 2007; Whitfield-Gabrieli et al., 2009), and a more generalized dysconnectivity syndrome involving both (Liu et al., 2008; Stephan et al., 2006; Wolf et al., 2009). Each type of abnormality may be plausibly linked to the disorder's phenomenology. For example, one proposed consequence of hypo-connectivity is reduced inter-regional functional integration, which is thought to result in the loosening of cognitive associations long viewed as a core feature of schizophrenia (Bleuler, 1911/1950; Friston and Frith, 1995). Conversely, hyper-connectivity of certain brain regions has been thought to reflect increased functional integration and the excessive salience of, and/or focus on, internal stimuli (Whitfield-Gabrieli et al., 2009). A more generalized state of dysconnectivity, reflecting both increases and decreases in connectivity, could point to either a diffuse dysregulation of neural dynamics or possible compensatory changes in response to primary deficits (e.g., an upregulation of certain types of connectivity to compensate for deficits elsewhere). The localization of these changes may determine the dominant form of symptomatology expressed at any given time.

The overwhelming majority of studies in schizophrenia have reported evidence for connectivity reductions in patients, as quantified using numerous techniques (reviewed in Pettersson-Yeo et al., 2011). Research using ga-fMRI is consistent with this trend (see Table 1), barring four exceptions (Liu et al., 2008, 2012; Salvador et al., 2010b; Zhou et al., 2007). These exceptions highlight the potential role that methodological choices can have on the findings. For example, three of these studies either corrected regional activity time courses for covariance with a global signal averaged across the entire brain (Liu et al., 2012; Zhou et al., 2007), or computed functional connectivity between regional pairs using a partial correlation approach that controlled for temporal covariance with all other *N*-2 regions

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(Liu et al., 2008). While these methods can increase the specificity of functional connectivity measures and correct for sources of non-neuronal physiological noise (Fox et al., 2009; Van Dijk et al., 2010), they also shift the distribution of connectivity weights c_{ij} in C so that it is approximately centered on zero. This results in a greater proportion of negative weights, some of which may be spurious (Fox et al., 2009; Murphy et al., 2009). As a result, a connectivity increase in patients could either be due to a stronger positive correlation, reflecting a genuine functional connectivity increase, or a weaker negative correlation, indicating a reduction in (negative) functional connectivity. These possibilities suggest distinct pathophysiological interpretations. Thus, while the appearance of negative weights in a connectivity matrix does not necessarily invalidate subsequent analyses (Fox et al., 2009), care should be taken to consider the sign of these weights when interpreting group differences in s_e or s_r.

Salvador et al. (2010a, 2010b) found evidence of increased medial PFC connectivity, as estimated using partial coherence, in patients using a hybrid parcellation method that enabled voxel-resolution mapping of connectivity differences. Other studies using more refined, functional or voxel-based node definitions have also reported increased connectivity in patients (Liu et al., 2012; Skudlarski et al., 2010; Zhou et al., 2007), suggesting that the resolution of analysis may also affect whether increases or decreases are observed. However, significant connectivity decreases in the absence of increases have been found in studies where global signal correction and/or high resolution, functionally defined nodes have been used (Repovs et al., 2011; Zalesky et al., 2011b), indicating that these methods do not always lead to abnormally increased connectivity in patients. Further work examining how variations in node and edge definition affect whether findings of increased or decreased connectivity are reported in schizophrenia will be necessary before firm conclusions can be drawn on the pathophysiological significance of these changes.

Symptomatology at the time of scanning may influence whether hyper- or hypo-connectivity is found in patients, as positive associations between increased connectivity and the severity of different symptom dimensions of schizophrenia have been found (Cole et al., 2010; Salvador et al., 2010a; Vercammen et al., 2010; Whitfield-Gabrieli et al., 2009). Negative correlations have also been reported however (Repovs et al., 2011; Salvador et al., 2010a), suggesting a complex relationship between functional connectivity measures and clinical status.

Is functional dysconnectivity in schizophrenia state-dependent?

The brain's functional dynamics are inherently transient. Neural ensembles synchronize and desynchronize in response to environmental stimulation and endogenous drives (Varela et al., 2001), while also being modulated by more prolonged changes in tonic arousal or mood states (Greicius et al., 2008; Harrison et al., 2008; Horovitz et al., 2008). Thus, an important issue for studies of functional dysconnectivity in schizophrenia concerns the degree to which the findings depend on the particular experimental paradigm used, as the paradigm may bias analyses to detect differences in the specific brain systems that it engages. This means that group differences may only be apparent in a given psychological context; i.e., they are context-dependent. Alternatively, the group differences may reflect a more generalized, context-independent dysconnection syndrome and bear little relation to the task being performed.

Complete characterization of the context-dependence of functional dysconnectivity in schizophrenia is only possible through the analysis of neural dynamics across multiple experimental paradigms. To our knowledge, no such ga-fMRI study has yet been published, though early positron emission tomography work did find consistent reductions in fronto-temporal connectivity across three different language tasks (Friston and Frith, 1995). Some studies have examined large-scale functional brain network interactions during cognitive task performance in patients, although they have not used measures that distinguish context-dependent, task-related modulations of

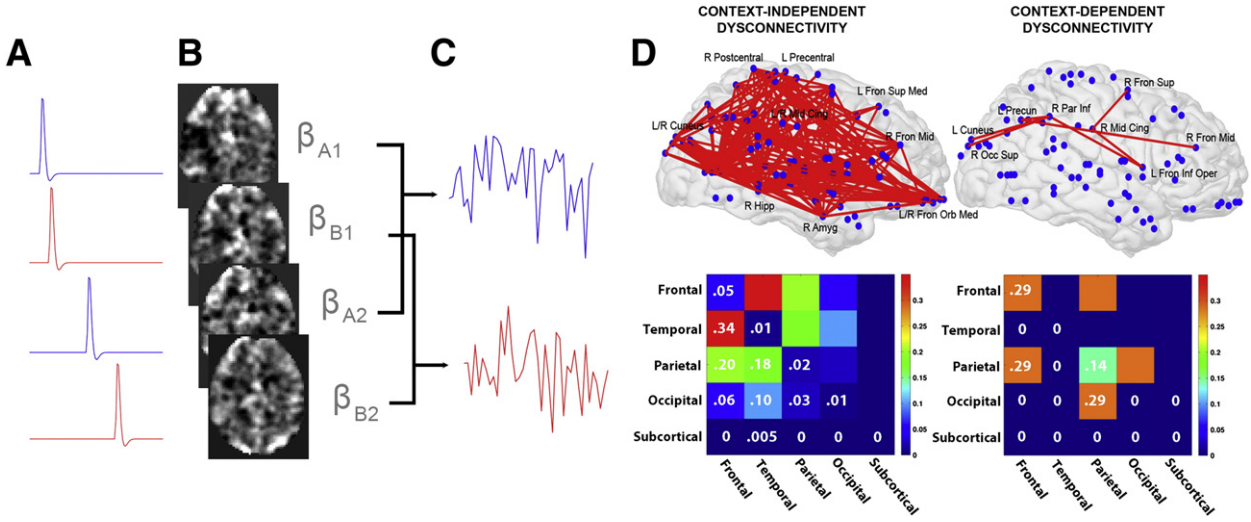

Fig. 5. Context-independent and context-dependent functional connectivity reductions observed in patients with first episode schizophrenia performing a cognitive control task. To generate event-related functional brain networks, each and every event was modeled with a unique regressor (A), resulting in a beta map for each event reflecting the degree to which each voxel's activity was modulated by that trial (B). These beta maps were then sorted by condition and concatenated to generate a beta series for each voxel, reflecting trial-to-trial variations in event-specific evoked responses (C). The resulting beta series maps were parcellated with an anatomical template and mean regional beta series were correlated for every pair of 78 regions. The NBS (Zalesky et al., 2010a, 2010b) was then used to identify sub-networks showing reduced functional connectivity in patients that were either constant across task conditions (context-independent) or specifically associated with the implementation of cognitive control (context-dependent). The sub-network showing context-independent dysconnectivity in patients comprised 200 edges linking 54 regions (D, top left). Classifying edges in this subnetwork based on the lobes that they interconnected and analyzing their relative frequencies indicated that the majority were fronto-temporal or fronto-parietal (D, bottom left). The sub-network showing context-dependent dysconnectivity comprised seven edges linking eight regions (D top right), and was primarily localized to fronto-parietal systems (D bottom right). Amyg = amygdala; Fron Inf Oper = inferior frontal operculum; Fron Mid = middle frontal gyrus; Fron Orb Med = medial orbital frontal gyrus; Fron Sup = superior frontal gyrus; Fron Sup Med = superior medial frontal gyrus; Hipp = hippocampus; L = left; Mid Cing = mid cingulate gyrus; Occ Sup = superior occipital gyrus; Par Inf = inferior parietal cortex; Precun = precuneus; R = right. Image adapted from Fornito et al. (2011a).

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functional connectivity from generic, task-unrelated dynamics (Lord et al., 2011; Wang et al., 2010; Yu et al., 2011).

We recently analyzed context-dependent and context-independent inter-regional functional interactions during performance of one specific task assessing cognitive control by using a beta series correlation approach (Rissman et al., 2004; Yoon et al., 2008) to generate measures of event-related functional connectivity for each task condition (Fornito et al., 2011c) (Figs. 5A–C). The method allowed us to test for main effects of group, task and their interaction, on functional connectivity measured using s_r and s_e. The main effect, reflecting differences between patients and controls that were insensitive to task demands (i.e., context-independent), revealed a marked, widespread reduction of both s_r and s_e in patients, with fronto-temporal and fronto-parietal connections being the most affected (see Fig. 5D). The interaction effect, reflecting group differences in connectivity associated specifically with the implementation of cognitive control (i.e., context-dependent), revealed a more circumscribed deficit affecting interactions between frontal and parietal cortices. Together, these findings suggest that circuit-specific, context-dependent alterations in functional coupling are superimposed on a background of pervasive, context-independent connectivity deficits in schizophrenia, consistent with the profile of domain-specific and generalized cognitive deficits known to characterize the disorder (Heinrichs and Zakzanis, 1998).

Though our analysis was focused on one specific cognitive task, other studies conducted in patients at different illness stages and during diverse cognitive states have also found evidence for a relatively global impairment of functional connectivity (Fig. 3). Moreover, dynamic causal modeling of networks comprising a small number of pre-defined brain regions has found that differences in endogenous (i.e., task-independent) inter-regional connectivity parameters are more replicable than context-dependent changes (Allen, et al., 2010; Mechelli et al., 2007; Benetti et al., 2009; Crossley et al., 2009). These convergent findings support the idea of a diffuse and generalized functional connectivity deficit in schizophrenia, though further replication across multiple experimental paradigms is required.

An alternative and common strategy for investigating putative context-independent functional dysconnectivity in schizophrenia has been to study spontaneous brain dynamics with resting-state fMRI. In this work, participants are scanned as they quietly lie in the scanner without performing any explicit task. The topography of functional connectivity networks measured under such conditions recapitulates well-known task-evoked co-activation patterns (Smith et al., 2009) and is correlated with underlying anatomical connectivity (Honey et al., 2009; Skudlarski et al., 2008; Zalesky and Fornito, 2009) and synchronized oscillations in neuronal activity (He et al., 2008). Resting-state connectivity measures are heritable (Glahn et al., 2010; Fornito et al., 2011b) and robust across individuals and over time (Damoiseaux et al., 2006; Shehzad et al., 2009), leading to the conclusion that they characterize a relatively stable and intrinsic property of brain function (Fox and Raichle, 2007). A corollary of this view is that case–control differences in such measures reflect a context-independent alteration of the brain's intrinsic functional organization, an assumption implicit in the widespread use of resting-state designs in most ga-fMRI studies of schizophrenia (Table 1). However, evidence that resting state measures correlate with pre-scan anxiety ratings (Seeley et al., 2007), and that they are affected by the performance of a prior task (Albert et al., 2009; Barnes et al., 2009; Lewis et al., 2009; Tambini et al., 2010) and induced changes in mood state (Harrison et al., 2008), suggest that such an interpretation may be too simplistic. Rather, such measures likely capture a stable, intrinsic component of functional brain dynamics as well as a more transient context-dependent component (Fransson, 2006; Fox and Raichle, 2007). Unfortunately, it can be difficult to discern which component contributes to any observed differences between patients and controls (Fornito and Bullmore, 2010), meaning that the functional and/or clinical significance of such differences should be validated using additional measures.

Does functional dysconnectivity in schizophrenia have a structural basis?

Alterations of anatomical connectivity in schizophrenia have been frequently reported (Pettersson-Yeo et al., 2011), with reduced integrity of fronto-temporal pathways emerging as the most robust finding (Ellison-Wright and Bullmore, 2009). This finding is consistent with repeated reports of functional dysconnectivity of these systems (Friston and Frith, 1995; Fornito et al., 2011c; Zalesky et al., 2010a). Relatively few ga-MRI studies of anatomical dysconnectivity have been conducted in schizophrenia, though they support this general trend; i.e., they have reported reduced connectivity of frontal and temporal regions, regardless of whether connectivity was measured at the level of individual regions (Bassett et al., 2008; van den Heuvel et al., 2010), edges (Skudlarski et al., 2010), or interconnected subnetworks (Zalesky et al., 2011a) (Table 2). Reduced connectivity of parietal, occipital and subcortical regions has also been reported in this work, which is again congruent with the ga-fMRI evidence.

We used the NBS to characterize sub-networks of altered functional and structural connectivity in two independent samples of patients using the same anatomical parcellation for network node definition (Zalesky et al., 2010a, 2011a). Despite the differences in samples and modalities, we found considerable overlap in the affected sub-networks, with both anatomical and functional sub-networks showing reduced connectivity between frontal and posterior brain regions (Fig. 6). Notably, the anatomical sub-network comprised a

Table 2
Summary of main findings of ga-MRI studies of structural dysconnectivity in schizophrenia.

Study	Modality	Sample	Illness duration (years)	Network	Node definition	Edge definition	Measures	Main findings
Bassett et al. (2008)	T1	203 SZ 259 HC	n/a	104 C and SC	A	GVC	k	↓ k primarily in frontal and temporal regions
Skudlarski et al. (2010)	DTI	27 SZ 27 HC	n/a	Hybrid	A/V	NIS	s_e	↓ s_e in frontal, temporal, parietal and occipital regions
van den Heuvel et al. (2010)	DTI/MTI	40 SZ 40 HC	2.08	108 BW	A	mMTR [a]	s_r	↓ s_r in frontal, temporal and striatal regions[b]
Zalesky et al. (2010a, 2010b)	DTI	74 SZ 32 HC	~15	82 C and SC	A	NIS	s_e	↓ s_e in a sub-network of frontal, temporal and occipital regions

↓ = decreased in schizophrenia; ↑ = increased in schizophrenia; ≈ = no significant difference; A = anatomical; A/V = combined anatomic and voxel-based parcellation; BW = brain-wide; C = cortical; DTI = diffusion tensor imaging; GVC = inter-regional covariance in gray matter volumes; HC = healthy control; k = nodal degree; mMTR = mean magnetic transfer ratio of the reconstructed tracts; MTI = magnetic transfer imaging; NIS = number of reconstructed streamlines intersecting each regional pair; SC = subcortical; s_e = edge connectivity strength; s_r = regional connectivity strength; SZ = schizophrenia.

[a] The authors also defined edges using tract-averaged fractional anisotropy.

[b] Differences were significant at uncorrected levels but did not survive correction for multiple comparisons.

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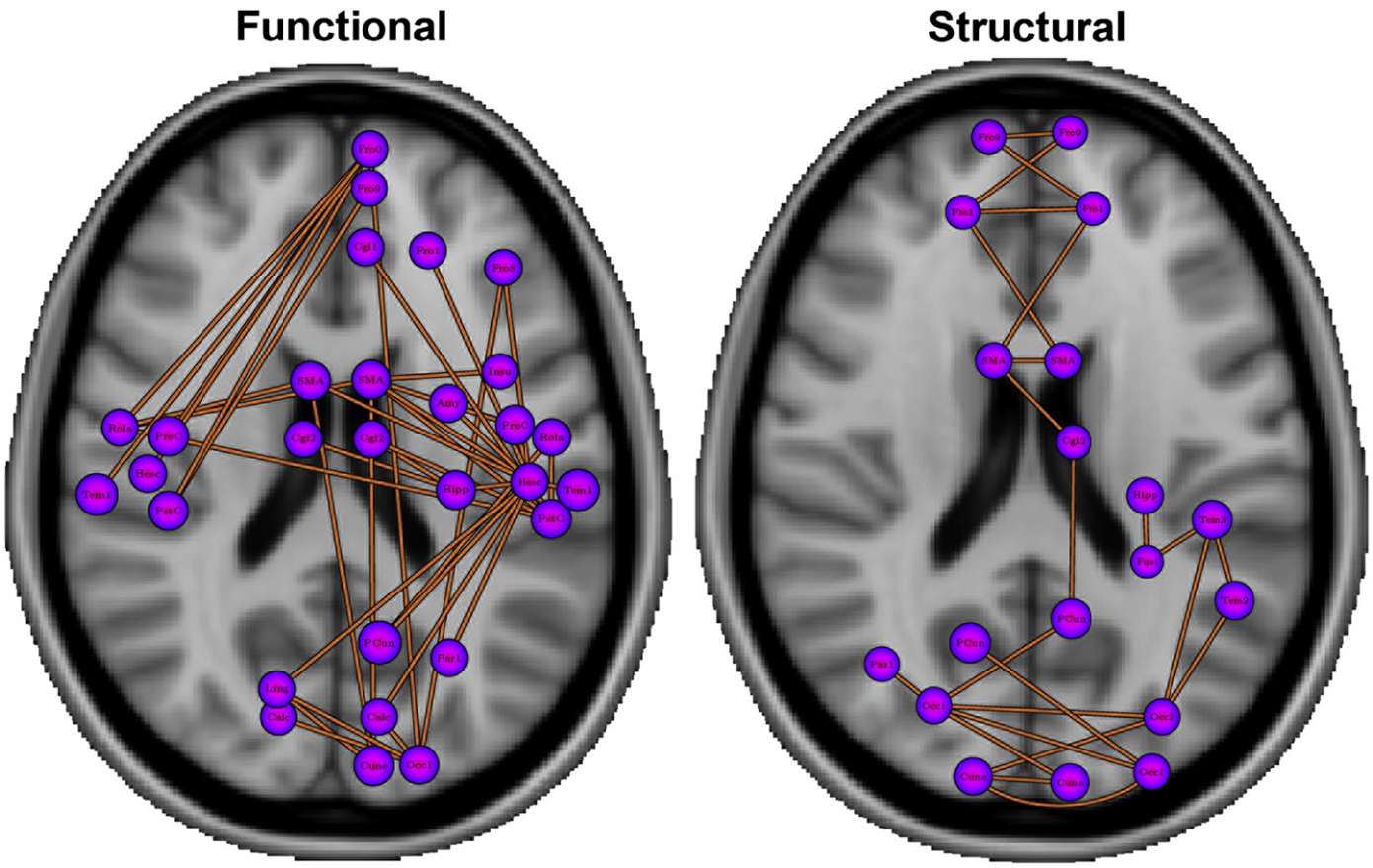

Fig. 6. Sub-networks of interconnected edges showing reduced resting-state functional (left) and structural (right) connectivity in two independent studies of people with schizophrenia. Data reproduced from Zalesky et al. (2010a, 2010b) and Zalesky et al. (2011a). Purple circles correspond to distinct brain regions defined using the same anatomical parcellation. Amy = amygdala; Calc = calcarine; Cgl1 = anterior cingulate gyrus; Cgl2 = mid anterior cingulate gyrus; Cune = cuneus; Fus = fusiform gyrus; Fro0 = medial orbital frontal gyrus; Fro1 = superior frontal gyrus; Fro8 = inferior orbital frontal gyrus; Fro9 = superior medial frontal gyrus; Hesc = heschl's gyrus; Hipp = hippocampus; Insu = insula; Ling = lingual gyrus; Occ1 = superior occipital gyrus; Occ2 = mid occipital gyrus; Par1 = superior parietal cortex; PCun = precuneus; PreC = precentral gyrus; PstC = postcentral gyrus; Rola = rolandic gyrus; SMA = supplementary motor area; Tem = superior temporal gyrus; Tem2 = middle temporal gyrus; Tem3 = inferior temporal gyrus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

subset of the affected functional connections and was principally localized to the midline. The restricted nature of the anatomical changes may reflect the greater abundance of functional 'connections' in the brain, indexing polysynaptic, indirect interactions between brain regions (Honey et al., 2009), or downstream functional effects of primary, more circumscribed anatomical deficits. The localization of the anatomical network to the midline may also reflect a limitation of diffusion-MRI for accurate whole-brain tract reconstruction, as pathways between medial and lateral regions can be difficult to reconstruct without algorithms that can track fibers over long distances and across voxels containing crossing fibers (e.g., Zalesky and Fornito, 2009).

Skudlarski et al. (2010) directly investigated the association between structural and functional connectivity in the same sample, reporting that the two are de-coupled in patients relative to controls. Separate comparison of structural and functional edge-wise connectivity revealed that anatomical connectivity was reduced while functional connectivity was both increased and decreased in patients across different pair-wise connections. These findings point to a complex interplay between structural and functional dysconnectivity in schizophrenia. Specifically, they demonstrate that reduced anatomical connectivity does not always lead to reduced function, and that abnormally increased connectivity may emerge as a possible compensatory response to a functional or anatomical deficit, though whether the primary deficit is anatomical or functional remains unclear. Altered anatomical connectivity between regions is likely to affect their functional dynamics, yet prolonged alterations in functional dynamics can also produce structural changes by affecting synaptic plasticity and, subsequently, long-range fiber integrity. Determining which takes precedence will likely only be possible through long-term longitudinal research attempting to pinpoint the onset of connectivity abnormalities as schizophrenia develops.

The measure used to quantify anatomical connectivity in imaging connectomic studies (e.g., Table 2) may affect the degree to which it correlates with function. For example, several studies have used the number of reconstructed streamlines intersecting each regional pair, as generated using diffusion MRI tractography, to infer anatomical connectivity. This is an abstract quantity contingent on the fidelity of the tractographic algorithm and may bear only an indirect relation to physiologic constraints on the functional capacity of a fiber pathway, such as its diameter and/or degree of myelination. The mean fractional anisotropy (FA) (or related measures) of the connecting fiber tract may be a more functionally relevant measure (Lowe et al., 2008), but it remains a relatively non-specific index of fiber integrity. One recent innovation, implemented by van den Heuvel et al. (2010), involved using the magnetization transfer ratio (MTR), a widely applied measure of white matter myelination (e.g., Giacomini et al., 2009). In this study, the mean MTR of fiber tracts reconstructed with DTI was more sensitive to differences between patients and controls than mean tract FA, suggesting it may indeed provide a more functionally meaningful index of anatomical connectivity. However, MTR values are also affected by tissue inflammation and edema (Vavasour et al., 2011), indicating that care should be exercised when interpreting these measures. More generally, tract-averaged

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Table 3
Summary of main findings of ga-MRI studies of functional brain network topology in schizophrenia.

Study	Paradigm	Sample	Illness duration (yrs)	Network	Node definition	Edge definition	Measures	Main findings
Liu et al. (2008)[a]	Rest	31 SZ 31 HC	2.25	90 C and SC	A	pTC	Cl, L, γ, λ, σ, E_g, E_l	Global: ↓ E_l, Cl, γ and σ; = L, λ and E_g. Regional: ↓ Cl in frontal, parietal, temporal and subcortical regions; ↓ E_l in frontal, parietal and subcortical regions; ≈ L and E_g in all but a few regions;
Alexander-Bloch et al. (2010)	Rest	13 COS 19 HC	n/a	111 BW	A	WC	E_g, E_l, Cl, σ, R, Q	Global: ↓ E_l, Cl, σ; and Q; ↑ E_g and R. Regional: ↓ Cl in cingulate, insula and temporal regions; ↑ E_g in temporal and parietal regions.
Lynall et al. (2010)	Rest	12 SZ 15 HC	n/a	72 BW	A	WC	E_g, Cl, σ, R, H, α, k_c	Global: ↓ Cl, σ, k_c; ↑ E_g, H, R, α. Regional: ↓ Cl in precuneus, ACC and OFC.
Wang et al. (2010)	Contextual recollection	23 SZ 33 HC	8.1	43 C and CER	A	pSC	E_g, E_l	Global: ↓ El; ≈ E_g.
Becerril et al. (2011)	Error processing	37 SZ 32 HC	17.4	13 C and CER	F	TC	E_g, Cl, BC	Global: ≈ E_g and Cl. Regional: ≈ Cl and BC in ACC and CER.
Fornito et al. (2011c)	Response inhibition	23 SZ 25 HC	FE	78 C and SC	A	BSC	γ, λ, σ, E_g, E_l	Global: ≈ γ, λ, σ, E_g, E_l.

↓ = decreased in schizophrenia; ↑ = increased in schizophrenia; ≈ = no significant difference; α = exponent of the power-law scaling regimen in the degree distribution; A = Anatomical; ACC = anterior cingulate cortex; BC = betweeness centrality, a path length based measure of how central a node is in the network (see Freeman, 1977); BSC = Beta series correlation (see Fig. 5); BW = brain-wide; C = cortical; Cl = clustering coefficient; COS = childhood-onset schizophrenia; CER = cerebellum; E_g = global efficiency; E_l = local efficiency; F = functional; FE = first episode; $\gamma = Cl/Cl_r$ where Cl_r is the clustering coefficient of a random graph; H = hierarchy, defined by the β coefficient of the logarithmic relationship between Cl and k (see Ravasz and Barabasi, 2003); HC = healthy control; k_c = exponential cut-off degree of the power-law scaling regimen in the degree distribution; L = mean path length; $\lambda = L/L_r$, where L_r is the path length of a random graph; OFC = orbitofrontal cortex; pSC = partial cross-subject correlation in task activation contrast values; pTC = partial temporal correlation, computed using the partial correlation between regional time courses; Q = modularity; R = robustness; SC = subcortical; σ = small-worldness, defined γ/λ; SZ = schizophrenia; TC = temporal correlation, computed as the Pearson correlation between regional time courses; WC = Pearson correlation between mean regional wavelet coefficients.

[a] These authors analyzed both τ- and κ-matched networks. Only results from the latter comparisons are presented here.

integrity measures may show low sensitivity when pathology is isolated to a restricted portion of the fiber pathway because such a change will be obscured when averaged with integrity estimates derived from healthy tissue.

Summary

The available findings indicate that schizophrenia is associated with a relatively diffuse, context-independent reduction in functional connectivity that particularly affects interactions between frontal cortex and posterior regions. This diffuse deficit acts as a background for more circumscribed, context-dependent alterations, in which abnormally increased connectivity may also be observed. Early work indicates that these functional abnormalities have an anatomical basis, although the relationship between anatomical and functional dysconnectivity in schizophrenia, at least on the basis of existing data, is not straightforward.

Brain network topology in schizophrenia

The application of graph analytic techniques to MRI data allows the computation of a wide range of measures that characterize diverse topological properties of the human connectome. Extensive treatments of these measures, including formal definitions, have been provided elsewhere (Albert and Barabasi, 2002; Boccaletti et al., 2006; Newman, 2003; Rubinov and Sporns, 2010). In the following, we provide a conceptual overview of some of the key topological properties investigated in imaging connectomic studies of schizophrenia (see Tables 3 and 4 for a summary).

Global and local integration, efficiency and cost

Two of the most widely studied topological properties of brain networks are the clustering coefficient, Cl, and the characteristic path length, L. The former corresponds to the probability that two nodes connected to an index node are also connected to each other. An analogy in social networks is the likelihood that two friends of a given person are also friends with each other. The measure provides an index of local clustering or cliquishness of network connectivity (Fig. 1). The characteristic path length of a network, L, represents the mean minimum path length between nodes in the graph and indexes the global topological integration of the network. If fewer edges must be traversed to move from one node to any other in the network, L is low and the network is globally integrated (i.e., information can propagate relatively quickly throughout the network).

Completely regular graphs such as lattices have high Cl and low L, whereas random graphs have high L and low Cl. The brain belongs to a class of networks falling in between these two extremes; i.e., it shows a small-world topology characterized by high Cl and comparable L relative to a random graph (Achard et al., 2006; Humphries et al., 2006; Watts and Strogatz, 1998). Small-world properties are found in a range of complex networks (Newman, 2003; Watts and Strogatz, 1998) and the combination of high Cl and low L is thought to provide the brain with an optimal structure to simultaneously support locally segregated and globally integrated processing (Bassett and Bullmore, 2006; Sporns, 2011; Sporns and Zwi, 2004).

Two related measures are network global and local efficiency (Latora and Marchiori, 2001, 2003). Global efficiency, E_g, is inversely related to L such that networks with lower mean path length are characterized by higher global efficiency, the intuition being that communication is more efficient when fewer connections must be traversed to pass information between any two nodes. E_g therefore provides a measure of globally integrated, parallel information-processing. Local efficiency, is defined as the mean efficiency of the subgraph defined by each node's neighbors after removal of that node. It is positively associated with Cl and is thought to index local information-processing or network fault tolerance. Small-world networks such as the brain are characterized by comparable E_g and high E_l relative to random graphs (Achard and Bullmore, 2007; Latora and Marchiori, 2003).

In schizophrenia, reductions in topological measures of local information processing (Cl and E_l) have been consistently found in ga-fMRI studies (Table 3). Two studies (Alexander-Bloch et al., 2010; Lynall et al., 2010) have also reported increased global efficiency, E_g. These findings accord with an earlier electroencephalographic report of reduced Cl and L in first episode patients, which was interpreted as evidence for a subtle randomization of network topology (Rubinov et

Table 4
Summary of main findings of ga-MRI studies of structural brain network topology in schizophrenia.

Study	Modality	Sample	Illness duration (yrs)	Network	Node definition	Edge definition	Measures	Main findings
Bassett et al. (2008)	T1	203 SZ 259 HC	n/a	104 C and SC	A	GVC	*Cl*, *H*, *As*	Global: ↑ *As* Regional: ↓ *H* of transmodal association cortex; ↓ and ↑ *Cl* mainly left frontal and temporal regions;↑ *D* of multimodal association cortex
van den Heuvel et al. (2010)	DTI/MTI	40 SZ 40 HC	2.08	108 BW	A	mMTR[a]	*L*, *Cl*, λ, γ, *BC*	Global: ≈ λ and γ. Regional: ↑ *L* in frontal, temporal and striatal regions; ↓ *L* in parietal cortex; ↓ *Cl* in frontal, temporal, parietal and cerebellar regions; ↑ *Cl* in visual cortex; ↓ *BC* in PFC; ↑ in temporal and parietal regions.
Zalesky et al. (2010a, 2010b)	DTI	74 SZ 32 HC	~15	82 C and SC	A	NIS	λ, γ, σ, E_g	Global: ≈ σ; ↓ γ and E_g; ↑ λ

↓ = decreased in schizophrenia; ↑ = increased in schizophrenia; ≈ = no significant difference; A = anatomical; *As* = assortativity, reflecting the correlation between a node an its neighbors; *BC* = betweeness centrality, a path length based measure of how central a node is in the network (see Freeman, 1977); BW = brain-wide; C = cortical; *Cl* = clustering coefficient; DTI = diffusion tensor imaging; E_g = global efficiency; $\gamma = Cl/Cl_r$ where Cl_r is the clustering coefficient of a random graph; GVC = inter-regional covariance in gray matter volumes; *H* = hierarchy, defined by the β coefficient of the logarithmic relationship between *Cl* and *k* (see Ravasz and Barabasi, 2003); HC = healthy control; $\lambda = L/L_r$, where L_r is the path length of a random graph; mMTR = mean magnetic transfer ratio of the reconstructed tracts; MTI = magnetic transfer imaging; NIS = number of reconstructed streamlines intersecting each regional pair; SC = subcortical; σ = small-wordlness, defined γ/λ; SZ = schizophrenia.

[a] The authors also defined edges using tract-averaged fractional anisotropy.

al., 2009). Such an effect may be context-dependent, as ga-fMRI studies of functional brain network interactions during task performance have failed to find evidence for global topological differences (Becerril et al., 2011; Fornito et al., 2011c; Wang et al., 2010).

As with fMRI, studies of structural dysconnectivity in schizophrenia have also reported reduced regional clustering in patients (Bassett et al., 2008; van den Heuvel et al., 2010; Table 4). (While Zalesky et al., 2011a, found evidence of increased *Cl*, the networks were not matched for κ and so the results may have been confounded to some extent by group differences in network sparsity.) In contrast to the functional findings however, *increased* regional path length has been observed in the structural brain networks of patients (van den Heuvel et al., 2010; Zalesky et al., 2011a). Collectively, these studies suggest that both structural and functional networks in schizophrenia are associated with reduced topological integration of local information-processing. However, while functional connectivity networks in patients may be characterized by a context-dependent increase in global integration, structural network topology is suggestive of a decrease. This discrepancy reiterates the potentially complex relationship between structural and functional brain network alterations in the disorder.

Another important property of small-world networks is their economy: they typically provide high topological efficiency for low connection cost (Latora and Marchiori, 2003). Connection costs in the brain arise from the metabolic resources required for forming and maintaining the brain's axonal wiring and are proportional to total wiring volume (Laughlin and Sejnowski, 2003). Accordingly, a diverse body of evidence shows strong evolutionary pressures on the brain to minimize wiring costs (Chen et al., 2006; Cherniak et al., 2004; Chklovskii et al., 2002). The brain does not minimize wiring costs in an absolute sense however, as it possesses long-range inter-regional projections that, though costly, provide topological short-cuts which greatly increase network efficiency (Buzsaki et al., 2004; Kaiser and Hilgetag, 2006). These considerations suggest that the connectome evolved to satisfy competitive selection criteria of minimizing connection cost and maximization communication efficiency, a balance that may be framed in terms of cost-efficiency optimization. Accordingly, recent evidence indicates that the human connectome is indeed configured in an optimally cost-efficient manner, subject to certain high-dimensional constraints (Bassett et al., 2010). Notably, reductions in functional brain network cost-efficiency have been found using magnetoencephalography in people with schizophrenia performing a working memory task (Bassett et al., 2009). A potential genetic basis for these changes is suggested by evidence that functional brain network cost-efficiency is highly heritable, with up to 60% of global and 80% of regional effects attributable to genetic factors (Fornito et al., 2011b). Thus, reduced cost-efficiency of functional brain network topology may represent a viable intermediate phenotype for schizophrenia.

The above findings should be interpreted with respect to certain caveats. First, putative measures of local information processing, such as *Cl* and E_l, are only local in a topological sense and take no account of spatial relationships between brain regions. It is therefore possible for two regions at opposite ends of the brain to be considered topological 'neighbors' simply because they are functionally or anatomically connected. In physically embedded networks such as the brain, spatially constrained measures of local information processing may provide more intuitive topological characterizations.

A second caveat is that the interpretation of efficiency and cost measures in functional brain networks can be ambiguous. Functional connections bear only a partial relationship with underlying anatomy (Honey et al., 2009) and so they do not directly reflect the physical wiring used to sustain inter-regional functional interactions. Thus, without anatomic or metabolic measures, the connection costs of a functional network can only be inferred indirectly (see Fornito et al., 2011b for a discussion). Similarly, measures based on shortest paths such as E_g and *L*, can be ambiguous in functional networks because the edge weights on which they are based are typically derived using continuous association metrics that directly index the degree of functional interaction between node pairs. It is therefore unclear whether measures based on indirect paths between nodes add any further information concerning their functional integration (Rubinov and Sporns, 2011). The interpretation of these measures ultimately depends on the treatment of low weight edges. Most functional studies treat such edges as reflecting noise that, for practical purposes, can be removed (via thresholding) and interpreted as an 'absent' connection. In this case, any communication between unconnected node pairs is assumed to propagate via indirect paths, and path length-based measures may therefore index a valuable topological property of the network (though see Telesford et al., 2011 for an alternative view). The high heritability of path length (and cost) based characterizations of functional network topology (Fornito et al., 2011b; Smit et al., 2008), as well as their associations with cognitive performance (Bassett et al., 2009; van den Heuvel et al., 2009) and disease (Bassett et al., 2009; He et al., 2009; Liu et al., 2008), support this contention. However, findings of a negative correlation between measures of global topological integration derived using E_g and global functional integration computed using principal component analysis of the connectivity weights c_{ij} (Lynall et al., 2010), suggest

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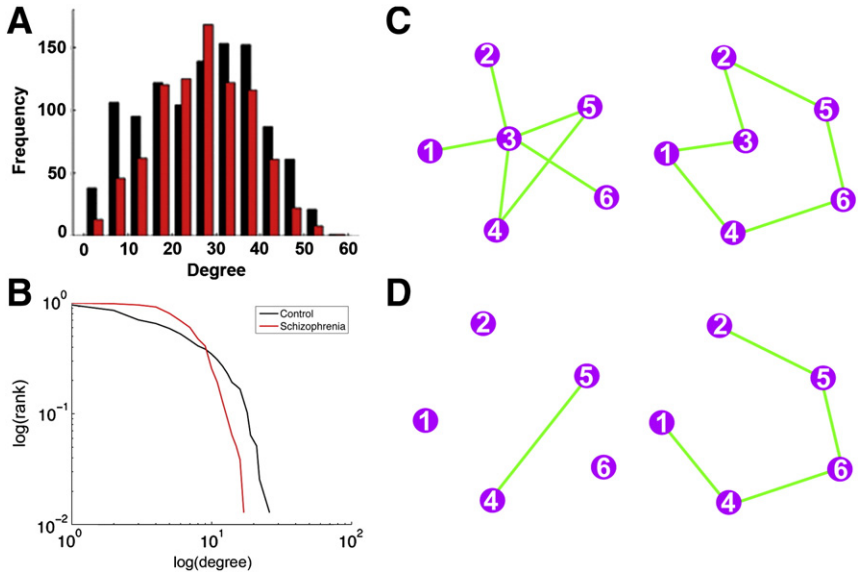

Fig. 7. Illustration of the relationship between network degree distribution, robustness and fragmentation. A, Pooled degree distributions of patients with schizophrenia (red) and healthy controls (black) showing a lower probability of highly connected nodes in the former group in resting-state functional networks (image reproduced from Lynall et al., 2010). B, Example of a rank-degree distribution plotted in doubly logarithmic axes for a task-related functional network of one first episode patient (red) and one control (black) studied in Fornito et al. (2010). The power-law scaling regimen is flatter and the exponential fall-off occurs earlier in patients, indicative of a lower probability of finding highly connected hubs (Lynall et al., 2010). C, Example graphs illustrating the relationship between degree distribution heterogeneity and robustness. The graph on the left is a variant of a star network, whereas the graph on the right is connected as a ring. Both have a total of six edges, though these are distributed differently. The star network has a heterogeneous degree distribution, such that node 3 is a major hub with $k=5$, node 5 has $k=2$, and all others have $k=1$. In contrast, the ring network has a homogeneous degree distribution with each node having $k=2$. D, The same two networks after node 3 and its incident edges have been removed. The star network (left) becomes completely fragmented because most of its edges were linked to node 3. In contrast, the ring network (right) remains connected. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

that the functional consequences of topological variations in path length based measures may not always be straightforward. As such, the putative functional effects of any topological differences should always be interpreted with respect to their relation to other measures of connectivity and topology (e.g., Alexander-Bloch et al., 2010; Lynall et al., 2010).

Degree distribution and robustness

The distribution of nodal connectivity in the brain, termed the degree distribution, is non-uniform, showing power-law scaling characteristics that can be described as either scale-free or broad-scale (Amaral et al., 2000; Barabasi and Albert, 1999). Scale-free networks have a degree distribution that follows the form $P(k) \sim k^{-\alpha}$, meaning that the network has a higher number of high degree nodes, termed hubs, than would be expected in a random graph. In broad-scale networks, the scaling regime is exponentially truncated such that the degree distribution follows the form $P(k) \sim k^{-\alpha-1} e^{k/k_c}$. The probability of finding highly connected hub nodes in these networks is lower than for a scale-free topology, but still higher than chance (Amaral et al., 2000). Reports of both scale-free (Eguiluz et al., 2005; van den Heuvel et al., 2008) and broad-scale (Achard et al., 2006; He et al., 2007; Fornito et al., 2010) properties in brain networks have been published, though the latter have been more common. In general, a broad-scale topology is characteristic of physically embedded networks, where spatial constraints (e.g., the skull) limit the total number of connections any single node can possess.

The degree distribution of a network has important implications for its robustness. Network robustness, *R*, is defined with reference to how a network fragments following removal of its constituent nodes and incident edges. *N*-1 nodes are removed either at random or in order of degree, and the robustness of the network can be defined in terms of how quickly it fragments following removal of these nodes (Chen et al., 2007; Figs. 7C–D). Random removal simulates stochastic failures in the network whereas ordered removal simulates targeted attack of the most highly connected nodes (Albert et al., 2000). Compared to random graphs, scale-free networks are more robust to random node failures but highly vulnerable to targeted attacks since the removal of just a few highly connected hubs quickly fragments the graph (Albert et al., 2000; Figs. 7C–D). Broad-scale networks are more resistant to targeted attack because hubs feature less prominently and connections are distributed more evenly across nodes, though this comes at the expense of a slight decrement in robustness to random node deletion (Achard et al., 2006).

Two studies have examined robustness in schizophrenia, both using resting-state ga-fMRI and both reporting that patients showed increased robustness to targeted and/or random node removal (Alexander-Bloch et al., 2010; Lynall et al., 2010). In one study, analysis of degree distribution properties indicated that this increased robustness was due to a lower probability of finding highly connected hubs in the patient group (Bassett et al., 2008; see also ; Lynall et al., 2010; Wang et al., 2010; Figs. 7A–B). A relative lack of hubs results in a more homogeneous distribution of connections across different network nodes, promoting greater robustness to targeted node removal (Figs. 7C–D). This increased robustness in patients may represent one potential functional benefit embedded within a general picture of dysfunction and deficit. Such a benefit, which implies greater resilience to focal neural damage, has been proposed as a potential explanation for the persistence of risk genes for schizophrenia despite strong contrary selection pressures on the disease (Lynall et al., 2010). It is as yet unclear however, whether robustness is a heritable property of brain network topology.

Related to the robustness finding is evidence that patients show a lower percolation threshold than controls, where percolation is defined as the connection density at which a network becomes node-connected (i.e., no longer fragmented) (Alexander-Bloch et al., 2010). Such differences in network fragmentation can confound group comparisons, particularly at sparse thresholds. For example, the clustering coefficient of an isolated node (i.e., a node with $k=0$) is zero, as is its local and global efficiency. Thus, if there are more isolated nodes in one group relative to the other, the global estimate of *Cl* (and E_l and E_g) will be down-weighted by the higher proportion of zero values. One solution may

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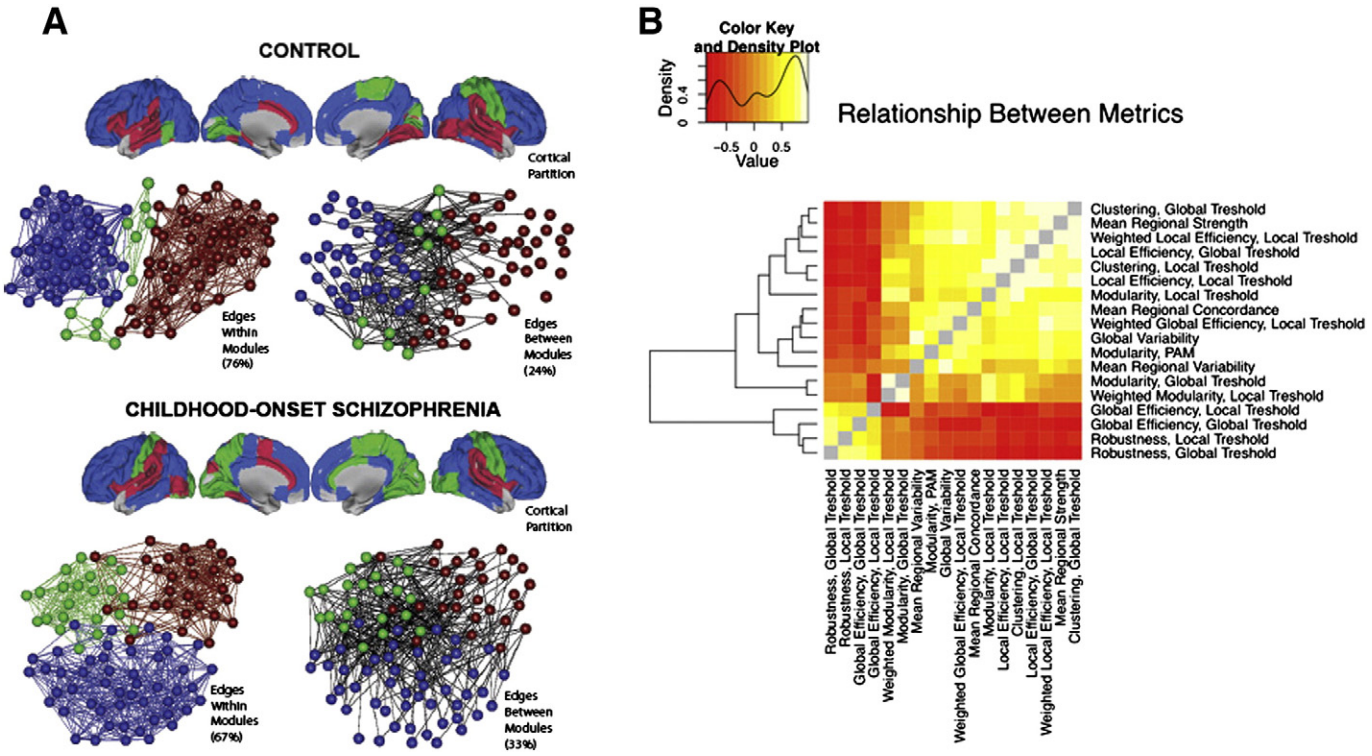

Fig. 8. Illustration of dysmodularity in schizophrenia and its correlations with other topological properties. A, The results of a modular decomposition of resting-state fMRI data from a representative patient with childhood-onset schizophrenia (bottom) and a healthy control (top). The surface maps color code each of 100 anatomical nodes according to the functional module they were assigned to. The graphs show intra-modular and inter-modular connectivity between nodes. The layouts of the nodes have been determined by a force-directed algorithm. B, Correlation matrix of global topological properties of functional brain networks in childhood-onset schizophrenia. Two broad clusters of measures are observed which are negatively correlated with each other but positively correlated with themselves. One comprises measures of robustness and global efficiency while the other comprises measures of local information processing, connectivity strength and modularity. Images adapted from Alexander-Bloch et al. (2010). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

be to use high resolution templates, which percolate at sparse connection densities (Fornito et al., 2010). An alternative is to compute a minimum spanning tree, which finds the minimum weighted combination of N-1 edges required to connect all nodes. Edges can then be added incrementally to reach a desired connection density while ensuring node-connectedness (Hagmann et al., 2008; Alexander-Bloch et al., 2010). Another alternative involves using weighted, unthresholded topological measures (e.g., Rubinov and Sporns, 2011).

Modularity

An important property of many complex networks, the brain included, is that they can be decomposed into subsets of nodes that have greater connectivity with each other than with other nodes; i.e., they are modular (Meunier et al., 2009, 2011; Newman, 2006). Many algorithms are available for characterizing the modular architecture of a graph (reviewed in Fortunato, 2010), their goal being to find an optimum decomposition that maximizes some modularity index. The most popular index, proposed by Newman and Girvan (2004), defines the goodness of a partition, Q, as the difference between the observed number of intra-modular connections and those expected by chance. Finding a partition that maximizes Q is a non-trivial (NP-hard) problem, so heuristics are often used. As a result, many alternative, similarly adequate, so-called degenerate, partitions may exist (Good et al., 2010). An analysis of possible degeneracies in the obtained decomposition is therefore important to understand its stability (Rubinov and Sporns, 2011).

David (1994) originally proposed that a dysmodularity of psychological functions may underlie the neuropsychological deficits of schizophrenia, where dysmodularity was defined as a breakdown of functionally segregated or encapsulated information processing. The correspondence between the modularity of cognitive processes and of brain network topology remains unclear, though parallels between the two provide an attractive avenue for further investigation. Only one study to date has quantified brain network modularity in patients with schizophrenia, finding consistent evidence for reduced modularity in patients using three different decomposition algorithms applied to resting-state fMRI data acquired in childhood-onset patients (Alexander-Bloch et al., 2010; Fig. 8A). Such findings imply a loss of intra-relative to inter-modular connectivity.

The modularity reductions observed in the study by Alexander-Bloch et al. (2010) were correlated with reduced local efficiency and connectivity strength, as well as increased global efficiency and robustness (Fig. 8B; note that similar associations between metrics were reported by Lynall et al., 2010). These associations point to some common disturbance exerting diffuse effects on brain network topology. The hypothesis that this common disturbance reflects a subtle randomization of network connectivity, as initially proposed by Rubinov et al. (2009), was supported by a simulation analysis in which the alterations observed in patients' networks were reproduced simply by randomizing ~5% of connections in controls' functional networks. However, four caveats limit the generality of this conclusion. First, anatomical studies have only been partially consistent with this hypothesis (see Table 4), underscoring the potentially complex relationship between structural and functional dysconnectivity in the disorder. Second, the few task-based ga-fMRI studies published to date have found limited evidence for altered functional network topology in schizophrenia (Table 3), suggesting the findings may be context-dependent. Third, most reported findings consistent with the randomization hypothesis have generally been observed in the presence of a global reduction of mean functional connectivity in patients. While this might indeed be expected under a hypothesis of connectivity randomization (i.e., a random organization will shift

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the distribution of patients' connectivity weights to be centered on zero), one consequence is that any analysis of graphs matched for connection density, κ, will result in the inclusion of proportionally more low-value (non-significant) edges in patients' networks (Fig. 2). If these values merely reflect noise, their inclusion will produce a more random topology. Evidence that profound reductions in functional connectivity can be observed in the absence of marked topological differences (Fornito et al., 2011a) suggests that topological alterations are not a necessary consequence of connectivity differences, although the two are often related (Alexander-Bloch et al., 2010; Lynall et al., 2010). Thus, care should be taken to distinguish *bona fide* topological disturbances from case–control differences in mean connectivity levels (e.g., van den Heuvel et al., 2010).

A final caveat is that a tendency towards a more random network architecture has been observed in several conditions other than schizophrenia, leading to the view that it may merely reflect a generic response to neural insult (Stam and Reijneveld, 2007). In schizophrenia, the insult could correspond to an early neurodevelopmental lesion or an aberration of later brain maturation, consistent with multi-hit developmental etiological models (Pantelis et al., 2005). Further work is therefore required to understand how topological variations in different disorders relate to similarities and differences in their phenotypic expression.

Summary

Numerous topological disturbances of structural and functional brain networks have been found in schizophrenia. Functional networks in particular may be characterized by a subtle randomization of network connectivity associated with reduced local connectivity and modularity and increased topological integration and robustness. These changes have not been observed during task-based studies (e.g., Fornito et al., 2011c), suggesting they may be context-dependent. The dependence of these topological changes on basic alterations of connectivity levels, and methodological procedures used for graph construction, needs to be clarified. Direct investigation of structural and functional topological disturbances in the same patients is an important avenue for future investigation. Finally, one important caveat affecting interpretation of all studies of functional network topology discussed here concerns the treatment of negative weights. Most commonly used graph theoretic measures of network topology are defined in relation to unsigned edge weights, and methods for accommodating negatively weighted edges between nodes are scarce. Consequently, investigators have either generated networks based on absolute correlation values or have excluded negative edge weights from further analysis. These practices may distort the actual topological properties of the network. The continued development of measures that can accommodate both positive and negative edge weights (Rubinov and Sporns, 2011) will be an important goal for future research.

Conclusions

The studies reviewed here add to the already extensive literature documenting connectivity abnormalities in schizophrenia (Ellison-Wright and Bullmore, 2009; Konrad and Winterer, 2008; Pettersson-Yeo et al., 2011). The power of the imaging connectomic methods we have considered lies in their ability to provide relatively succinct, multidimensional characterizations of regional and whole-brain disturbances in brain network connectivity and topology. The findings suggest that schizophrenia is associated with a relatively diffuse and possibly context-independent functional connectivity deficit, upon which are superimposed more circumscribed, context-dependent changes resulting in transient hypo- and/or hyper-connected states. The causes of these changes in inter-regional functional coupling remain unclear, but in some cases appear related to localized intra-regional dysfunction. These abnormalities are also associated with widespread topological changes broadly characterized by reductions in measures of local information-processing and, to a lesser extent, increases in measures of global functional integration. Some of these functional abnormalities may have an anatomical basis, though the relationship between functional and anatomical dysconnectivity in the disorder is complex.

While several consistent themes emerged in the reviewed findings, discrepancies were also apparent. These discrepancies may partly reflect the heterogeneous nature of schizophrenia, which is an umbrella term that likely describes multiple disease processes with distinct etiologies and overlapping clinical manifestations. Such heterogeneity is compounded by the small samples usually studied in the literature. The discrepancies may also reflect variations in the clinical status of the patients at the time of scanning, including differences in symptomatology, medication status, and/or illness stage. As previously mentioned, positive and negative associations between connectivity levels and various symptom dimensions of schizophrenia have been reported (Cole et al., 2010; Salvador et al., 2010a; Vercammen et al., 2010; Whitfield-Gabrieli et al., 2009) suggesting the findings may, to some extent, be associated with transient variations in the clinical expression of the disease. Antipsychotic treatment has also been shown to modulate functional connectivity (Achard and Bullmore, 2007; Lui et al., 2010), and represents a potentially serious confound in many studies. However, reports of connectivity disturbances in patients' unaffected siblings (Liu et al., 2012; Repovs et al., 2011; Whitfield-Gabrieli et al., 2009) suggest that at least some connectomic abnormalities may reflect an inherited susceptibility to the disease. These changes may represent viable intermediate phenotypes, consistent with evidence for high heritability of brain network connectivity and topology measures (Glahn et al., 2010; Fornito et al., 2011b; Smit et al., 2008) and their association with schizophrenia risk genes (Esslinger et al., 2009). Further delineation of state- and trait-related effects on brain connectivity in the disorder will be an important avenue of further investigation.

Heterogeneity across studies may also be caused by generic methodological issues common to all case–control neuroimaging studies, such as differences in image processing and quality assurance protocols. Methods for dealing with the problems posed by physiological or scanner related noise in both functional and structural studies vary considerably across different research groups, and it is often difficult to ascertain the impact that these variations have on the findings. In particular, the problems posed by head motion are not always accounted for with traditional pre-processing strategies (Van Dijk et al., 2012), and may require more detailed analysis than the simple (and commonplace) exclusion of participants exceeding some pre-specified motion threshold.

While the studies reviewed here demonstrate the utility of imaging connectomics and ga-MRI in particular for characterizing connectivity disturbances in schizophrenia, considerable work remains. A glaring omission from the reviewed literature is longitudinal data. Brain changes in schizophrenia have a dynamic trajectory, beginning before disease onset and progressing with ongoing illness (Hulshoff Pol and Kahn, 2008; Olabi, et al., 2011; Pantelis et al., 2005; Wood et al., 2008). The findings listed in Tables 1–4 indicate that changes in brain connectivity and topology are present in both early and late stages of schizophrenia. Evidence that these changes are manifest prior to illness onset has been provided by one recent study reporting increased nodal degree, k, of the anterior cingulate cortex in high-risk individuals displaying elevated levels of psychotic symptoms (Lord et al., 2011). Whether these changes are predictive of which individuals subsequently develop schizophrenia is unclear, though volumetric changes in the region do show predictive utility (Borgwardt et al., 2007; Fornito et al., 2008; Koutsouleris et al., 2009) consistent with the known role that this region plays in the disorder's pathophysiology (Fornito et al., 2009a, 2009b). Such findings point to a potential convergence of volumetric and connectivity changes in the earliest stages of the illness. Whether the documented progression of volumetric changes in schizophrenia is associated with connectomic abnormalities has not yet been studied, but associations between

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functional connectivity and volumetric losses in other brain disorders (Seeley et al., 2009) suggest that this relationship warrants further investigation.

Longitudinal work will prove particularly valuable for understanding the generative mechanisms of connectomic disturbances in schizophrenia. The literature reviewed here suggests that investigation of these mechanisms can be broadly framed in three terms: (1) whether brain network changes in schizophrenia are a global phenomenon, or a secondary consequence of a localized dysfunction propagating throughout the network; (2) whether altered inter-regional connectivity is a cause or consequence of intra-regional dysfunction; and (3) whether functional deficits are caused by anatomical abnormalities or vice-versa. All these changes have been observed in schizophrenia and relations between each of them have been established (e.g., Skudlarski et al., 2010; Zalesky et al., 2011b). Establishing the temporal sequence of these abnormalities will be a critical step in understanding their causal relationships.

Finally, an important issue concerns the specificity of the findings to schizophrenia. Altered functional and structural connectivity levels, as well as network topological properties, have been reported in a range of psychiatric and neurological conditions (e.g., Di Martino, et al., 2011; Lin, et al., 2011; Lo, et al., 2010; Wang et al., 2009b), though similarities and differences between the disorders have seldom been examined directly. Preliminary work suggests that connectivity measures may indeed be useful in discriminating schizophrenia from other patient groups (Calhoun et al., 2008), although no study to date has used the connectomic measures described in this article for these purposes.

In summary, imaging connectomics offers a rich conceptual and analytic framework for the comprehensive study of brain network abnormalities in schizophrenia. The findings reported to date are consistent with the ideas first proposed by Wernicke a century ago (1906), and have extended contemporary pathophysiological models by demonstrating the highly distributed character of brain dysfunction associated with the disease. The continued refinement and application of these methods is likely to yield increasingly detailed insights into the dysconnection syndrome that characterizes schizophrenia.

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