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REVIEW

Brain Networks in Schizophrenia

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Abstract Schizophrenia—a severe psychiatric condition characterized by hallucinations, delusions, loss of initiative and cognitive function—is hypothesized to result from abnormal anatomical neural connectivity and a consequent decoupling of the brain's integrative thought processes. The rise of in vivo neuroimaging techniques has refueled the formulation of dysconnectivity hypotheses, linking schizophrenia to abnormal structural and functional connectivity in the brain at both microscopic and macroscopic levels. Over the past few years, advances in high-field structural and functional neuroimaging techniques have made it increasingly feasible to reconstruct comprehensive maps of the macroscopic neural wiring system of the human brain, know as the connectome. In parallel, advances in network science and graph theory have improved our ability to study the spatial and topological organizational layout of such neural connectivity maps in detail. Combined, the field of neural connectomics has created a novel platform that provides a deeper understanding of the overall organization of brain wiring, its relation to healthy brain function and human cognition, and conversely, how brain disorders such as schizophrenia arise from abnormal brain network wiring and dynamics. In this review we discuss recent findings of connectomic studies in schizophrenia that examine how the disorder relates to disruptions of brain connectivity.

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Schizophrenia—A Disorder of Brain Connectivity

Schizophrenia is a severe psychiatric disease characterized by hallucinations, delusions, loss of initiative and cognitive dysfunction. The notion that schizophrenia may be related to disrupted brain connectivity dates back to work of pioneering anatomists and psychiatrists in the 19th and 20th century. Early thinkers like Theodor Meynert (1833–1892), Carl Wernicke (1848–1905) and Emil Kraepelin (1856–1926) were among the first to notice that brain function and higher-order cognitive processes are the result of functional integration between multiple, spatially distributed brain regions (Wernicke 1885), and that conversely neural dysfunction need not necessarily be the product of focal lesions in specific brain regions, but could also equivalently be related to damage of their interconnecting axonal pathways. Emil Kraepelin gained notoriety as the father of modern descriptive psychiatry by providing one of the first systematic clinical descriptions of dementia praecox – a degenerative neuropsychiatric condition with early onset (Kraepelin 1919) which is widely recognized as a foundation for current diagnostic formulations of schizophrenia. The Swiss psychiatrist Eugen Bleuler (1857–1939) later redefined the illness as a disease whose core involves a de-coupling of the brain's normally integrated processes. He coined the name 'schizophrenia' to describe the characteristic 'split' (schizo) of the 'mind' (phrenia) that he viewed as fundamental to the disorder (Bleuler 1911).

Despite the insights of these early neuronatomists, psychiatry had to wait until the end of the 20th century for techniques that would allow detailed interrogation of in vivo brain connectivity. The development of Magnetic Resonance Imaging

(MRI) and Positron Emission Tomography (PET) offered an unprecedented capacity for examining the anatomy and function of discrete brain regions in living patients. In the past 30 years, MRI and PET studies have provided a wealth of imaging results suggesting that schizophrenia does not solely arise from isolated damage to one or a few brain regions; rather, it is likely the product of pathological alterations distributed throughout interconnected neural systems (e.g. Bora et al. 2011; Ellison-Wright and Bullmore 2009; Fornito et al. 2012; Friston 2005; Glahn et al. 2008; van den Heuvel and Kahn 2012). The development of techniques such as diffusion weighted imaging (DWI) and magnetic transfer ratio imaging have further allowed more detailed in vivo characterization of the brain's the white matter projections, and have been used to demonstrate an array of white matter volume, axonal microstructure and myelination changes in patients, particularly in frontal and parietal areas (see for review: Ellison-Wright and Bullmore 2009; Fornito et al. 2009; Kubicki et al. 2005). In parallel, advances in functional MRI techniques have enabled the examination of widespread disruptions of brain functional organization (see for review: Fornito et al. 2012; Greicius 2008; Karbasforoushan and Woodward 2013; Pearlson and Calhoun 2009).

These imaging techniques played a central role in reviving disconnectivity theories of schizophrenia, following initial PET research demonstrating an altered covariance structure of inter-regional cerebral metabolism and blood flow measures (Friston and Frith 1995)(Volkow et al. 1988). These findings led to a formal disconnection hypothesis being proposed by Friston (Friston 1998), which was subsequently extended to incorporate a broader pattern of dysconnectivity by Stephan et al. (Stephan et al. 2006)[1]. Andreasen et al. (1999) later proposed a connectivity model centered on cortico-subcortico-cerebellar systems, while Bullmore et al. (1997) suggested that wiring abnormalities in patients' brains may arise form a dysplastic developmental lesion. A large number of studies since then have confirmed the presence of wide-range of connectivity disturbances in the disorder (e.g.Fornito et al. 2012b; Pettersson-Yeo et al. 2011). The common thread linking contemporary theories with early writings is an emphasis on the role of the brain's integrative processes—the substrate of which is connectivity—in the pathophysiology of schizophrenia.

On the microscopic scale, neurons are connected to other neurons through axonal and dendritic connections and synaptic terminals, forming both local and global neuronal circuits. At meso- and macro- scopic scales, neural columns and large-scale brain regions are interconnected by short-range and long-range axonal white matter projections, forming a brain-wide network of neural interactions. The 'connectome' describes a complete map of the neural elements and structural interactions that comprise a neural system, together forming the anatomical substrate for neural communication, functional processing and information integration in the brain (Sporns et al. 2005). The field of 'connectomics' is concerned with accurately mapping the brain's connectivity architecture and understanding how the architectural organization of these neural maps underlies brain function. The emerging discipline of network science, centered on the mathematical theory of graphs, has emerged as a generic framework for studying brain networks and their relation to other complex systems (Bullmore et al. 2009; Bullmore and Sporns 2009; Sporns 2011; van den Heuvel and Hulshoff Pol 2010). This work describes the brain as a graph consisting of nodes (neurons and/or brain regions) linked by edges (their inter-connecting synapses/axons). Neuroimaging, and MRI in particular, has played a prominent role in these efforts, and is currently the only tool available for rapid and cost-effective characterization of macro-scale connectome architecture in living humans (Bullmore and Bassett 2011; de Reus and van den Heuvel 2013a; Fornito et al. 2013b; Hagmann et al. 2010a; Johansen-Berg 2013; Sporns 2012a; Van Essen and Ugurbil 2013).

In this review, we highlight recent findings reported in MRI-based whole-brain connectomic studies of schizophrenia, with a particular emphasis on analyses employing graph theoretic techniques. We begin with a brief overview of the advances in neuroimaging techniques and network analysis that together form the basis of MRI-based macroscopic connectomics. We then summarize recent empirical findings of network abnormalities in schizophrenia, as measured through structural and functional imaging, and consider how these findings might inform clinical decision-making. We discuss evidence of network disruptions representing a possible vulnerability marker of disease risk, and include an overview of promising work aiming at devising quantitative, generative models that provide insight into the causal mechanisms explaining the observed network changes. We conclude by remarking on some of the insights that modern connectomics has contributed to the concept of schizophrenia, and with a brief consideration of remaining open questions.

Imaging and Brain Network Analysis

Structural Connectivity

As originally proposed, the connectome refers to a comprehensive description of anatomical (i.e., structural) brain connectivity (Sporns 2012a, b; Sporns et al. 2005). In vivo investigation of anatomical brain connectivity on the macroscopic

[1] The distinction between the prefixes 'dis' and 'dys' was drawn on etymological grounds by Stephan et al.: in Latin, 'dis' refers to a reduction or breakdown; in Greek, 'dys' connotes bad or ill and implies that changes could involve both abnormal decreases and/or increases.

level can be performed by the use of Diffusion Weighted Imaging (DWI) (Basser et al. 2000; Basser and Pierpaoli 1996; Beaulieu and Allen 1994; Mori and Barker 1999), a technique that measures how the diffusion of water molecules in brain tissue is constrained by large-scale white matter fiber tracts.

A commonly used metric of the strength of interregional connectivity includes the number of reconstructed trajectories intersecting two regions (Cammoun et al. 2011; Hagmann et al. 2010a, b; Zalesky et al. 2011a). Alternative measures attempt to index various aspects of fiber tract integrity, including the local level of *mean diffusivity* (MD) (i.e., the level of water diffusion along each point of a tract), *fractional anisotropy* (FA) (how constrained the water diffusion is), *radial diffusivity* (RD) (i.e., the degree of diffusion perpendicular to the primary tract axis; often taken as an indirect estimate of myelin integrity) and *axial diffusivity* (AD; the degree of water diffusion parallel to the tract trajectory; often taken as an indirect measure of local fiber organization)(e.g. (van den Heuvel et al. 2010; Hagmann et al. 2010a, b; Verstraete et al. 2012)). Combining tractography with additional imaging sequences, such as Magnetic Transfer Imaging (Kubicki et al. 2005; Mandl et al. 2010; van Buchem 1999; van den Heuvel et al. 2010), CEST (Verstraete et al. 2013) and complex analysis of multiple diffusion images (Mandl et al. 2010) can be used to obtain more direct measures of physiologically relevant parameters such as myelin content and axon diameter distributions (Assaf et al. 2013; Assaf et al. 2008; Barazany et al. 2009). (See for reviews on diffusion imaging and tractography: (Beaulieu 2002; Jbabdi and Johansen-Berg 2011; Jones 2008; Le Bihan et al. 2001; Mori and van Zijl 2002)).

Primary advantages of diffusion imaging techniques for mapping brain connectivity include the relative ease of acquisition (~10–20 min) and analysis, and its capacity for in vivo measurement, which enables large-scale cross-sectional and longitudinal case–control studies. Limitations include the relatively indirect nature of the resulting connectivity estimates, which leave room for false positive and false negative reconstructions in connectome reconstruction (de Reus and van den Heuvel 2013a), the mm-scale resolution, and the lack of information about the directionality of the reconstructed projections (Hagmann et al. 2010a, b; Jbabdi and Johansen-Berg 2011; Jones 2008) (Fornito et al. 2013b).

Functional Connectivity

Functional connectivity refers to a statistical dependence between spatially distinct neurophysiological signals, as recorded using techniques such as functional MRI and M/EEG (Friston 1994). The construct assumes that synchronized activity between two or more brain regions reflects some degree of communication occurring between them. Most commonly, functional connectivity is inferred from a simple Pearson or partial correlation analysis between regional time-series, though alternative measures such coherence and mutual information have also been employed (Bassett et al. 2011; Boersma et al. 2013; Micheloyannis et al. 2006; Salvador et al. 2008; Stam et al. 2006; Stam and Reijneveld 2007). On longer timescales (accumulating measurements over several minutes) studies have shown that spontaneous activity recorded during rest is highly organized and reproducible (Damoiseaux et al. 2006; Shehzad et al. 2009; van den Heuvel and Hulshoff Pol 2010), overlaps with patterns of task-evoked activity and behavior (Fox and Raichle 2007; Fox et al. 2006; Hesselmann et al. 2008), and is under strong genetic control (Fornito et al. 2011b; Glahn et al. 2010; Jahanshad et al. 2013b; van den Heuvel et al. 2012b). Functional connectivity can be measured either during cognitive task performance (Fornito et al. 2012a; Friston et al. 1997) or during task-free, so-called resting-states (Fox and Raichle 2007), using appropriately adapted techniques.

Though functional connectivity is constrained by anatomical connectivity, they are not isomorphic (Hagmann et al. 2008; Honey and Sporns 2008; Honey et al. 2009; Skudlarski et al. 2010; van den Heuvel and Sporns 2013a). At the scales accessible with MRI, functional connectivity tends to be more prevalent than structural connectivity—two regions can show strongly correlated activity in the absence of a direct anatomical link (Honey et al. 2007; Skudlarski et al. 2008; Vincent et al. 2007). In some cases these excess connections may reflect polysynaptic transmission; in others, they may simply be artifacts of the metric used to index functional connectivity. For example, measures such as the Pearson correlation coefficient cannot distinguish whether a strong correlation between two regions is driven by a direct connection, or the indirect influence of a third area. Accordingly, the various measures used to capture the statistical dependencies that characterize functional connectivity vary in their accuracy (Smith et al. 2011) and can often bias network analyses (Friston et al. 2011; Power et al. 2013; Van den Heuvel et al. 2012a; Zalesky et al. 2012). Moreover, anatomical and functional connectivity differ along a temporal dimension: anatomical connectivity changes over a relatively slower timescale (e.g. hours to days), whereas functional connectivity patterns are context-dependent and can change on very short time scales (e.g., milliseconds).

Graph Theory, Brain Networks, and Their Relation to Brain Function

The structural or functional connections between every pair of regions comprising the brain can be represented in the form of a graph—a mathematical construct consisting of a set of nodes (representing neurons, or macroscopic cortical regions) and edges, which describe the interactions between nodes

(being axons, macroscopic white matter pathways, level of inter-regional functional coupling etc.) (Fig. 1 gives an illustration of the steps involved to form structural and functional brain networks; Bullmore and Sporns 2009). Once a formal, mathematical description of a network is established, graph theory can be used to describe the overall organization or topology of the network (Fig. 2). Such description enables investigation of emergent features that are otherwise not measurable by focusing exclusively on information from single brain regions or single pair-wise connections.

Several network attributes appear to be of particular value in describing brain networks (Bullmore and Sporns 2009) (Fig. 2 shows a basic graph and illustrates a number of commonly used network attributes). Attributes like clustering or path length express respectively, the overall tendency of nodes of the network to locally cluster, and the average length of shortest communication paths integrating otherwise spatially disparate node pairs. Community structure expresses the tendency of nodes to form locally connected clusters of connectivity or modules (Newman 2006; Newmann 2010), expressing a level of network ordering. In brain networks, modules are thought to represent functionally specialized neuronal ensembles and thus provide a topological foundation for functional segregation (Damoiseaux et al. 2006; Salvador et al. 2005; Smith et al. 2009; Sporns 2012a, b; Van den Heuvel et al. 2008a). Furthermore, degree and centrality metrics provide information on the role of each node and edge in the overall communication architecture of the network. Degree measures the number of edges each node possesses and the level of closeness centrality provides an indication of the travel distance from a node to every other node in the network. In addition, a node's betweenness centrality is a ratio of number of all shortest paths between any two nodes in the network that travel through an index node, providing an indication of how topologically central a node's role is in overall network communication.

Nodes with a central placement in the network -meaning they display a high degree and high of centrality- are often referred to as 'hubs' (Buckner et al. 2009; Bullmore and Sporns 2012; Gong et al. 2009; Iturria-Medina et al. 2008; Sporns et al. 2007; van den Heuvel and Sporns 2011; van den Heuvel and Sporns 2011, 2013b) (Fig. 2). Using graph theoretical approaches, studies have identified a small set of putative 'brain hubs' that display a high and diverse pattern of connectivity, and a high level of network centrality. Besides being individually 'rich' in connectivity, recent studies have suggested that these brain hubs are densely interconnected amongst themselves, together forming a central rich club or core (de Reus and van den Heuvel 2013b; Towlson et al. 2013; van den Heuvel and Sporns 2011; Zamora-Lopez et al. 2009) (Fig. 2). Due to their central embedding in the overall network, brain hubs have been suggested to play a pivotal role in global brain communication, and to form putative central points for neural convergence and global integration of information (van den Heuvel and Sporns 2013b).

Empirical Findings of Network Alterations in Schizophrenia

Structural Findings

Structural studies have reported clear volumetric and morphological changes in schizophrenia. Volumetric studies have consistently shown reduced white matter volumes (besides clear changes in grey matter) in patients, together with deviant developmental trajectories during adolescence and aging (e.g. (Gogtay et al. 2012; Hulshoff Pol et al. 2004; Kuperberg et al. 2003; van Haren et al. 2012)). Together, these studies provided relatively non-specific evidence for white matter alterations in schizophrenia. Later network studies examining the architecture of structural brain networks derived from diffusion weighted data have verified reduced levels of overall structural connectivity in patients (Skudlarski et al. 2010; van den Heuvel et al. 2010; Zalesky et al. 2011b). In particular, white matter projections linking frontal, temporal and parietal regions seem to be the most affected. A wealth of evidence from voxel-based morphometry (VBM) studies on white matter density and tract-based diffusion studies point to altered white matter microstructure of the unscinate fasciculus, the arcuate fasciculus, the cingulum and the corpus callosal genu tract (see for review (Ellison-Wright and Bullmore 2009; Kubicki et al. 2007)). Among other aspects, these studies have reported reduced fractional anisotropy, believed to be an indicator of affected overall microstructure, together with increased mean and radial diffusivity, which has been suggested to reflect possible decreases in level of myelination and organization of these tracts (e.g. (Ellison-Wright and Bullmore 2009; Kubicki et al. 2007; Skudlarski et al. 2013)). Studies utilizing magnetic transfer imaging (MTI) have indeed suggested affected levels of myelination and hypothesized abundant levels of free-water and glutamate concentrations in some of these tracts (Foong et al. 2001; Kubicki et al. 2005; Mandl et al. 2010). Although limited in number (likely related to the difficulty of performing such studies), tissue histology studies of white matter connectivity in schizophrenia reveal evidence of an increased count of pathological myelinated fibers in prefrontal cortical regions of patients (Uranova et al. 2013). Volume, tract-based and network studies thus point to overall reduced white matter volume as well as reduced white matter microstructure of large-scale white matter projections as playing an important role in the disease pathology of schizophrenia.

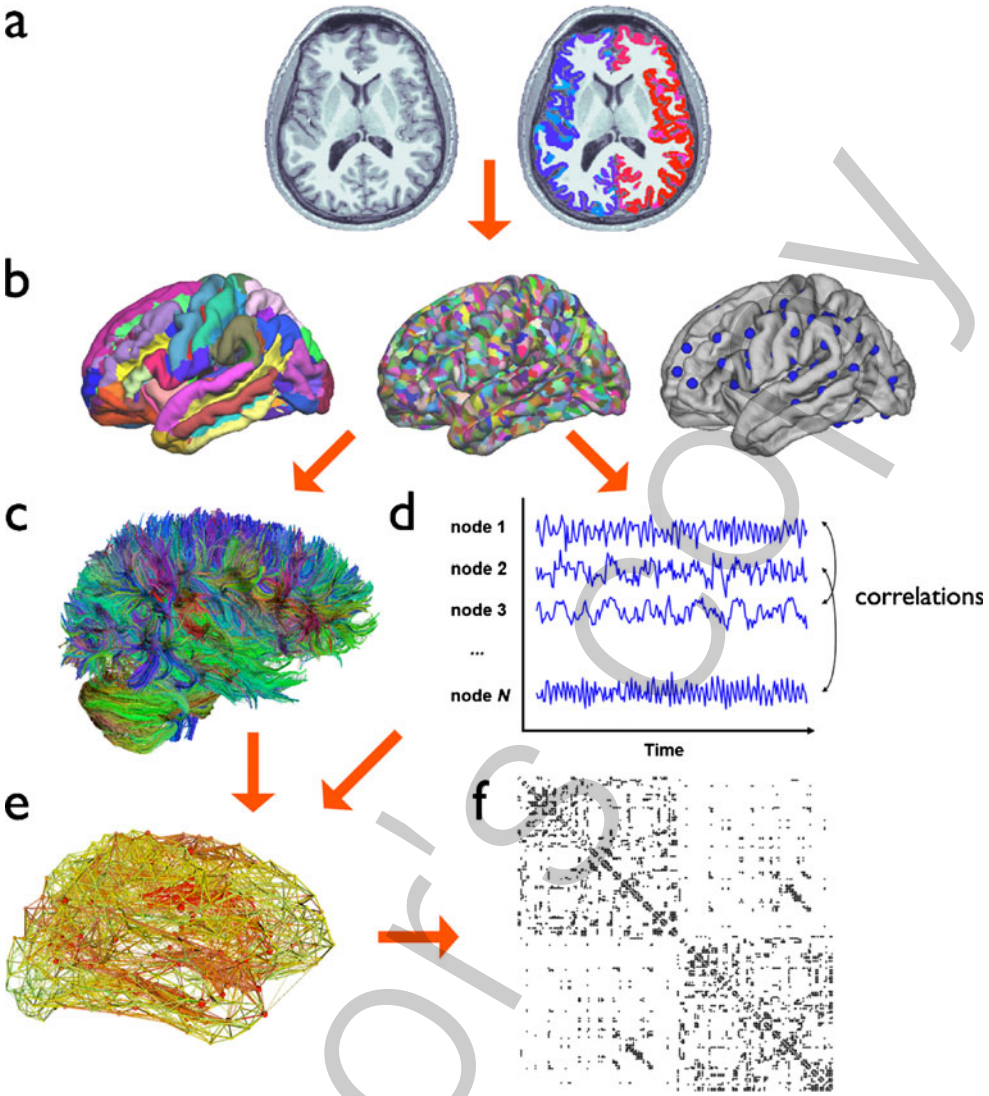

Fig. 1 Structural and functional brain networks derived from neuroimaging data. A typical network reconstruction derived from MR data involves the following steps. **a** *Grey matter regions* are selected on basis of a anatomical T1 image in combination with a parcellation scheme, which can be voxel-based, derived from a priori anatomical landmarks (left), or random parcellation of the cortical mantle (middle) or a priori defined functional regions-of-interest (de Reus and van den Heuvel 2013a, b)). **b** Selected regions are interpreted as the 'nodes' of the network. **c** Anatomical or structural connectivity between brain regions can be derived from diffusion imaging, enabling the reconstruction of the white matter fiber pathways between the nodes (here brain regions derived from the used parcellation scheme) of the network (panel **e**). **d** Functional connectivity is often derived from correlation analysis between the recorded time-series (fMRI or M/EEG) of each brain region. **e** The reconstructed anatomical connections and/or functional connections are taken as 'connections' between the nodes, together forming a structural or functional brain network. **f** To examine a network's architectural organization, a network is often mathematically described as a 'graph', a mathematical construct consisting of a collection of 'nodes' (describing the brain regions) and 'edges' (describing the collection of connections). A brain graph is often presented in the form of a 'connectivity matrix', describing the nodes of the network as columns and rows in the matrix (i.e. each column/row describing one of the brain regions) and the level of connectivity of each connecting edge as a cell entry in the connectivity matrix. Panel **a–d** adapted and modified from (Filippi et al. 2013)

Abnormal Network Organization

These changes in white matter microstructure and connectivity have pronounced effects on the topological organization of the connectome in schizophrenia patients. Examining brain networks derived from diffusion imaging data, clustering (Zalesky et al. 2011b) and modularity structure (van den Heuvel et al. 2013) are elevated, suggesting an overall more segregated pattern of network organization. Consistent with this hypothesis, network studies have revealed longer average path length (Ottet et al. 2013; van den Heuvel et al. 2010; Zhang et al. 2012) and corresponding reductions in global communication efficiency (Zalesky et al. 2011b), suggesting reduced communication between more segregated parts of the brain.

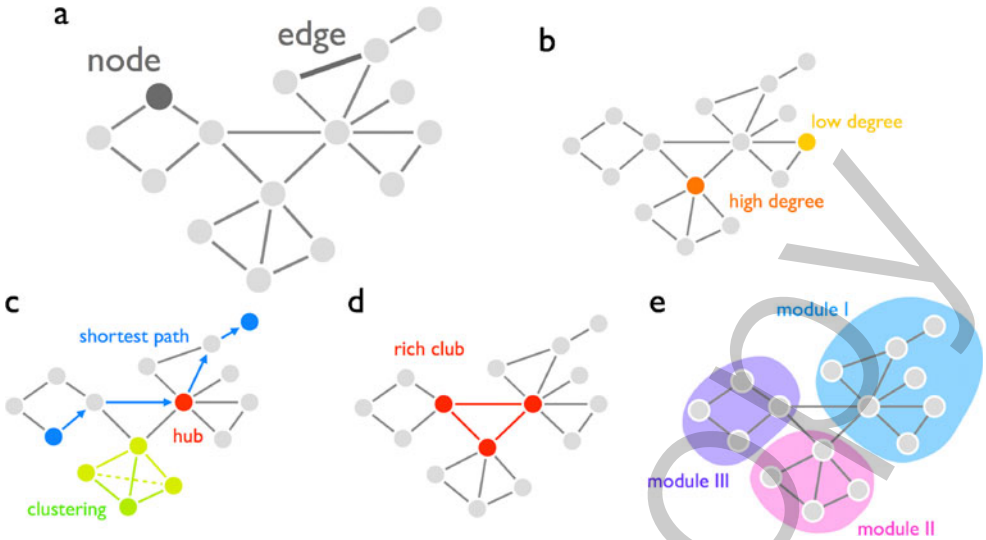

Fig. 2 A graph and examples of basic graph attributes. **a** A network can be mathematically described as a graph, consisting of a collection of 'nodes', and a collection of 'edges' describing the collection of connections between the nodes of the network. When the number of network edges is sparse the layout of the edges describes the topological organization of the network. Basic network attributes include a network's degree distribution (panel **b**), clustering, characteristic path length and modular structure **b**. The degree of a node describes its number of connections to other nodes in the graph. Nodes with a high degree that take on a central position in the graph are often referred to as 'hubs'. **c** The 'clustering' of a graph provides insight into the level of local connectedness of the graph, describing how strong the connected neighbors of a node are connected themselves. In **c**, the node depicted in green has three connected neighbors (*light green nodes*) together sharing two of the possible three edges between them (the *dotted edges* is missing), resulting in a clustering coefficient of two-thirds. The 'characteristic path length' of a graph describes the average number of edges that have to be crossed to travel between any two nodes in the network. In **c**, the shortest path between the two blue nodes is depicted by the *blue arrows*, which defines the shortest path traveling along four edges and three nodes of the network. The *red node* reflects an exemplary hub node, displaying a high degree, a short global path length and being involved in a large number of communication paths in the network. **d** Besides being individually rich in connectivity, high degree nodes can display an above chance level of interconnectivity, forming a densely connected 'rich club'. A closely related concept is the formation of a 'core' within networks (Hagmann et al. 2008). **d** The modular structure of the network describes the tendency of nodes to form local connected clusters that share a relative high level of connectivity with each other than with other regions. In d, three modules can be distinguished, consisting of subsets of nodes predominantly connected to nodes within their own module

Focusing on the role of individual nodes in the overall network structure reveals altered connectivity profiles in several cortical regions (Fig. 3). Frontal and temporal brain regions show altered clustering (Bassett et al. 2008), as well as longer communication paths (van den Heuvel et al. 2010) and reduced global efficiency (Wang et al. 2012). Moreover, centrality reductions have been found particularly in medial frontal and medial parietal regions. Analyses of structural covariance networks –connectivity networks derived from inter-regional covariations in morphometric parameters such as grey matte volume or cortical thickness (Alexander-Bloch et al. 2013a, b; He et al. 2007) – have revealed altered network topology (Collin et al. 2012) and a reduced hierarchical structure, indicative of a disruption in the connectivity organization of cortical regions (Bassett et al. 2008). Furthermore, regions of superior frontal cortex, lateral precuneus and overlapping parts of the default mode network have been noted to show reduced levels of closeness and betweenness centrality, suggesting a less central role for these regions in the overall communication structure of the network (Zhang et al. 2012).

Focusing on specific edges, connectome-wide analyses have found that decreases in connectivity strength are centered on a frontal-parietal-occipital network, mostly involving genu, cingulum and interhemispheric parietal and occipital tracts, interconnecting medial regions of the frontal and parietal cortex (Zalesky et al. 2011b).

Caution may be warranted when examining network properties in the context of reduced overall connectivity strength (Fornito et al. 2012b). In weighted network analyses, which incorporate variations in the strength of connectivity into the computation of topological measures, reductions in overall white matter microstructure -as regularly reported in schizophrenia- might have a pronounced effect on network metrics. Indeed, two studies comparing the observed reduction in network organizational metrics directly to the reductions one could expect in randomly connected networks (which to some extent corrects for global differences in connectivity) revealed an attenuation of the reported effects, revealing no clear alteration of in global efficiency or clustering metrics (van den Heuvel et al. 2010; Zalesky et al. 2011b). However, differences in overall clustering and path length have also been found when no information on connectivity strength was included (Zalesky et al. 2011b), when the overall level of connectivity strength was normalized across groups

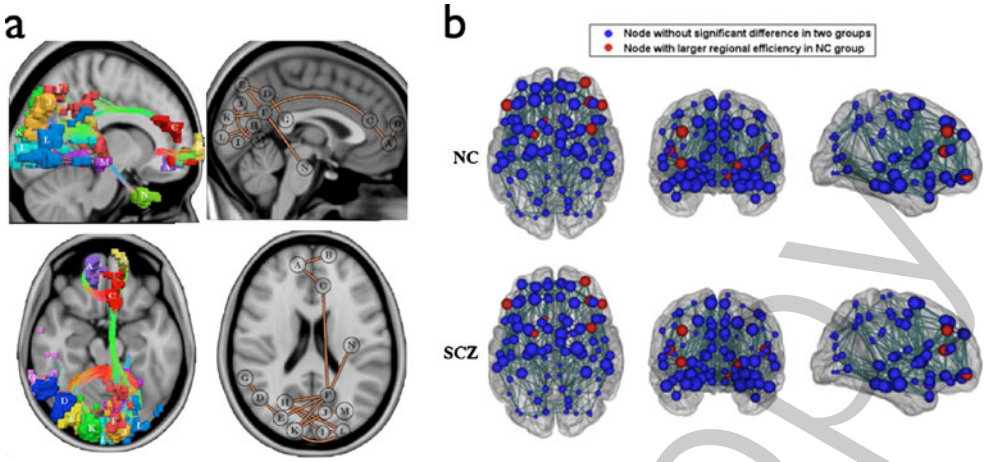

Fig. 3 Empirical findings of disturbed structural brain networks in schizophrenia. **a** Panel **a** shows a sub network of reduced anatomical connectivity as observed in patients with schizophrenia, derived from a network-based statistic analysis of diffusion tractography data. Right panels show a graph representation of the affected network edges, including two interconnected clusters of occipital/parietal and frontal regions. **b** Figure illustrates nodes (i.e. brain regions) that show reduced network global network efficiency (i.e. longer communication paths) in patients with schizophrenia. In particular frontal regions showed reduced global network efficiency. Panel **a** adapted and modified from (Zalesky et al. 2011b), panel **b** adapted and modified from (Wang et al. 2012)

(van den Heuvel et al. 2010), and in the absence of an overall difference in the number of reconstructed network edges between groups (van den Heuvel et al. 2010; Wang et al. 2012), suggesting that the reported network changes in schizophrenia are not solely related to a relative global reduction in connectivity strength, but likely also involve topological changes of the brain network. In addition, adopting a graph modeling approach in which reductions in edge weights were modeled in the control network revealed that the observed effects in path length and centrality of frontal and parietal regions in patients are not solely the result of reductions in connectivity strength, but are likely also related to a possible change in the overall connectivity profile of these regions (van den Heuvel et al. 2010). Thus, although topological measures are sensitive to changes in overall connectivity strength, there is consistent evidence for topological alterations that exist above and beyond lower-order connectivity differences.

Functional Findings

Studies of functional connectivity disturbances in schizophrenia, whether using whole-brain mapping or seed-based analysis techniques, have reported alterations in a wide-variety of systems, many of which involve prefrontal brain regions (Cole et al. 2011; Fornito et al. 2012b, 2013a; Liang et al. 2006; Zalesky et al. 2011a, b). These systems include fronto-parietal networks implicated in cognitive function (Repovs et al. 2011), cingulo-opercular systems involved in interoception and salience processing (Palaniyappan et al. 2013), the default mode network, which is involved in introspective processing (Whitfield-Gabrieli et al. 2009), and specific fronto-striatal (Dandash et al. 2013; Fornito et al. 2013) and fronto-temporal circuits (Hoffman et al. 2011). Together, these findings are consistent with studies of structural brain connectivity in suggesting that pathology of (mostly frontal) hub regions may be a core characteristic of schizophrenia. However, while structural findings overwhelmingly implicate reduced anatomical connectivity in the pathophysiology of the disorder (Pettersson-Yeo et al. 2011), studies of functional connectivity have included reports of both abnormally increased and abnormally decreased functional connectivity, even in the same sample (e.g., Liu et al. 2008; Skudlarski et al. 2010). Functional connectivity reductions are more common however (Fornito et al. 2012b; Pettersson-Yeo et al. 2011; van den Heuvel et al. 2013).

Structural studies have generally found evidence of increased segregation (i.e., clustering and modularity) and reduced integration (higher path length and lower global efficiency and rich-club organization) (Fig. 4). In contrast, many functional studies have reported seemingly contradictory results, such as reduced clustering, local efficiency and/or modularity (Alexander-Bloch et al. 2010; Liu et al. 2008; Wang et al. 2010, Yu et al. 2011) along with increased or unchanged global efficiency (most commonly when analyzing binary networks) (Alexander-Bloch et al. 2010; Becerril et al. 2011; Fornito et al. 2011a; Lynall et al. 2010) (though see (Micheloyannis et al. 2006; Yu et al. 2013) for exceptions) and affected modular organization (Yu et al. 2012). Similarly, while structural studies suggest a prominent reduction of long-distance association pathways in schizophrenia (van den Heuvel and Kahn 2012; van den Heuvel et al. 2013), studies of functional network topology suggest that (early-onset) schizophrenia patients display an excess of long-distance functional couplings between brain regions (Alexander-Bloch

et al. 2013a, b). In some cases, these changes have been accompanied by increased topological efficiency (Lynall), in other cases, global efficiency and longer path lengths have been found (Yu et al. 2011).

There are several possible reasons for these discrepancies. Certain pre-processing steps for fMRI, such as correction of regional activity time courses for covariations with global mean signal fluctuations, can introduce artifactual correlations (Fox et al. 2009; Murphy et al. 2009), distort case–control differences (Saad et al. 2012), and tend to be more frequently used in studies finding functional connectivity increases in patients (Fornito et al. 2012b). Variations in methods used to define functional connectivity, as well as network nodes, may also play a role (e.g. Liu et al. 2008; Lynall et al. 2010; Yu et al. 2011; Yu et al. 2012; Van den Heuvel et al. 2013; Liu et al. 2008; de Reus and Van den Heuvel 2013a; Smith et al. 2013; Fornito et al. 2010). Furthermore, as functional connectivity measures are continuously weighted, networks are typically thresholded prior to analysis in order to remove spurious connections. When there are mean group differences in overall functional connectivity, this thresholding procedure can bias group comparisons. For example, if patients show a global reduction in connectivity, thresholding patient and control matrices may lead to the inclusion of more low-weight and thus potentially spurious connections to achieve the same connection density in the patient group. A higher proportion of spurious connections will result in a network with a more random topology (see for a detailed discussion Fornito et al. 2012b). Finally, a reduction in structural connectivity need not always result in reduced functional connectivity. The brain adapts to pathology such that dysfunction in one site can lead to a compensatory up-regulation of activity and/or connectivity in other areas (Johansen-Berg et al. 2002; Riecker et al. 2010). Accordingly, computational work shows that lesions to specific brain regions can result in both decreases and increases of inter-regional functional connectivity extending beyond the affected site (Alstott et al. 2009). In some cases, up-regulation of functional connectivity may be even related to the onset of schizophrenia-like symptoms (Hoffman et al. 2011).

Affected Hub Organization

Several lines of evidence suggest that a critical factor in determining topological alterations appears to be an altered organization of hub nodes in schizophrenia (Fig. 5). Analyses of anatomical covariance networks point to a less prominent role of high degree hub regions in the prefrontal and parietal cortex of patients, coupled with the emergence of non-frontal hubs in other brain regions (Bassett et al. 2008; Collin et al. 2012; Zhang et al. 2012). Examination of functional and anatomical connectivity confirmed a less central role for frontal and parietal hubs in the overall network (Lynall et al. 2010, Collin et al. 2013, Yu et al. 2012). A direct comparison between the spatial location of hubs as defined on basis of diffusion imaging data and network nodes showing the strongest reductions in efficiency and centrality in patients revealed high overlap, suggesting a prominent role of these regions in disease pathology (van den Heuvel et al. 2010). In addition, node-level topological changes centre on frontal associative regions (Wang et al. 2012), regions commonly identified as structural and functional brain hubs.

Further evidence implicating disrupted hub organization in the topological disturbances associated with schizophrenia comes from recent studies focusing on the rich club organization of hubs in the connectome. As a collective of hubs, the brain's rich club possesses a dense level of connectivity that spans spatially distributed hubs and interconnects many functional networks (de Reus and van den Heuvel 2013b; van den Heuvel and Sporns 2013b), forming a putative anatomical backbone for global neural communication (van den Heuvel and Sporns 2011; van den Heuvel et al. 2012a). The rich club is thus thought to play a crucial role in neural signaling and information integration between different functional subdomains of the human brain (van den Heuvel and Sporns 2013a, b; Zamora-Lopez et al. 2009). A recent structural network study revealed pronounced rich club reductions in patients, with the level of connectivity strength between frontal, parietal and insular hubs to be among the most strongly affected connections in the brain (van den Heuvel and Sporns 2013b). Moreover, the strongest reductions were found for edges linking two rich club nodes (named 'rich club connections'), when compared with connections linking hub regions to non-hub regions (named 'feeder connections') or connections linking non-hub to non-hub regions (named 'local connections')(van den Heuvel et al. 2013, Collin et al. 2013)(Fig. 5). Across patients, stronger reductions in rich club strength were related to lower levels of network efficiency (van den Heuvel et al. 2013), a more pronounced alteration of functional dynamics (van den Heuvel et al. 2013) and worse disease outcome (Collin et al. 2013). Moreover, functional studies have shown reduced levels of functional coupling and disrupted low frequency power of rich club regions in patients (Yu et al. 2013). One recent structural network study of patients with a 22q11DS deletion resulting a clinical phenotype that is nearly indistinguishable from schizophrenia noted a disproportionate loss of connectivity in a large proportion of cortical and sub-cortical hubs compared to other low-degree brain regions (Ottet et al. 2013)(Fig. 5). Collectively, these findings thus suggest that a core disturbance of hub connectivity and topology may underlie a broad range of network abnormalities observed in patients, having a pronounced effect on the functional dynamics and functional capacity of the

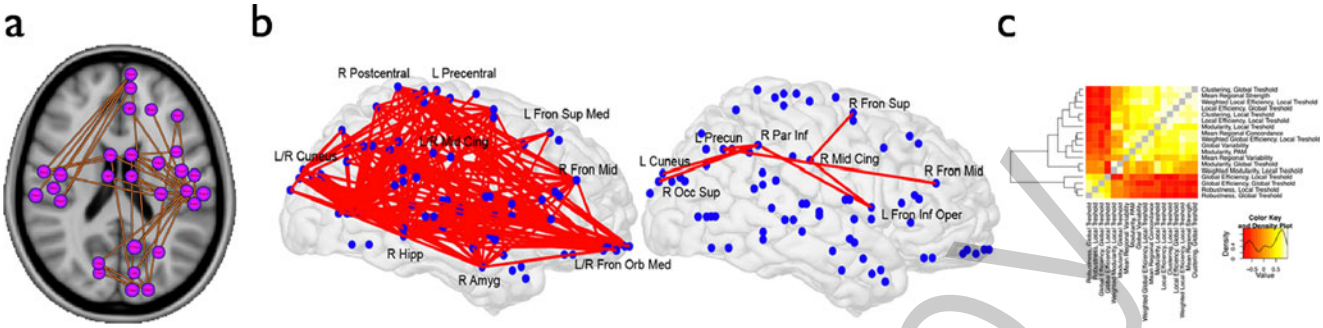

Fig. 4 Empirical findings of disturbed functional brain networks in schizophrenia. Whole-brain studies of functional connectivity changes have revealed widespread reductions in chronic patients during rest (**a**) and first episode patients during cognitive task performance (**b**), particularly in networks linking frontal and posterior areas. Studies of task-related functional connectivity have reported context-specific changes in fronto-parietal systems during the implementation of cognitive control (**b**, *right*), which are superimposed on a more diffuse, context-independent disruption of functional connectivity that persists across task conditions and which affects fronto-posterior connectivity in particular (**a**, *left*). Studies of childhood onset schizophrenia indicate that measures of brain functional network topology fall into two clusters: measures of functional segregation (clustering, modularity, etc.) or integration (path length, efficiency, etc.) (**c**). In patients, brain functional networks generally show reductions of the former and increases of the latter. Images in a adapted and modified from (Zalesky et al. 2010); images in b adapted and modified from (Fornito et al. 2011a); and in images in **c** adapted and modified from (Alexander-Bloch et al. 2010)

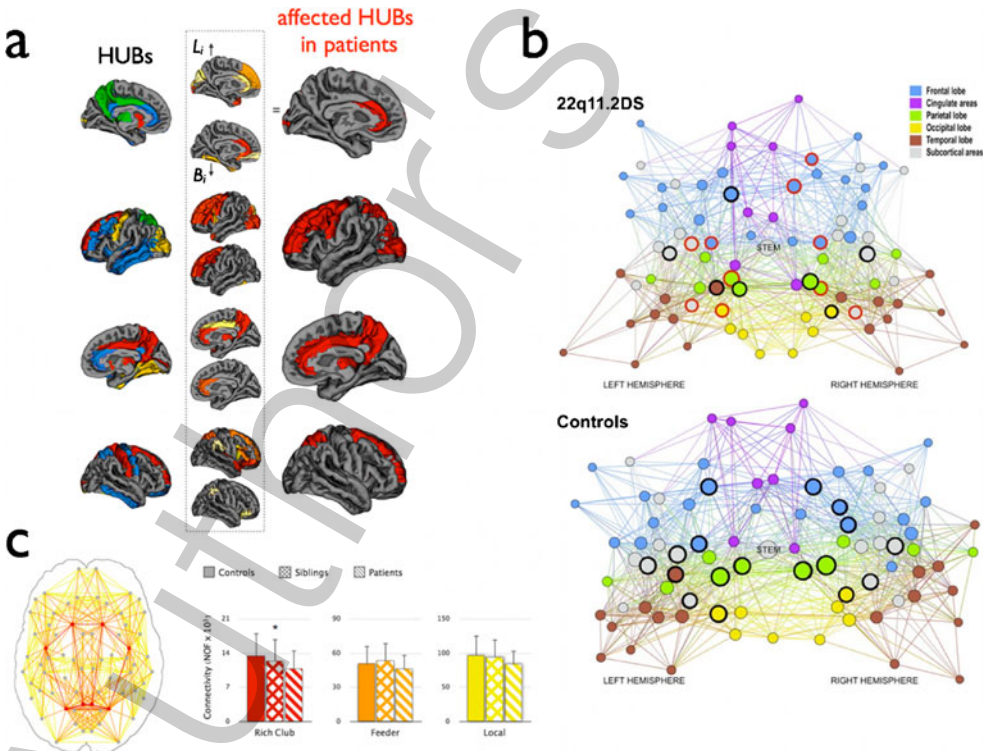

Fig. 5 Empirical findings of disturbed hub connectivity in schizophrenia. **a** Analysis of anatomical connectivity derived from diffusion-weighted imaging provided further evidence of a possible reduced hub connectivity in schizophrenia. Comparing regions that showed increased path length (reflecting longer communication paths) and reduced centrality (reflecting a less central role in the overall network) in patients (shown in the middle column) with hub regions as detected in a group of healthy participants (*left column*) revealed a high level of overlap (*right column*). **b** Reduced hub structure was observed in schizophrenia patients with 22q11.2DS (brain network shown in *upper panel*) as compared to a group of healthy controls (brain network shown in *lower panel*). **c** Categorizing the edges of the brain network into connections interconnecting hub nodes ('rich club connections'), edges that connect hub nodes to peripheral nodes ('feeder connections') and edges that connect peripheral nodes ('local connections') revealed reduced connectivity predominantly in the class of rich club connections in patients, with intermediate levels in non-affected siblings of patients. Panel **a** adapted and modified from (van den Heuvel et al. 2010), panel **b** adapted and modified from (Ottet et al. 2013), panel **c** adapted and modified from (Collin et al. 2013)

brain (van den Heuvel et al. 2013), and conversely global (cognitive) brain functioning.

Abnormal Network Organization and Clinical Symptoms

Demonstrating differences in network connectivity or topology is useful for mapping brain disturbances in schizophrenia. However, if these measures are to provide insight in to the clinical manifestations of the disease, they should correlate with variations in symptom strength or illness course. In the ideal case, they would also predict some relevant feature of the illness, such as outcome, treatment response or risk of disease onset.

In healthy individuals, variations in brain network organization are robustly related to inter-individual differences in cognitive function. Both connectivity and topological measures of network integration have been related to individual differences in intelligence (Bassett et al. 2009; Li et al. 2009; van den Heuvel et al. 2009; Zalesky et al. 2011a, b), performance in specific cognitive domains (Bassett et al. 2009; Cole et al. 2012), information processing speed (Reijmer et al. 2013), as well as differences in personality traits (Adelstein et al. 2011; Van Horn et al. 2013).

In patients, positive symptom severity has been linked to reduced levels of overall structural connectivity (Skudlarski et al. 2010), both decreases and increases in structural and functional coupling (Skudlarski et al. 2010), connectivity strength of temporal and frontal region pairs (Skudlarski et al. 2010), reduced global network efficiency (Wang et al. 2012) and reduced levels of clustering (Wang et al. 2012). The severity of negative symptoms has been associated with reductions in global functional connectivity (Skudlarski et al. 2010), increases in global structural-functional coupling (Skudlarski et al. 2010), increases in structural-functional coupling in default mode subnetworks (Skudlarski et al. 2010), as well as reduced levels of global network efficiency (Wang et al. 2012, Yu et al. 2011) and global clustering (Wang et al. 2012). Lower functional connectivity has also been associated with poorer cognitive performance (Cole et al. 2011; Repovs et al. 2011). Topological studies have mostly been focused on attributes relating to network efficiency. One study found an absence of the normal relationship between structural network efficiency and intelligence in patients (Zalesky et al. 2011b). A second study of functional networks assessed using MEG found that patients with schizophrenia show reduced network cost-efficiency—a metric that balances the competing constraints of maintaining and integrated network while minimizing connection costs—and that this reduction was correlated with poorer working memory performance (Bassett et al. 2009). Brain functional network cost-efficiency is strongly heritable (e.g. Fornito et al. 2011b, see also van den Heuvel et al. 2012b) suggesting a possible genetic basis for these deficits.

There also appears to be some degree of specificity in the way that distinct symptoms correlate with connectivity variations in different neural systems. For example, reduced functional connectivity between dorsal regions of the caudate and dorsolateral prefrontal cortex has been associated with the severity of positive symptoms in first episode psychosis patients (Fornito et al. 2013a) and prodromal positive symptoms in individuals experiencing an at-risk mental state (Dandash et al. 2013). In contrast, positive symptom severity has also been associated with *increased* functional connectivity of medial prefrontal components of the default mode network (Whitfield-Gabrieli et al. 2009). Similarly, increased functional connectivity and topological efficiency of fronto-striato-temporal systems has been associated with more severe auditory hallucinations schizophrenia and 22q.11 deletion patients (Hoffman et al. 2011; Ottet et al. 2013). These findings are consistent with the view that variations in distinct symptom domains arise from alterations of different neural circuits (Meyer-Lindenberg and Weinberger 2006).

It is tempting to conclude that functional measures are perhaps a more specific index of state-related changes in brain function, perhaps more closely tracking the onset and offset of symptom expression, whereas structural measures are more stable and thus may related to more enduring illness characteristics. Indeed, there is some evidence to suggest that long-term disease outcome and clinical functioning relate to lower levels of structural rich club organization in the absence of clear correlations with symptom severity (Collin et al. 2013). However, accumulating evidence that both structural as well as functional changes found in patients are also apparent in unaffected or minimally-affected risk populations, (Collin et al. 2013; Dandash et al. 2013; Fornito et al. 2013a; Whitfield-Gabrieli et al. 2009) suggest that functional connectivity alterations may capture stable or intrinsic components of disease pathophysiology as well.

Brain Connectivity, Genetics and Disease Vulnerability

With brain wiring and brain network organization being subject to clear alterations during early development and adolescence (see for review Collin and van den Heuvel 2013; Dennis and Thompson 2013), deviation from normative developmental trajectories at specific periods may enhance vulnerability for schizophrenia. Several lines of evidence suggest that abnormal development of brain connectivity plays an important role in the etiology of schizophrenia. First, structural and functional studies have revealed that unaffected relatives of patients often show brain network alterations that parallel those observed in affected probands, suggesting a genetic basis (e.g. Boos et al. 2013; Clemm von Hohenberg et al. 2013; Kubicki et al. 2013; Skudlarski et al. 2013; Repovs et al. 2011; Collin

et al.; Fornito et al. 2013a; Whitfield-Gabrieli et al. 2009). Second, young children with childhood-onset schizophrenia (COS) show topological alterations of functional brain networks that parallel those seen in adult patients (Alexander-Bloch et al. 2013a, b). Third, neonatal offspring of schizophrenia patients already show lower levels of connectivity strength, communication efficiency and hub strength as assessed via analysis of anatomical covariance networks (Shi et al. 2012). Finally, putative genetic risk variants for schizophrenia, as identified through genome-wide association and linkage analyses have also been associated with connectivity and topological alterations that mimic those seen in schizophrenia (Esslinger et al. 2009; Li et al. 2013). These findings converge to suggest that genetically inherited vulnerabilities in specific neural circuits interact with environmental factors to bring on the disease (Buckholtz and Meyer-Lindenberg 2012; Collin et al. 2013; Fornito and Bullmore 2012).

Though these studies have proven useful in understanding the neurobiological impact of putative genetic risk variants, and for identifying potential risk biomarkers for illness onset, no dysconnectivity phenotype has yet been translated into a clinical useful predictor. Though the same could be said for most other putative biomarkers of schizophrenia, recent studies applying multivariate classifiers to measures of grey matter volume have demonstrated promising results, suggesting that relative high accuracy (>80 %) can be achieved in making clinically important distinctions, such as which high-risk individuals will subsequently transition to diagnosable psychotic disorder (Koutsouleris et al. 2009). If connectomic measures are to be useful in this regard, they must allow similar distinctions with an accuracy superior to that afforded by simpler measures (e.g., grey matter volume). Thus far, preliminary work has shown that classifiers composed of whole-brain functional connectivity measures can distinguish between patients and controls with 80 % accuracy, patients and their unaffected relatives with 79 % accuracy, and relatives and controls with 77 % accuracy (Liu et al. 2012). These results are in the same range as classifiers based on morphological metrics (Nieuwenhuis et al. 2013; Schnack et al. 2013), suggesting promise not only in identifying people at-risk, but in also distinguishing between at-risk individuals and patients with frank disorder. The generalizability and comparative efficacy of these classifiers remains an open question for future study.

Modeling Dysconnectivity in Schizophrenia

A particular advantage of a graph theoretic approach is that it readily allows the formulation and evaluation of generative models designed to model the ontogeny and functional consequences of an observed set of altered network properties. Two broad classes of models have been studied. Growth models attempt to deduce the developmental anomalies that may lead to a particular pattern of aberrant network organization by growing networks according to a pre-specified set of rules. Dynamical models attempt to understand the underlying causes of dysregulated activity by using biophysically plausible models of neural activation and interactions (Breakspear et al. 2011).

In one study, a simple model that grew networks subject to two constraints—a bias towards clustered connectivity and a penalty on the formation of long-distance links—was able to reproduce a diverse range of topological properties observed experimentally in healthy functional brain networks. Moreover, adjusting model parameters to relax the clustering bias and reduce the penalty on long-distance connections accurately modeled the topological alterations observed in COS patients (Vertes et al. 2012). An implication of this study is that small variations in the developmental rules guiding network formation may create a vulnerability for non-optimal brain network topology, forming a pathogenetic mechanism for the development of the disorder (Collin et al. 2013; van den Heuvel and Kahn 2012). Such growth models are particularly pertinent for neurodevelopmental disorders such as schizophrenia, and may prove useful in understanding the developmental processes leading to the onset of the disorder, which typically occurs in the adolescent to early adulthood period.

Dynamical models take into account known biophysical properties of neuronal populations to simulate brain functional dynamics (Breakspear et al. 2011; Deco et al. 2012; Jirsa et al. 2010). When simulated on network architectures using empirically derived structural network topologies, they can be used to model the consequences of dysfunction in specific structural elements (Alstott et al. 2009; Honey and Sporns 2008). Dynamical models have shown that certain network configurations allow for a more dynamic and more diverse functional pattern of brain activity (Deco et al. 2012) and, conversely, that disrupted anatomical connectivity may explain a wide range of functional alterations. One recent study found that artificially reducing the degree of anatomical connectivity, either globally or locally, effected changes in functional network topology redolent of those seen in schizophrenia; specifically, a reduction in clustering and increase in global efficiency of brain functional network topology (Cabral et al. 2012). Recent developments and application of novel dynamic models (Deco et al. 2013; Deco et al. 2012; Honey et al. 2009; Senden et al. 2012), coupled with open-source platforms for large-scale neural modeling (e.g., http://thevirtualbrain.org) are likely to enhance the proliferation and application of these techniques to mental disorders such as schizophrenia. In particular, the specification of models that can accurately capture hypothesized mechanistic

disturbances thought to underlie schizophrenia, such as dopamine dysregulation (Howes and Kapur 2009) or deficient GABAergic and N-methyl-d-aspartate (NMDA) receptor signaling (Lisman et al. 2008), will facilitate attempts to bridge the gap between molecular pathology and large-scale connectomic disturbances.

Closing Remarks and Open Questions

Decades of active research into brain connectivity alterations in schizophrenia have revealed a wealth of evidence suggesting that dysconnectivity plays an important role in the pathophysiology of the disorder. More recently, network studies have indicated that the disorder is characterized both by altered network connectivity and topological organization, including disrupted global network communication, segregation and a deficient structural and functional hub connectivity.

Many of the network abnormalities observed in people with schizophrenia seem to converge on highly connected hub regions. Indeed, recent conceptual studies have suggested that abnormal connectivity of brain hubs and disrupted integration of information may be a core aspect of the disorder (Lynall et al. 2010; Rubinov and Bullmore 2013; van den Heuvel and Kahn 2013; van den Heuvel and Sporns 2013b). However, whether schizophrenia is a disorder that specifically targets hubs and the extent to which these hub effects are specific to schizophrenia remain open questions. In any case, the evidence points to a genetic basis for many of these network disturbances, suggesting that a fruitful approach will involve characterization of the effects of putative risk variants for schizophrenia on brain network connectivity and development. In this context, a key challenge for the field will be the development of analytic frameworks appropriate fusing highly multivariate datasets such as those acquired in connectomic and genomic studies (Jahanshad et al. 2013a, b). Other important challenges include determining whether connectomic measures can inform clinically relevant classifications (e.g., predicting treatment response and/or transition to illness in at-risk populations) formulating generative models that are able to replicate the complex range of network disturbances in schizophrenia, as well as their dynamical consequences. Studies incorporating information on the dynamical configuration of functional brain networks (e.g. Hutchison et al. 2013, Bassett et al. 2011), which delineate system-level aspects of healthy and affected network organization (de Lange et al. 2014) and make use of cross-model approaches (e.g. Van den Heuvel et al. 2013, Liang et al. 2013) are of particular interest. Surmounting these challenges will be necessary to move beyond simple mapping of connectivity changes to elucidate underlying disease mechanisms.

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