Network Neuroscience: A Framework for Developing Biomarkers in Psychiatry

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Abstract Psychiatric disorders are disturbances of cognitive and behavioral processes mediated by the brain. Emerging evidence suggests that accurate biomarkers for psychiatric disorders might benefit from incorporating information regarding multiple brain regions and their interactions with one another, rather than considering local perturbations in brain structure and function alone. Recent advances in the field of applied mathematics generally – and network science specifically – provide a language to capture the complexity of interacting brain regions, and the application of this language to fundamental questions in neuroscience forms the emerging field of network neuroscience. This chapter provides an overview of the use and utility of network neuroscience for building biomarkers in psychiatry. The chapter begins with an overview of the theoretical frameworks and tools that encompass network neuroscience before describing applications of network neuroscience to the

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study of schizophrenia and major depressive disorder. With reference to work on genetic, molecular, and environmental correlates of network neuroscience features, the promises and challenges of network neuroscience for providing tools that aid in the diagnosis and the evaluation of treatment response in psychiatric disorders are discussed.

Keywords Cognitive neuroscience · Depression · Graph theory · Network neuroscience · Schizophrenia

1 Introduction

Psychiatric disorders are disturbances of cognitive and behavioral processes mediated by the brain. Biomarkers for such disorders are objective indications of medical state; their clinical utility lies in the potential to diagnose the disorder, to determine its prognosis, and to predict and monitor a patient's response to interventions (Biomarkers Definitions Working Group 2001; Strimbu and Tavel 2010). Promising approaches for the development of biomarkers include noninvasive neuroimaging techniques, which have the capacity to capture the structure and function of the brain in health and disease, without requiring the injection of contrast agents or radiation exposure that may not be particularly well-tolerated by patient populations with mental illness. Historically, such approaches have focused on delineating regions whose anatomy or physiology – as estimated from imaging measurements – is altered in the disease. Yet, emerging evidence suggests that accurate biomarkers might benefit from incorporating information from both imaging and non-imaging modalities regarding not a single region but multiple regions and their interactions with one another. The complexity of building such a biomarker can initially seem quite daunting, largely because it requires the development of a language in which to describe, quantify, and predict multi-region, multimodal, interacting networks.

Recent advances in the field of applied mathematics generally – and network science specifically – have begun to provide just such a language. Their application to fundamental questions in neuroscience forms the emerging field of network neuroscience (Bassett and Sporns 2017). There are several features that render network neuroscience approaches to neuroimaging data exquisitely suited to the task of identifying mental illness (Fornito and Bullmore 2015). First, many psychiatric disorders have a genetic component, with heritability estimates as high as 80–90% observed for some disorders (e.g., schizophrenia and bipolar disorder; Cannon et al. 1998; McGuffin et al. 2003). The association between genetic variants and liability for mental illness is complex, arising from the combined effects of many genes exerting small effects. As such, identifying genetic markers of risk is difficult. Given that genes exert their effects on behavior via their influence on brain regions and their complex patterns of interactions (Esslinger et al. 2009; Richiardi et al. 2015), neuroimaging and network approaches to it provide a way forward by allowing the examination of intermediate phenotypes through which genetic risk for disorder is conferred (Meyer-Lindenberg and Weinberger 2006). Second, healthy brain function depends on complex interactions among distributed brain

regions (Sporns 2014), and psychiatric disorders are conceptualized as dysfunctions in the dynamics across regions of the brain (Friston et al. 2016; Kana et al. 2011; Woodward and Cascio 2015), rather than resulting from pathological perturbations to individual regions (Fornito et al. 2015). Methodological approaches such as network neuroscience, which are capable of capturing aberrant connectivity across regions of the brain, provide a good match to theories of psychiatric disorders.

In this chapter, we provide an overview of the use and utility of network neuroscience for building biomarkers in psychiatry. We begin by describing the fundamentals of the field of network neuroscience. We then turn to a brief review of the application of theoretical frameworks and mathematical tools from network neuroscience to the study of schizophrenia and major depressive disorder. We close by highlighting the value of the network neuroscience approach for understanding the biological underpinnings of psychiatric disorders more generally and the construction of novel biomarkers specifically.

2 Network Neuroscience: A Primer

The emerging field of network neuroscience pursues new ways to map, record, analyze, and model the elements and interactions of neurobiological systems (Bassett and Sporns 2017). Many types of elements and their interactions are examined in network neuroscience, reflecting the multi-scale nature of brain networks (Betzel and Bassett 2017). However, the tools available for observing the brain and its constituent parts place limits on the scales that may be examined. Imaging connectivity approaches often make use of magnetic resonance imaging (MRI) data. From that data, one can construct a graph, which is a simple mathematical representation of a network composed of nodes representing system elements and edges representing element relations or interactions. In imaging-derived networks, the nodes are typically parcels of gray matter voxels, ranging from single voxels to the entire brain. Associations among nodes (edges) may be established in a number of ways, which are typically categorized into structural or functional connectivity approaches.

Structural connectivity approaches aim to understand the network architecture of anatomically connected regions. There are two main approaches available for constructing anatomical networks. Diffusion imaging tractography aims to reconstruct the trajectory of axonal tracts using indices of the diffusion of water molecules within neural fibers (Li et al. 2016; Mukherjee et al. 2008). In this approach, edges reflect estimates of the probability with which a node is physically connected to another via a white matter tract. Structural connectivity may also be established via structural covariance analysis (Mechelli et al. 2005). In this approach, the covariance between morphometric features (e.g., gray matter thickness) of each possible pair of nodes in an anatomical network is estimated. In structural covariance networks, edges represent shared morphometric features between nodes that are thought to indicate physical connectivity of white matter tracts or functional connectivity related to synchronous neural activation between regions (Alexander-Bloch et al.

2013). Functional connectivity, in contrast, can be used to define network edges based on statistical similarities in the time series of nodes at rest or during task performance (Friston 2011). The edges in functional brain networks represent communication or coordination between nodes. With appropriate analytic techniques, causal relations between nodes can also be established. This form of connectivity is typically referred to as effective connectivity (Stephan and Friston 2010).

Once nodes and edges have been estimated, structural and functional connectivity networks are represented with an adjacency matrix **A** (see Fig. 1). For an unweighted and undirected graph, the element A_{ij} indicates the presence (1) or absence (0) of an edge between node i and node j. For a weighted graph, the element A_{ij} takes on a value corresponding to the strength of the association between node i and node j. The adjacency matrix for an undirected graph is symmetric, but in a directed graph, in which the direction of the associations between node i and node j are specified, the adjacency matrix may not be symmetric. In this case, A_{ij} represents the edge weight from node j to node i. This general graph construction can be used to represent a time-invariant network, one that describes network organization across the entire length of the scan, which is one typical object of study in network neuroscience. Yet, more recently the time-varying nature of network organization has been increasingly recognized (Calhoun et al. 2014), and tools with which to examine the changing organization of the brain over time have emerged (Khambhati et al. 2017; Mucha et al. 2010; Sizemore and Bassett 2017). In the case of time-varying networks, multiple adjacency matrices may be constructed, by applying a sliding window across smaller sections of imaging time series to extract a time-ordered graph ensemble, providing the basis for analyses focused on capturing changes in network organization across time (De Domenico 2017).

Following adjacency matrix construction, graph theory is applied to examine the properties of brain networks (for a recent overview, see Fornito et al. 2016). The application of graph theory to imaging data has led to the discovery of fundamental

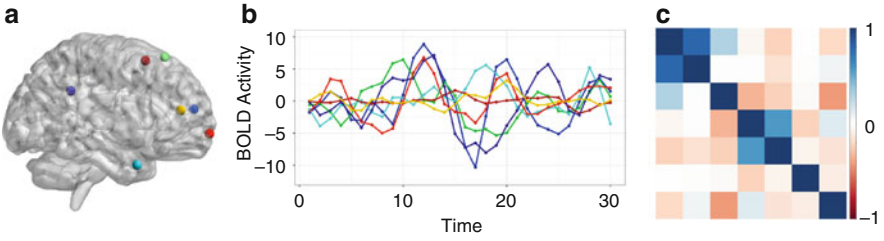

Fig. 1 Panels (**a**) through (**c**) provide an overview of the main steps involved in transforming functional brain data into an adjacency matrix that encodes the associations among brain regions. In panel (**a**), nodes are denoted by colored spheres. Spherical node parcellations are commonly used (e.g., Power et al. 2011) although other options exist (e.g., areal pacellations; Gordon et al. 2014). In panel (**b**), the mean time series of the BOLD response across the length of the scan is depicted for each node of panel (**a**). Edges, or an estimation of the extent or strength of connectivity between nodes, are created by estimating pair-wise correlations (or alternative statistical indices of association, e.g., coherence; Bassett et al. 2011) among the time series of all node pairs. Nodes and edges of the network are parsimoniously represented as an N-by-N adjacency matrix (where N is the number of nodes) in panel (**c**); here color indicates edge strength

organizational features of the brain. Structural and functional brain networks show a small-world architecture, characterized by a combination of high clustering with short characteristic path length (Watts and Strogatz 1998). The clustering coefficient captures the extent to which neighboring nodes of a network tend to be densely interconnected, or *cluster,* together. More formally, clustering in a binary graph indicates the probability that nodes *j* and *k*, which are both connected to node *i*, are also connected to each other (Chalancon et al. 2013). The shortest path length between node *i* and node *j* describes the minimum number of edges that must be traversed to travel from node *i* to node *j* in the graph. The characteristic path length of a network is then defined as the average shortest path lengths across all possible pairs of nodes in the network (Schreiber 2013). Based on the clustering coefficient and the characteristic path length of a network, a network can be likened to a regular graph (high local clustering and long path length), small-world graph (high local clustering and short path length), or random graph (low local clustering and short path length).

Small-world architecture has been observed in human structural and functional brain networks across a number of imaging modalities (for reviews, see Bassett and Bullmore 2006, 2016), as well as across a number of methods for network construction. A few pioneering early examples of such studies examined connectivity patterns of cortical thickness across the cerebral cortex using MRI (He et al. 2007), white matter connection probabilities between gray matter volumes using diffusion-weighted imaging (Iturria-Medina et al. 2008), and functional connectivity at rest (Achard et al. 2006; Salvador et al. 2005) as well as across task conditions (Eguíluz et al. 2005). Small-world architecture, as evidenced by a combination of high clustering and short path length, is thought to confer the capacity for specialized processing in local regions as well as the ability to integrate processes across the entire network, mapping onto the functional segregation and integration thought to enable efficient cognition (Sporns et al. 2004).

In addition to exhibiting small-world characteristics, the brain exhibits community structure, such that the large-scale network of the brain can be decomposed into communities or modules. Modules are made up of nodes with dense connectivity with each other and sparse connectivity with nodes in other modules. Both structural and functional graphs of human brains exhibit modularity (Bassett et al. 2010; Chen et al. 2008; Meunier et al. 2009). Functional connectivity studies, for example, have uncovered multiple functional modules at rest characterized by relatively dense internode connectivity (Nelson et al. 2010; Power et al. 2011). Named to reflect the functions typically associated with the constituent nodes, these functional systems include salience, central executive, default mode, dorsal attention, ventral attention, subcortical, cingulo-opercular, memory, visual, auditory, motor, and cerebellar systems (although the systems are not consistently labeled). Modular organization is thought to confer significant advantages to cognitive functioning (Meunier et al. 2010; Sporns and Betzel 2016). From an evolutionary perspective, modular organization allows adaptation of the system in response to changing environments one module at a time, allowing for system change without risking loss of function in already well-adapted modules (Simon 1962). In terms of its relevance to cognition, modular organization contributes to efficient local

information processing within functionally specialized modules as well as to the rapid exchange of information between modules, allowing for a balance between the functional segregation and integration important for cognition (Cohen and D'Esposito 2016; He et al. 2009).

The availability of tools to examine time-varying aspects of network organization has provided insight into changes in network organization over time and how these changes relate to cognitive performance (for a recent review, see Cohen 2017). Brain network organization varies across task contexts but also within scan sessions over the course of seconds (Calhoun et al. 2014; Medaglia et al. 2015a). Dynamics in brain network organization at these timescales have implications for cognition and behavior. In an auditory detection task, for example, reduced modularity of the brain was observed prior to trials on which the target was missed relative to trials on which the target was heard (Sadaghiani et al. 2015). In addition, performance on a broad range of cognitive tasks was related to the flexibility with which the salience system interacted with other modules over time at rest (Chen et al. 2016). The salience system is a module involved in facilitating access to executive functions by signaling the engagement and disengagement of task-relevant and task-irrelevant modules, respectively (Menon and Uddin 2010; Sridharan et al. 2008). These and similar data further highlight the role of dynamic changes in brain organization in cognition and behavior. Emerging frameworks linking dynamic features of brain organization to both behavior and cognition emphasize that a brain that can flexibly traverse many states of organization while also maintaining a preference for a few states will support consistently accurate but also adaptable behavior (Medaglia et al. 2015b).

3 Network Features as Biomarkers of Disease

Network neuroscience has revealed organizational principles of healthy brains (e.g., small-world architecture and modularity) that allow for efficient, flexible, and robust information processing. The fundamental insights into brain network organization conferred by network neuroscience hold great promise for providing biomarkers of disease. Studies comparing the networks of individuals with psychiatric disorders to those of healthy controls have observed disease-related deviations from the network topology that defines healthy networks. In this section, we present an overview of findings in schizophrenia and major depression disorder that have emerged from graph theory applications to neuroimaging data.

Schizophrenia Schizophrenia is a mental disorder characterized by positive symptoms, including delusions and hallucinations, and negative symptoms, such as flattened affect, as well as deficits in cognitive functions (Kahn et al. 2015). It has an average lifetime prevalence of approximately 1% (Perälä et al. 2007) and is associated with a shorter life-span relative to the general population (McGrath et al. 2008). Brain network features may be particularly well suited as biomarkers

of schizophrenia given current, and longstanding, dysconnectivity hypotheses of schizophrenia (Andreasen et al. 1998; Friston and Frith 1995; Wernicke 1906; Stephan et al. 2009). From the dysconnectivity perspective, it is an abnormal functional integration between distinct brain regions, rather than simply focal brain abnormalities, that are thought to underpin the disorder.

The advent of techniques capable of capturing connectivity disturbances provided early evidence for dysconnectivity in schizophrenia (Volkow et al. 1988). Since then, dysconnectivity in the organization of brain networks has been observed across a range of scales in schizophrenia. Small-world network architecture has been observed in people with schizophrenia as well as healthy volunteers using inter-regional covariation of gray matter volume (Bassett et al. 2008) as well as resting state functional connectivity (Liu et al. 2008; Lynall et al. 2010), suggesting that small-world organization is conserved across individuals with schizophrenia and healthy controls. However, quantitative differences in small-world network architecture among people with schizophrenia and healthy controls have emerged. Small-worldness is significantly reduced in people with schizophrenia relative to healthy controls across rest and task states (Liu et al. 2008; Lynall et al. 2010; Ma et al. 2012), and the extent of this reduction may be associated with the length of illness (Fornito et al. 2011a). Significant reductions in clustering (and the related notion of local efficiency) have also been observed in people with schizophrenia (Liu et al. 2008; Wang et al. 2010; Zhu et al. 2016) and some evidence for increased global efficiency (the harmonic mean of the inverse of the average shortest path) in schizophrenia has emerged, although this is a less consistent finding (Alexander-Bloch et al. 2012, 2010; He et al. 2012).

Analyses of topological disturbances in structural connectivity related to schizophrenia have not mapped onto the functional network findings for schizophrenia in a straight-forward fashion, reinforcing the complex relationship between structural and functional connectivity observed in the field more broadly (Honey et al. 2010; Damoiseaux and Greicius 2009). Few differences in the overall topology of structural brain networks, as operationalized through clustering coefficients and path length, were observed between people with schizophrenia and healthy controls (van den Heuvel et al. 2010). A diffusion tensor imaging study observed reduced global efficiency in people with schizophrenia relative to healthy controls (Wang et al. 2012), a result that differs from functional connectivity findings. In sum, schizophrenia is characterized by differences in the small-world architecture of functional brain organization, marked by a subtle randomization of network topology (Rubinov et al. 2009), although findings for structural networks are not as clear.

A variation on the dysconnectivity hypothesis of schizophrenia specific to brain network modularity was proposed by David (1994) and focused on abnormalities in the segregation of specialized processing regions. From this perspective, symptoms of schizophrenia reflect a breakdown in the encapsulation of brain systems that are specialized to carry out different processes. Hallucinations, for example, may result from cross-communication between inner speech and auditory modules. In line with this hypothesis, people with childhood-onset schizophrenia exhibit reduced

modularity in resting state functional connectivity networks relative to healthy controls (Alexander-Bloch et al. 2010). Indeed, some studies have reported more and smaller modules in people with schizophrenia relative to healthy controls (Yu et al. 2012), again providing evidence for altered modular architecture in the functional networks of schizophrenia. Recent work examining community structure in individuals with schizophrenia and healthy controls at rest, paired with rigorous preprocessing techniques to minimize the effects of motion, have also observed alterations in community structure in individuals with schizophrenia relative to controls (Lerman-Sinkoff and Barch 2016).

Alongside dysconnectivity in static graphs, deficits in the coordination of large-scale networks across time have also been proposed to underlie schizophrenia (Uhlhaas 2013). Braun et al. (2016) examined the reconfiguration of large-scale brain networks during a working memory paradigm in people with schizophrenia, unaffected first-degree relatives, and healthy controls. Dynamic changes in the interactions among brain regions with other regions were captured using a network flexibility measure that indicated the frequency with which a brain region changed its allegiance to a community of nodes over the course of the scan. Both patients with schizophrenia and their relatives showed increased brain-wide, network flexibility relative to controls. Findings suggest an excess of network flexibility in schizophrenia and deficits in the temporal coordination of large-scale networks that underpin efficient cognitive function. Further evidence for dysconnectivity in dynamic brain network organization in people with schizophrenia relative to healthy controls has been observed during resting state scans (Damaraju et al. 2014).

In sum (see Table 1 for overview), network neuroscience has provided tools to test dysconnectivity hypotheses of schizophrenia across multiple levels of brain organization. Findings indicate a greater randomization of large-scale brain networks in schizophrenia relative to healthy controls as well as alterations in the modularity of both static and time-varying networks. Notably, approaches aiming to characterize patients with schizophrenia relative to healthy controls based on network organization indices (e.g., clustering coefficient) show promising levels of classification accuracy (Anderson and Cohen 2013), suggesting that network neuroscience indices may have future clinical utility as biomarkers of schizophrenia.

Major Depressive Disorder Major depressive disorder is a prevalent psychiatric disorder associated with extensive personal and societal costs (Greenberg et al. 2015; Kessler 2012), affecting approximately 6% of the adult population worldwide each year (Bromet et al. 2011). Depressed mood and diminished interest or pleasure are core symptoms of depression, with other symptoms including diminished ability to concentrate, recurrent thoughts of death, and psychomotor agitation or retardation (see Otte et al. 2016 for a recent review). Contemporary models of major depressive disorder emphasize dysfunctional interactions between brain networks that are critical for the regulation of mood, as well as general cognitive, motor, and somatic behaviors (e.g., Mayberg 1997).

Table 1 Summary of network neuroscience findings for schizophrenia

Study	Modality	Sample	Main findings
Bassett et al. (2008)	sMRI	203 SZ 259 HC	• Small-world properties similar in SZ and HC
Van den Heuvel et al. (2010)	DTI	40 SZ 40 HC	• Small-world properties similar in SZ and HC
Wang et al. (2012)	DTI	79 SZ 96 HC	• Small-world properties reduced in SZ relative to HC
Alexander-Bloch et al. (2012)	rsfMRI	19 SZ 20 HC	• More connections between modules and fewer connections within modules in SZ relative to HC
Alexander-Bloch et al. (2010)	rsfMRI	13 SZ 19 HC	• Small-world properties reduced in SZ relative to HC • Reduced density of intra-modular connections in SZ relative to HC
Damaraju et al. (2014)	rsfMRI	151 SZ 163 HC	• SZ spend more time in more sparsely connected brain states relative to HC
Lerman-Sinkoff and Barch (2016)	rsfMRI	44 SZ 41 HC	• Small changes in modularity across SZ and HC. Differences in node community participation in subcortical, somatosensory, auditory, default mode, and salience networks
Liu et al. (2008)	rsfMRI	31 SZ 31 HC	• Small-world properties reduced in SZ relative to HC
Lynall et al. (2010)	rsfMRI	12 SZ 15 HC	• Small-world properties reduced in SZ relative to HC
Yu et al. (2012)	rsfMRI	24 SZ 24 HC	• More numerous and smaller modules in SZ relative to HC
Zhu et al. (2016)	rsfMRI	26 FSZ 26 SSZ 26 HC	• Small-world properties reduced in FSZ relative to SSZ and HC
Braun et al. (2016)	Task	28 SZ 37 UR 139 HC	• Increased flexibility of dynamic community structure in SZ and UR relative to HC
Fornito et al. (2011a)	Task	23 SZ 25 HC	• Small-world properties similar in SZ and HC
He et al. (2012)	Task	35 SZ 35 HC	• Small-world properties reduced in SZ relative to HC at medium difficulty • Small-world properties more variable across conditions in SZ than HC
Wang et al. (2010)	Task	23 SZ 33 HC	• Small-world properties reduced in SZ and HC
Ma et al. (2012)	Task; rsfMRI	28 SZ 28 HC	• Small-world properties reduced in SZ relative to HC

sMRI structural MRI, *DTI* diffusion tensor imaging, *rsfMRI* resting state fMRI, *SZ* schizophrenia, *HC* healthy controls, *FSZ* familial schizophrenia, *SSZ* sporadic schizophrenia, *UR* unaffected first-degree relatives

While small-world organization has been observed in participants with major depressive disorder as well as healthy controls, findings have been mixed as to whether there are quantitative differences between patients and controls based on whether functional or structural networks are under consideration. Indications of

reduced small-world architecture and a shift to randomization in brain networks have been observed in the functional networks of participants with major depressive disorder relative to healthy controls (Jin et al. 2011; Zhang et al. 2011). For structural networks, in contrast, no significant differences in small-world organization or associated features (e.g., global efficiency, path length, clustering coefficient) were observed between individuals with major depressive disorders and non-depressed controls in two studies (Korgaonkar et al. 2014; Sacchet et al. 2014).

While findings are mixed for whole-brain topology in major depressive disorder across functional and structural networks, examinations of connectivity within and between modules associated with both emotional and cognitive functions are providing insight into major depressive disorder (Ye et al. 2015). Interactions among three modules in particular have been the focus of much attention in network neuroscience studies of major depressive disorder. These modules include the salience system (SN), central executive system (CEN), and the default mode system (DMN). The DMN (for review see Buckner et al. 2008) is characterized by deactivation during task and activation during both rest and self-referential tasks (Mazoyer et al. 2001; Shulman et al. 1997) and encompasses many regions, including posterior cingulate cortex, precuneus, medial prefrontal cortex, orbital frontal gyrus, anterior cingulate cortex, inferolateral temporal cortex, parahippocampal gyrus, and bilateral parietal cortex (Raichle et al. 2001; Thomason et al. 2008; Van Den Heuvel et al. 2009). In contrast to the DMN and its characteristic deactivation during tasks and activation at rest is the CEN. The fronto-parietal CEN is characterized by nodes showing increased, rather than decreased, activation during the performance of cognitive tasks. The nodes of the CEN have established roles in a range of executive functions, including sustained attention and response suppression (Curtis and D'Esposito 2003; Jiang and Kanwisher 2003; Ridderinkhof et al. 2004). Due to the associations between its nodes and executive functions, the CEN is viewed as essential for guiding goal-directed behavior. Core nodes of the CEN include the dorsolateral, dorsomedial prefrontal cortex, and the posterior parietal cortex. A core function of the SN is salience detection, with nodes of the SN activating in response to different forms of salient stimulation (Uddin 2015; Menon 2015). The SN is also thought to facilitate access to executive functions by signaling the engagement of the CEN while suppressing DMN activity (Menon and Uddin 2010; Sridharan et al. 2008).

The putative functions of these three modules as well as the functions resulting from interactions among them map well onto core aspects of depressive symptomatology, including rumination (DMN), emotional disinhibition (CEN), and responses to salient, emotional events (SN). Importantly, these observations have led to an integrative model of neural dysfunction in depression focused on the connectivity among these networks (Hamilton et al. 2013). Despite observing few differences between patients with major depressive disorder and healthy controls in global features of structural connectivity, Korgaonkar et al. (2014) observed lowered structural connectivity in two distinct brain modules. The first contained regions primarily of the DMN, while the second was comprised of regions in the frontal cortex, thalamus, and caudate regions – areas central to cognitive and emotional

processing. Increased levels of DMN dominance over CEN have been observed to be associated with higher levels of depressive rumination in participants with major depressive disorder (Hamilton et al. 2011). Findings also highlight a potential role for the SN in the balance of activity between DMN and CEN, with activity of right fronto-insular cortex (a core component of the SN) exhibiting increasing activation at the onset of increases in CEN activity and decreases in DMN activity, while the opposite pattern was observed in healthy controls.

In terms of the reward deficits observed in major depressive disorder, two studies have observed a role for disturbances in the functional connectivity of the salience network, default mode network, and a broader reward network (encompassing nodes such as the ventral striatum) with depression symptom severity (Satterthwaite et al. 2015; Sharma et al. 2017). Satterthwaite and colleagues observed that depression severity was associated with diminished activity in core nodes of the reward and reward salience systems during a monetary incentive task, as well as with reduced connectivity between the ventral striatum and other nodes of the reward system during rest. Sharma and colleagues focused on symptoms of anhedonia and observed that reward deficits were associated with hyperconnectivity within the DMN, diminished connectivity between the DMN and regions of a cingulo-opercular system involved in salience detection, as well as a decoupling of the nucleus accumbens from DMN system regions. Notably, these two studies included participants with diagnoses spanning a range of disorders, allowing for the identification of network features common to reward deficits across a range of disorders that included depression.

Dynamic connectivity studies indicate that time-varying network organization of DMN, CEN, and SAL systems deviates from organization observed in healthy controls in major depressive disorder. Increased connectivity variability has been observed between regions of the DMN in patients with major depressive disorder relative to controls, an association that was replicated in a second sample (Wise et al. 2017). In terms of connectivity across modules, patients with major depressive disorder exhibit decreased variability in the functional connectivity between nodes of the DMN and CEN relative to healthy controls at rest (Demirtaş et al. 2016). Increased variability between nodes of the DMN and SAL networks was observed in people with major depressive disorder relative to healthy controls, and, notably, higher levels of rumination were also associated with increased variability between DMN and SAL nodes (Kaiser et al. 2016).

In sum (see Table 2 for overview), large-scale organization features (e.g., small-world organization) seem less impacted in major depressive disorder relative to schizophrenia. An emerging finding is that major depressive disorder is characterized by dysconnectivity across both static and dynamic measures of connectivity among three functional modules that map onto core symptoms of the disorder. Efforts to classify major depressive disorder patients relative to controls based on these features of network organization show promising results (Demirtaş et al. 2016), indicating potential future clinical utility of network neuroscience findings in major depressive disorder.

Table 2 Summary of network neuroscience findings for major depressive disorder

Study	Modality	Sample	Main findings
Sacchet et al. (2014)	DWI	14 MD 18 HC	• Small-world properties similar in MD and HC
Korgaonkar et al. (2014)	DTI	95 MD 102 HC	• Small-world properties similar in MD and HC • Connectivity in two networks, one involving DMN regions and a second comprising frontal cortex, thalamus, and caudate regions, was reduced in MD relative to HC
Demirtaş et al. (2016)	rsfMRI	27 MD 27 HC	• Connectivity variability between DMN and FPN decreased in MD relative to HC
Hamilton et al. (2011)	rsfMRI	17 MD 17 HC	• DMN dominance over CEN similar in MD and HC • rFIC showed increased activity during initiation of rise in CEN activity in MD but not in HC • rFIC showed increased activity during initiation of rise in DMN activity in HC but not in MD • Greater DMN dominance over CEN associated with greater depressive rumination in MD
Jin et al. (2011)	rsfMRI	16 MD 16 HC	• Small-world properties reduced in MD relative to HC
Kaiser et al. (2016)	rsfMRI	100 MD 109 HC	• Connectivity variability among mPFC and DMN regions decreased in MD relative to HC • Connectivity variability among mPFC and a region of the right insula
Satterthwaite et al. (2015)	rsfMRI	27 BPD 25 UPD 37 HC	• Depression severity correlated with diminished reward network connectivity
Sharma et al. (2017)	rsfMRI	32 MD 32 BD 51 SZ 51 PR 39 HC	• Reward deficits were associated with decreased connectivity between NAcc and DMN and increased connectivity between NAcc and CON across all groups, including MD • Reward deficits were associated with DMN hyper-connectivity and diminished connectivity between DMN and CON
Wise et al. (2017)	rsfMRI	20 MD 19 HC	• Connectivity variability between mPFC and PCC (nodes of DMN) greater in MD relative to HC
Zhang et al. (2011)	rsfMRI	30 MD 63 HC	• Small-world properties reduced in MD relative to HC

DWI diffusion-weighted imaging, *DTI* diffusion tensor imaging, *rsfMRI* resting state fMRI, *MD* major depression, *HC* healthy controls, *BD* bipolar disorder, *SZ* schizophrenia, *PR* psychosis risk, *BPD* bipolar depression, *UPD* unipolar depression, *DMN* default mode network, *FPN* fronto-parietal network, *CEN* central executive network, *rFIC* right fronto-insular cortex, *mPFC* medial prefrontal cortex, *NAcc* nucleus accumbens, *CON* cingulo-opercular network, *PCC* posterior cingulate cortex

The review of imaging connectivity features in schizophrenia and major depressive disorder indicates that network neuroscience is providing insight into psychiatric disorders. Identifying differences across participants with psychiatric disorders compared to healthy controls may lead to the discovery of features that

aid in diagnosis – a key aim for biomarkers. Differences across patients and healthy controls in the organization of brain networks may also provide insight into the mechanisms underlying the disorders, as molecular correlates of network features are beginning to be uncovered. To provide a richer intuition for these relations, we next examine genetic, molecular, and environmental correlates of brain network features.

4 Genetic and Molecular Correlates

Imaging genetic approaches aim to identify genes that are associated with network features of interest. The identification of genes associated with features of network organization allows a greater understanding of how that feature is related to biological processes by considering the biological actions of the associated genes. A number of quantitative and molecular genetic approaches have been enlisted in network neuroscience efforts, from establishing that brain network features are under some degree of genetic control to examining the mechanisms of individual genes (see Thompson et al. 2013).

Foundational work has demonstrated that there is substantial heritability of brain network organization (Bohlken et al. 2014). Notably, the genetic factors involved in network organization have been observed to be independent of the genetic factors associated with gray matter density of nodes within particular regions (i.e., local features of the brain; Glahn et al. 2010). Global network features, such as cost-efficiency, path length, and the small-world organization of both structural and functional brain networks, have all been demonstrated to exhibit substantial heritability (Fornito et al. 2011b; Jahanshad et al. 2012; Schmitt et al. 2008).

Findings of heritability provide important initial evidence that brain network organization is under genetic control. However, heritability estimates provide little information concerning the specific genes that contribute to the observed heritability. Candidate gene approaches examine the influence of variations in genotypes, chosen based on biologically plausible mechanisms, to determine how specific genetic factors affect the organization of brain networks. These approaches are beginning to shed light on how genetic variation may influence risk for psychopathology through associations with network connectivity. A number of studies have examined associations between genetic variants and a number of indices of brain connectivity. These studies have implicated a number of genetic variants in between-person differences in connectivity across regions of the brain (see Fornito and Bullmore 2012 for a recent review).

Much less work has examined associations between genetic variants and large-scale network organization. We discuss two noteworthy exceptions. Li et al. (2013) examined how variation in the disrupted-in-schizophrenia 1 (DISC1) gene was related to the efficiency of structural brain networks in healthy participants. DISC1 is involved in a number of neurodevelopmental processes with implications for brain connectivity, including neurite outgrowth, myelination, and axon guidance (Chen

et al. 2011; Jaaro-Peled et al. 2009). A common missense variant, ser704Cys (rs821616), in the DISC1 gene has been associated with schizophrenia and also affective disorders (Arias et al. 2014; DeRosse et al. 2007; Qu et al. 2007). Li and colleagues observed that Cys-allele carriers, relative to Ser homozygotes, exhibited longer shortest path length and lower global efficiency of structural networks, suggesting a role for DISC1 in the topological properties of brain network features implicated in psychiatric disorders.

In another noteworthy study, Markett et al. (2016) examined associations between variation on the tryptophane hydroxylase 2 gene's promotor region (TPH2 rs4570625) and structural connectivity of rich-club pathways. The rich club is a collection of nodes that are particularly rich in connections, tend to connect to one another, and thereby play a prominent role in the brain's overall network organization (Van Den Heuvel and Sporns 2011). The focus on TPH2 was chosen due to its role as a regulatory enzyme involved in limiting the rate of serotonin biosynthesis in the brain (Zhang et al. 2004). Based on findings of decreased mRNA expression for TPH2 in TPH2-703 T-allele carriers relative to G/G carriers and resultant reductions in levels of TPH2 concentrations throughout serotonergic neurons (Scheuch et al. 2007), Markett and colleagues hypothesized that reduced serotonin biosynthesis would be present in the T-allele carriers. Given that serotonin inhibits axonal growth (Trakhtenberg and Goldberg 2012), increased structural connectivity was hypothesized in T-allele carriers relative to G/G carriers due to decreased inhibition of axonal growth. In line with this hypothesis, higher connectivity in the rich club was observed in carriers of the TPH2 T-variant relative to G/G carriers.

While the candidate gene approach has been popular in work to date, genome-wide association studies (GWAS) will be useful to identify novel genetic determinants of network features (Bush and Moore 2012). GWAS approaches involve genotyping markers spanning the genome and searching for *loci* that influence phenotypes (e.g., network features). These approaches are beginning to provide insight into the genetic variants that are associated with features of brain network organization that are disrupted in disorders. For example, using a GWAS approach, O'Donovan et al. (2008) identified a single nucleotide polymorphism, rs1344706, in ZNF804A that was associated with schizophrenia. A later study, by establishing an association between rs1344706 genotype variation and functional connectivity among regions of the dorsolateral prefrontal cortex and hippocampal formation, provided evidence that the genetic risk for schizophrenia associated with variation in rs1344706 may be conferred through impacting brain network organization (Esslinger et al. 2009).

Findings of associations between genetic variants and features of brain organization from either candidate gene or GWAS approaches are compelling, especially in the context of plausible biological mechanisms. However, experimental approaches that manipulate or observe the proposed mediating mechanisms linking genetic variation to network organization (e.g., neurotransmitter activity) are important for establishing the viability of the proposed mechanisms and also, in turn, for highlighting other potential candidate genes that may confer risk for

psychopathology. This will be especially important for major depressive disorder for which, in contrast to schizophrenia, it has been relatively difficult to identify associated genetic variants (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium 2013; but see also Hyde et al. 2016; Okbay et al. 2016).

Studies using a range of techniques have established roles for dopamine, glutamate, and norepinephrine in preserving efficient network organization. A key role for dopamine in modulating spontaneous oscillations in basal ganglia and the coherence of neuronal activity between components of cortico-striato-thalamic circuits has emerged from nonhuman animal studies (Dejean et al. 2008; Walters et al. 2000). Recent work is further establishing a role for dopamine in brain networks in humans. Carbonell et al. (2014) examined how alterations in the dopamine system related to resting state network modularity and overall patterns of connectivity. Participants were scanned twice, once following a balanced amino acid mixture and once following a mixture that was tyrosine and phenylalanine deficient. This acute tyrosine and phenylalanine depletion technique decreases dopamine synthesis and reduces baseline dopamine levels as well as dopamine release in response to stimulation (Montgomery et al. 2003). Blood samples drawn to measure plasma amino acid concentrations indicated that the amino acid precursors of dopamine were indeed reduced following the tyrosine and phenylalanine deficient mixture relative to the balanced mixture. In the lowered dopamine state, following the tyrosine and phenylalanine deficient mixture, a number of effects on brain network connectivity were observed. The global and local efficiency of brain networks, as well as the modularity of brain networks, were reduced following dopamine precursor depletion. Short-range connections within the frontal lobe were reduced in the lowered dopamine state, and reduced connectivity between the frontal lobe and posterior association areas was observed. Finally, connectivity between the default mode network and the task positive network was increased in the low dopamine state. This experimental manipulation and its associated results highlight a role for dopamine in maintaining the modularity and efficiency of resting state brain networks, as well as in maintaining segregation of the default mode and task positive networks. Reductions in functional network efficiency have also been observed following a dose of a dopamine receptor antagonist (Achard and Bullmore 2007).

In terms of the role of glutamate, alterations in the cellular excitation-inhibitory balance have been theorized to disturb the neural synchrony of large-scale cell ensembles, giving rise to dysconnectivity at the level of neural ensembles that has been observed in psychopathology (Krystal et al. 2003; Uhlhaas 2013; Yizhar et al. 2011). As neural excitation-inhibitory balance is dependent on glutamatergic *N*-methyl-D-aspartate (NMDA) receptor function (Carlén et al. 2012), the effects of NMDA receptor antagonists on brain network organization have been examined. Braun et al. (2016) tested the effects of a single dose of the NMDA antagonist

dextromethorphan (DXM) on functional network flexibility during a working memory task in healthy participants. Note that while DXM binds to NMDA receptors, it may also impact serotonin transporters and other targets, including sigma-1 receptors (Werling et al. 2007). Network flexibility was increased following application of DXM relative to a placebo condition. Notably, the association between DXM and network flexibility was observed as a brain-wide effect and was not driven by changes in the flexibility of a single system. Thus, the hypo-glutamatergic state induced a network hyper-flexibility consistent with differences in network flexibility observed across patients with schizophrenia and healthy individuals (Braun et al. 2016). Further evidence for a role for NMDA receptor function in the organization of functional networks has emerged in work showing that administration of ketamine (an NMDA receptor antagonist) disrupted the association between CEN and DMN neural systems in a way that correlated with working memory performance, as well as the expression of symptoms of schizophrenia (Anticevic et al. 2012).

Pharmacological intervention approaches are not always feasible for examining the neuromodulatory systems that underpin network features due to ethical issues but also due to the timescales on which certain network features change. An example of a non-pharmacological intervention approach comes from Shine et al. (2016) who examined coupled changes in functional connectivity and pupil diameter over the course of a resting state scan. Fluctuations in pupil diameter co-vary with locus coeruleus activation, an activation that is linked to norepinephrine release that results in coordinated neural activity patterns throughout many parts of the brain via modulation of neural gain (Aston-Jones and Cohen 2005; Eldar et al. 2013; Joshi et al. 2016). By classifying brain network organization into two states characterized by either integration or segregation and capturing both fluctuations in these two states and in pupil diameter across the resting state scan, Shine and colleagues observed that brain network integration correlated with increases in pupil diameter. These findings highlight a role for norepinephrine in the relatively fast fluctuations in network organization that underpin fast and accurate cognitive performance. Further support for a role for norepinephrine and fluctuations in network organization comes from a study by Betzel et al. (2017) that observed an association between level of arousal (a state known to be associated with norepinephrine; España et al. 2016) and the flexibility with which nodes changed communities across time.

In sum, a combination of candidate gene, GWAS, and experimental studies is providing insight into the extent to which brain organization is heritable, associated with certain genetic variants, and with differences in neurochemical functioning. The focus on genetic drivers of network features is in line with the high heritability estimates of psychiatric disorders. However, there are also environmental risk factors for psychopathology (Rutter 2000), and the effects of genotype on psychiatric disorders may be conditional on environmental experiences (Kendler et al. 1995). As such, we turn to a discussion of the role that environmental factors play in psychopathology and brain network organization.

5 Environmental Factors

In terms of environmental factors involved in schizophrenia, approximately 60% of patients with schizophrenia do not have an affected first-degree relative and heritability estimates range between 60–80% (Brown 2011; Sullivan et al. 2003). For major depressive disorder, heritability estimates are in the range of 31–42% indicating substantial environmental factors in the disorder (Lohoff 2010; Sullivan et al. 2000). The substantial variance in psychopathology associated with environmental experiences necessitates a consideration of factors beyond genetics. Emerging work is examining how environmental factors may lead to changes in network connectivity indices observed to be associated with psychopathology. We provide an overview of two environmental factors, socioeconomic status and social network structure, that exhibit associations with both psychopathology and brain network organization.

Socioeconomic status (SES) is a multidimensional construct that includes measures of economic resources and is typically assessed with income, education, occupation, as well as combinations of these indicators (Braveman et al. 2005; Krieger et al. 1997). Low SES is associated with greater risk for schizophrenia (Werner et al. 2007) and major depressive disorder (Lorant et al. 2003), as well as psychopathology more generally (Kohn et al. 1998). The mechanisms driving associations between low SES and psychopathology may be articulated as social causation and social selection hypotheses. Social causation hypotheses posit that people with low SES develop psychological problems in response to exposure to adverse life circumstances. Social selection hypotheses, in contrast, posit that people with psychopathology drift down the SES ladder due to an inability to fulfill role obligations resulting from their psychopathology or by inheriting risk through genetic pathways. Of course, either hypothesis alone is unlikely to capture the complex, reciprocal dynamics between selection and causation processes that may operate across development, leading to interactionist perspectives of SES that consider both processes (Conger and Donnellan 2007). Tests of interactionist models of the effects of SES require complex study designs over long periods of time (e.g., Capaldi et al. 2003) to disentangle the contributions of social selection, social causation, or a combination of the two to psychopathology and brain network organization.

The difficulties in establishing causality notwithstanding, network neuroscience is in a prime position to examine the structural and functional brain network features that are impacted by low SES experiences, which place individuals at risk for psychopathology. There is substantial evidence from nonhuman animal work that exposure to deprived environments modifies the brain (Mohammed et al. 2002; Van Praag et al. 2000). There is also human work showing local structural and functional brain differences across levels of SES (Gianaros et al. 2011; Kishiyama et al. 2009).

Much less work has examined large-scale network features but two noteworthy exceptions exist. Krishnadas et al. (2013) examined the modular architecture of brain network structure in men from the most deprived and least deprived neighborhoods

of Glasgow, Scotland. Using region-wise cortical thickness correlations, they observed differences in the modular structure of brain graphs. Structural networks of the least deprived group showed stronger modular organization relative to random graphs, while structural networks of the most deprived group showed the same number of modules relative to their corresponding random network. The most deprived group, then, exhibited a weakened modular structure, with more edges between modules relative to the least deprived group. The least deprived group also had greater indications, relative to the most deprived group, of brain network architecture that would facilitate efficient information transfer between modules. The results, as a whole, establish evidence of a relationship between socioeconomic status and network topology.

A second study examined the implications of SES for the development of functional networks during the first year of life (Gao et al. 2015). Longitudinal growth trajectories of nine functional modules (Smith et al. 2009) were examined in terms of their within-module connectivity, between-module connectivity, and overall similarity to adult references at five time points during the first year of life. At age 6 months, both higher income and higher maternal education were associated with greater similarity to adult references and higher within-module connectivity. Further, higher income was associated with lower between-module connectivity. Thus, indications of reduced modular structure across functional brain networks were associated with low SES – in line with findings of structural connectivity in adults. An important future direction for work on SES is to examine the mechanisms through which low SES "gets under the skin" to influence network connectivity. Candidate mechanisms for SES effects on the brain include exposure to stressful experiences, social support, toxins, and stimulating activities (Hackman et al. 2010).

An additional environmental factor that is beginning to receive attention for its impact on brain networks is one's social network structure. Social support is the emotional support, guidance, and tangible aid available to the individual through social ties to other individuals, groups, and the larger community (Lin et al. 1979; Wills 1991). Social support has long been known to have beneficial effects on mental and physical health (for review see Taylor 2011). In schizophrenia, positive relationships with the individuals in one's social network are associated with fewer symptoms and greater levels of functioning (Pahwa et al. 2016). Further, social networks of greater size, containing a greater number of individuals outside of the family and that provide greater levels of support, are associated with greater quality of life in people with schizophrenia (Cechnicki et al. 2008). Lower levels of social support may also act as a risk factor for major depressive disorder (Wade and Kendler 2000). Increased contact with one's social network is associated with fewer depressive symptoms (Sugisawa et al. 2002), and multiple aspects of social network characteristics are associated with depression recovery over a 2-year period (van den Brink et al. 2017).

In terms of etiology, frameworks for understanding the role of social network stress and support in impacting both schizophrenia and major depressive disorder have implicated the engagement of neural stress regulatory circuits that, with chronic stress, lead to long-term physiological and neurobiological changes that increase

the risk for pathological states (Akdeniz et al. 2014; Slavich and Irwin 2014). In these frameworks, social networks play stress-buffering roles, attenuating the physiological stress response (Cohen and Wills 1985; Seeman and McEwen 1996; Young et al. 2014).

The extent to which social network structure and function buffers experiences of stress to protect against brain network changes that increase vulnerability to developing psychopathology remains to be seen. However, a number of groundbreaking studies linking brain network function to social network structure have laid the foundations for future work in this area (see Falk and Bassett 2017 for review). Schmälzle et al. (2017), for example, examined the moderating role of social network structure on the effect of social exclusion on functional brain network architecture. The experience of social exclusion was simulated through the use of a well-validated game referred to as Cyberball (Williams et al. 2000) in neurotypical adolescent males. Functional connectivity within the mentalizing network – a group of regions involved in the process of inferring others' affective states encompassing the medial prefrontal cortex, precuneus/posterior cingulate cortex, and the temporoparietal junction (Frith and Frith 2006; Schnell et al. 2011) – increased during social exclusion. Notably, the strength of functional connectivity between two key nodes of the mentalizing network was related to social network structure as measured by ego-network density based on objective social media data. A dense ego-network indicates a close-knit social network in which participants' friends are also friends with one another (Hurlbert et al. 2000). Less dense ego-networks, in contrast, reflect social networks in which a participant's friends do not know each other. Participants with a less dense social network exhibited stronger coupling between key regions of the mentalizing network during social exclusion. The findings highlight differences in the brain network response to social exclusion, a potent source of stress, based on preexisting social network characteristics.

Important foundational work remains to be conducted to examine the extent to which network features, especially large-scale topological features, are associated with environmental factors such as SES and social network structure and function. Establishing the mechanisms through which environmental factors impact brain network structure and function will also be integral for a better understanding of the causes and consequences of psychopathology. In considering these mechanisms, it will be valuable for both our understanding of mechanisms and for intervention possibilities to work within frameworks that emphasize the bidirectional interplay among intra- and extra-organismic levels of analysis across development (Magnusson and Cairns 1996). Observed brain network features reflect, in part, experience-dependent organization (Sporns 2013). Indeed, patterns of structural and functional connectivity are thought to result from histories of co-activation of regions across cognitive processes and actions. The more frequently processes are used, the more entrenched they are thought to become in functional modules detectable during resting state analyses. This proposition stems from a network-level application of Hebbian theory in which "neurons that fire together, wire together" and is consistent with observations of training-induced changes in network organization (e.g., Bassett et al. 2015; Takeuchi et al. 2010; Taubert et al. 2010).

The experiences available across different environments also likely impact network features given that behavior can be conceived of as the leading edge of adaptation – with the individual's activity at the boundary of the individual and their environment capable of inducing change in the environment and the structures of the individual to facilitate adaptation (Gariepy 1996). As such, incorporating measures of everyday behaviors, using experience-sampling designs, for example (Bolger et al. 2003; Shiffman et al. 2008), into studies examining network organization changes in response to the environment will be key for establishing mechanisms underlying change.

6 Open Frontiers

Work to date suggests that network neuroscience has the potential to inform our understanding of psychiatric disorders. In this section, a number of open frontiers are described that will bring the field closer to its aims of providing tools that aid in the diagnosis, determination of prognosis, and prediction and monitoring of responses to intervention.

A key challenge for the study of network neuroscience in psychiatry is to adopt designs that move beyond an examination of associations between genetic variants and environmental factors and the presence or absence of psychopathology. Developmental psychopathology perspectives hold that psychiatric disorders constitute end points of interactions between genetic and environmental risk factors that impact normal brain development, leading researchers to highlight that adult imaging phenotypes represent systems resulting from a developmental process in which environmental stressors interact with genetic vulnerability to contribute to the emergence of psychopathology (Viding et al. 2006). From this perspective, an understanding of psychopathology and its causes will be bolstered by situating the study of network neuroscience and psychiatry within a developmental framework and making use of intensive longitudinal data to capture within-person change in brain network organization across typical and atypical development (Bergman and Magnusson 1997; Menon 2013).

Existing classification systems in psychiatry are descriptive, relying on identifying combinations of symptoms to reach a diagnosis of a disorder, and provide a challenge for network neuroscience applications. There is tremendous heterogeneity in brain network organization among individuals with the same diagnostic label (Fried and Nesse 2015; Galatzer-Levy and Bryant 2013). Work to date has relied on diagnostic categories to define patient versus healthy control groups and, as such, has inherited existing difficulties in identifying the mechanisms underlying heterogeneous disorders. Going forward, imaging connectivity approaches must be paired with innovations in theoretical frameworks that rely less on monothetic diagnostic criteria and more on approaches that recognize the dimensional nature of mental disorders. The theoretical components of such an approach are emerging in RDoC (Insel et al. 2010) and in network approaches to psychopathology (Borsboom 2017; Fried and Cramer 2016).

To date, imaging connectivity approaches have provided insight into the network features that distinguish healthy controls from participants with psychiatric diagnoses. Much less work has examined the ability for network features to contribute to differential diagnoses of psychiatric disorders. Given that the standard of care differs across diagnostic categories, this will be an important achievement to meet in order for imaging connectivity features to act as feasible biomarkers (Savitz et al. 2013). This aim will be met by including participants across diagnosis categories to identify common and dissociable aspects of connectivity (e.g., Satterthwaite et al. 2015).

There are a number of challenges associated with network neuroscience methodologies that place limitations on their capacity to act as biomarkers. Chiefly, there are many freely selectable parameters during the analysis of imaging data. Small variations in the implementation of connectivity analyses can impact resulting features to the extent that associations with genetic variation and network features, for example, can be observed for specific implementations of connectivity analyses but not others (Bedenbender et al. 2011). While this will be an ongoing challenge, work providing a better understanding of the effects of differing data processing pipelines is emerging that will aid in establishing guidelines for best practices in the analysis of brain networks (Ciric et al. 2017; Zhang et al. 2016).

7 Conclusion

Network neuroscience provides an array of tools and concepts capable of capturing the complex features of brain (dys-)organization that have been long-theorized to underpin psychiatric disorders. Applications of network analysis have revealed organizational principles of healthy brains that allow for efficient, flexible, and robust information processing. These mathematical tools and conceptual frameworks have allowed for fruitful research into how brain organization deviates from optimal organization in psychiatric disorders. There is promising potential for network neuroscience to highlight the mechanisms associated with psychopathology and to provide tools that aid in diagnosis and in evaluating treatment response. Further progress will be gained by incorporating network neuroscience techniques within developmental psychopathology frameworks that recognize the limitations of current clinical nosology.

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