Review

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Large-scale brain networks and psychopathology: a unifying triple network model

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The science of large-scale brain networks offers a powerful paradigm for investigating cognitive and affective dysfunction in psychiatric and neurological disorders. This review examines recent conceptual and methodological developments which are contributing to a paradigm shift in the study of psychopathology. I summarize methods for characterizing aberrant brain networks and demonstrate how network analysis provides novel insights into dysfunctional brain architecture. Deficits in access, engagement and disengagement of large-scale neurocognitive networks are shown to play a prominent role in several disorders including schizophrenia, depression, anxiety, dementia and autism. Synthesizing recent research, I propose a triple network model of aberrant saliency mapping and cognitive dysfunction in psychopathology, emphasizing the surprising parallels that are beginning to emerge across psychiatric and neurological disorders.

Towards a neurocognitive network perspective on psychopathology

Understanding how the human brain produces cognition depends on knowledge of its large-scale (see Glossary) organization [1]. The human brain is a complex patchwork of interconnected regions, and network approaches have become increasingly useful for understanding how functionally connected systems engender, and constrain, cognitive functions. These network approaches are also providing new insights into aberrant brain organization in several psychiatric and neurological disorders. Methodological advances in this area are propelling new ways of thinking about disorders of brain connectivity such as autism, schizophrenia and dementia. Studies of psychopathology are now increasingly focused on understanding how disturbances in distributed brain areas operating within large-scale networks contribute to cognitive and affective dysfunction. These advances offer the possibility of broad synthesis and integration from a systems neuroscience perspective: a perspective that has been largely absent in the clinical neuroscience literature until recently and is now beginning to have a major impact on how brain systems impacted by psychopathology are examined.

Most, if not all, major psychopathologies involve dysfunction of cognitive and emotion regulation processes relying on distributed brain regions spanning multiple lobes. In this review, I examine how large-scale brain networks provide integrative models of cognitive and affective dysfunction in psychopathology. I begin by reviewing recent conceptual and methodological developments contributing to a paradigm shift in the study of brain function and dysfunction. I discuss different approaches and methods for characterizing brain networks in psychopathology and describe how network analyses are providing novel insights into global brain architecture and organization in psychopathology. I then turn to a description of large-scale neurocognitive networks and show how their systematic investigation provides a synthesis of cognitive dysfunction across several disorders. I describe the surprising parallels and dissociations that are beginning to emerge across psychiatric and neurological disorders. Finally, I propose a 'triple network' model that helps synthesize extant findings into a common framework for understanding dysfunction in core neurocognitive networks across multiple disorders. The review focuses on autism, schizophrenia, depression, anxiety, Alzheimer's disease (AD) and frontotemporal dementia (FTD), disorders associated with major cognitive impairments and relatively high prevalence rates. However, rather than discussing the unique characteristics of individual disorders, this review focuses on common motifs and their unifying empirical, neurobiological and conceptual underpinnings. As such, many of the techniques and general principles described are likely to apply to other psychopathologies in which disturbances of interoception, cognition, consciousness and the self are prominent.

A paradigm shift in the study of psychopathology

Multiple brain imaging techniques have contributed to our understanding of aberrant perception, cognition and

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Glossary

Alzheimer's disease (AD): AD is an age-related nonreversible brain disorder that develops over a period of years. Initially associated with memory loss and confusion, the symptoms of AD gradually lead to behavior and personality changes, a decline in cognitive abilities such as decision making and language skills, and problems recognizing family and friends.
Attention deficit hyperactivity disorder (ADHD): ADHD is one of the most common childhood disorders and can continue through adolescence and adulthood. Symptoms include difficulty staying focused and paying attention, difficulty controlling behavior and hyperactivity.
Autism: autism is a neurodevelopmental disorder that appears in the first three years of life, and affects the normal development of social and communication skills of the brain. Individuals with autism have difficulties with social interaction, display problems with verbal and nonverbal communication, and exhibit repetitive behaviors or narrow obsessive interests.
Central executive network (CEN): a brain network that is responsible for high-level cognitive functions such as planning, decision making, and the control of attention and working memory.
Centrality: a property of a node in a network that measures the relative importance of the node in the network. Nodes that occur on many shortest paths between other nodes have higher centrality than those that do not.
Clustering coefficient: a property of a node in a network. Clustering coefficient is a measure of the extent to which nodes in a graph tend to cluster together, and is based on measures of how connected the neighborhood of the node is.
Default-mode network (DMN): a large-scale network of brain areas that form an integrated system for self-related cognitive activity, including autobiographical, self-monitoring and social functions. The DMN is typically deactivated during stimulus-driven cognitive processing.
Depression: major depression is characterized by a combination of symptoms that interfere with an individual's ability to enjoy once-pleasurable activities. Prominent symptoms include persistent sad, anxious or 'empty' feelings, feelings of hopelessness and pessimism, feelings of guilt, worthlessness and/or helplessness, rumination and suicidality.
Diffusion tensor imaging (DTI): a type of noninvasive MRI technique that measures white matter tracts in the human brain *in vivo,* based on diffusion properties of water molecules in the local tissue microstructure.
Frontotemporal dementia (FTD): FTD describes a clinical syndrome associated with shrinking of the frontal and temporal anterior lobes of the brain. The symptoms of FTD fall into two clinical patterns that involve changes in behavior or problems with language.
Functional connectivity: the statistical interrelation of variables representing temporal changes in different network nodes. The functional interdependency of brain network nodes refers to joint activity in different brain structures that is codependent under variation of a functional or behavioral parameter.
Functional magnetic resonance imaging (fMRI): a form of noninvasive neuroimaging based on blood-oxygen-level-dependent signals in the brain *in vivo*.
Generalized anxiety disorder (GAD): GAD is a pattern of frequent constant worry and anxiety triggered by many different activities and events. The main symptom is the almost constant presence of worry or tension, even when there is little or no cause.
Independent component analysis (ICA): a computational technique that separates a multivariate signal into additive components based on the assumption that the components arise from statistically independent non-Gaussian sources.
Intrinsic connectivity network (ICN): a large-scale network of interdependent brain areas observed in subjects at rest.
Large-scale: a term referring to neural systems that are distributed across most of the brain.
Network: a physical system that can be represented by a graph consisting of nodes and edges.
Path length: a property of a node in a network that is the average number of steps between a node and all other nodes in the network.
Salience network (SN): a large-scale brain network involved in detecting and orienting to salient external stimuli and internal events.
Schizophrenia: schizophrenia is a complex mental disorder associated with auditory hallucinations, paranoid or bizarre delusions, disorganized speech and thinking, poor social behaviors and blunt affect.
Small-world network: a graph in which most nodes are not neighbors of one another but most nodes can be reached from every other by a small number of steps.
Structural connectivity: physical connectivity between brain areas measured using DTI tractography *in vivo* or tracer studies on *postmortem* tissue.

emotion in psychiatric and neurological disorders such as schizophrenia, depression and dementia. It is now well established that many such disorders are associated with multiple and distributed foci of structural brain abnormalities (Figure 1). Schizophrenia, for example, a complex mental disorder whose symptoms include disordered thought and blunted affect, is associated with significant reductions in whole-brain volume, whole-brain gray matter, frontal gray and white matter, parietal and temporal lobe white matter, as well as large differences in lateral ventricular volume [2–4]. These reductions are also associated with progressive cognitive decline [5]. In autism, another major neurodevelopmental disorder affecting social development, verbal and nonverbal communication and motor behaviors, multiple brain systems are aberrant from an early age [6]. For decades, structural brain imaging has been the mainstay for identifying abnormalities in individuals with autism and schizophrenia. Most of the earlier studies were limited to univariate models of localized deficits or unconstrained measures of global change involving metrics such as overall brain volume. In the ensuing years, multivariate techniques involving principal components analyses or structural equation modeling were brought to bear on identifying distributed structural patterns of deficits [7].

The advent of functional magnetic resonance imaging (fMRI) has brought an ever increasing armamentarium of methodological tools for investigating both cognitive function and dysfunction. The first two decades of fMRI research were largely focused on localization of brain responses in relation to specific experimental manipulations in individual disorders. Similar to structural brain imaging, fMRI studies have identified multiple brain foci underlying deficits in cognitive, affective and social information processing in various disorders. Over the years, these studies have focused on identifying the neural bases of specific symptoms and cognitive deficits by using experimental manipulations borrowed from the cognitive neuroscience literature. Nevertheless, functional localization of dysfunction as measured by increased or decreased blood-oxygenation-level-dependent signal levels has been the mainstay of this approach.

It has become increasingly apparent that the original goal of mapping dysfunctional cognitive and psychological processes associated with psychiatric disorders onto individual brain areas is now widely considered implausible. This is not surprising given that most psychiatric conditions are syndromes or 'disorders' encompassing multiple, heterogeneous, behavioral phenotypic features. In schizophrenia, for example, key phenotypic features include positive symptoms, such as thought disorder and hallucinations, and negative symptoms, such as flat affect, in addition to ubiquitous executive functioning deficits [8]. Furthermore, different symptom clusters can have different levels of prominence across time and across individuals, as in schizophrenia with changing presentations of disorganized, positive and negative symptoms [9]. Beyond the complexity represented by such heterogeneous presentations, even specific symptoms such as auditory hallucinations cannot be ascribed to isolated operations of single brain areas such as the primary or secondary auditory cortex [10].

Increasingly, researchers have turned their attention to investigations of how multiple brain regions interact over time. Functional connectivity analyses based on temporal

Figure 1. Distributed structural deficits in major psychopathology. Both convergent and divergent patterns of deficits are readily seen in structural brain imaging studies of schizophrenia, bipolar disorder, mild cognitive impairment and AD. Convergent patterns of deficits are particularly evident in the insula and medial PFC. **(a) Schizophrenia:** patients with schizophrenia have reduced gray matter density relative to control subjects in a distributed network of regions, including bilateral insular cortex, anterior cingulate, left parahippocampal gyrus, left middle frontal gyrus, postcentral gyrus and thalamus. Meta-analysis of voxel-based morphometric data reveals consistent patterns of anatomical deficits across 42 studies. Adapted from [164]. **(b) Bipolar disorder:** in patients with bipolar disorder, gray matter reduction in left rostral ACC and right FIC were consistently observed across 21 studies. Adapted from [165]. **(c) Mild cognitive impairment:** in patients with mild cognitive impairment, meta-analysis of 22 studies has revealed convergent patterns on gray matter atrophy, which were mainly situated in the amygdala, hippocampus, parahippocampal gyrus, medial temporal pole, thalamus, precuneus and PCC. Adapted from [166]. **(d) Alzheimer's disease (AD):** patients with AD show progressive gray matter tissue loss throughout the brain and most notably in the DMN, frontoparietal and salience networks. Prominent nodes include the PCC, hippocampus, entorhinal cortex, precuneus, parieto-occipital sulcus and insula and lateral PFC. Adapted from [167].

coupling of fMRI responses have been widely used in the past decade to examine context- and stimulus-dependent interactions between brain regions [11,12]. Naturally, the distributed patterns of deficits observed in task-related activation paradigms have led to the suggestion that abnormal functional integration and aberrant connectivity is a core feature of psychiatric disorders. The most concerted effort in this direction, lasting almost two decades now, has been in studies which have provided strong evidence for reduced connectivity between multiple frontotemporal and frontoparietal regions of patients with schizophrenia [13] (Figure 1).

Functional dysconnectivity models have also increasingly taken center stage in explanations of the etiology of autism. In autism, structural and functional brain imaging studies have variably described abnormalities in the superior temporal sulcus, prefrontal cortex (PFC), and subcortical areas including the basal ganglia, amygdala and cerebellum. However, findings from these studies are generally not well replicated [14–16]. Moreover, the focus

on differences in single brain regions does not recognize the emerging view that autism is a disorder of multiple brain systems and that the disturbance lies in the interactions among these systems [17–19]. In contrast to the late adolescent onset of schizophrenia, the effects of autism on brain structure and function can be detected as early as infancy and altered connectivity can result from multiple genetic and epigenetic influences that extend over decades, resulting in both aberrant synaptic pruning during early childhood and altered brain wiring during childhood and adolescence [20].

The upshot of these and related studies across multiple disorders is that complex psychiatric and neurological disorders are characterized by structural and functional abnormalities in multiple brain areas involving several distinct brain systems. Although such research has provided insights into the multiple brain regions activated by particular tasks, a systematic understanding of dysfunctional brain circuits has remained elusive because of the variability in the locus of deficits with symptoms and lack of consistency in the cognitive experimental paradigms used to investigate them.

A paradigm shift in the study of brain dysfunction is now emerging, led by several recent conceptual and methodological developments. First is the emerging science of large-scale networks and the discovery that the human brain is intrinsically organized into coherent functional networks [1] (Figure 2). The discovery of task-positive and task-negative networks in fMRI data, for example, has highlighted bottlenecks arising from network access, conflict and resources due to the oppositional nature of brain networks [21–24]. Second is the discovery of the default-mode network (DMN) which plays an important role in monitoring the internal mental landscape [21,25,26]. Third, the discovery of the salience network (SN): a system that plays an important role in attentional capture of biologically and cognitively relevant events and in the subsequent engagement of frontoparietal systems for working memory and higher-order cognitive control [27–29]. Fourth, dynamic interactions between these networks regulate shifts in attention and access to domain-general and domain-specific cognitive resources [30]. These processes have important implications for psychopathology not only in attentional disorders such as attention deficit hyperactivity disorder (ADHD), but also many other disorders involving dysfunctional saliency processing which can lead to aberrant allocation of attentional resources and consequently to diminished goal-relevant cognitive capabilities. Fifth, graph-theoretical formulations and techniques have become important for understanding fundamental aspects of global brain architecture in healthy individuals [31–33]. This approach is now providing crucial insights into the aberrant brain architecture in neuropsychiatric and neurological disorders and, most importantly, in identifying dysfunctional phenotype-specific subsystems [34–36]. Finally, ongoing local baseline fluctuations and intrinsic functional circuits impose strong biases on information processing in the brain [22,27,37], and these functional circuits in turn are constrained by anatomical pathways that mature in specific ways during childhood and adolescence [38,39]. Additionally, task-based functional and effective connectivity studies, although informative and essential, can sometimes not only miss but also lead to poor and incomplete characterization of basic features of dysfunctional brain systems and circuits. A glaring example of this is illustrated by AD in which episodic memory performance is often at floor levels [40]. Furthermore, titrating task difficulty to optimal levels can be especially challenging in cases where symptoms fluctuate over time and across individuals. In such cases, alternate methods are needed to assess dysfunctional brain circuits. A proper characterization of intrinsic anatomical and functional circuitry is therefore essential for a more principled characterization of cognitive and affective dysfunction in psychopathology.

Characterizing brain networks in psychopathology

Brain networks can be characterized by a collection of brain regions (nodes) and the connections (edges) that link them [32]. A brain network can be defined based on structural connectivity as measured in the human brain with diffusion tensor imaging (DTI), or functional connectivity as typically measured by fMRI [1,41]. Aberrant brain networks can arise from damage either to individual nodes or edges that link them. In the context of large-scale brain network architecture, there are different ways of defining nodes and multiple approaches for characterizing both the structural and functional edges linking them. Implicit in all neuroimaging studies of brain networks in psychopathology is the notion that dysfunctional nodes or edges result in aberrant signaling which can then propagate to the whole network or subnetworks across the brain.

Aberrant nodes

The functions of a node are determined by its intrinsic properties and its extrinsic connections [42]. Each brain region has a unique fingerprint that distinguishes its connectivity from other brain regions, endowing it with specific functional properties. Understanding network-level dysfunctions arising from node-level deficits therefore requires analysis of how its connectivity differs from the pattern of connections in other functionally related brain areas. Decades-long research findings of altered gray and white matter suggest the presence of abnormalities in multiple network nodes spanning several lobes in many psychopathologies. Even in the case of focal lesions following stroke, network analysis suggests disrupted information processing across widely distributed regions including those in the contralesional hemisphere [43]. Thus, functional deficits can extend much further downstream than predicted solely on the basis of focal node damage. Furthermore, there is evidence to suggest that structural abnormalities propagate over time because of reductions in synchronized neuronal activity. Disorders such as FTD and AD initially arise from focal structural abnormalities that become more diffusive and extensive over time [44]. The recent availability of cytoarchitectonic mapping [45] and neurochemical receptor mapping [46] offers new possibilities for better characterizing network nodes and brain connectivity [47]. However, it is not clear at this time whether cytoarchitectonic boundaries are similar in patient groups and healthy controls. Nevertheless, these

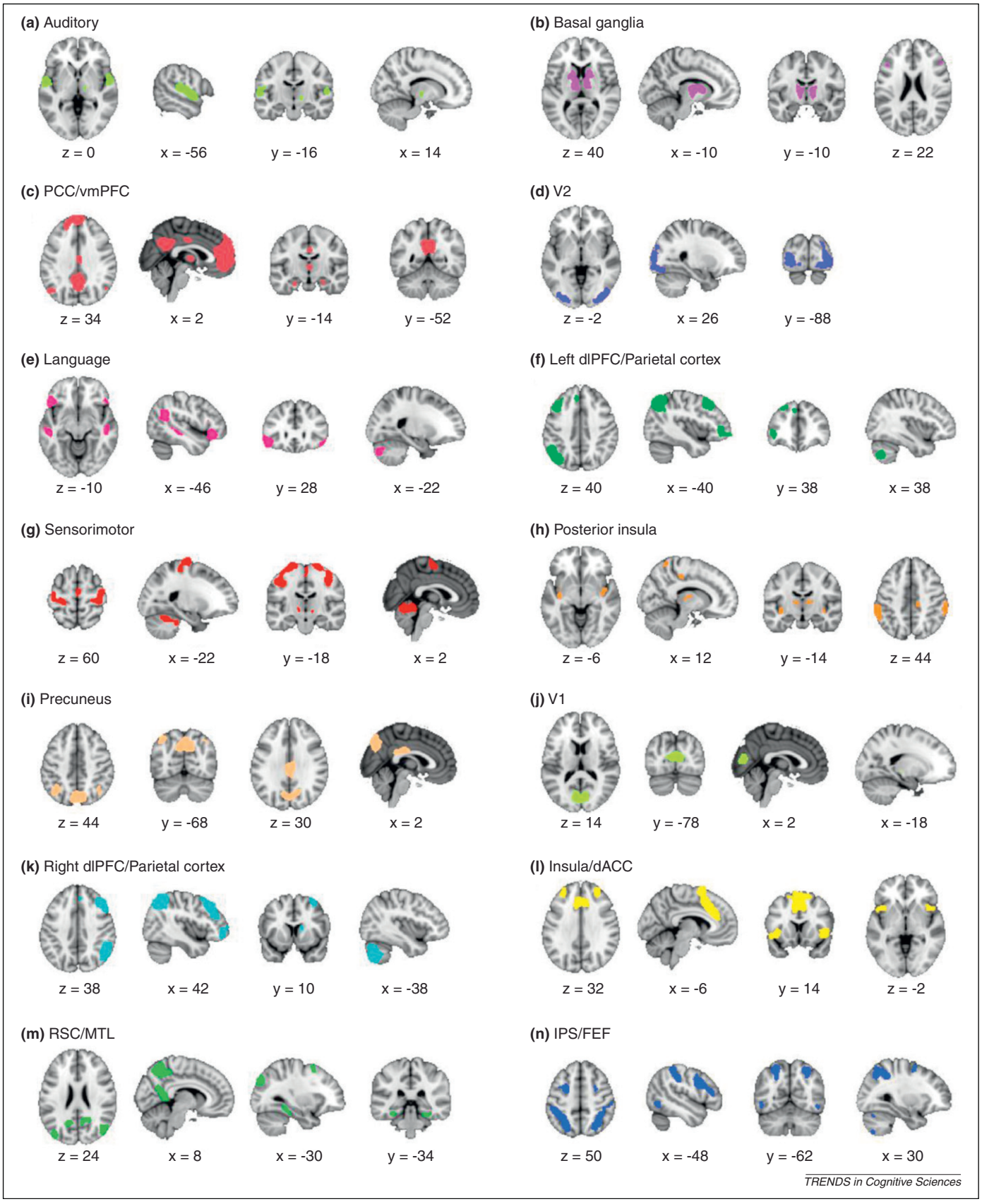

Figure 2. ICNs. The human brain is intrinsically organized into distinct functional networks that impose strong constraints on information processing. Disruptions to the nodes and edges of these networks contribute to specific patterns of cognitive and behavioral impairments. Recently identified ICNs include **(a)** Auditory, **(b)** Basal ganglia, **(c)** PCC/vmPFC, **(d)** Secondary visual cortex (V2), **(e)** Language, **(f)** Left dlPFC/Left parietal cortex, **(g)** Sensorimotor, **(h)** Posterior insula, **(i)** Precuneus, **(j)** Primary visual cortex (V1), **(k)** Right dlPFC/Right parietal cortex, **(l)** Insula/dACC, **(m)** Retrosplenial cortex (RSC)/MTL, **(n)** Intraparietal sulcus (IPS)/FEF. Adapted from [168].

developments offer interesting possibilities for exploring computational models of how pathology at the level of intrinsic node-level properties alters network function [48]. Local circuit dysfunction can contribute to abnormal signaling and temporal interactions between brain regions even in the presence of intact structural edges. However, the contributions of local circuit properties to psychopathology are virtually impossible to examine noninvasively at this time, although some progress has been made using *postmortem* brains in schizophrenia [49], autism [50], FTD [51] and depression [52] (Figure 3). More detailed characterization of intrinsic node properties in terms of cell size, boundaries, neuronal and synaptic density, and the canonical profile of local circuits remains a challenge, and biophysically realistic simulations remain the only possible approach in the foreseeable future.

Aberrant edges

Dysfunctional edges can arise from: weak axonal pathways linking nodes taken pairwise, altered computations in individual nodes which are transmitted to other connected nodes, and altered emergent network dynamics arising from complex nonlinear interactions between edges. Investigations of dysfunctional edges are being propelled by advances in DTI, which are providing increasingly sophisticated methods for measuring the integrity of white matter pathways linking nodes *in vivo*. Inspired by recent developments in intrinsic fMRI approaches for characterizing abnormal connectivity, DTI studies are now beginning to examine anatomical networks in which edge strength is measured using density of white matter tracts as well as myelination [53]. Most studies of large-scale brain network dysfunction in psychopathology have, however, been based on dysfunctional edges using task-related and intrinsic functional connectivity.

I now turn to two different approaches for characterizing large-scale brain networks and discuss recent advances in understanding psychopathology using each approach; both involve using whole-brain data. The first approach uses graph-theoretical analysis of functional or structural

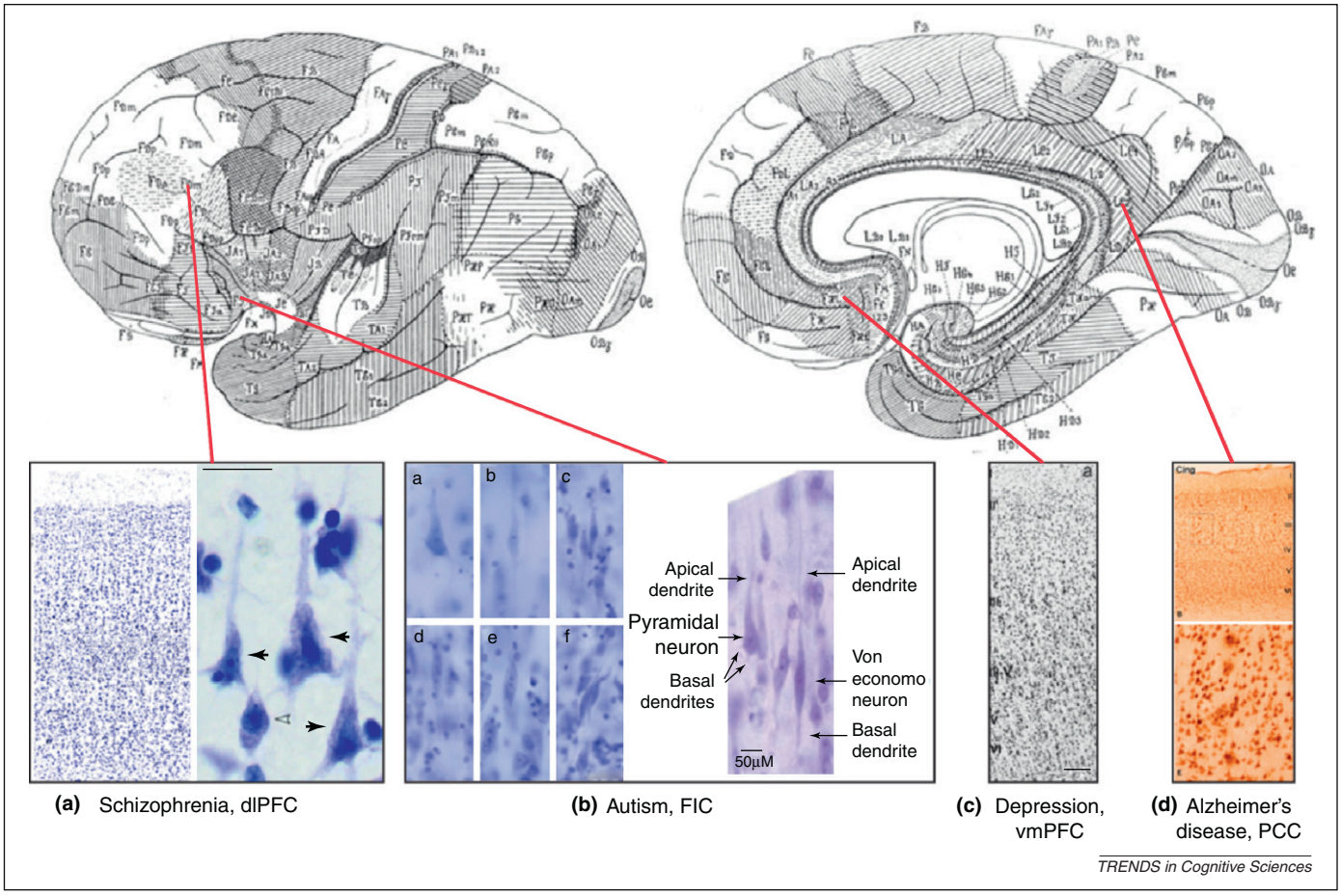

Figure 3. Node-level vulnerability in psychopathology. Node-level abnormalities alter the balance of excitation–inhibition in local neurocircuitry and impact global signaling. Progress in identifying node-level cytoarchitectonic organization and local circuit abnormalities in major psychopathology has been slow and only a few brain areas have been mapped despite decades of research. This figure shows select examples of dysfunctional nodes in schizophrenia, autism, depression and AD. **(a) Schizophrenia:** deficits in working memory in schizophrenia are attributable, at least in part, to specific pathological alterations in the neuronal circuitry of the dlPFC that involve abnormalities in pyramidal neurons and disturbances in glutamate and dopamine signaling. Pyramidal neurons (light blue) in deep layer 3 have smaller somal size, shorter basilar dendrites, lower dendritic spine density, and a reduced axonal arbor in schizophrenia. Adapted from [49]. **(b) Autism:** abnormalities in distinctive von Economo neurons (VEN) of the FIC and ACC have been implicated in autism and frontotemporal dementia. Photomicrographs showing the typical morphology of pyramidal neurons (panel a) and VENs (panel b) in control subjects, and atypical morphologies of VENs in patients with autism (panels c–f). Adapted from [50,169]. **(c) Depression:** altered pregenual and subgenual anterior cingulate/vmPFC glutamatergic signaling in major depression. Nissl staining of a perpendicular section showing subgenual cingulate cytoarchitecture. Adapted from [52]. **(d) AD:** the formation of plaques of extracellular fibrillar amyloid beta peptide (Aβ) in the PCC is one of the main pathological signatures of AD. AD is characterized by dementia that begins with formation of plaques in the MTL and PCC, leading to progressive deterioration of behavioral and cognitive functions. Adapted from [170].

connectivity to characterize the topology, modularity and hierarchy of the whole brain as a single network, whereas the second approach is based on identifying circumscribed neurocognitive networks for targeted explorations of dedicated cognitive functions.

Graph-theoretical analysis of large-scale brain networks in psychopathology

Graphs are data structures which have nodes and edges that link the nodes [32]. In a graphical representation of a brain network, a node corresponds to a brain region whereas an edge corresponds to the functional interactions between two brain regions. In recent years, there has been increasing interest in the use and application of graph metrics to characterize aberrant large-scale brain networks. Graph-theoretical metrics such as clustering coefficient, path length, degree and centrality provide quantitative measures to characterize large-scale networks represented as a graph (see [32,41] for a detailed review of various graph metrics and their interpretation). Clinical studies are now beginning to examine how these network metrics are altered in psychiatric and neurological disorders (Figure 4).

The human brain is a highly nonrandom network [32]. In normal healthy adults, converging evidence from several studies has shown that the brain has a small-world architecture characterized by dense local clustering of connections between neighboring nodes and a short path length between nodes, due to the existence of relatively few long-range connections [34,41]. Small-world networks are economical, tending to minimize wiring costs while supporting efficient processing of complex information. The combination of these attributes simultaneously promotes high specialization and high integration within a modular architecture [31].

Brain networks can be characterized on the basis of either their structural or functional covariance structure. The former relies on data pooled across individuals whereas studies using resting fMRI (rfMRI) are based on temporal covariance structure derived from each individual, and are therefore likely to be more useful in clinical settings. The power of rfMRI-based methods also relates to simultaneous *in vivo* examination of the entire brain regions, the intrinsic interactions among them and the demonstration that patterns of rfMRI correlations are tightly linked to the

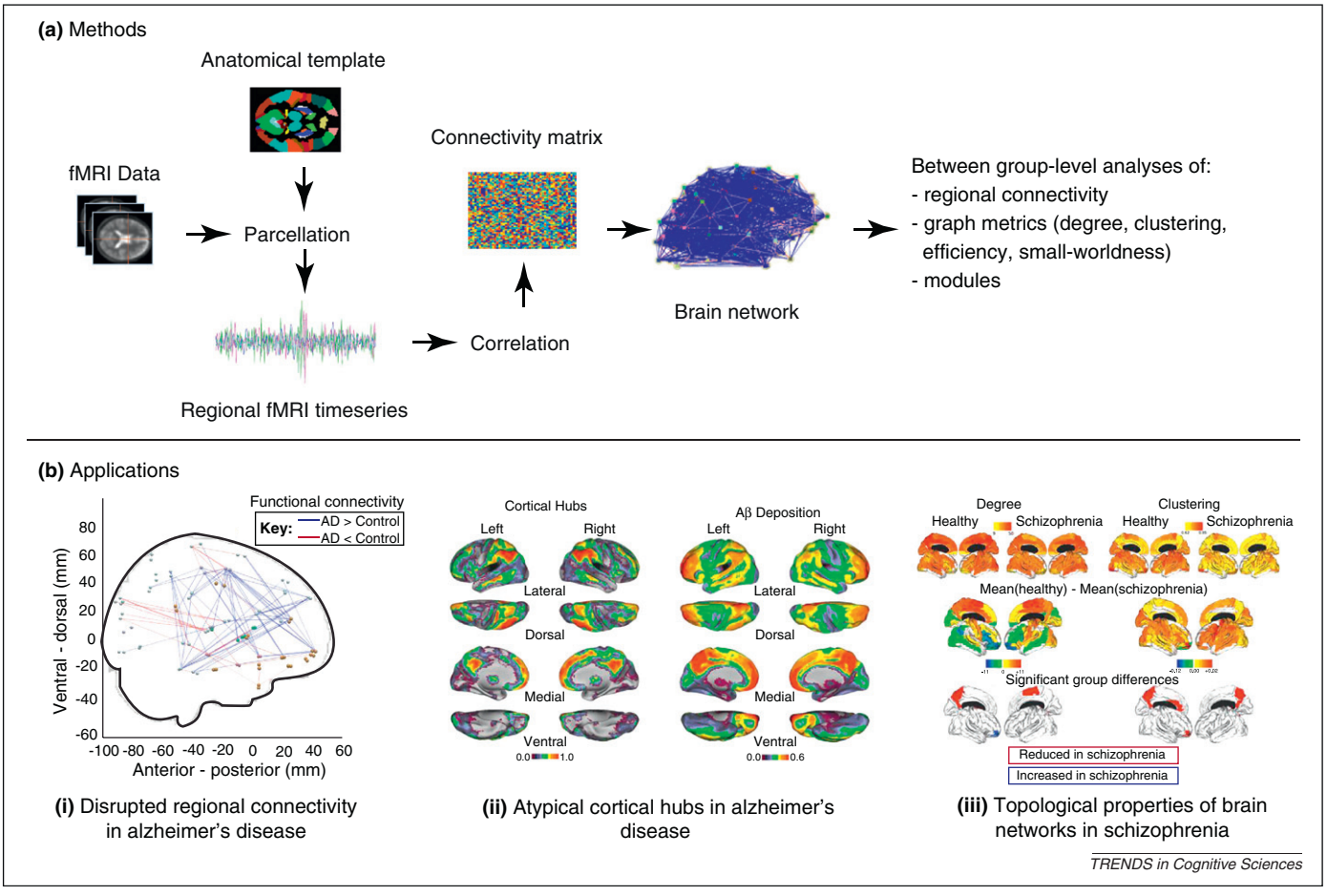

Figure 4. Graph-theoretical analysis of large-scale brain networks in psychopathology. Network metrics such as path length, clustering and modularity are used to detect aberrant network topology, modularity and efficiency of communication. They are also useful for identifying dysfunctional and compensatory subnetworks and hubs in patients. **(a)** Schematic of major steps in graph-based fMRI data analysis: parcellation of data into nodes of the large-scale brain network, construction of functional association matrix by calculating the pairwise association between nodes, computation of graph-theoretical metrics and statistical analysis to determine whether network metrics are different in patients with psychopathology from healthy controls. Adapted from [34]. **(b)** Application of the graph-based analysis to psychopathology in AD and schizophrenia. **(i)** Graphical representation of altered functional connectivity along the posterior–anterior and ventral–dorsal axes, highlighting higher connectivity within the prefrontal areas and lower connectivity within the temporal areas in AD, compared with healthy elderly controls. Adapted from [34]. **(ii)** Brain regions showing high functional connectivity ('cortical hubs') overlap with the regions showing Aβ deposition. Adapted from [114]. **(iii)** Cortical surface rendering of differences in topological properties – degree and clustering – of whole-brain networks in schizophrenia, compared with healthy controls. Adapted from [171].

gross functional architecture of the brain [54–56]. Thus, damage to part of the network can propagate throughout the whole network or large-scale subnetworks [57], and systematically impact a spectrum of cognitive functions. Clinically relevant measures include those that detect functional integration and segregation, quantify centrality of individual brain regions or pathways, characterize patterns of disrupted anatomical circuitry, and test resilience of networks to insult [58]. I focus below on five major aspects of dysfunctional brain organization that this approach provides, using recent findings in AD and schizophrenia as illustrative examples. Taken together, these features help to uncover loci of altered local and global network connectivity in psychopathology and help identify specific nodes for more targeted structural and functional analysis.

Abnormal small-world architecture Deviance from small-world architecture is a tell-tale sign of significant global deficits in brain organization. The three most commonly used metrics of overall network architecture are path length, clustering coefficient and the cumulative metric sigma: the ratio of normalized clustering coefficient to the characteristic path length, a measure of small-world organization. In patients with AD, network analysis using rfMRI has shown that sigma and path length do not differ between AD and healthy control groups [34,59]. However, AD patients show a significantly lower clustering coefficient indicative of disrupted local connectivity [34]. Surprisingly, global connectivity is relatively intact and whole-brain synchronization does not differ between AD and healthy aging groups. Patients with schizophrenia, by contrast, show both global and local connectivity deficits, and multiple network metrics, including sigma, clustering coefficient and path length are reduced, reflecting progressive neurodevelopmental changes that impact multimodal cortical systems [60].

Dysfunctional subsystems The absence of global connectivity differences does not, however, preclude the existence of dysfunctional subnetworks. Network analysis has provided useful tools for identification of such subnetworks. Division of the brain into known functional subsystems can be used to examine functional organization in key subdivisions such as primary sensory, subcortical, limbic, paralimbic and association areas [61]. In addition, examining the global connectivity of regions with known structural pathology such as the posterior cingulate cortex (PCC) and hippocampus in AD, or the insular cortex in FTD, can help identify disrupted subnetworks and cognitive systems differentially impacted by each disorder. For example, in AD, subnetwork analysis has identified the hippocampus as a particular locus of connectivity deficits characterized by significantly lower clustering coefficients of both the left and right hippocampus [34]. Crucially, this finding suggests that a similar approach might help to uncover major foci of nodal deficits in other neurological and psychiatric disorders.

Compensatory subsystems Regional and subnetwork analysis can provide evidence for compensatory subsystems. For example, increased connectivity within the frontal lobe has been reported in patients with AD [34,62] in spite of disrupted long distance interregional correlations. This may help compensate for reduced connectivity between the temporal and parietal lobes in these patients. Interestingly, this reorganization is mirrored in task-related studies showing increased PFC activation in AD during successful encoding and retrieval of visuospatial paired associates [63]. A shift towards increased semantic processing during autobiographical memory retrieval supported by greater activity in the left inferior frontal gyrus has also been reported to be enhanced in patients with AD [64]. Quantitative meta-analysis of episodic memory in AD further suggests that patients demonstrate increased activation likelihood in the inferior frontal gyrus [65], and there is also evidence emerging for training-related brain plasticity in the PFC in patients with AD [66]. At the other end of the age spectrum, enhanced mnemonic and visuospatial skills have been reported in children with autism [67,68]. Very little is currently known about the compensatory subsystems that promote such skills, and it remains an important area of investigation. Identifying preserved, compensatory and enhanced subsystems can be useful for designing cognitive remediation, particularly in developmental disorders such as autism where early diagnosis and treatment is crucial. Graph-theoretical measures offer novel tools for such discovery.

Identification of dysfunctional hubs Graph-theoretical methods provide metrics for identifying vulnerable hubs that are crucial for integrating information from many other brain areas. The PCC is one such hub, and disruptions in information processing within this region have been implicated in AD [34] and schizophrenia [60]. Cortical hubs in the PCC and temporal lobe are particularly impaired in AD, yet these patients retain hubs in the frontal lobe [62]. The spatial overlap between hypometabolism and disruption of connectivity in cortical hubs points to a particular susceptibility of these regions to early Alzheimer's-type neurodegeneration, and may reflect a link between loci of initial synaptic dysfunction and large-scale functional disconnection [69]. By contrast, patients with schizophrenia show many more dysfunctional hubs distributed across frontal, parietal and temporal lobes [53].

Disease identification, onset and progression Network metrics can potentially be used as biomarkers to distinguish between disease stages. In AD, small-world metrics have been successfully used to distinguish between patients with AD and mild cognitive impairment, and to characterize changes in the functional organization of the brain in early and late phases of AD. Small-world measures of global brain connectivity in patients with mild cognitive impairment exhibit intermediate values between healthy controls and patients with AD [62]. Similar to previous studies of functional connectivity in AD, patients with mild cognitive impairment also show increased interregional correlations within the local brain lobes and disrupted long distance interregional correlations [62]. Thus, network metrics could be useful in providing prognostic information about disease presence and progression.

In summary, graph-theoretical network metrics help to uncover loci of altered local and global network connectivity in psychopathology and help identify specific nodes for more targeted structural and functional connectivity analysis.

I have focused on recent studies in AD and schizophrenia as examples of how this approach can inform our understanding of disruptions in network, subnetwork and node-level organization. The study of many other disorders is likely to benefit from such investigations in the future, even those that do not show significant deficits in small-world architecture at the whole-brain level. Network analysis not only provides information about disruption of global organization but also helps identify both subnetworks that are compromised and subnetworks that potentially compensate for dysfunction. Network metrics also hold promise as biomarkers for distinguishing symptom clusters and for early detection and potential treatment. Although graph-theoretical methods provide useful metrics for characterizing the gross topology of brain disorganization, they are less successful in relating specific brain systems to crucial aspects of cognitive dysfunction.

Large-scale neurocognitive networks

Neurocognitive networks are brain systems dedicated to a more or less distinct cognitive function [70]. Examples of such networks are the language network anchored in the middle temporal gyrus, Broca's, Wernicke's and Geschwind's areas, the working memory–executive function network anchored in the dorsolateral PFC (dlPFC) and posterior parietal cortex (PPC), and the spatial attention network anchored in dorsal PPC and frontal eye fields (FEFs). The nodes of such neurocognitive networks were initially identified using lesion studies [71]. Although these studies in patients with neurological disorders have taken on increasing sophistication over the years with voxel-based lesion-symptom mapping [72], their anatomical precision remains relatively poor. Further, lesion mapping does not lend itself to identification of common patterns of distributed brain processes associated with precise cognitive functions. More recently, fMRI activation studies have been used to more precisely demarcate nodes of specific functional circuits associated with such dedicated networks. However, regions of interest (ROIs) identified in this manner tend to vary considerably with task demands, patient groups used, and the specific control or baseline conditions used to identify them. As a result, uncovering the nodes of neurocognitive networks in a principled and reliable manner has turned out to be elusive.

Analysis of intrinsic functional connectivity has facilitated the isolation of neurocognitive networks that have not yet been captured with more sophisticated tract-tracing techniques such as diffusion spectrum imaging and autoradiography [73,74]. Since the discovery of coherent fluctuations within the somatomotor system [75], a growing number of studies have shown that many of the brain areas engaged during various cognitive tasks also form coherent large-scale brain networks that can be readily identified using intrinsic functional connectivity [22,76] (Figure 2). There are two distinct approaches to analysis of intrinsic functional connectivity, both of which have proven useful in characterizing convergent and divergent patterns of aberrant network connectivity. Intrinsic connectivity analysis of disease-relevant nodes is one important approach for examining aberrant functional circuitry, and for demarcating divergent networks targeted by related disorders with unique phenotypic features. Amygdala hyperactivation is a common feature of several different types of anxiety disorders, including generalized anxiety disorder (GAD), social anxiety, specific phobia, fear and posttraumatic stress disorder (PTSD) (Figure 5). Studies of negative emotion processing in these patients have pointed to a common underlying circuitry involving the amygdala, insula and medial PFC (mPFC) [77]. Analysis of functional connectivity at the level of individual nuclei of the amygdala has provided new insights into the functional neuroanatomy of the human amygdala convergent with connectivity studies in animal models [78]. Using this approach, greater intra-amygdala interconnectivity, weak segregation of target functional circuits, and engagement of a compensatory frontoparietal network has been identified in patients with GAD (Figure 5). Similar analyses in other anxiety disorders are likely to clarify the precise functional circuits impaired in each disorder and to identify similarities and distinctions between different types of anxiety disorders, thereby facilitating more targeted pharmacological and behavioral interventions. A second example comes from studies of patients with dementia where selective vulnerability of different brain regions to neurodegeneration has been associated with divergent network connectivity patterns [79,80]. Connectivity analysis of disease-specific nodes associated with five different neurodegenerative syndromes has provided evidence for circumscribed atrophy within five distinct intrinsic networks: consistent with known functional neuroanatomy in healthy adults (Figure 6). Identification of unique connectivity fingerprints will also facilitate the development of biomarkers for differential diagnosis of related disorders [80].

Analysis of rfMRI data using independent component analysis (ICA) has turned out to be another useful tool for identifying intrinsic connectivity networks (ICNs) [27,81]. ICNs reflect strong coupling of spontaneous fluctuations in ongoing activity and they remain robust under different mental states including sleep and loss of consciousness [82–84] (Figure 3). Importantly, ICNs are less sensitive to physiological noise and other artifacts and they offer a more reliable and robust way to characterize large-scale brain organization [1]. As I discuss below, these ICNs provide a common neuroanatomical framework for understanding fundamental aspects of behavioral and cognitive dysfunction.

Three core neurocognitive networks and their dysfunctions

Of the many stable ICNs identified in the human brain thus far, three have turned out to be particularly important for understanding higher cognitive function, and dysfunction, in fundamental ways; hence the use of the term 'core' neurocognitive networks. They are the central executive network (CEN), the DMN and the SN [21,27,85] (Figure 7). Importantly, ICNs show close correspondence in independent analyses of resting and task-related connectivity patterns [76], suggesting that intrinsically coupled functional networks are also systematically engaged during cognition. This allows intrinsic and task-related fMRI activation patterns to be identified and studied in a common framework. Crucially, they provide useful models for

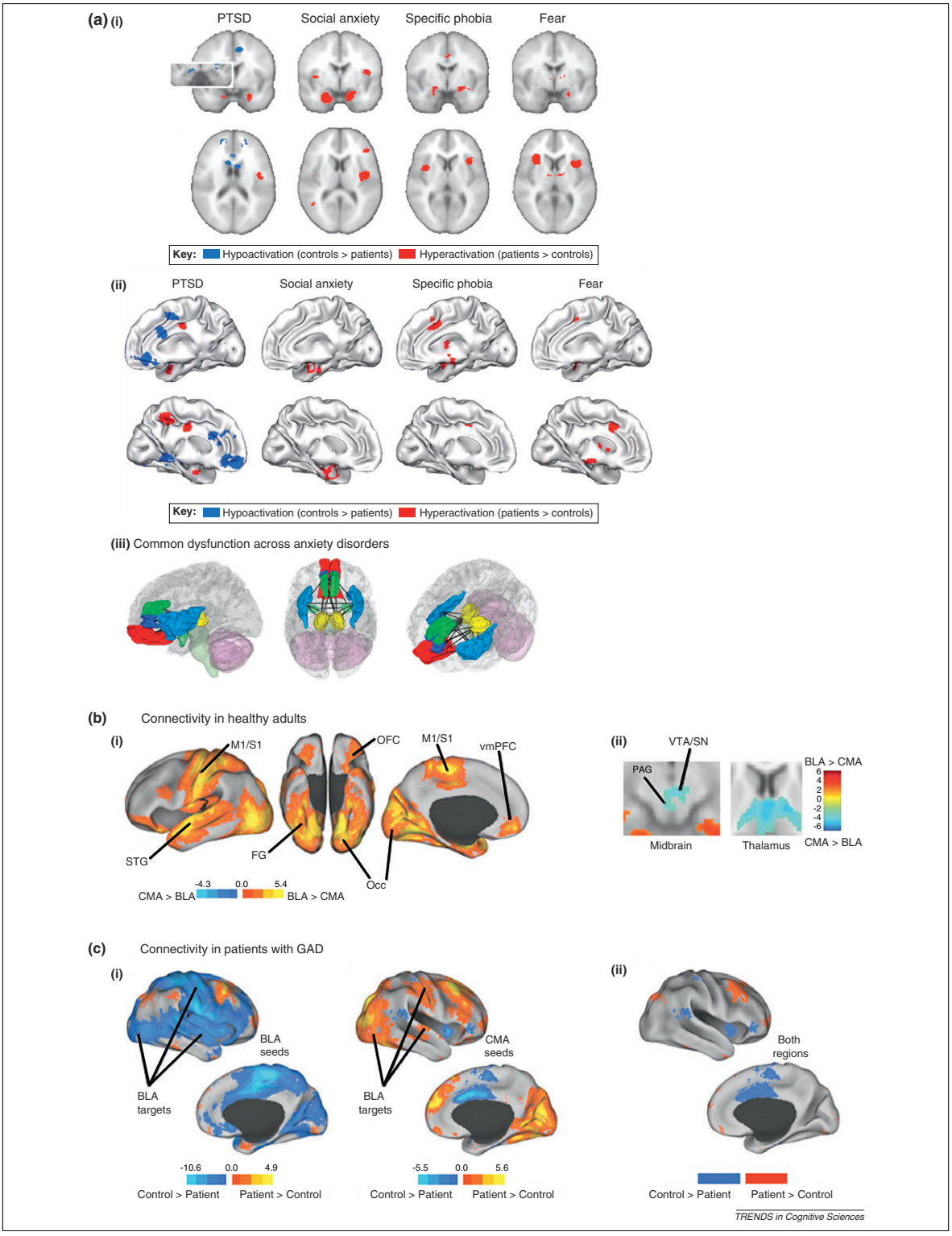

Figure 5. **Amygdala circuit dysfunction in anxiety disorder.** Connectivity analysis identifies novel patterns of aberrant amygdala circuits and cross-network coupling in patients with anxiety disorder. **(a)** Common patterns of aberrant emotional processing based on meta-analysis of patients with posttraumatic stress disorder (PTSD), social anxiety disorder and specific phobia. **(i)** and **(ii)** Hyperactivation of amygdala and insular cortex in patients with anxiety disorder. **(iii)** Model of amygdala-medial PFC dysfunction across anxiety disorders provides a limited view of dysfunctional amygdala circuitry. Adapted from [77]. **(b)** Differential intrinsic connectivity of the basolateral (BLA) and centromedial (CMA) nuclei of the amygdala with cortical **(i)** and subcortical regions **(ii)** involved in emotion processing and regulation. The BLA is differentially connected with primary and higher-order sensory and medial prefrontal cortices. The CMA is differentially connected with the midbrain, thalamus and cerebellum. Adapted from [78]. **(c) (i)** and **(ii)** In patients with generalized anxiety disorder (GAD), BLA and CMA connectivity patterns are significantly less distinct, and are characterized by greater cross-network coupling, increased connectivity with the frontoparietal CEN and decreased connectivity with cingulate-insular SN. Adapted from [78].

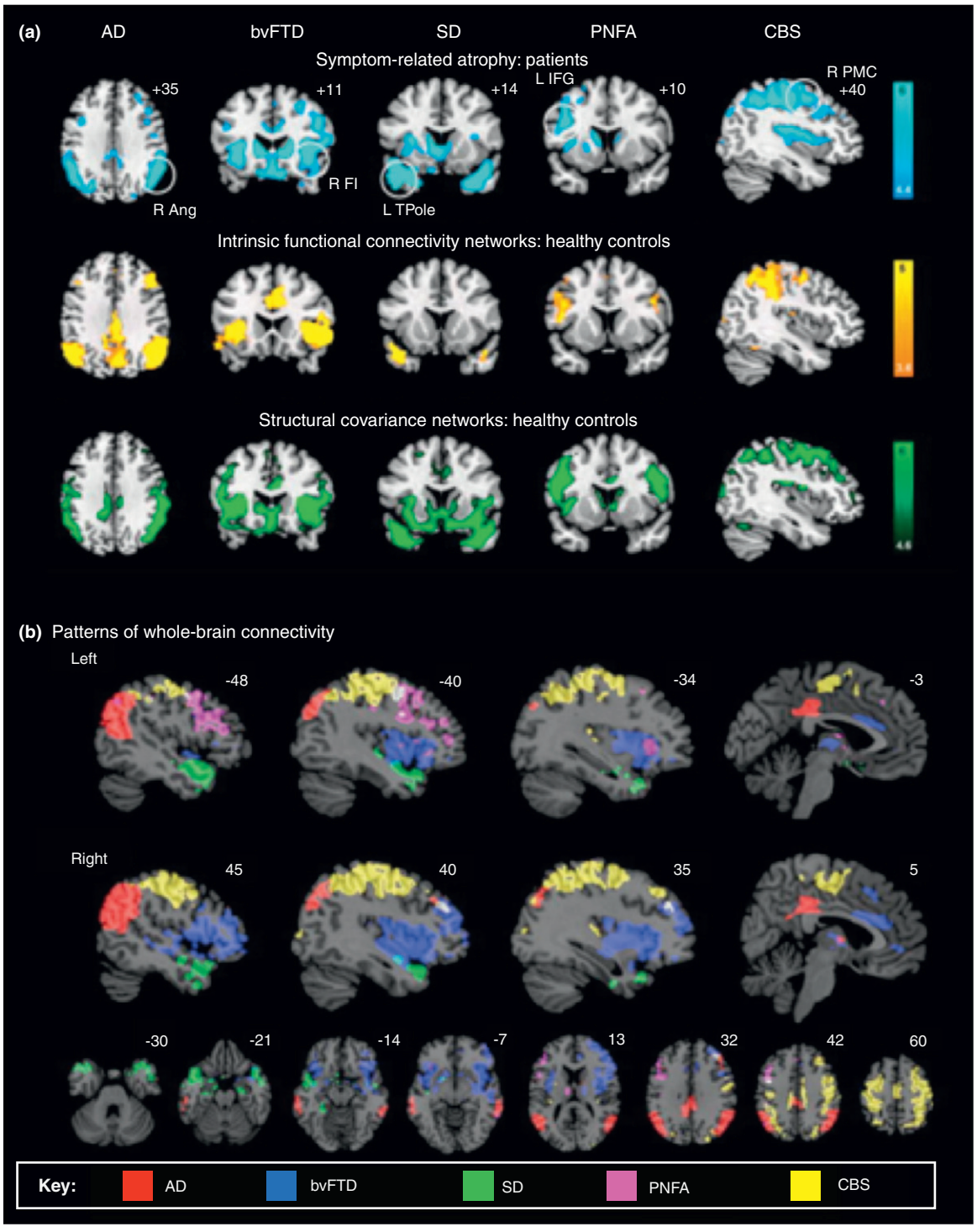

Figure 6. Neurodegenerative diseases target distinct large-scale human brain networks. Five major dementias – AD, bvFTD), semantic dementia (SD), progressive nonfluent aphasia (PNFA) and corticobasal syndrome (CBS) – have unique fingerprints of cortical and subcortical degeneration. **(a)** Distinct syndrome-related atrophy (top row). Healthy controls showed intrinsic functional connectivity patterns (middle row) and gray matter volume covariance patterns (bottom row) consistent with networks targeted by individual neurodegenerative syndromes. **(b)** Distinct patterns of whole-brain connectivity associated with the five clinical syndromes. Colored regions highlight voxels found within associated maps of syndromic atrophy, ICNs and structural covariance patterns. The color code refers to the atrophy map used to derive the relevant seed ROI. The resulting maps demonstrate the dissociable nature of brain systems associated with the five different types of dementia. Adapted from [172].

investigating network features of cognitive dysfunction in psychopathology. Although these networks are identified on the basis of ICNs, their application to brain disorders extends beyond the investigation of aberrant intrinsic network organization. They can also be used to identify both normal and abnormal nodes related to large-scale brain organization, and to investigate aberrant task-related information processing in specific cognitive and affective domains in a more principled manner. More specifically, the intrinsic wiring and connectivity of the brain imposes

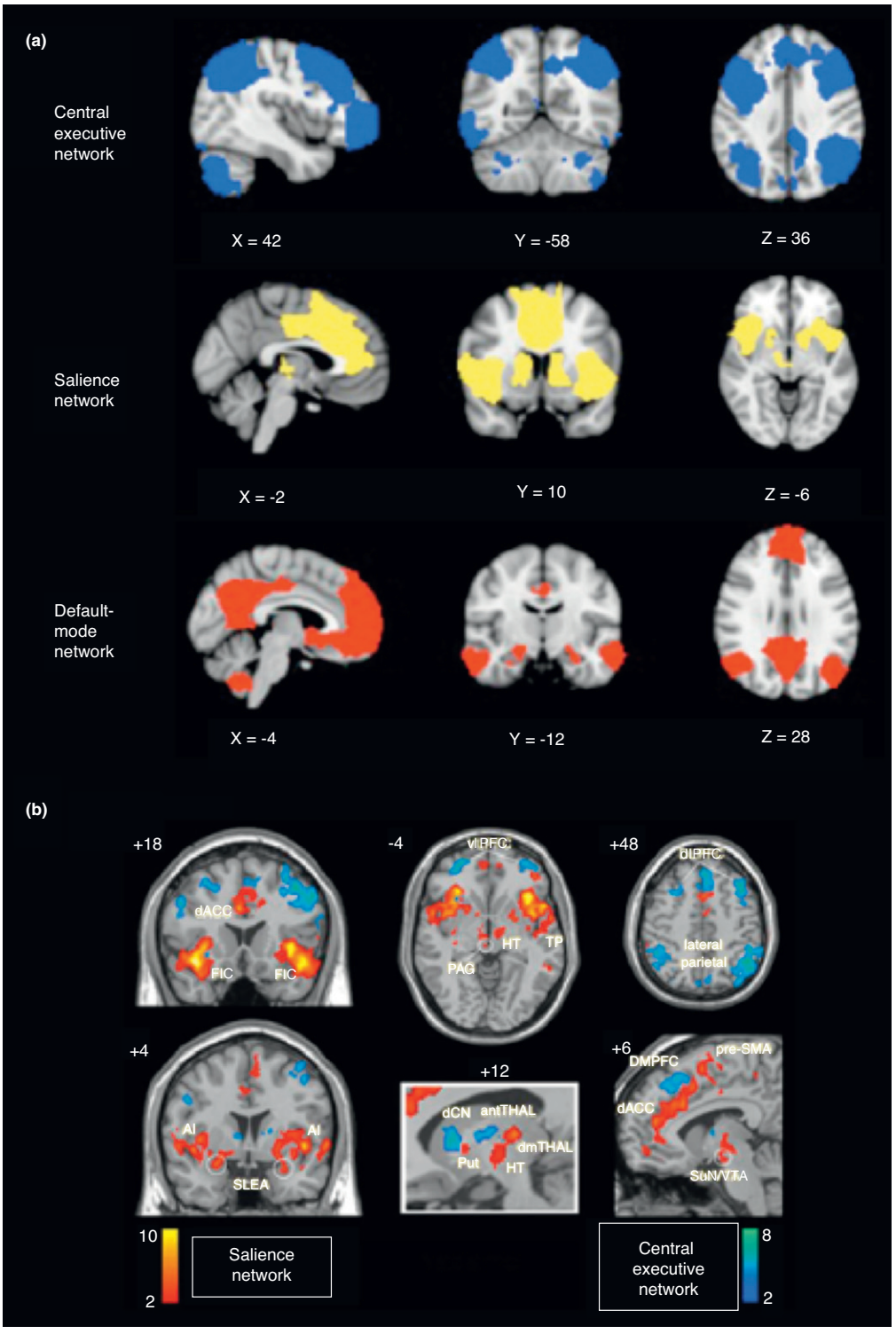

Figure 7. **Three core neurocognitive networks. (a)** The CEN, SN and DMN. The frontoparietal CEN (shown in blue), anchored in the dlPFC and the PPC, plays an important role in working memory and attention. The SN, shown in yellow, is important for detection and mapping of salient external inputs and internal brain events. The SN is anchored in the FIC and dorsal dACC and features extensive connectivity with subcortical and limbic structures involved in reward and motivation. The DMN (shown in red), anchored in the PCC and medial PFC, is important for self-referential mental activity. Adapted from [27,28,38] **(b)** The CEN and SN are both coactivated during a wide range of cognitive tasks but have distinct patterns of intrinsic cortical connectivity in the dorsomedial prefrontal cortex (DMPFC) dACC, dlPFC, vlPFC and lateral parietal cortex and subcortical connectivity in the anterior thalamus (antTHAL), dorsal caudate nucleus (dCN), dorsomedial thalamus (dmTHAL), hypothalamus (HT), periaqueductal gray (PAG), putamen (Put), sublenticular extended amygdala (SLEA), SuN/VTA and the temporal pole (TP). Adapted from [27].

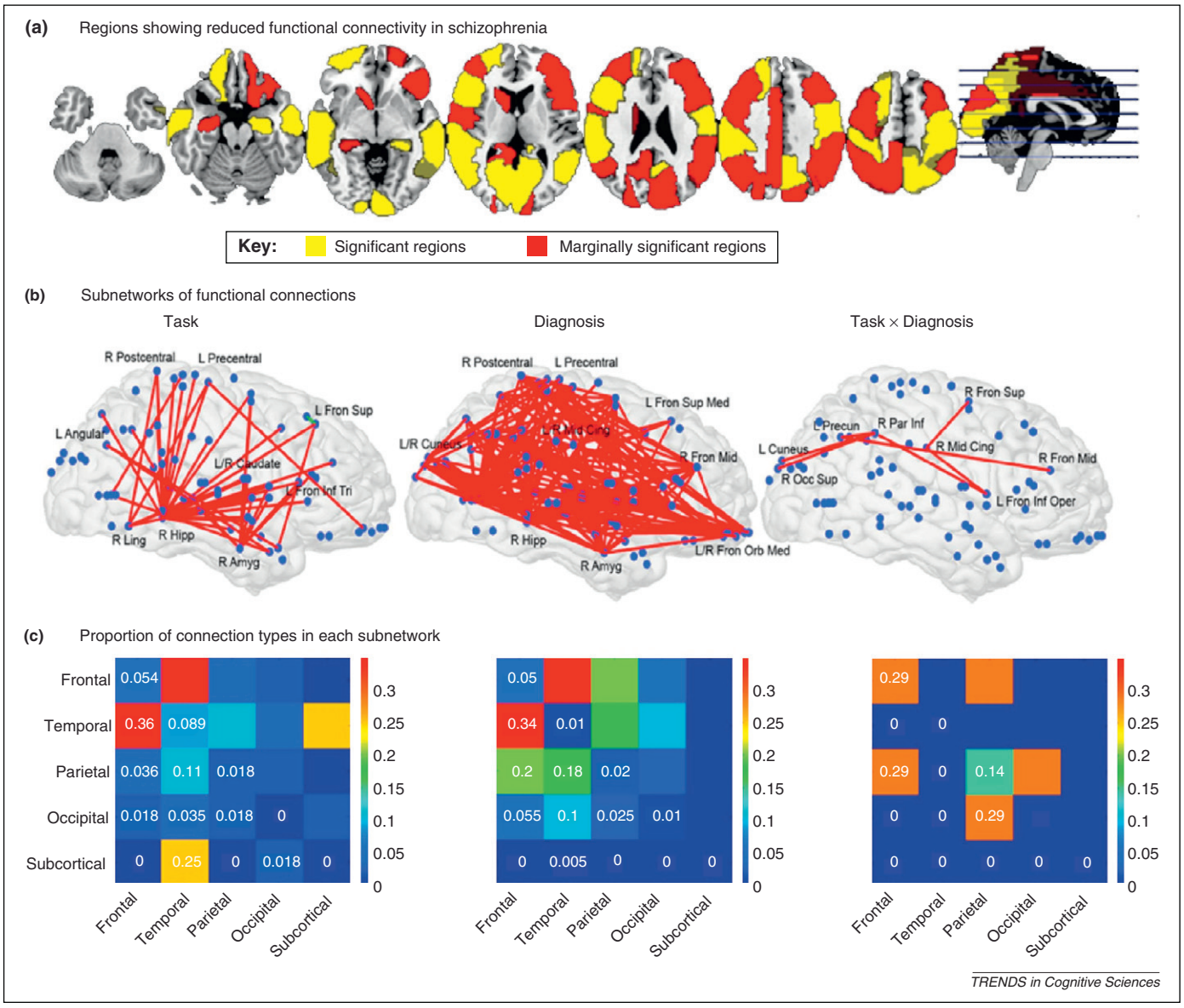

Figure 8. CEN dysfunction. Impaired cognition arising from frontoparietal CEN deficits are a prominent feature of many psychiatric and neurological disorders. In schizophrenia, for example, although deficits in activation of prefrontal and parietal cortices have been widely reported, functional dynamics of large-scale brain networks during cognitive task performance provide novel insights into functional connectivity reductions in specific subnetworks during cognitive control. **(a)** Widespread frontoparietal functional connectivity deficits connectivity in patients with schizophrenia compared with healthy controls. Effects surviving false-positive correction for multiple comparisons are shown in yellow; weaker effects are shown in red. **(b)** Patients showed widespread functional connectivity deficits in a large-scale network of brain regions, which primarily affected connectivity between frontal cortex and posterior regions and occurred irrespective of task context. Frontoparietal systems showed the strongest deficits in patients for more complex cognitive tasks. Subnetworks of functional connections showing a significant main effect of task (left column), main effect of diagnosis (middle column) and task × diagnosis interaction (right column). Amyg: Amygdala; Cing: Cingulate; Fron: Frontal; Hipp: Hippocampus; L: left; Ling: Lingual; Mid: Middle; Occ: Occipital; Oper: Opercularis; Par: Parietal; Precun: Precuneus; R: Right; Sup: Superior; Tri: Triangularis; **(c)** Proportion of connection deficits in each subnetwork, categorized by lobe, highlights frontoparietal connectivity deficits. All panels adapted from [173].

dynamic constraints and biases on information processing [37], and probing the integrity of network interactions and aberrant crosstalk between them provides a unique window into brain disorders.

CEN

The CEN is a frontoparietal system anchored in dlPFC and the lateral PPC [27,86]. CEN nodes that show strong intrinsic functional coupling also show strong coactivation during a wide range of cognitively demanding tasks. The CEN is crucial for actively maintaining and manipulating information in working memory, for rule-based problem solving and for decision making in the context of goal-directed behavior [87–90]. Many psychiatric disorders are characterized by deficits in these processes [91–93]. For example, much of the research into working memory deficits in patients with schizophrenia has focused on dlPFC and PPC regions that overlap with the CEN [49]. CEN disruption is widespread in virtually every major psychiatric and neurological disorder, including depression, AD, schizophrenia [94,95], FTD and autism (Figure 8). It should be noted, however, that most of these studies have been focused on activation deficits in the dlPFC and the PPC, and less on frontoparietal connectivity deficits associated with the coherent network characterized and demarcated by the CEN. Paradoxically, although the nodes of the CEN have been most widely studied in relation

to cognitive disorders that accompany psychopathology, it is the nodes of the DMN and the SN that have most consistently been investigated from a network perspective. Deficits in the CEN can arise as a result of at least three factors: (i) weak intrinsic connectivity between its nodes, (ii) abnormal recruitment of other brain nodes into the network that are not typically part of the CEN or (iii) impaired access to salient task-relevant stimuli, a process which the SN has an important role in, as described below. A systematic investigation of these and other related factors in psychopathology in relation to aberrant cognitive processing and task-related modulation of network activity remains an important area of research for the future.

DMN

In contrast to the CEN, the DMN is typically deactivated during most stimulus-driven cognitive tasks [21,96]. Of the three ICNs, the DMN was the first to be identified using rfMRI [21]. It is anchored in the PCC and mPFC, with prominent nodes in the medial temporal lobe (MTL) and the angular gyrus. A range of functions, some based on above 'rest' baseline activations and others based on reduced levels of deactivation with respect to control tasks, have been ascribed to DMN nodes in the functional imaging literature [26]. Nodes in the PCC, hippocampus and angular gyrus have been typically associated with episodic memory retrieval [97,98], autobiographical memory [99,100] and semantic memory related to internal thought [101], whereas specific nodes in the mPFC have been differentially associated with self-related and social cognitive processes [99,102], value-based decision making [103] and emotion regulation [104]. Together, the DMN collectively comprises an integrated system for different aspects of self-referential mental processes. Abnormalities in intrinsic functional connectivity within the DMN have now been identified in virtually every major psychiatric disorder including dementia, schizophrenia, epilepsy, anxiety and depression, and autism and ADHD[105] (Figure 9). I review important findings below, starting with studies in AD [25] and depression [106].

Major depression is characterized by persistent, pervasive feelings of sadness, guilt and worthlessness [107]. Consistent with reports of elevated glucose metabolism in the subgenual cingulate [108,109], abnormal functional connectivity within the DMN has been identified in patients with major depression. Deficits are most prominent in the subgenual cingulate, which has become a particular area of interest in depression research over the past decade as more and more studies implicate it as a locus of dysfunction. Furthermore, the degree of abnormal subgenual functional connectivity is also correlated with the length of the current depressive episode. Most previous studies of the DMN in healthy controls [21,23,96,110], dementia patients [25,111,112] or autistic patients [113] have not detected DMN connectivity in the subgenual cingulate. Thus, over-recruitment of this region into the DMN seems to be a feature unique to depression [105,106].

AD and major depression both involve dysfunction of the DMN; however, they impact different nodes of the key midline structures of the DMN. In depression, the subgenual cingulate and the adjoining ventromedial PFC (vmPFC) show enhanced connectivity with other nodes of the DMN, whereas in AD the PCC and MTL structures show significantly reduced network connectivity [25]. This dissociation seems to be related to different aspects of episodic memory dysfunction in the two disorders. Episodic and autobiographical memory loss are the cardinal features of AD and the most common presenting symptom [44], and both the hippocampus and PCC connectivity have been implicated in memory deficits in AD [25,44,98,114]. By contrast, depression, which is characterized by rumination and the recurrent reflective focus on the self [115], differentially impacts the PFC nodes of the DMN. These clinical studies, together with recent developments in memory tasks that upregulate the DMN [97,98], provide converging evidence that dysfunction in different nodes of the DMN plays an important role in self-related episodic memory retrieval.

In schizophrenia patients, reduced functional and anatomical connectivity within the DMN, with the mPFC as a particular locus of dysfunction, has been shown in several studies [116,117]. These deficits seem to also be related to morphological changes and changes in gray matter density [118]. Crucially, aberrant functional connectivity in the DMN is also associated with positive symptoms including the severity of hallucinations and delusions [117,119].

The DMN has also been shown to be selectively impaired during epileptic seizures associated with loss of consciousness. Decreased fMRI and electrophysiological activity in the DMN has been detected during complex partial generalized tonic-clonic and absence seizures [120]. Importantly, although the specific mechanisms of onset and propagation differ considerably across these seizure types, the resulting loss of consciousness in all three types of seizures has been linked to abnormal maintenance and engagement of the DMN [120] and specifically to structural and functional connectivity deficits between tracts linking the hippocampus and the PCC nodes of this network [121].

Dysfunctional DMN connectivity is also prominent in adolescents and young adults with autism, suggesting that manifestation of DMN dysfunction can occur early in development. Several recent studies have suggested a role for the DMN in the pathophysiology of autism. In young adults with autism, deactivation of the DMN during task performance is abnormal [113], and the network shows reduced intrinsic functional connectivity [122,123]. Several recent studies have implicated the DMN in the pathophysiology of autism [123,124]. A recent meta-analysis points to decreased gray matter in the MTL, both the hippocampus and amygdala as well as the posterior medial cortex in autism [14]. Altered social information processing has also been related to DMN dysfunction and a recent meta-analysis of 24 neuroimaging studies examining social processing in autism found that the PCC and the mPFC, two main nodes of the DMN, are hypoactive relative to neurotypical adults [125].

This overview suggests that DMN abnormalities are widespread in psychiatric and neurological disorders. The question of how different subnetworks within the DMN contribute to common and diverse phenotypic features

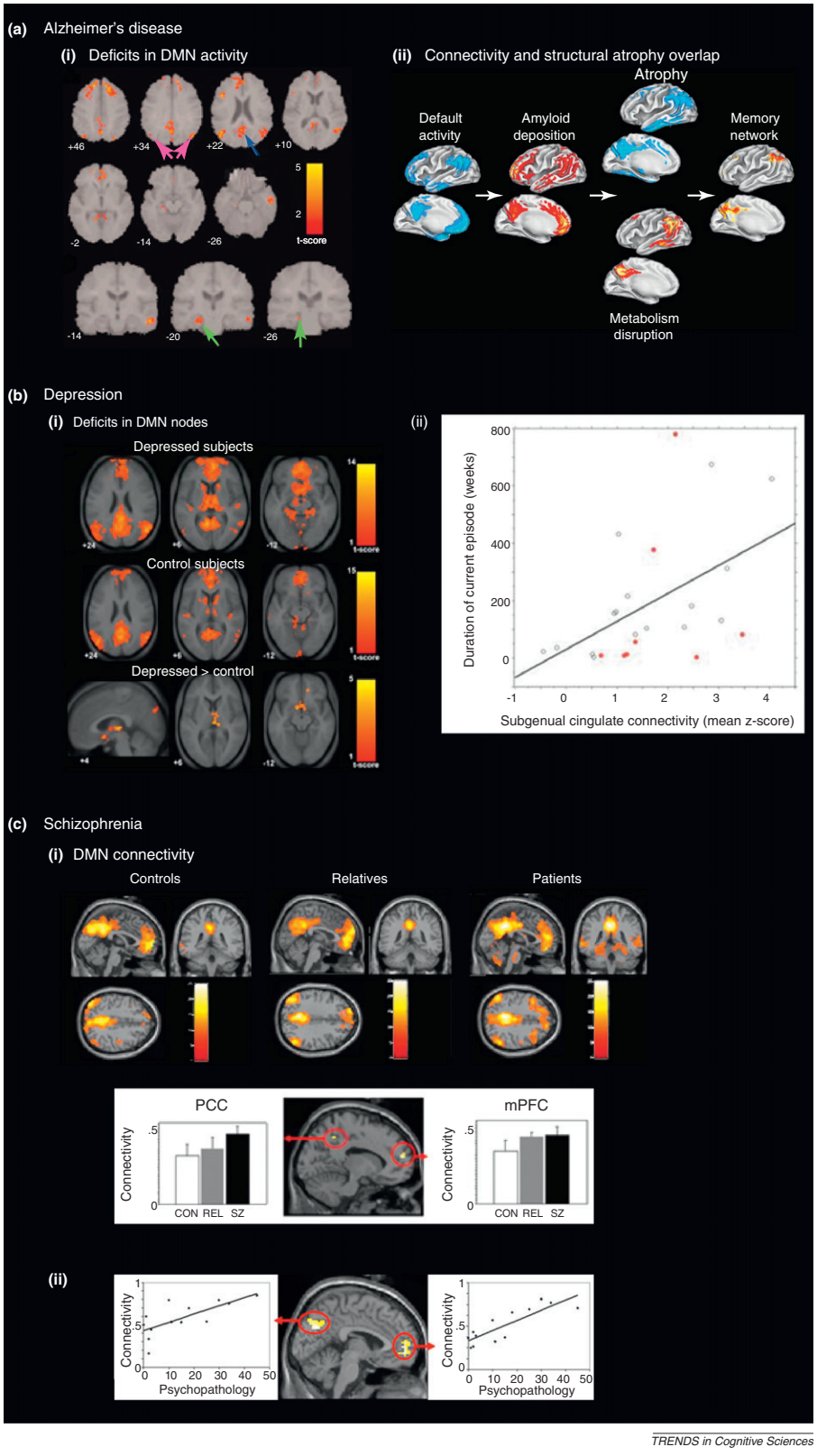

Figure 9. **DMN dysfunction in multiple disorders. (a) AD: (i)** Deficits in DMN activity in patients with AD compared with age-matched healthy elderly. The PCC (green arrow), angular gyrus in the inferior parietal cortex (magenta arrow) and hippocampus (green arrow) show prominent DMN deficits in AD. Adapted from [21]. **(ii)** Functional connectivity in the DMN shows prominent overlap with structural atrophy and amyloid deposition in older patients with AD. Adapted from [174]. **(b) Depression: (i)** Significant deficits in subgenual cingulate, thalamus, and precuneus nodes of the DMN in patients with depression. **(ii)** Deficits in subgenual cingulate functional connectivity in the DMN are related to duration of the current depressive episode. Adapted from [106]. **(c) Schizophrenia: (i)** Both patients and their first degree relatives show increased connectivity within the DMN. PCC connectivity with mPFC was significantly greater for relatives and patients than for controls. **(ii)** Connectivity between these regions was significantly correlated with severity of psychopathology. Adapted from [175].

across disorders is an important area for further research. Nonetheless, it is now sufficiently clear that DMN dysfunction is a major and consistent feature of disorders that alter episodic memory, autobiographical memory and self-related mental processes.

SN

The SN is a cingulate-frontal operculum system anchored in the dorsal anterior cingulate cortex (dACC) and frontoinsular cortex (FIC), and is involved in detecting, integrating and filtering relevant interoceptive, autonomic and emotional information [27]. In task-based functional imaging, the SN and CEN have been difficult to isolate because coactivations of the anterior insula (AI), ACC, the dlPFC and the ventrolateral PFC (vlPFC) are very common across a wide range of cognitive tasks. Functional connectivity analysis has shown, however, that these regions form distinct frontoparietal and cingulo-opercular networks [27,126]. ICA of rfMRI data clearly distinguishes an ICN comprising the AI and dACC that is distinct from the CEN [27]. The SN also includes two key subcortical structures: the amygdala and the substantia nigra/ventral tegmental area (SuN/VTA), which are important for detecting emotional and reward saliency (Figure 7).

Until recently, the AI and dACC were thought to be part of distinct brain systems, with the AI playing a greater role in social and affective information processing tasks that involved functions such as pain, empathy and disgust [127] whereas the dACC was most closely associated with conflict resolution and cognitive control [128]. However, recent developments have suggested that the AI and dACC are part of a functional circuit involved in both attention as well as interoceptive and affective processes [29]. Recent research has also suggested that a key function of this network is to identify the most homeostatically relevant among several internal and extrapersonal stimuli to guide behavior [27–29,129].

Even outside the context of tasks involving explicit experimental manipulations of cognitive control, the behavioral domains in which SN dysfunction has been demonstrated is staggering (Figure 10). For example, AI dysfunction is now thought to be a core feature of anxiety, pain and addiction. Furthermore, multiple disturbances following lesions of the insula, including those related to autonomic function, gustatory, olfactory, auditory, somatosensory and multimodal perception, as well as body awareness, the emotion of disgust, mood and willed action, addiction behavior and language have been reported in the literature [130].

Hyperactivity of the AI node of the SN has been consistently implicated in anxiety disorders [131,132]. In this disorder, altered prediction of an aversive body state is thought to trigger an increase in negative and worrisome thoughts as well as avoidance behaviors in individuals who are prone to anxiety, and the AI is proposed to play a key role in this process [131]. Individuals scoring high on the trait neuroticism, defined as the tendency to experience negative emotional states, demonstrate greater right AI activation during decision making, even when the outcome of the decision is certain [133]. These findings are important because anxiety disorders are a common comorbid feature of many psychiatric disorders, including depression, phobia, PTSD and autism [134].

The operculo-insular cortex has been rediscovered as a main area of pain integration, and these areas are abnormally recruited, bilaterally, in response to innocuous stimuli [135,136]. It is important, however, to recognize that it is not only physical pain but the same core network consisting of bilateral AI and ACC is also associated with empathy for pain [137]. Although previous studies have mainly focused on hyperactivation of these regions, increasingly, connectivity analysis studies are suggesting that the AI and cingulate cortex are part of a network that integrates information about the significance of an impending stimulation into perceptual decision making in the context of pain [138].

Cue reactivity seen in addiction is also associated with aberrant AI activation [139]. Most prior research on the neurobiology of addiction has focused on the role of subcortical systems, such as the amygdala, the ventral striatum (VStr) and mesolimbic dopamine system, in promoting the motivation to seek drugs. Recent evidence indicates that the AI also plays a crucial part in the conscious urges to take drugs [140]. Crucially, the AI and these subcortical systems are an integral part of the SN, suggesting that addiction is associated with significant dysfunction of multiple nodes in the SN [141].

Both functional and structural studies have pointed to dysfunctional SN in schizophrenia [142]. Bilateral volume reduction has been seen in the AI and ACC in patients with schizophrenia. Furthermore, reduced volume in the SN has been reported to be significantly correlated with the severity of reality distortion [143]. Auditory verbal hallucinations constitute severe incapacitating symptoms of schizophrenia [10]; patients experiencing such hallucinations demonstrate significantly increased activation in the AI and the frontal operculum suggesting that abnormal monitoring of saliency of internal stimuli might be associated with these symptoms [144]. AI and ACC deficits in patients with schizophrenia have also been linked to reality distortion, leading to the suggestion that SN abnormality leads to an impaired attribution of salience to stimuli that is associated with delusions and hallucinations in schizophrenia [142,143,145,146]. Systematic investigation of the SN has also provided better differentiation of neurodegenerative disorders such as AD and different forms of FTD [80] (Figure 10). In particular, the behavioral variant FTD (bvFTD), an early-stage frontoinsular degeneration, has been implicated in progressive SN breakdown that leaves patients unable to model the emotional impact of their own actions or inactions [147]. Finally, a comprehensive meta-analysis of functional neuroimaging studies of social processing in autism has demonstrated that across a group of studies examining various aspects of social processing, one of the regions consistently showing significant hypoactivity in autism was the right AI [125]. Taken together, these findings suggest that SN dysfunction is a prominent feature of several psychiatric and neurological disorders. As discussed below, such dysfunction results in impaired detection and mapping of salient external stimuli and internal events, with significant consequences for both cognition and self-monitoring.

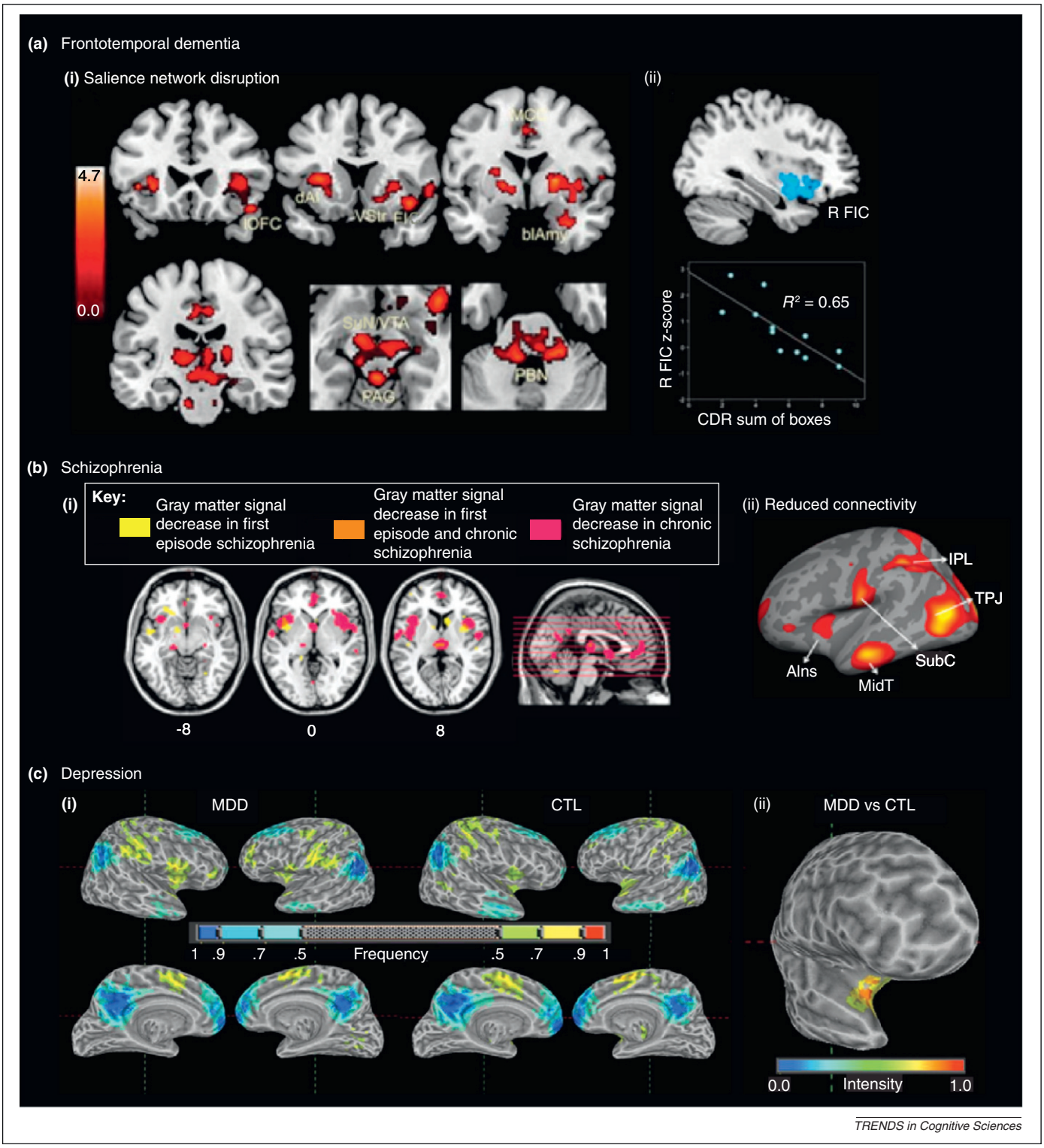

Figure 10. SN dysfunction in major psychopathology. (a) Frontotemporal dementia: (i) SN connectivity disruption in patients with bvFTD. Multiple nodes of the SN, including the FIC, lateral orbitofrontal cortex (lOFC), dorsal AI (dAI), midcingulate cortex (MCC), VStr, basolateral amygdala (blAmy), thalamus, SuN/VTA, PAG, and dorsal pons and parabrachial nuclei (PBN) showed deficits in the patient group. **(ii)** Of these regions, only the right FIC responses were associated with functional severity, as measured by the Clinical Dementia Rating (CDR) scale, sum of boxes score. Adapted from [80]. **(b) Schizophrenia: (i)** Both functional and anatomical deficits are prominent in patients with schizophrenia. SN structural deficits in insula and ACC are prominent in both the early and late stages of schizophrenia, with progressive increase in gray matter deficits in chronic schizophrenia. Adapted from [176]. **(ii)** Significantly reduced functional connectivity in patients compared with controls both within the SN (between AI and ACC) and with other networks (AI and vmPFC). AIns: Anterior Insula; IPL: Inferior Parietal Lobule; MidT: Middle Temporal; SubC: SubCentral; TPJ: Temporal-Parietal Junction. Adapted from [142]. **(c) Depression: (i)** SN and CEN activation (yellow-red) and DMN deactivation (blue-cyan) in patients with major depressive disorder (MDD) and control (CTL) participants. **(ii)** Chi-square statistic map showing increased frequency of inclusion of right FIC in the SN and CEN in the MDD group. Adapted from [177].

Triple network model of psychopathology

Neurocognitive network models provide a common framework for examining stable and reliable patterns of large-scale connectivity. Although these networks are most prominently identified in relation to the intrinsic organization of the brain, they suggest new avenues for synthesis of disparate findings on abnormal regulation of cognitive function in the clinical neuroscience literature. The research findings summarized in the previous section suggest that aberrant organization and functioning of the CEN, SN and DMN are prominent features of several major psychiatric and neurological disorders. How can the same set of networks be impacted across so many disorders that differ widely in symptom profiles? In this section, I propose a triple network model which helps synthesize extant findings into a common framework for understanding dysfunction in these core networks across multiple disorders (Figure 11).

The triple network model focuses on the CEN, SN and DMN; these networks are unique in that they can be readily identified across an extremely wide range of cognitive tasks, and their responses increase and decrease proportionately, and often antagonistically, with general cognitive task demands. The CEN and SN typically show increases in activation during stimulus-driven cognitive and affective information processing, whereas the DMN shows decreases in activation during tasks in which self-referential and stimulus-independent memory recall is not crucial [2122,96]. The model proposes that deficits in engagement and disengagement of these three core neurocognitive networks play a significant role in many psychiatric and neurological disorders. An important aspect of this model is the inappropriate assignment of saliency to external stimuli or internal mental events, a process that the SN seems to play a particularly important role in [29].

Emerging evidence suggests that SN, and most notably the AI, is an integral hub in mediating dynamic interactions between other large-scale brain networks involved in externally oriented attention and internally oriented self-related mental processes. These discoveries point to a model in which the SN plays an important role in saliency detection, attentional capture enhanced by error signals and dynamic cognitive control [29]. The model highlights

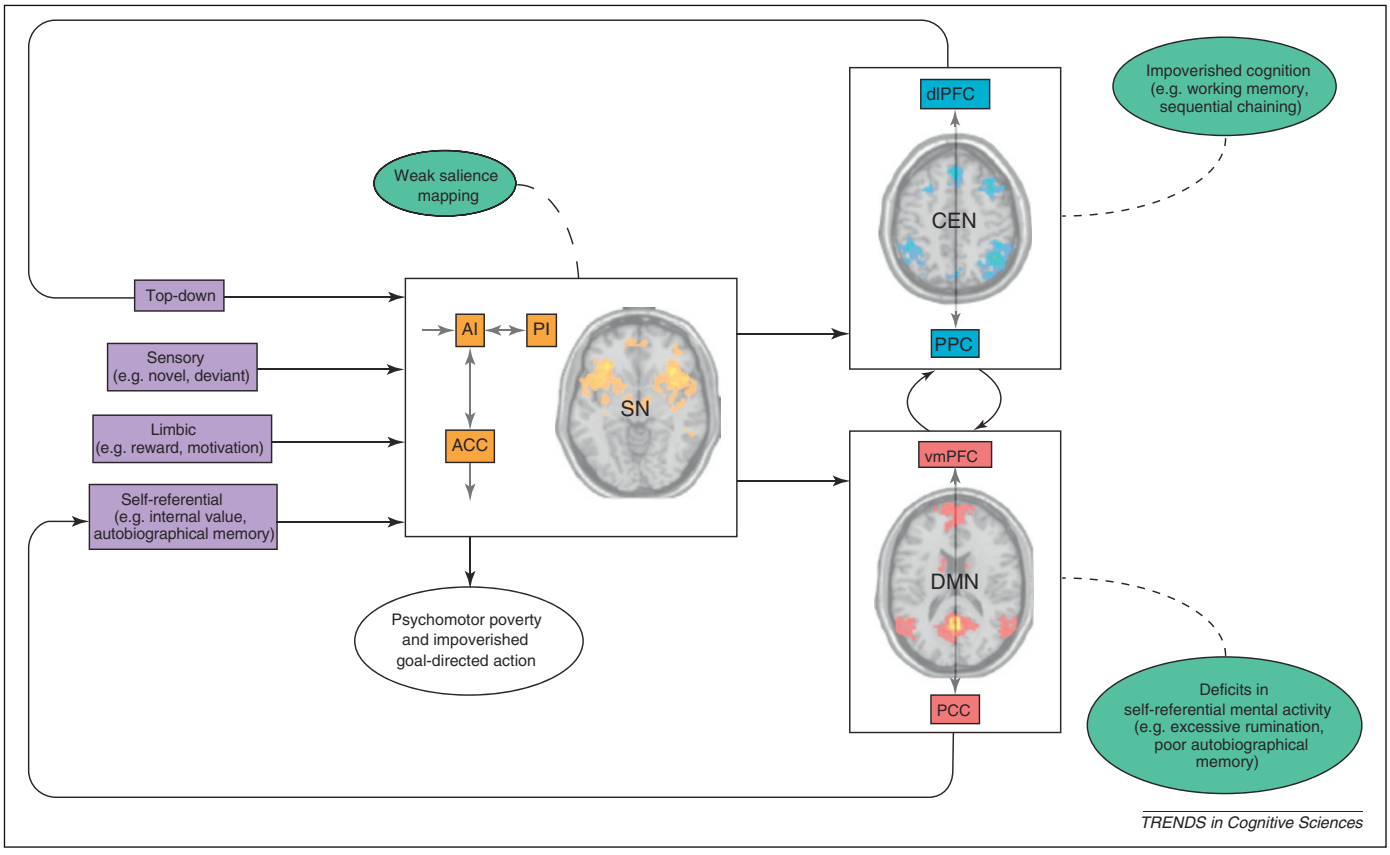

Figure 11. Triple network model of major psychopathology. Aberrant intrinsic organization and interconnectivity of the SN, CEN and DMN is characteristic of many psychiatric and neurological disorders. The model proposes that weak salience detection and mapping of goal-relevant external stimuli and internal mental events from, and into, the SN plays a major role in psychopathology. Weak mapping from the insular-cingulate SN gives rise to aberrant engagement of the frontoparietal CEN, compromising cognition and goal-relevant adaptive behavior. Aberrant DMN organization as well as weak engagement or disengagement of the DMN by salient events is associated with altered self-referential mental activity (e.g. excessive rumination in patients with depression). Weak salience mapping can arise from at least three input factors: (i) aberrant stimulus mapping, such as weak or enhanced cue signaling and novelty detection; (ii) aberrant limbic reward and motivational signals and (iii) aberrant self-referential mental processes representing internal value and autobiographical memory. The SN maps such events and initiates appropriate control signals that facilitate access to attentional and working memory resources needed for cognitively demanding tasks, such as those requiring rule-based manipulation of stimuli. Within the SN, the AI also facilitates access to the motor system to regulate behavior via its coupling with the ACC and homeostatic state via the mid- and posterior insular (PI) cortex. The ACC facilitates response selection and motor response via its links to the midcingulate cortex, supplementary motor cortex and other motor areas. Diminished outflow from the cingulate cortex results in psychomotor poverty and impoverished goal-directed action. Weak interactions along the anterior–posterior axis of the insular cortex contribute to altered introspective awareness and physiological monitoring of the internal milieu. Key nodes of the SN: AI and ACC; key nodes of the CEN: dlPFC and the (PPC; key nodes of the DMN: vmPFC and PCC.

the crucial role of the SN and, in particular, the right AI, for initiating network switching leading to the engagement of the CEN and the disengagement of the DMN. In this model, the SN, with the AI as its integral causal outflow hub, assists target brain regions in the generation of appropriate behavioral responses to salient stimuli. Once such a stimulus or event is detected, the AI facilitates task-related information processing by initiating appropriate transient control signals. These signals engage brain areas that mediate attentional, working memory and higher-order cognitive processes while disengaging the DMN.

The mechanisms by which weak mapping from the SN can contribute to cognitive and affective dysfunction include:

(i) aberrant bottom-up detection of salient events,
(ii) aberrant control signals to other large-scale networks that facilitate access to attention and working memory resources,
(iii) aberrant interaction of the anterior and posterior insula to modulate physiological reactivity to salient stimuli and
(iv) aberrant functional coupling with the ACC that facilitates rapid access to the motor system.

This new understanding of the right AI as a crucial node for initiating network switching provides insights into mechanisms underlying deficits in cognitive functioning should: (i) SN integrity and/or connectivity be compromised as in FTD or (ii) stimulus/event salience be weakly mapped as in autism, or erroneously mapped as in addiction, anxiety or pain. Signaling deficits can arise from aberrant filtering and mapping of salient stimulus cues into the SN (especially its AI and amygdala nodes) and weak signaling mechanisms from the SN to the CEN to trigger appropriate dorsal attentional system responses. These signaling mechanisms together with (i) poor integrity of network nodes, for example PCC and MTL nodes of the DMN as in AD, or vmPFC as in depression and (ii) weak anatomical connectivity within- and across-network nodes can compromise the dynamic interaction of these core networks. The consequence of abnormalities at any of these levels is deficient context-dependent engagement and disengagement of cognitive systems important for attending to salient external stimuli or internal mental events.

Recent clinical studies suggest that an appropriate level of AI activity is necessary to provide an alerting signal to initiate brain responses to salient stimuli but this signal can be overactive in the case of anxiety, or underactive as in autism [18]. Thus, in individuals with autism ineffective salience mapping of a specific class of stimulus features can result in reduced attention to socially relevant cues [125]. By contrast, hyperactivity of the AI or other nodes of the SN, such as the amygdala, may be the basis for pathologically enhanced salience detection. Increased anxiety or neuroticism, for example, may be the consequence of the AI misattributing emotional salience to mundane events.

In the context of psychopathology, it should be noted that what is salient in one group may not be for another. In autism, the relative salience of social stimuli may be diminished, and this could be the basis for a cascade of developmental events that result in weak social skills [20]. For an individual with autism, social stimuli may not be salient enough to drive attention to another's face, eyes and gaze. By contrast, for a hypersocial child with Williams syndrome exactly the opposite may be true. Specific drug paraphernalia may be uniquely salient to individuals with cocaine addiction but not to an individual with anxiety or pain. Although saliency is hard to define precisely and has many subjective attributes, the general consequences for psychopathology are surprisingly simple: aberrant saliency filtering, detection and mapping result in deviant signaling into and out of the SN. This in turn has important repercussions for how attentional resources are allocated and consequently for cognition and behavior. I suggest that these are fundamental mechanisms underlying cognitive dysfunction in many psychiatric disorders. Each disorder has different and often unique symptomatology, in autism deficits might be in signaling social cues, in auditory hallucinations it might be monitoring saliency of internal cues, however, in each case this process is accompanied by observable dysfunction in not only the SN but also the DMN and the CEN.

The triple network model predicts that dysfunction in one core network can impact the other two networks, with clinical manifestations that may transcend the primary deficit. For example, the SN is the primary network impacted in pain, yet abnormalities in the DMN have also been reported [148]. Indeed, chronic pain patients suffer from more than only pain; depression and anxiety, and decision-making abnormalities are also common [149]. Similarly, in depressed patients, activity in the DMN is excessively coupled to activity in the SN [150]. DMN deficits arise as a natural outcome of the inability to cycle out of internal mental processes to attend to salient task-relevant external stimuli, as manifest most prominently in depressed patients in whom rumination leads to impaired cognitive resource allocation [115,150]. Finally, in perhaps one of the most extreme examples of debilitating psychopathology, patients with schizophrenia show both structural and functional deficits in all three networks [118].

Within the triple network model, besides the AI and adjoining FIC, two subcortical nodes of the SN are particularly relevant for psychopathology. The two nodes are the amygdala, which is crucial for detection of biologically salient affective cues such as fear, and the nucleus accumbens/ventral tegmental area, which is important for reward prediction. The insula, however, is unique in that it is situated at the interface of the cognitive, homeostatic and affective systems of the human brain, providing a link between stimulus-driven processing and brain regions involved in monitoring the internal milieu and interoceptive awareness of physiological changes in the body [151]. Understanding the flow and integration of information between these regions will be important in linking the concomitant 'cognitive' and 'affective' features of psychopathology [152].

The triple network model provides a parsimonious account that may explain various clinical symptoms as a function of enhanced, reduced or otherwise altered salience detection. These deficits have cascading consequences in

terms of attentional allocation and engagement of hierarchical frontoparietal and frontotemporal systems important for higher-order cognition and decision making. A particularly striking illustration of this view of psychopathology comes from the finding, discussed above, that the AI is a crucial node for initiating network switching. This key insight reveals the potential for profound deficits in cognitive functioning should AI integrity or connectivity be compromised. Characterization of the SN and its interactions with the DMN and CEN is beginning to identify an important aspect of dysfunction in psychopathology. In autism, such a description is beginning to provide a parsimonious account of the recent neuroimaging literature [18]. In major depression, studies of altered glutamatergic metabolism within these networks are providing novel insights into how aberrant nodes influence within- and across-network interactions, and how this in turn influences disease severity and core symptoms such as anhedonia [153,154]. In dementia, symptom-specific deficits in SN and DMN connectivity are associated with unique patterns of social-emotional and episodic memory deficits [155] (Figure 10). Additional investigations of disruptions to dynamical processes inherent in the triple network model are likely to lead to greater understanding of fundamental brain mechanisms underlying psychopathology in several neurological and psychiatric disorders, including schizophrenia, depression, autism and anxiety disorders.

Concluding remarks

Network models are now increasingly being used to study psychopathology. Analysis of large-scale networks has shown them to be powerful tools for investigating the core features of disorders such as autism, schizophrenia, depression and dementia. The developments reviewed suggest that a systematic exploration of large-scale functional brain networks is likely to yield novel insights into major psychiatric and neurological disorders. At the network level, surprising parallels are also beginning to emerge between psychiatric and neurological disorders.

Anatomical connectivity imposes strong constraints on functional connectivity at both the interregional and global level. These constraints impose stereotypic alterations in cognitive and affective functions, which manifest as clinical symptom clusters. We have seen that there are unifying motifs in brain systems impacted by psychopathology, which may help to better pinpoint unique and common brain networks that are disrupted in relation to specific symptoms or symptom clusters. Collective deficits and disruptions in intrinsic large-scale networks are associated with parallel patterns of cognitive information processing deficits. This review has also highlighted several avenues of synthesis afforded by network analysis of brain connectivity that are emerging in the literature. Such an approach not only promises a better understanding of individual disorders but also opens new avenues for synthesis and theory building. The triple network model offers a powerful approach to the synthesis of a wide range of studies that have identified deficits in the DMN, SN and CEN. The core networks that are yielding reliable and robust patterns of aberration in individual psychopathology are among the most stable and easiest to identify. Other systems that are uniquely dysfunctional in specific disorders may yet remain to be identified, and will likely offer other avenues for synthesis.

Analysis of large-scale networks has already brought in a rigorous quantitative framework, which offers improved tools for better characterization of neuropsychiatric and neurological disorders. As models of network characterization mature in the next few years, we can expect to gain deeper insights into aberrant functional and structural organization of coherent large-scale networks in the human brain and the perturbations that accompany individual symptoms (Box 1). From a graph-theoretical point of view, we can expect network-derived metrics to facilitate identification of symptom heterogeneity and eventually aid in development of more targeted pharmacological and cognitive interventions. Technological advances and improved characterization of the structural wiring diagram of the entire human brain resulting from efforts such as the Human Connectome Project [31] will undoubtedly drive much of the progress. But this alone will be insufficient; a crucial characterization of impaired dynamics within and across networks in relation to specific symptoms will be necessary for advancing our understanding of psychopathology in the coming decades.

This review has emphasized MRI-based techniques for probing brain connectivity; a deeper understanding of dysfunctional neurocognitive networks will require characterization of the rapid coupling of oscillatory dynamics that takes place on the order of tens of milliseconds [156]. Evidence to date suggests that fMRI connectivity arises from low frequency ($f < 0.1$ Hz) modulation of fluctuations in local field potential in the alpha, beta and gamma bands [157,158]. Methods that incorporate slow (seconds to minutes) and fast (milliseconds) timescales are both likely to be useful for the investigation of large-scale brain networks in psychopathology in unique ways. At the slow timescale, functional network analysis of neurophysiological signals at specific frequency bands can yield more precise information about the neurophysiological basis of altered brain architecture in psychopathology [60,159,160]. At the fast timescale, combined electroencephalographic (EEG)–fMRI recordings and analysis have the potential to provide important information about how aberrant brain architecture changes dynamic causal interactions underlying cognitive processes which unfold over tens of milliseconds. At intermediate timescales, analysis of neuronal synchrony can reveal how aberrant distributed processing disrupts the maintenance of coherent mental representations during cognitive information processing [161]. Combined EEG–fMRI studies in patients with epilepsy provide additional opportunities not only for investigating fundamental aspects of the relation between neuronal spiking, local field potentials and fMRI activity [100] but also for investigating the electrophysiological correlates of abnormalities in core neurocognitive networks [162]. For example, electrophysiological studies of the onset and propagation of seizures are beginning to provide unique insights into how abnormal DMN activity results in loss of consciousness [120]. Finally, as we noted in Section 3.1, node level abnormalities in psychiatric disorders such as autism and schizophrenia have been

Box 1. Crucial questions for examining psychopathology from a network perspective

- What are the intrinsic node-level cytoarchitectonic abnormalities associated with major brain disorders and how do they impact brain wiring and the functional architecture of large-scale networks?
- How does the abnormal balance of excitation and inhibition in local neural circuits alter the formation and maintenance of large-scale brain networks?
- How do aberrant large-scale brain networks alter faster timescale dynamics and interareal synchrony needed for cognitive information processing on the timescale of tens of milliseconds?
- How does cognitive dysfunction emerge from aberrant large-scale brain networks?
- Can large-scale brain networks be used to identify disease subtypes and classify heterogeneity of symptom clusters within a syndrome?
- What mechanisms underlie abnormal engagement and disengagement of distributed brain areas and how do failures of these mechanisms impair cognition and emotion?
- How do developmental vulnerabilities contribute to aberrant brain wiring and maturation of functional connectivity between childhood and adulthood?
- What are the convergent and divergent brain networks that discriminate and unify related symptoms across different types of psychiatric and neurological disorders?
- How can functional circuits in related disorders be disentangled (e.g. generalized anxiety vs social anxiety)?
- How do we differentiate symptomatic features across disorders (e.g. ADHD in autism vs ADHD without autism; anxiety in depression versus anxiety in autism)?
- Can large-scale brain networks help us understand gender differences in vulnerabilities to psychiatric disorders?
- How do genes and epigenetic factors influence large-scale brain connectivity and how do they increase risk factors for specific psychiatric and neurological disorders?

linked to altered cellular organization and elevations in the balance of excitation and inhibition within neural microcircuitry. How such alterations impact information processing at the network level remains largely unknown but optogenetics offers promising new tools for such investigations. For example, altering the neuronal balance of excitation and inhibition in mPFC regions homologous to key nodes of the DMN elicits increased high-frequency oscillations in the gamma range with concomitant impairments in social function similar to those observed in clinical conditions in humans [163]. Such experimental tools together with the analytic methods reviewed here provide new avenues for the study of the neurophysiological underpinnings of large-scale brain network dysfunction in psychopathology.

The study of large-scale networks and the linking of them to brain function in disease states promises to not only uncover core aspects of major brain disorders but also to provide novel insights into brain function much like classical lesion studies did in the past two centuries. Rapid progress in the domain of disorders of consciousness and internalizing disorders is likely to be a particularly fruitful domain of scientific and clinical investigations. Perhaps most exciting are prospects of theory building and developing links between core features of symptoms rather than syndromes, be they classified as psychiatric or neurological disorders.

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