Review

Biological Psychiatry

Depression, Neuroimaging and Connectomics: A Selective Overview

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ABSTRACT

Depression is a multifactorial disorder with clinically heterogeneous features involving disturbances of mood and cognitive function. Noninvasive neuroimaging studies have provided rich evidence that these behavioral deficits in depression are associated with structural and functional abnormalities in specific regions and connections. Recent advances in brain connectomics through the use of graph theory highlight disrupted topological organization of large-scale functional and structural brain networks in depression, involving global topology (e.g., local clustering, shortest-path lengths, and global and local efficiencies), modular structure, and network hubs. These system-level disruptions show important correlates with genetic and environmental factors, which provide an integrative perspective on mood and cognitive deficits in depressive syndrome. Moreover, research suggests that the pathologic networks associated with depression represent potentially valuable biomarkers for early detection of this disorder and they are likely to be regulated and recalibrated by using pharmacologic, psychological, and brain stimulation therapies. These connectome-based imaging studies present new opportunities to reconceptualize the pathogenesis of depression, improve our knowledge of the biological mechanisms of therapeutic effects, and identify appropriate stimulation targets to optimize the clinical response in depression treatment. Here, we summarize the current findings and historical understanding of structural and functional connectomes in depression, focusing on graph analyses of depressive brain networks. We also consider methodological factors such as sample heterogeneity and poor test-retest reliability of recordings due to physiological, head motion, and imaging artifacts to discuss result inconsistencies among studies. We conclude with suggestions for future research directions on the emerging field of imaging connectomics in depression.

Keywords: Connectivity, Connectome, Graph theory, Hub, Mood disorder, Network, Rich club

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Depression is a globally prevalent psychiatric disorder characterized by affective, cognitive, and somatic symptoms. Neuropsychological evidence suggests impairments in executive function, memory, and emotional processing in patients with depression (1). Neuroimaging studies demonstrate that these impairments are accompanied by focal functional and structural abnormalities in many regions (2–4), including the hippocampus (5,6), medial prefrontal cortex (mPFC) (3), dorsolateral prefrontal cortex (DLPFC) (7), anterior cingulate cortex (ACC) (8), posterior cingulate cortex/precuneus (PCC/PCu) (9), amygdala (9,10), and caudate nucleus (11–13). Also reported were abnormal functional associations between regions, involving default mode network (DMN) (14–20), ACC-thalamus (21), ACC-insula (20), and prefrontal-limbic-thalamic (22); structural covariance between prefrontal regions (23); and anatomical connectivity in the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, posterior thalamic radiation, and corpus callosum (24,25), suggesting that depression involves alterations of brain connectivity in multiple neuronal circuits.

The human brain is structurally and functionally organized into a complex network that facilitates the effective segregation and integration of information processing. Recently, the topological description of the network was referred to as the human connectome (26). Combined with neuroimaging, connectome-based approaches revealed many nontrivial topological properties of healthy human brains, such as small-world efficiency, modular structure, and highly connected hubs (27–32). These features are disrupted in various brain disorders, such as schizophrenia (33,34) and Alzheimer's disease (35–37). Depression is also associated with abnormal topological organization of brain networks, including disrupted global integrity and regional connectivity (38–51) (Table 1). These network dysfunctions are valuable for studies of diagnosis biomarkers (52–55) and treatment evaluation (56) and significantly advanced our understanding of the neuropsychopathology of depression. Here, we provide an overview of imaging depressive connectomes, focusing especially on graph-based network analysis.

GRAPH THEORY AND BRAIN CONNECTOMICS

Measurement of Brain Connectivity

There are three classes of brain connectivity: functional, effective, and structural connectivity (Table S1 in Supplement 1) (26–32,57–59). Structural connectivity includes gray matter (GM) structural covariance and white matter (WM) anatomical con-

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Table 1. Neuroimaging Studies of Graph-Based Brain Connectomes in Depression

Study	Imaging Modality	Patients		Control Subjects		Node Definition	Edge Definition	Network Type
		n	Age	*n*	Age			
Zhang *et al.* (2011) (38)	fMRI	30	36.1 ± 12.3 (18–60)	63	35.1 ± 15.9 (16–81)	AAL (90)	Partial correlation	B
Jin *et al.* (2011) (43)	fMRI	16	17.1 ± 1.3 (NA)	16	17.3 ± 1.5 (NA)	AAL (90)	Partial correlation	B
Lord *et al.* (2012) (40)	fMRI	22	37.9 ± 11.4 (NA)	22	34.5 ± 6.2 (NA)	AAL (95)	Pearson correlation	W
Perrin *et al.* (2012) (56)	fMRI	9	46.8 ± N/A (17–54)	NA	NA	Voxels (27,600)	Pearson correlation	W
Guo *et al.* (2012) (55)	fMRI	38	28.4 ± 9.7 (17–54)	28	26.6 ± 9.4 (17–51)	AAL (90)	Partial correlation	B
Tao *et al.* (2013) (42)	fMRI	15/24	28.3 ± 7.5/27.8 ± 7.9 (NA)	37	28.2 ± 6.5 (NA)	AAL (90)	Partial correlation	B
Bohr *et al.* (2013) (41)	fMRI	14	76.6 ± 7.7 (NA)	16	75.8 ± 7.8 (NA)	HOA (110)	Pearson correlation	B
Cisler *et al.* (2013) (50)	fMRI	19/7	31.3 ± 8.6/27.4 ± 7.4 (NA)	12	25.92 ± 5.33 (NA)	ACN (21)	Pearson correlation	B
Wang *et al.* (2014) (49)	fMRI	20/18	28.2 ± 8.7/28.3 ± 6.2	20	27.9 ± 4.4	Voxels (67,632)	Pearson correlation	W
Meng *et al.* (2014) (39)	fMRI	25	48.76 ± 14.83 (N/A)	25	44.08 ± 14.78 (NA)	HOA (112)	Wavelet correlation	B
Singh *et al.* (2013) (44)	sMRI	93	38.59 ± 11.71 (18–60)	151	33.08 ± 10.53 (18–60)	AAL (90)	Pearson correlation	B
Ajilore *et al.* (2013) (45)	sMRI	53	69.36 ± 8.52 (60–91)	73	70.64 ± 7.15 (60–91)	FreeSurfer (82)	Pearson correlation	B
Bai *et al.* (2012) (46)	DTI	35	67.90 ± 4.50 (NA)	30	71.30 ± 4.40 (NA)	AAL (90/1024)	WM tractography	W
Qin *et al.* (2013) (47)	DTI	29	38.97 ± 9.95 (22–53)	30	35.57 ± 11.73 (23–54)	AAL (396)	WM tractography	W
Korgaonkar *et al.* (2014) (48)	DTI	95	33.8 ± 13.1 (19–65)	102	33.9 ± 13.0 (18–62)	FreeSurfer (84)	WM tractography	W

AAL, Automated Anatomical Labeling; ACN, affective cognition network; B, binarized; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; HOA, Harvard-Oxford Probabilistic MRI Atlas; NA, not available; sMRI, structural magnetic resonance imaging; W, weighted; WM, white matter.

nectivity (28,29,59). Effective connectivity is not commonly used for graph-based brain network analysis due to its complexity and will not be detailed here. Based on the brain connectivity information extracted from neuroimaging data (e.g., functional, structural, and diffusion magnetic resonance imaging [MRI]), functional or structural networks can be generated (Figure 1) and their topological properties can be described using graph theory approaches (Figure 2).

Brain Connectome Analysis Based on Graph Theory

Graph theory provides a powerful mathematical framework to quantify the topological organization of the brain networks or connectomes. In graph theory, the brain is modeled as a graph composed of nodes, representing structurally or functionally defined regions of interest or imaging voxels and edges, representing functional or structural connectivity (27–32). Topological architectures of the brain networks (binarized or weighted) are usually depicted at three levels: global properties (e.g., clustering coefficient, shortest path length, local efficiency, and global efficiency), modularity, and regional nodal properties (e.g., degree, efficiency, and betweenness centralities) (26–32,60–62) (Figure 2 and Table S1 in Supplement 1). The global metrics measure the capacity of the overall information segregation or integrity of the networks. Detecting the brain's modular structures allow the identification of groups of anatomically and/or functionally associated regions that perform specific functions. Regional nodal properties are often used to identify network hubs that are critical for establishing and maintaining efficient information transfer across regions.

Using imaging connectomics, recent studies have demonstrated that the healthy brain networks have higher local clustering and smaller shortest path lengths (i.e., high local and global efficiencies) than their random counterparts (63–65), suggesting an optimized small-world configuration that supports both segregated and integrated information processing. The networks are also found to contain cohesive modules, such as the somatosensory/motor, auditory, attention, visual, subcortical, and DMN systems (65–67), and highly centralized hub nodes predominantly located in the PCC/PCu, mPFC, DLPFC, and insula (Figure 3) (63–70). These network architectures are crucial for maintaining brain function but are disrupted in neuropsychiatric disorders, such as Alzheimer's disease, schizophrenia, and depression (27–31).

DISRUPTED FUNCTIONAL CONNECTOMICS IN DEPRESSION

Several resting-state functional MRI (R-fMRI) studies reported aberrant topological organization of whole-brain functional networks in adult depressive patients involving the global, modular, and nodal properties (Table 1). In the first such study, Zhang *et al.* (38) measured partial correlation coefficients of R-fMRI signals between 90 cortical and subcortical regions in 30 first-episode, drug-naive depressive patients. They observed that the depressed group showed altered global properties including smaller path lengths and higher global efficiency, indicating a shift toward randomization in their brain networks. The opposite pattern (increased path lengths and decreased

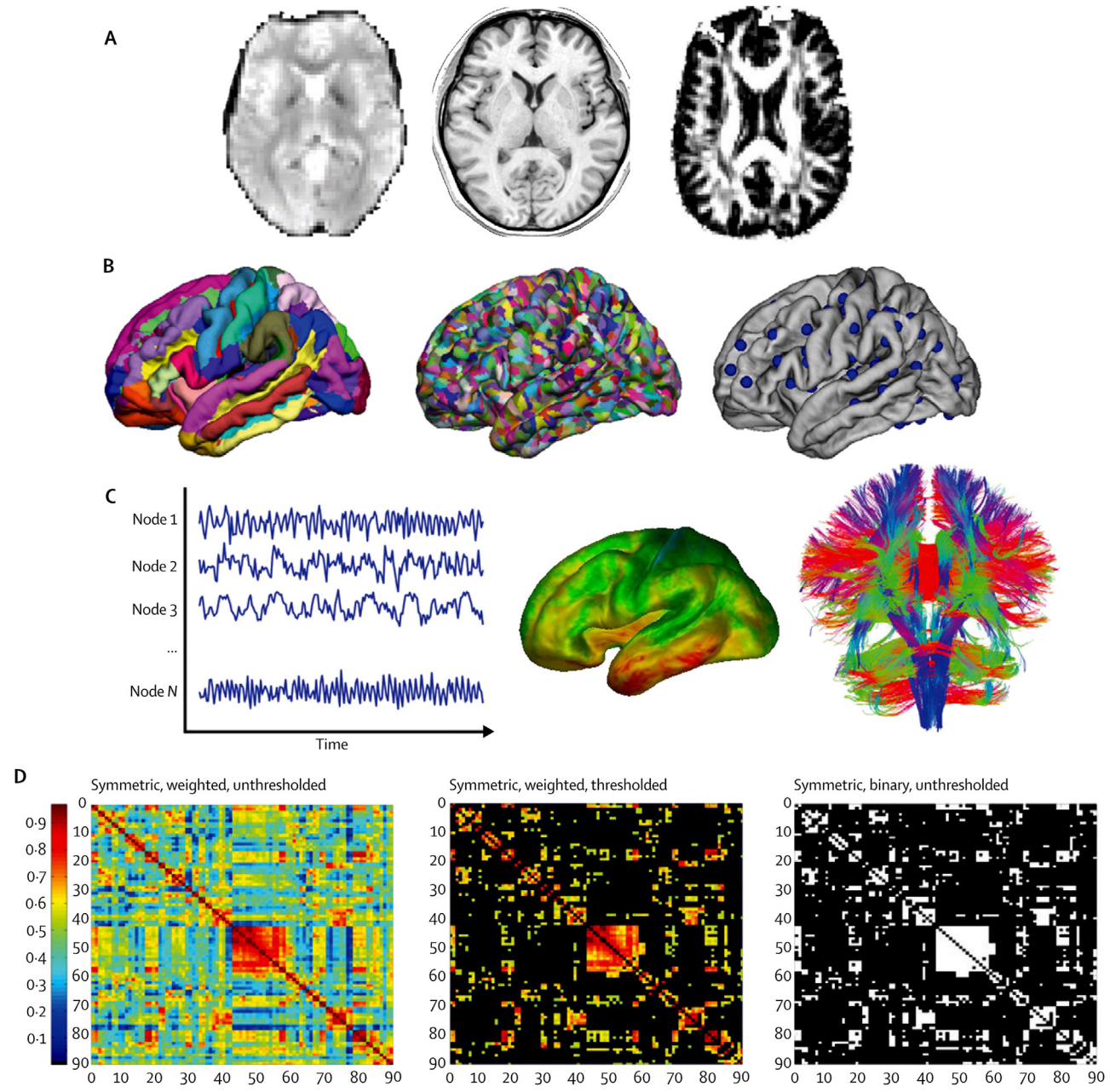

Figure 1. Illustration of brain network construction with magnetic resonance imaging (MRI). **(A)** Functional MRI data (left) can be used to estimate functional connectivity; structural MRI data (middle) can be used to estimate morphological connectivity or structural covariance; diffusion tensor imaging data (right) can be used to generate anatomical connectivity. **(B)** Network nodes, corresponding to different brain regions, are identified by division of the brain into sections with a range of strategies, e.g., a priori anatomical templates (left), random division (middle), and functionally defined regions of interest (right). **(C)** After definition of brain regions, interregional connectivity is typically measured with functional associations in regional-activity time courses for functional MRI (left), statistical dependencies in interregional morphological features (e.g., cortical thickness) for structural MRI (middle), or whole-brain tractography for diffusion tensor imaging (right). **(D)** After some measure of connectivity has been calculated for every pair of brain regions, connectome architecture can be represented by a connectivity matrix encoding the strength and type of connectivity between each regional pair. In MRI studies, these matrices are typically symmetric (i.e., connections are undirected), weighted (i.e., variations in the strength of interregional connectivity are captured), and unthresholded (i.e., the values are continuous, with few zero entries; left). A threshold is usually applied to distinguish the real from spurious connections (middle) and to binarize the resulting matrix to encode the presence or absence of a connection (right). [Reproduced with permission from Filippi *et al.* (31) with a slight modification.]

global efficiency) was observed by Meng *et al.* (39), where wavelet correlations were computed between 112 regions in 25 recurrent depressed patients. Two additional R-fMRI studies by Lord *et al.* (40) and Bohr *et al.* (41) employed Pearson's correlation for connectivity metric and reported no significant depression-associated differences in these global measures.

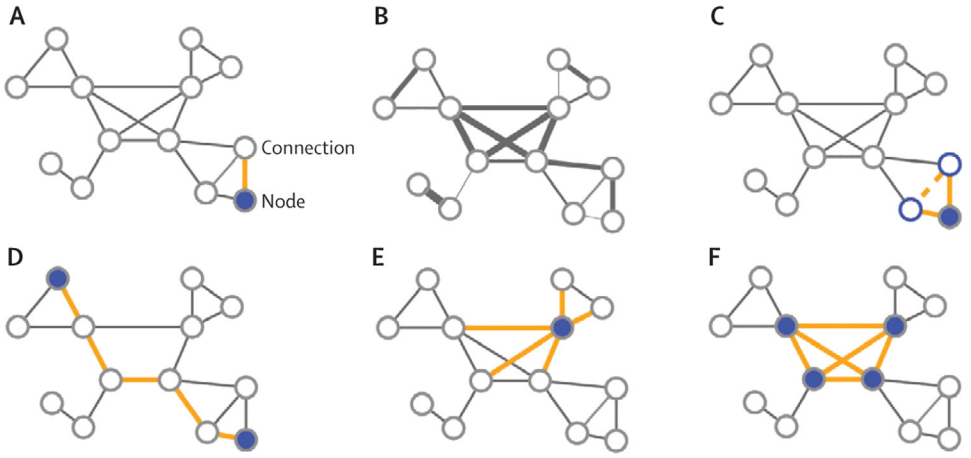

Figure 2. Summary of the main measures with graph theoretical analysis. **(A)** A graph is a mathematical description of a network, consisting of a collection of nodes and connections. **(B)** A weighted graph includes information about the strength of the connections. **(C–F)** Local and global metrics can provide insight into the topological organization of a network. **(C)** The clustering coefficient describes the tendency of nodes to form local triangles, providing insight into the local organization of the network. **(D)** The shortest path length describes the minimum number of steps needed to travel between two nodes (dots in blue) and provides insight into the capacity of the network to communicate between remote regions. **(E)** The degree of a node describes its number of connections (lines in yellow). The existence of a small set of high-degree nodes with a central position in the network can suggest the existence of hub nodes. **(F)** High-level connectivity (lines in yellow) between hub nodes (dots in blue) can suggest the existence of a central so-called rich club within the overall network structure. [Reproduced with permission from Filippi *et al.* (31).]

Notably, there were important differences in the patient samples across these studies: in the Meng *et al.* (39) study, the patients were highly heterogeneous, varying in many factors including depressive episode number (n = 2–10) and medication type (antidepressant monotherapy, dual therapy, or triple therapy); in the Lord *et al.* (40) study, some patients (n = 4) were experiencing their first episodes and the others were recurrent, and all patients were treated using different types of antidepressants; in the Bohr *et al.* (41) study, all patients were taking antidepressants, antipsychotics, nonbenzodiazepine hypnotics, or antiepileptic drugs at the time of the study. Thus, sample heterogeneity in age, depressive episode, or medication at the time of scan or in the patients' prior records is a highly likely source of the result inconsistency; other potential sources include the use of different network node and edge definitions (Table 1) or changes in arousal, cardiorespiratory, and motion artifacts, all of which are correlated with the global properties of brain networks (71–73).

Tao *et al.* (42) specifically investigated intrinsic modular structure of 90-node brain networks in two depressed groups (15 first-episode, drug-naive and 24 long-term, drug-resistant). The greatest change in both depressed groups was the uncoupling of the hate circuitry, including the superior frontal gyrus, insula, and putamen. Other major changes were located in circuitry related to risk-taking, emotion, and reward processing. These findings may reflect an impaired ability for cognitive control over negative feelings in patients. Zhang *et al.* (38) showed decreased regional connectivity (degree,

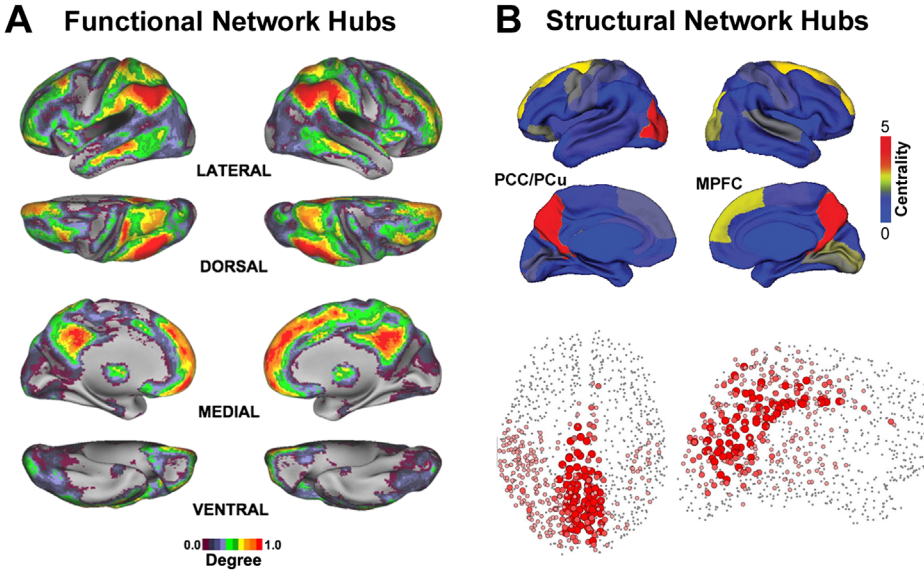

Figure 3. Functional and structural network hubs of the human brain. **(A)** Functional brain hubs were identified by using degree connectivity from resting-state functional magnetic resonance imaging (R-fMRI) data of 127 participants. Higher degree values were primarily located at the default mode network (including the medial prefrontal cortex [MPFC], posterior cingulate cortex/precuneus [PCC/PCu], and lateral parietal cortex), dorsolateral prefrontal cortex, and insula. Figure adapted from (69). **(B)** Structural brain hubs were identified by using betweenness centrality from diffusion tensor imaging (68) and diffusion spectrum imaging data (65) (upper and lower panels, respectively). Structural hubs were mainly located in the MPFC, PCC/PCu, and visual cortex. [**(A)** Reproduced with permission from Buckner *et al.* (31); **(B)** Reproduced with permission from Hagmann *et al.* (65) and Gong *et al.* (68) with slight modifications.]

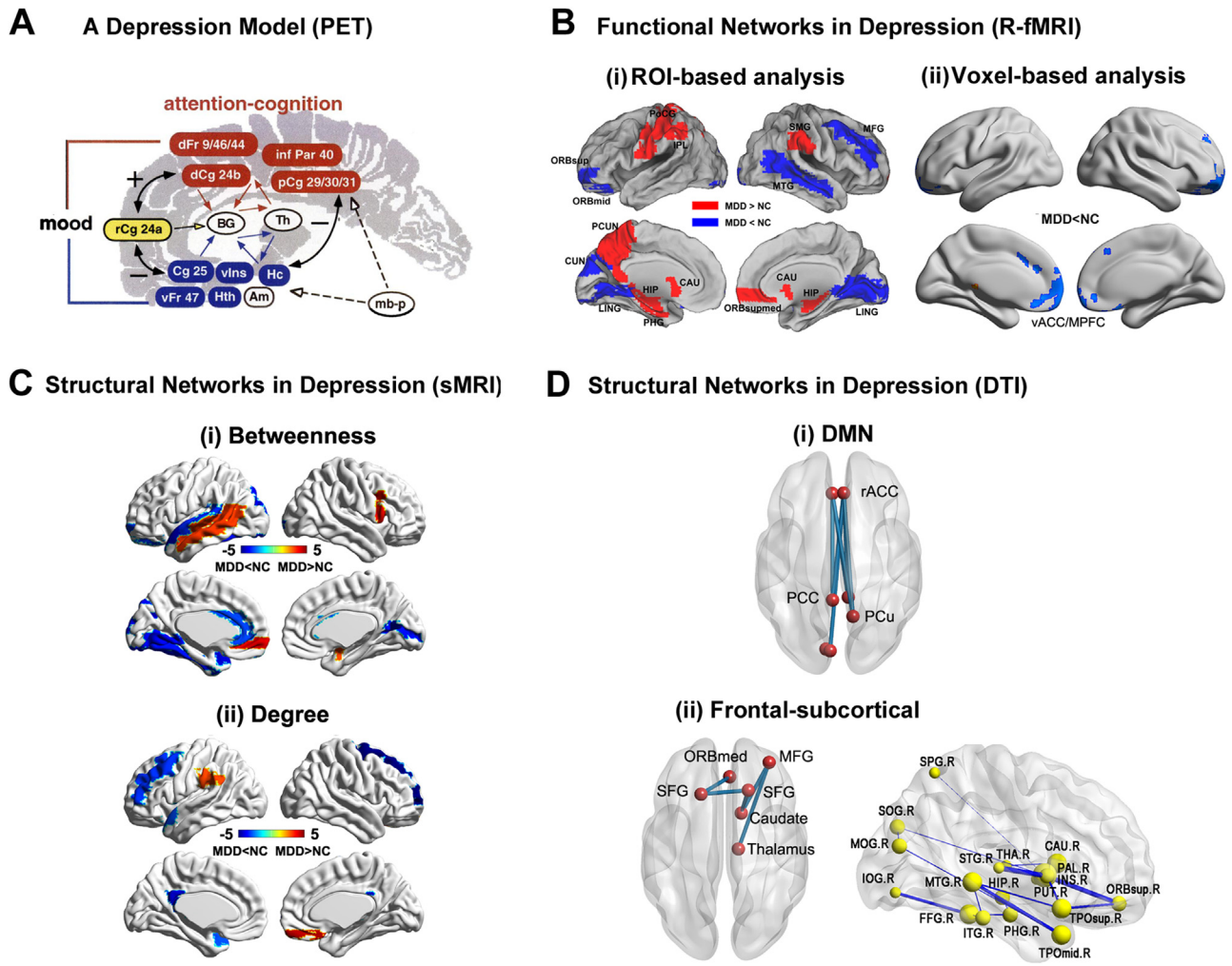

Figure 4. Disrupted regional and connectivity patterns of structural and functional brain networks using various imaging modalities. **(A)** A working depression model based on positron emission tomography (PET) studies. Regions showing functional changes using PET were grouped into three main compartments: dorsal (red), ventral (blue), and rostral (yellow). Sadness and depressive illness are associated with decreased activities in dorsal limbic and neocortical regions (red) and increased in ventral paralimbic areas (blue). **(B)** (i) Brain regions showing abnormal nodal betweenness centralities in the whole-brain functional networks with 90 regions of interest (ROIs) in depression patients. The red colors represent higher nodal centralities in brain networks in depression patients than control subjects. The blue colors represent lower nodal centralities in brain networks in depression patients than control subjects. (ii) Brain regions (e.g., ventral anterior cingulate cortex/medial prefrontal cortex [vACC/MPFC]) showing decreased connectivity degree in the whole-brain networks with 67,632 nodes (i.e., voxels). **(C)** Depression patients showed altered regional betweenness (i) and degree (ii) centralities in whole-brain structural correlation networks derived from structural magnetic resonance imaging (sMRI) data. Hot colors denote higher nodal centrality values in the patients than the control subjects, while cold colors denote lower values in the patients. **(D)** Diffusion tensor imaging (DTI)-based network analysis revealed decreased white-matter structural connectivity in the default mode network (DMN) (48) and frontal-subcortical (46,48) networks. Am, amygdala; BG, basal ganglia; CAU, caudate nucleus; CAU.R, right caudate nucleus; Cg 25, subgenual cingulate; CUN, cuneus; dCg, dorsal anterior cingulate; dFr, dorsolateral prefrontal; FFG.R, right fusiform gyrus; Hc, hippocampus; HIP, hippocampus; HIP.R, right hippocampus; Hth, hypothalamus; inf Par, inferior parietal; INS.R, right insula; IOG.R, right inferior occipital gyrus; IPL, inferior parietal, but supramarginal and angular gyri; ITG.R, right inferior temporal gyrus; LING, lingual gyrus; mb-p, midbrain-pons; MDD, major depressive disorder; MFG, middle frontal gyrus; MOG.R, right middle occipital gyrus; MTG, middle temporal gyrus; MTG.R, right middle temporal gyrus; NC, normal controls subjects; ORBmed, medial orbital frontal gyrus; ORBmid, middle frontal gyrus, orbital part; ORBsup, superior frontal gyrus, orbital part; ORBsupmed, superior frontal gyrus, medial orbital; ORBsup.R, right superior frontal gyrus, orbital part; PAL.R, right pallidium; PCC, posterior cingulate cortex; pCg, posterior cingulate; PCu, precuneus; PCUN, precuneus; PHG, parahippocampal gyrus; PHG.R, right parahippocampus; PoCG, postcentral gyrus; PUT.R, right putamen; rACC, rostral anterior cingulate cortex; rCg, rostral anterior cingulate; R-fMRI, resting state functional magnetic resonance imaging; SFG, superior frontal gyrus; SMG, supramarginal gyrus; SOG.R, right superior occipital gyrus; SPG.R, right superior parietal gyrus; STG.R, right superior temporal gyrus; Th, thalamus; THA.R, right thalamus; TPOmid.R, right temporal pole (middle temporal gyrus); TPOsup.R, right temporal pole (superior temporal gyrus); vFr, ventral frontal; vIns, ventral anterior insula. [**(A)** Reproduced with permission from Mayberg (2); **(B)** (i) Reproduced with permission from Zhang *et al.* (38); **(B)** (ii) Reproduced with permission from Wang *et al.* (49); **(C)** Reproduced with permission from Singh *et al.* (44) with modifications; **(D)** Reproduced with permission from Bai *et al.* (46) and Korgaonkar *et al.* (48) with slight modifications with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/) (136).]

efficiency, and betweenness) in the DLPFC and occipital regions (Figure 4B). The DLPFC plays a critical role in mood regulation and cognitive functioning (3,74) and is frequently implicated in the pathophysiology of depression (18,22,25) (Figure 4A). Abnormal occipital activity was reported in depression (75). Notably, increased regional connectivity was found in the caudate nucleus and DMN (Figure 4B), and these increases significantly correlated with disease duration and severity (38). The caudate nucleus, through its afferent and efferent connections, plays a key role in the regulation of attention and reward (76). Depression-related GM atrophy (11,12) and functional abnormalities during specific tasks (13) and rest (40,77,78) have been found in this region. The DMN regions, a set of core areas in the brain (30,69,79) (Figure 3), have frequently been found to show increases of regional cerebral blood flow (5), cerebral glucose metabolic metabolism (9), and functional connectivity (18,19) in depressed patients. These increases of DMN connectivity suggest their strengthened roles in coordinating information transfer in brain networks, which may reflect pathologic adaptations. Depressed patients also exhibited increased nodal connectivity in the putamen and this increase positively correlated with depressive episode number, independent of current symptoms, medication status, and disease duration (39), indicating that the reorganization of striatal connectivity may interact with the course of episodes. Notably, Jin *et al.* (43) constructed 90-node whole-brain networks in 16 first-episode, drug-naive adolescent patients and reported higher nodal degree in the DMN, DLPFC, insula, and amygdala. The degree connectivity of the amygdala positively correlated with depression duration. These findings are largely compatible with adult depression studies showing increased glucose metabolism and functional connectivity in these regions (5,9,10,18,19), supporting the notion that symptoms of depression in adolescents are an early sign of adult depressive disorders (80).

Together, these R-fMRI studies suggest topological disorganization of brain functional networks in depression. Given the several inconsistent findings among studies (38–41), further validation using independent data sets and the same analysis strategy is important. Depression individuals suffer from behavioral deficits such as biased cognitive processing and dysregulation of emotion (1). Although functional dysconnectivity has been reported when depressed patients perform specific emotional or cognitive tasks (17,81), topological alterations of brain networks during task states are rarely studied and need to be further investigated. These works will add to our understanding of how the system-level disruption of functional brain networks underlies the mood and cognitive impairments associated with depression.

DISRUPTED STRUCTURAL CONNECTOMICS IN DEPRESSION

Two structural MRI studies by Singh *et al.* (44) and Ajilore *et al.* (45) investigated topological organization of depressive GM networks (with 90 or 82 nodes) (Table 1). Singh *et al.* (44) reported that the depressed patients had smaller clustering coefficients in their GM networks, which suggests a less specialized or segregated topological organization. Higher regional connectivity was primarily found in the components of the prefrontal-limbic circuit (amygdala and ventral mPFC) (Figure 4C). These highly interactive regions could be vital in maintaining or adapting to depressive pathology. Reduced regional connectivity was observed in the DMN and DLPFC. Ajilore *et al.* (45) reported disrupted GM networks in late-life depressed patients involving the DMN and limbic regions. These regions are frequently implicated in functional imaging studies of depression (18,19,82,83). Different from the Singh *et al.* (44) study, higher local clustering was found in the late-life depressive networks, possibly due to different age distributions and regional parcellation approaches (Table 1).

Three diffusion tensor imaging (DTI) studies (46–48) examined whole-brain WM networks in depression (Table 1). Bai *et al.* (46) reported disrupted global properties in patients with remitted geriatric depression, including reduced network strength and increased path length. This result was compatible with the Korgaonkar *et al.* (48) study and suggests that widespread disconnections between regions may cause depressed patients to have reduced global network integrity. However, Qin *et al.* (47) did not detect any significant depression-related abnormalities in these global measures. Using network-based statistical analysis (84), Korgaonkar *et al.* (48) reported disrupted WM connectivity in the DMN (e.g., ACC/mPFC and PCC/PCu) and frontal-subcortical (e.g., DLPFC, thalamus, and caudate) networks (Figure 4D). As aforementioned, the DMN engages in emotional and self processing (3,85), and the frontal-subcortical network is critical for mood regulation and cognitive functioning (3,74). These aberrations could be the structural basis underlying the functional and behavioral deficits in depressive individuals.

Overall, depressed patients exhibit disrupted topological organization in both structural GM and WM networks. Although GM morphology displays similar topological principles with the WM connectivity network (86), they capture different information about interregional association, possibly reflecting developmental changes or environment-related plasticity (59,87). Future research should combine structural and diffusion MRI techniques as well as R-fMRI (34,88) to better understand network dysfunction in depression.

GENETIC AND ENVIRONMENTAL INFLUENCES ON BRAIN CONNECTOMICS IN DEPRESSION

Genetic Effects on Depressive Brain Networks

Depression is a highly heritable disorder with a reported heritability of 31% to 42% (89). Specifically, several susceptibility genes are relevant to depression, including apolipoprotein E, dopamine receptor D4, dopamine transporter, and serotonin transporter (90). Neuroimaging studies have demonstrated that these genetic variations are associated with different brain connectivity patterns. In a large sample of healthy human subjects, Pezawas *et al.* (91) reported that compared with individuals with two long alleles (L/L genotype), individuals with one or two short alleles (S carriers) of the promoter region (serotonin transporter [5-HTT]) of the serotonin transporter gene had significantly reduced structural covariance and functional connectivity between the amygdala and the rostral subgenual portion of the ACC. These genotype-related alterations in the amygdala-cingulate circuit

for emotion regulation implicate a system-level mechanism that underlies genetic susceptibility for depression. In another study, Pezawas *et al.* (92) showed that the brain-derived neurotrophic factor (BDNF) genotypes significantly impacted the influences of 5-HTT S allele on the structural covariance of this circuitry: in comparison with a group that was at low risk of depression (5-HTT L/L genotype and BDNF methionine allele carrier), high-risk genotypes (5-HTT S allele carrier and BDNF valine/valine genotype) had reduced structural covariance between the amygdala and the subgenual ACC. Although the influences of genetic variations have been demonstrated in the DMN in health (93) and depression (16), few studies have directly examined the effects of these susceptibility genes on the brain network topology. Two R-fMRI studies based on twin datasets (94,95) reported that the global efficiency of brain networks and regional connectivity in the DMN and DLPFC are heritable. A DTI study showed that apolipoprotein E4 carriers displayed an accelerated age-related loss of mean local WM interconnectivity and regional nodal interconnectivity decreases in several DMN regions (96). We speculate that these susceptibility genes associated with depression may affect the brain network topology underlying preclinical or clinical phenotypes of depression, which can be further explored by combining neuroimaging and molecular genetic methods.

Environmental Effects on Depressive Brain Networks

Depression is also highly associated with environmental factors, such as early life stress (ELS). Converging evidence suggests that ELS (e.g., sexual, physical, and emotional maltreatment) markedly elevates the risk of developing depression (97–99) and influences many aspects of the disease process including the appearance of symptoms, frequency of recurrence and treatment outcome (100–102). Neuroimaging studies show that ELS affects the brain networks in ways that are similar to those in adults with depression. Several R-fMRI studies have reported that ELS-exposed individuals without any psychiatric or medical illness exhibit decreased PCC-mPFC connectivity (103), amygdala-mPFC connectivity (104), and dorsal ACC-related salience network connectivity (105,106). DTI studies in primates and humans demonstrated that ELS leads to disrupted WM integrity in the genu of the corpus callosum (107) and the anterior limb of the internal capsule (108). ELS effects on the brain network topology were also reported in both healthy and depressed individuals. Using R-fMRI, Wang *et al.* (49) investigated whole-brain networks with 67,632 nodes in 18 depressed patients with a history of childhood maltreatment and 20 depressed patients without childhood maltreatment (Table 1). They found that the depressed groups showed overlapping reduced regional degree connectivity in the ventral ACC/mPFC (Figure 4B). However, the maltreated group exhibited remarkably reduced degree connectivity relative to the nonmaltreated patients, especially in regions within the prefrontal-limbic-thalamic-cerebellar circuitry; these reductions significantly correlated with measures of childhood neglect. Also using R-fMRI, Cisler *et al.* (50) examined a 21-node emotion regulation brain network in 7 resilient individuals with ELS and 19 individuals who were susceptible to ELS (Table 1), observing decreased degree connectivity and hub-like properties (in terms of betweenness) in the ventrolateral prefrontal cortex in the resilient individuals and decreased hub-like properties in the dorsal ACC and increased hub-like properties in the amygdala in

the susceptible individuals. Using a large-sample structural MRI dataset, Teicher *et al.* (51) examined the ELS effects on 112-node GM networks in 142 childhood-maltreated individuals and 123 nonmaltreated control subjects (Table 1). They found that the dorsal ACC had the second highest degree centrality and was a major component of the "rich club" in the control network but not in the maltreated network. Conversely, both the precuneus and anterior insula were major hub regions in the maltreated network but not in the control network. Although the neurobiological basis underlying these ELS-associated network alterations remains unclear, ELS may induce long-term hyperactivity or hypoactivity of corticotropin-releasing factor systems and/or other neurotransmitter systems, thereby resulting in brain network dysfunction and increases of stress responsiveness (97–101). The manifestation of depression in relation to ELS can be moderated by age, gender, and genetic factors (100,101). Collectively, these findings suggest not only the relationship between ELS exposure and the impaired brain connectivity in depression but that ELS may lead to a more serious level (or compounds) of impairment in brain connectivity than does depression alone.

The genetic and environmental variables may also influence depressive symptoms and brain networks in an interactive fashion (89,109–111). In a prospective longitudinal study, Caspi *et al*. (112) reported that individuals with the 5-HTT S allele were more stress-sensitive than those with two long alleles (L/L genotype), suggesting that the influence of ELS on depressive symptoms could be moderated by specific genes. Using an fMRI stressful/threatening paradigm, Alexander *et al.* (113) reported the interaction of the 5-HTT gene and environmental adversity as characterized by higher amygdala-hypothalamus connectivity in the 5-HTT S/S allele carriers with ELS. Future works should include intensive, systematic studies of how gene-environment interactions influence depressive connectomes.

DEVELOPING DIAGNOSTIC BIOMARKERS USING CONNECTOME-BASED METRICS

Early diagnosis of depression is important, as treatment is most effective in the early stages. However, depression is traditionally diagnosed mainly focused on clinical interviews and patient ratings and underrecognized and often misdiagnosed (114). Recent advances in machine learning and neuroimaging techniques provide potential for the clinical diagnosis of this disorder. Of these, multivariate pattern analysis based on support vector machine is one of the most popular machine learning methods, in part because of high prediction accuracy and low sensitivity to noise in comparison with conventional univariate analysis (115). In support vector machine models, the selection of the optimal set of features is essential to reduce prediction errors and improve the results interpretability (52,115). Recently, structural and functional connectivity and graph network metrics have been shown to be promising measures for depressive classification analysis (Table 1). Using a whole-brain DTI tractography method, Korgaonkar *et al.* (53) mapped 70-node WM connectivity matrices in

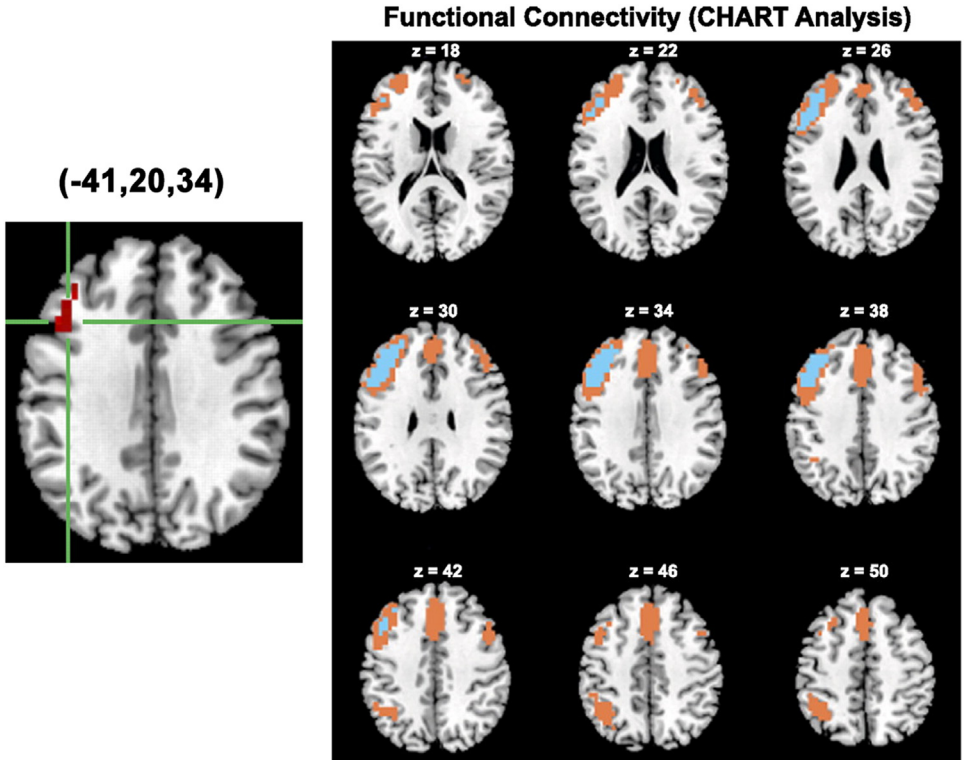

Figure 5. Modulation of functional connectivity in depressive brain networks by electroconvulsive therapy (ECT) treatment. Three-dimensional orthogonal representation of the left dorsolateral prefrontal cortex cluster of voxels (in red) for which a significant reduction in the average global functional connectivity was observed after ECT treatment (left). The coordinates (x, y, and z) refer to Montreal Neurological Institute standard space. Functional connectivity in severely depressed patients before ECT (displayed in orange) and persisting connectivity after ECT (displayed in cyan), showing a substantial reduction in cortical connectivity after ECT treatment ($p < .001$, corrected; right). CHART, cortical hub and related network topology. [Reproduced with permission from Perrin *et al.* (56) with a slight modification.]

depressed patients and yielded a high discriminating accuracy. The most discriminating features were found in the superior longitudinal fasciculus, corpus callosum, and posterior thalamic radiation. Using R-fMRI, several studies of depression also achieved high classification accuracy by training functional connectivity matrices (52,54) or regional nodal measures (40,55). The most discriminating features were primarily in the DMN and the affective networks that underlie emotional processing and cognitive function. While only with small sample sizes, these data demonstrated how the alterations of network connectivity might aid diagnostic biomarker studies of depression. Importantly, future works should be conducted to validate these studies with larger samples and examine whether connectome-based metrics could discriminate subtypes of depression and solve the problem of heterogeneity of this clinical syndrome.

UNDERSTANDING TREATMENT MECHANISMS AND IDENTIFYING POTENTIAL THERAPEUTIC TARGETS FROM A CONNECTOME PERSPECTIVE

Numerous antidepressant treatments are currently available in clinical practice, including pharmacologic and psychotherapeutic interventions and brain stimulation therapies (e.g., electroconvulsive therapy, repetitive transcranial magnetic stimulation, and deep brain stimulation). Although the biological mechanisms of action underlying their therapeutic effects remain incompletely understood, one possible explanation is that these treatment methods selectively modulate the activities of pathologic neuronal circuitries, thereby improving depressive symptoms (116–119). Such a putative mechanism has gained crucial support from brain imaging studies. Using R-fMRI, Li *et al.* (120) reported that unmedicated depressed patients showed elevated functional connectivity in posterior components of DMN, which was significantly normalized after 12 weeks of antidepressant medication. Sheline *et al.* (18) observed that in depressed patients, the dorsal mPFC exhibited dramatically high functional connectivity with several systems (DMN, cognitive control, and affective networks) and argued that antidepressant treatment may be involved in the "hotwiring" normalization. This hypothesis was tested by R-fMRI studies in healthy individuals: the mPFC exhibited reduced functional connectivity following a ketamine and selective serotonin reuptake inhibitor (citalopram) administration (121–123). Using fMRI, Perrin *et al.* (56) observed the strongest reduction of degree connectivity in the DLPFC (involving DLPFC-mPFC connectivity) in patients with severe depressive disorder after electroconvulsive therapy treatment (Figure 5 and Table 1). These connectivity-based studies suggest that several frontal regions (e.g., DLPFC and mPFC) are accessible therapeutic targets in depression treatment. Importantly, different stimulation targets are associated with varying levels of clinical efficacy: several DLPFC stimulation sites, such as the lateral and anterior parts, are more effective than others (124), presumably due to different connectivity profiles in these subregions (125). Together, these neuroimaging studies not only increase our understanding of the biological mechanisms underlying therapeutic effects but also show promise for identifying the appropriate stimulation targets to optimize the clinical response in depression treatment. Future work should investigate from a connectome perspective the effects of psychotherapy and multimodal interventions (combined medications and psychotherapy), which is the mainstay of treatment for the vast majority of individuals with depression.

FUTURE PERSPECTIVES

Addressing Sample Heterogeneity

As described above, there have been mixed results showing decreased, increased, and unchanged global and regional properties in depressive brain networks. The heterogeneity of the patient samples may be a major reason for these discrepancies (Table 1). Researchers need to select more homogeneous samples with detailed consideration of demographic variables (e.g., age, gender, medication, socioeconomic status, childhood experiences, and disease duration) and symptom dimensions.

Relationship between Structural and Functional Connectivity

Depression is characterized by disrupted structural and functional connectivity. However, the structural-functional relationship remains largely unclear (126,127). Using a multimodal imaging approach, de Kwaasteniet *et al.* (128) reported that depressed patients showed higher functional connectivity between the subgenual ACC and the hippocampus and decreased WM connectivity in the uncinate fasciculus that links the two regions. Importantly, these structural and functional changes were negatively correlated in patients, indicating that structural abnormalities may contribute to increased functional connectivity in the frontolimbic network. Both neuroimaging and computational modeling studies suggest that human brain structural and functional networks share similar topological mechanisms such as hubs (65,129). Future multimodal imaging studies should be conducted to ascertain topological associations between structural and functional abnormalities in depression.

Physiological Basis of Network Topology

The preferentially disrupted sites in depression are primarily distributed in the DMN (e.g., ACC/mPFC and PCC/PCu), DLPFC, insula, and amygdala (Figure 4) (38–51). Most of these areas are heavily connected and serve as global hubs of human brain networks that support integrative processing and information communication (63–70), raising the possibility that depression mainly targets network hubs. The brain hubs exhibit important correlates with the physiological measures such as aerobic glycolysis (27), regional cerebral blood flow (79), and regional cerebral metabolic rate of glucose (2,130). The clearance and metabolism of glutamate, which is a primary mediator of depression pathology and a target for antidepressants, are associated with volumetric changes in these regions in depression (131). Preclinical studies in stress and depression models have reported dendritic remodeling and synapse/circuitry alterations and found that these maladaptive changes can be reversed by antidepressants (131). All of these studies indicate a physiological and neurochemical basis underlying the network dysfunctions in depression, but future work is necessary to clarify these issues.

Specificity of Connectomics-Based Findings in Depression

Besides depression, other disorders such as schizophrenia (33,34) and Alzheimer's disease (35–37) also exhibit network abnormalities but have distinct topological patterns. For instance, brain network alterations in schizophrenia point to reduced local clustering and increased global efficiency, namely a randomization configuration (33,34), whereas those in Alzheimer's disease show reduced global efficiency, namely a regular configuration (35–37). Intriguingly, both diseases tend to have hub-concentrated GM lesion distributions, with distinct subsets of brain hubs targeted: lesions are mainly associated with frontal and temporal hubs in schizophrenia, whereas in Alzheimer's disease, lesions are concentrated in temporal lobe hubs (132). In depression, brain hubs also appear to be abnormal, especially in the DMN and frontal-subcortical regions (38–51). Undoubtedly, it would be of interest to chart a comprehensive picture of connectome changes in these brain disorders and further explore the commonalities and specificities of their network dysfunctions.

Reliable Connectome Analysis Approaches and Novel Imaging Protocols

Brain connectome analysis could be influenced by several important sources of variances, including poor test-retest reliability of recordings due to factors such as changes in arousal, cardiorespiratory, and motion artifacts, as well as the noisiness of imaging recordings more generally. Specifically, this analysis involves choosing various network node definitions and connectivity metrics and imaging preprocessing such as head-motion correction (27–32). These choices are associated with variation in test-retest reliability of network measures (73,133–135). Caution should be taken in choosing the most reliable analysis strategies in imaging depressive connectomes. For R-fMRI studies, higher test-retest network reliabilities could be obtained using the following schemes: functionally rather than structurally defined nodes, Pearson rather than partial-based correlations, and nodal degree rather than betweenness metrics (73,133,134). Finally, the emergence of novel connectome analysis approaches (e.g., dynamic connectivity) and imaging protocols (e.g., multiband fMRI) will dramatically increase our knowledge of network dysfunction in depression.

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