Received: 23 November 2017 | Revised: 29 May 2018 | Accepted: 29 May 2018

DOI: 10.1111/cns.12998

REVIEW ARTICLE

WILEY CNS Neuroscience & Therapeutics

A brain network model for depression: From symptom understanding to disease intervention

Bao-Juan Li[1,2] | Karl Friston[3] | Maria Mody[2] | Hua-Ning Wang[4] | Hong-Bing Lu[1] | De-Wen Hu[5]

[1]School of Biomedical Engineering, Fourth Military Medical University, Xi'an, Shaanxi, China

[2]Department of Radiology, Athinoula A Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA

[3]The Wellcome Trust Centre for Neuroimaging, University College London, London, UK

[4]Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, China

[5]Department of Automatic Control, College of Mechatronics and Automation, National University of Defense Technology, Changsha, Hunan, China

Correspondence
Dewen Hu, Department of Automatic Control, College of Mechatronics and Automation, National University of Defense Technology, Changsha, Hunan, China.
Email: dwhu@nudt.edu.cn
and
Hongbing Lu, School of Biomedical Engineering, Fourth Military Medical University, Xi'an, Shaanxi, China.
Email: luhb@fmmu.edu.cn

Funding information
NLM Family Foundation; National Key Technologies R & D Program of China, Grant/Award Number: 2015BAI13B00 and 2015BAI13B01; National Natural Science Foundation of China, Grant/Award Number: 61420106001, 81230035, 81301199 and 81630032; Wellcome Trust Principal Research Fellowship, Grant/Award Number: 088130/Z/09/Z; National Clinical Research Center on Mental Disorders, Grant/Award Number: 2015BAI13B02

Abstract

Understanding the neural substrates of depression is crucial for diagnosis and treatment. Here, we review recent studies of functional and effective connectivity in depression, in terms of functional integration in the brain. Findings from these studies, including our own, point to the involvement of at least four networks in patients with depression. Elevated connectivity of a ventral limbic affective network appears to be associated with excessive negative mood (dysphoria) in the patients; decreased connectivity of a frontal-striatal reward network has been suggested to account for loss of interest, motivation, and pleasure (anhedonia); enhanced default mode network connectivity seems to be associated with depressive rumination; and diminished connectivity of a dorsal cognitive control network is thought to underlie cognitive deficits especially ineffective top-down control of negative thoughts and emotions in depressed patients. Moreover, the restoration of connectivity of these networks—and corresponding symptom improvement—following antidepressant treatment (including medication, psychotherapy, and brain stimulation techniques) serves as evidence for the crucial role of these networks in the pathophysiology of depression.

KEYWORDS
affective network, cognitive control network, default mode network, depression, reward network

1 | INTRODUCTION

Depression is one of the most common psychiatric disorders, with a lifetime prevalence of up to 20% and 30% in men and women, respectively.[1] A key step toward developing effective diagnosis and intervention techniques is to uncover the neural substrates of this disorder. For example, which brain systems are associated with affective and cognitive dysfunction in depression? How do distributed regions interact to produce the symptoms of depression? What is the neural mechanism underlying remission following antidepressant treatment? Why is the relapse rate so high in remitted depressed patients? Advances in neuroimaging techniques and brain connectivity analysis are now making it possible to address these questions, thereby tackling one of the greatest mysteries of the human mind.

A growing literature supports the notion that the symptoms of depression are associated with widespread network dysconnectivity rather than the aberrant responses of individual brain regions. Here, we review recent advances in functional magnetic resonance imaging (fMRI) studies that have tried to elucidate the neurobiological underpinnings of depression, from the perspective of functional integration. Depression—frequently seen as withdrawal from the prosocial environment—is characterized by aberrant emotional and affective processing, excessive self-focus, and diminished cognitive control. To this end, we pay special attention to four core networks that have been implicated in these processes: the affective network (AN), reward network (RN), default mode network (DMN), and cognitive control network (CCN), respectively. First, we briefly summarize brain connectivity analysis methods. Detailed descriptions of the different methods we refer to can be found in Reference (2-9). We then review findings from recent fMRI studies that have investigated abnormalities in brain connectivity in depression. This is followed by a short discussion on how brain connectivity studies can help with the treatment of the disease. Finally, we suggest that future studies should elucidate the structural and metabolic substrates of depression-related dysconnectivity and try to develop an extended model of depression for improved diagnosis, treatment, and prevention of the disorder.

2 | A BRIEF SUMMARY OF BRAIN CONNECTIVITY ANALYSIS METHODS

Characterizations of brain connectivity include structural connectivity, functional connectivity, and effective connectivity. For the most part, structural connectivity analysis relies on techniques such as diffusion magnetic resonance imaging (dMRI) and tractography, which report the integrity of white matter fiber tracts. The remaining distinction between functional and effective connectivity is important to understand.[2-4] The former refers to (undirected) correlations between the activity of two brain regions, while the latter refers to (directed and usually reciprocal) causal influences among brain regions within a network (Figure 1).

Specifically, functional connectivity corresponds to the temporal correlations (or statistical dependencies) between the activity

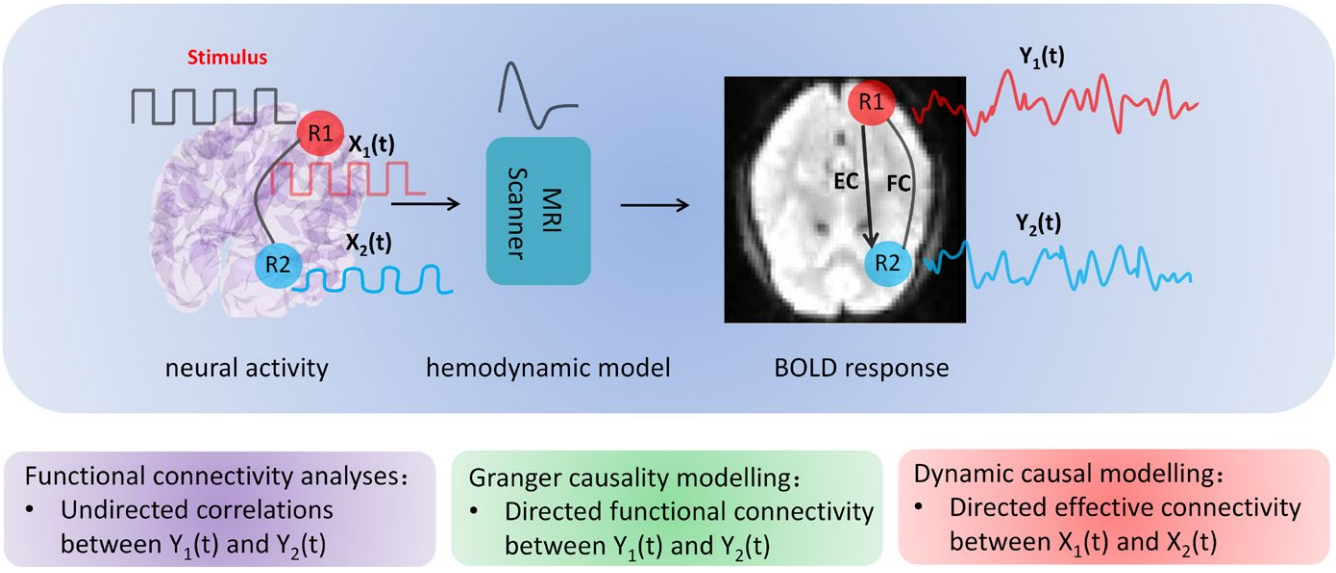

FIGURE 1 Characterization of different approaches to examine brain connectivity. Experimental inputs usually enter into sensory cortex and cause changes in neuronal activity X_1 in the region (R1). Activity in R1 will then be propagated to a second region R2 which is connected to R1 and causes changes in X_2. The neuronal activity X_1 and X_2 are hidden neuronal states because they cannot be observed directly using fMRI. Instead, the BOLD signals recorded in fMRI images are a convolution of the neuronal states with a hemodynamic function. Functional connectivity analyses simply measure the undirected temporal correlations (or statistical dependencies) among observed BOLD signals of different brain regions. Granger causality modeling (GCM) tries to infer directed connectivity using autoregressive models. Strictly speaking, GCM measures directed functional connectivity because it operates on observed hemodynamic (BOLD) responses. In contrast, dynamic causal modeling (DCM) estimates the influence that the neural activity of one brain region exerts on another. FC: functional connectivity; EC: effective connectivity

of different brain regions.[3,4] It is a simple characterization of brain connectivity and can be measured directly from fMRI data using different methods. The easiest way to measure functional connectivity is to use a seed-based method. Usually, one extracts the mean time series of a region of interest (ROI) and computes the correlation between the time series of the ROI and all other voxels (or regions) in the brain. The ensuing (thresholded) correlation map represents functional connectivity between the ROI and all other voxels (or regions). Lately, researchers have started to map whole-brain functional connectivity using fMRI. Usually, the brain is segmented into many (about 100) regions according to a template (eg, the automated anatomical labeling atlas, AAL.[10] Whole-brain functional connectivity can then be summarized with a correlation matrix. The topological properties of the functionally connected networks can then be studied using graph theory approaches. Graphs are constructed to describe the brain networks with the nodes denoting brain regions and the edges denoting significant connections among these regions. Properties such as node degree, efficiency, clustering coefficient, path length, and modularity can be calculated and compared across different groups.[11-13] Finally, independent component analysis (ICA) is widely used to derive coherent patterns or modes of activity from neuroimaging data that correspond to functionally connected brain networks. This sort of characterization decomposes the fMRI images of the whole brain into a series of spatially independent modes or networks.

Unlike functional connectivity, effective connectivity infers directed (ie, causal) interactions within a brain network. Effective connectivity is defined as the influence one neural system exerts on another.[2,4] In the past decade, different approaches to measure effective connectivity such as psychophysiological interaction (PPI) analysis, structural equation modeling (SEM), Granger causality modeling (GCM), and dynamic causal modeling (DCM) have been developed. GCM tries to infer directed connectivity from observed BOLD signals using autoregressive models.[5] In contrast, DCM treats the brain as a dynamic system of (unobserved or hidden) neuronal states, which are driven by experimental inputs or endogenous fluctuations

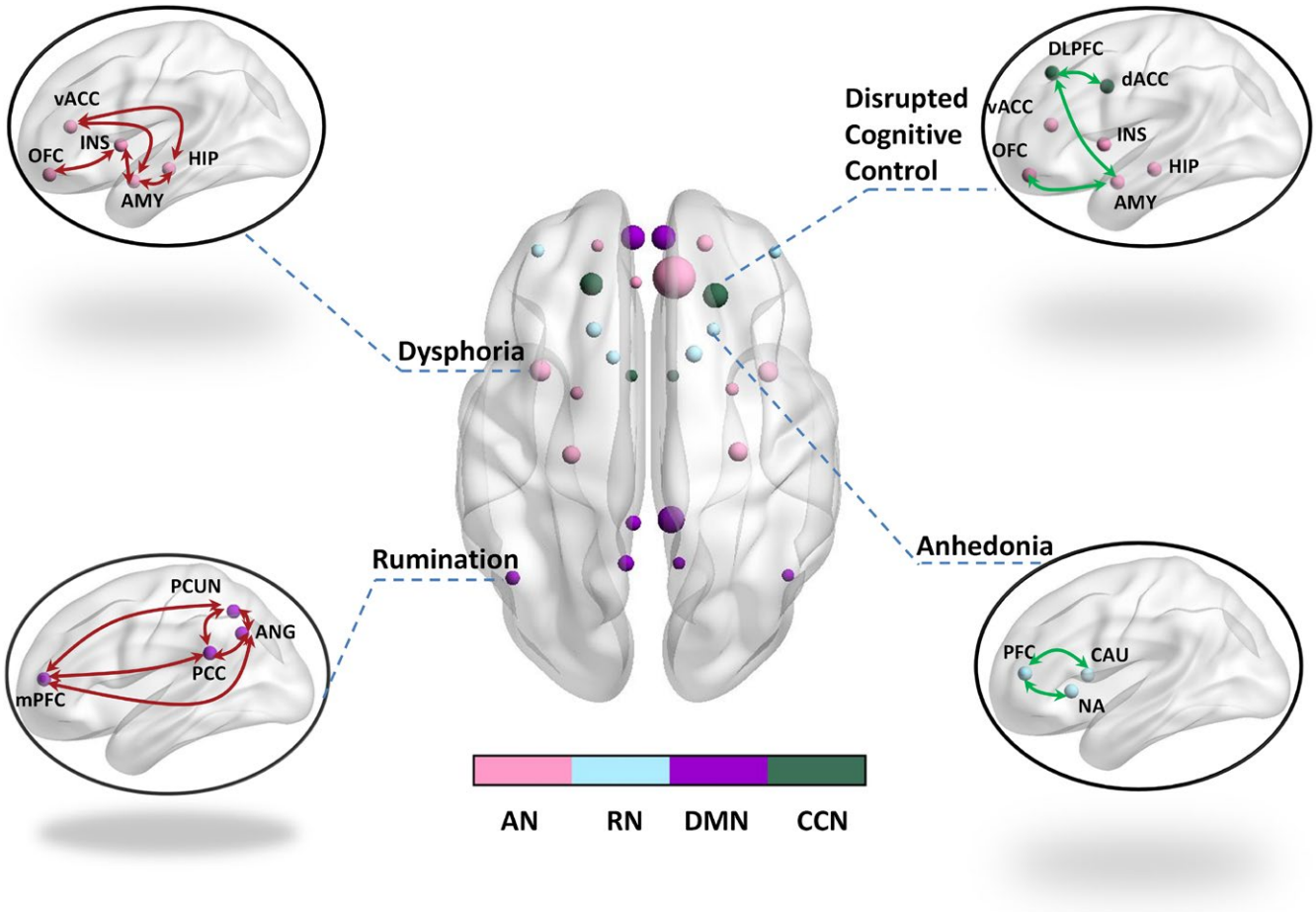

FIGURE 2 Dysconnectivity and depression. Four networks including the affective network (AN), reward network (RN), default mode network (DMN), and cognitive control network (CCN) have been mainly associated with the neural substrates of depression, with hyperconnectivity (marked in red) of the AN and DMN and attenuated connectivity (marked in green) of the RN and CCN observed in the patients. OFC: orbitofrontal cortex; INS: insula; AMY: amygdala; HIP: hippocampus; vACC: ventral anterior cingulate cortex; mPFC: medial prefrontal cortex; PCC: posterior cingulate cortex; PCUN: precuneus; ANG: Angular; DLPFC: dorsolateral prefrontal cortex; dACC: dorsal anterior cingulate cortex; PFC: prefrontal cortex; CAU: caudate; NA: nucleus accumbens. This figure was prepared with the BrainNet Viewer[132]

to produce BOLD responses.[6,7] DCM estimates neural interactions using state-space models based on (deterministic or random) differential equations. These equations describe neural dynamics and are supplemented with hemodynamic equations to transform regional neuronal activity into the observed BOLD response (Figure 1).[6] Both empirical and simulated data suggest DCM may be more robust than GCM, when estimating directed connectivity.[14,15]

3 | A NETWORK MODEL OF MAJOR DEPRESSION

Major depressive disorder is characterized by prominent affective disruptions and cognitive impairments. Neuroimaging studies suggested that these deficits may be associated with altered connectivity of four brain networks (Figure 2): Elevated connectivity of a ventral limbic affective network appears to be associated with excessive negative feeling (dysphoria); decreased connectivity of a frontal-striatal reward network has been suggested to account for loss of interest, motivation, and pleasure (anhedonia); enhanced default mode network connectivity seems to be associated with depressive rumination; and diminished connectivity of a dorsal cognitive control network is thought to underlie cognitive deficits especially ineffective top-down control of negative thoughts and emotions in depressed patients. In this section, we examine these core networks affected in depression, focusing on the pattern of disruption within each—as related to the symptoms of depression.

3.1 | Elevated affective network connectivity and persistent sad mood

The orbitofrontal cortex (OFC), the affective division of the anterior cingulate cortex (ACC), and limbic regions including the amygdala, hippocampus, and insula form a ventral network which is also known as the brain's affective network (AN).[16,17] Crucially, the AN has been associated with processing and regulation of emotions. Emerging neuroimaging findings suggest an involvement of the AN in the pathophysiology of depression.[18,19] Previous studies have found hyperactivation of the amygdala and subgenual ACC, associated with dysfunctional affective processing in depressed patients. Functional neuroimaging also points to aberrant connectivity within the AN (Figure 2, Table 1), which may underlie emotion dysregulation, a hallmark of depression.

Increased resting-state interactions between regions of the AN have been consistently reported in depression. The patients showed enhanced functional connectivity between the dorsal midinsula cortex and the amygdala, subgenual prefrontal cortex, and OFC[20]; between the subgenual ACC and dorsomedial frontal cortex[16,21]; between pregenual ACC and left dorsolateral frontal cortex[21]; and between lateral orbitofrontal cortex and the precuneus, angular gyrus, and temporal visual cortex,[22] with connectivity strength positively correlated with illness severity.[20,21,23] Notably, the strength of the amygdala-sgACC connectivity was positively correlated with negative affectivity, while an increase in this connection was associated with the onset of depression.[23] In addition, enhanced OFC connectivity with the precuneus and angular gyrus was also related to affectively negative sense of the self in the patients.[22] Attempts have also been made to determine the directionality of the influences among these regions at rest. Granger causality analysis revealed increased excitatory influences from hippocampus to ventral anterior cingulate cortex and reciprocal interactions between the medial prefrontal cortex and ventral anterior cingulate cortex in major depressive disorder (MDD).[24]

When presented with sad and happy faces, individuals with depression demonstrated an attentional bias for sad faces,[25,26] whereas healthy controls show a positive bias toward happy faces.[26] Related to these findings, an opposite pattern of limbic network connectivity was found during processing of emotional stimuli. Specifically, happy faces modulated bidirectional OFC-amygdala and OFC-fusiform gyrus connectivity in depressed subjects. The same pattern of modulation was observed when healthy controls viewed sad faces. Similarly, the connection from the fusiform gyrus to orbitofrontal cortex was modulated when healthy subjects were presented with happy faces and depressed patients were processing sad faces.[27] Depressed patients also show increased memory sensitivity for negative information associated with increased amygdala-hippocampus and amygdala-caudate-putamen connectivity.[28] Admon et al[29] found an increased susceptibility to negative stimuli in remitted patients compared with controls. The increases in cortisol and anxiety levels were higher in the remitted MDD individuals than the controls in a stress task. It is worth noting that elevated caudate-amygdala and caudate-hippocampus connectivity during processing of negative stimuli was only seen in remitted subjects, but not the control group.[29]

3.2 | Attenuated frontal-striatal reward network connectivity and anhedonia

Symptoms such as loss of pleasure, interest, or motivation (anhedonia) are also typical in depression. Evidence from neuroimaging studies suggests that anhedonia seen in the patients may be attributed to diminished interactions in the frontal-striatal reward network (Figure 2, Table 1). The frontal cortex and striatal regions including the caudate, putmen, and nucleus accumbens form a brain's reward network. Interactions among regions in this network have been shown to be attenuated in patients with depression,[22] with reduction in connectivity being in proportion to depression severity.[30] Interestingly, nodal efficiency of the right putamen's resting-state functional connectivity network was associated with the course of depressive episodes—an important predictor of depressive relapse.[31] Recently, a study by Felger and colleagues further suggested that anhedonia and hypoconnectvity of the reward network may be caused by elevated inflammation, increased biomarkers of which were seen in depression.[32]

When exposed to positive stimuli, depressed patients demonstrated reduced magnitude and duration of positive affect.[33] The

TABLE 1 Altered connectivity in brain networks (AN, RN, DMN, and CCN) in patients with depression

References	Subjects	Paradigms	Methods	Main findings
The affective network (AN)				
Avery et al[20]	20 MDD vs 20 controls	Resting-state fMRI; Focused awareness task	Seed-based functional connectivity analysis	Increased resting-state functional connectivity between the dorsal midinsula cortex and the amygdala, subgenual prefrontal cortex, and orbitofrontal cortex
Davey et al[21]	18 MDD vs 20 controls	Resting-state fMRI	Seed-based functional connectivity analysis	Enhanced functional connectivity between the sgACC and dorsomedial frontal cortex, between the pregenual ACC and left dorsolateral frontal cortex; Reduced connectivity between the pregenual ACC and caudate nucleus
Cheng et al[22]	421 MDD vs 488 controls	Resting-state fMRI	Voxel level functional connectivity analysis	Increased connectivity between the lateral OFC and the precuneus, angular gyrus, and temporal visual cortex
Davey et al[23]	56 adolescents, of whom 8 developed depression during a 2-y follow-up period	Resting-state fMRI	Seed-based functional connectivity analysis	Increased connectivity between the sgACC and amygdala in subjects who developed depression at follow-up compared with baseline
Hamilton et al[24]	16 MDD and 14 controls	Resting-state fMRI	Granger causality analysis	Increased excitatory influences among limbic and paralimbic regions and inhibitory influences from limbic regions to dorsal cortical regions
Admon et al[29]	33 remitted MDD vs 35 controls	Mild psychological stress task	Psychophysical interaction analyses	Enhanced caudate-amygdala and caudate-hippocampus connectivity was only observed in remitted MDD subjects during processing of negative stimuli
Goulden et al[27]	22 remitted MDD vs 21 controls	Face emotion processing task	Dynamic causal modeling	Reversed pattern of frontotemporal effective connectivity in remitted MDD and controls during processing of happy and sad faces
Hamilton et al[28]	14 MDD vs 12 controls	Picture encoding task; Incidental recognition memory task	Psychophysical interaction analysis	Increased memory sensitivity for negative stimuli in the patients which was associated with enhanced amygdala-hippocampus and amygdala-caudate-putamen connectivity
The reward network (RN)				
Cheng et al[22]	421 MDD vs 488 controls	Resting-state fMRI	Voxel level functional connectivity analysis	Decreased connectivity between the medial orbitofrontal cortex and the parahippocampal gyrus and medial temporal lobe
Satterthwaite et al[30]	27 bipolar depression, 25 MDD, and 37 controls	Resting-state fMRI; Monetary reward task	Functional connectivity among 11 nodes	Disrupted resting-state connectivity of the reward network was correlated with depression severity in both patient groups

(Continues)

TABLE 1 (Continued)

References	Subjects	Paradigms	Methods	Main findings
Meng et al[31]	25 recurrent MDD vs 25 controls	Resting-state fMRI	Whole-brain functional connectivity analysis	Abnormal nodal efficiency of the right putamen was associated with the course of depressive episodes
Simmons et al[37]	16 patients with MDD and increased appetite, 16 patients with MDD and decreased appetite, and 16 controls	Resting-state fMRI; Food/nonfood picture task	Seed-based functional connectivity analysis	Patients with increased appetite demonstrated greater activation of the reward regions in response to food pictures; Patients with decreased appetite demonstrated weakened activation of the midinsula; Connectivity of the midinsula and reward regions was correlated with food pleasantness ratings
Manelis et al[36]	31 bipolar depression, 39 MDD, and 36 controls	Number guessing reward task	Independent Multiple sample Greedy Equivalence Search (IMaGES); Linear non-Gaussian Orientation, Fixed Structure (LOFS) algorithms	Win/loss anticipation was characterized differently in patients and controls, with bottom-up connectivity and top-down connectivity observed in the MDD patients and controls, respectively
Admon et al[35]	26 MDD vs 29 controls	Monetary incentive delay task	Psychophysical interaction analysis	Reduced caudate connectivity to gains and greater caudate connectivity to penalties
Heller et al[34]	27 MDD vs 19 controls	Emotion regulation task	Seed-based functional connectivity analysis	Abnormal connectivity between the left NAcc and left middle frontal gyrus
The default mode network (DMN)				
Greicius et al[41]	28 MDD vs 20 controls	Resting-state fMRI	Independent component analysis	Increased subgenual cingulate and thalamic connectivity
Berman et al[42]	15 MDD vs 15 controls	Resting-state fMRI; Short-term memory task	Seed-based functional connectivity analysis	Enhanced subgenual cingulate-PCC connectivity in the patients was observed at rest but not during performance of the short-term memory task
Li et al[43]	24 MDD vs 29 controls	Resting-state fMRI	Independent component analysis	The default mode network dissociated into an anterior and another posterior subnetwork; Functional connectivity of both subnetworks was elevated in the patients.
Ho et al[44]	26 adolescents with MDD vs 37 controls	Resting-state fMRI; Emotion identification task	Psychophysical interaction analysis	Greater mPFC and PCC connectivity during task performance, as well as increased PCC-subcallosal cingulate connectivity at rest
Belleau et al[46]	16 MDD vs 16 controls	Self-focus thought induction task; External-focus thought induction task	Seed-based functional connectivity analysis	Enhanced connectivity of the default mode network and weakened connectivity of the executive and salience network during the external-focus thought induction task; No significant differences in connectivity were observed between the patients and controls during performance of the self-focus thought induction task

(Continues)

TABLE 1 (Continued)

References	Subjects	Paradigms	Methods	Main findings
Lemogne et al[47]	15 MDD vs 15 controls	Self-referential processing task	Seed-based functional connectivity analysis	Elevated MFC-dACC and MFC-DLPFC connectivity
Zamoscik et al[48]	29 remitted MDD vs 29 controls	Resting-state fMRI; Mood induction task; Rumination phase; Distraction phase	Seed-based functional connectivity analysis	Increased connectivity between the PCC and parahippocampal gyri
Nixon et al[49]	20 recovered MDD vs 20 controls	Go/No-Go task	Seed-based functional connectivity analysis	Increased precuneus connectivity in right dorsomedial prefrontal cortex and right frontal pole
Gaffrey et al[50]	21 children with a history of preschool depression and 18 controls	Resting-state fMRI	Seed-based functional connectivity analysis	Greater PCC connectivity in the sgACC and anterior middle temporal gyrus; Reduced PCC connectivity in the middle temporal gyrus, inferior parietal lobule, and cerebellum
Zhu et al[54]	35 MDD vs 35 controls	Resting-state fMRI	Independent component analysis	Increased connectivity in anterior part and decreased connectivity in posterior part of the default mode network
Sambataro et al[58]	20 MDD vs 20 controls	Resting-state fMRI	Independent component analysis	Increased connectivity within the posterior, ventral subsystems of the DMN; Decreased connectivity from anterior to ventral subsystems.
Zhang et al[45]	30 MDD vs 63 controls	Resting-state fMRI	Whole-brain functional connectivity analysis	Reduced path length and increased global efficiency; Greater nodal centralities in the hippocampus, inferior parietal, medial frontal, and parietal regions, as well as lower nodal centralities in the occipital, frontal and temporal regions.
The cognitive control network (CCN)				
Vasic et al[69]	14 MDD vs 14 controls	Verbal working memory	Independent component analysis	Decreased connectivity in the ACC, ventrolateral and superior prefrontal cortex, inferior parietal, superior prefrontal, and frontopolar regions; Increased connectivity in the DLPFC and cerebellum
Aizenstein et al[70]	13 late-life depression vs 13 controls	Executive-control task	Seed-based functional connectivity analysis	Reduced connectivity between the DLPFC and dACC
Kerestes et al[72]	21 MDD vs 21 controls	Resting-state fMRI	Seed-based functional connectivity analysis	Elevated connectivity between dorsal caudate nucleus and ventrolateral prefrontal cortex
Alexopoulos et al[73]	16 late-life MDD vs 10 controls	Resting-state fMRI	Seed-based functional connectivity analysis	Reduced connectivity of the CCN and increased connectivity of the DMN characterized the patients

(Continues)

TABLE 1 (Continued)

References	Subjects	Paradigms	Methods	Main findings
Stange et al[75]	52 remitted MDD vs 47 controls	Resting-state fMRI	Seed-based functional connectivity analysis; Independent component analysis	Weakened CCN connectivity pattern seen in the patients was stable over time
Anand et al[77]	15 MDD vs 15 controls	Resting-state fMRI; Emotion processing task	Seed-based functional connectivity analysis	Attenuated connectivity between the ACC and limbic regions both at rest and during task performance
Tang et al[78]	28 MDD vs 30 controls	Resting-state fMRI	Seed-based functional connectivity analysis	Weakened connectivity between bilateral amygdala and left ventral prefrontal cortex
Kong et al[79]	28 MDD vs 30 controls	Emotional face processing task	Seed-based functional connectivity analysis	Reduced connectivity between the amygdala and left rostral prefrontal cortex in the patients during processing of fear faces
Lui et al[80]	28 refractory MDD, 32 nonrefractory MDD, and 48 controls	Resting-state fMRI	Seed-based functional connectivity analysis	Attenuated bilateral connectivity in prefrontal-limbic-thalamic regions in both patient group
Song et al[81]	28 MDD vs 27 controls	Resting-state fMRI	Voxel-based eigenvector centrality mapping	Decreased connectivity in bilateral middle frontal gyrus, insula, hippocampus, amygdala and cerebellum; Increased connectivity in the medial prefrontal cortex; Attenuated frontal–subcortical connection and stronger insula–medial prefrontal cortex connection
Carballedo et al[82]	15 MDD vs 15 controls	Face-matching task	Structural equation modeling	Decreased bilateral connectivity from amygdala to orbitofrontal cortex; Reduced connectivity from right amygdala to ACC, and from ACC to prefrontal cortex
Moses-Kolko et al[83]	14 depressed mothers vs 16 postpartum healthy mothers	Face vs shape matching task	Granger causality analysis	The connection from left dorsomedial prefrontal cortex to amygdala seen in controls was absent in the patients
Erk et al[84]	17 MDD vs 17 controls	Emotion regulation task	Psychophysiological interaction analysis	Attenuated prefrontolimbic connectivity during active regulation
Grant et al[85]	20 MDD vs 19 controls	Affective variant of the flanker task	Granger causality analysis	Reduced mPFC–amygdala connectivity was only presented in subjects with a history of early life trauma (ELT). For those without ELT, mPFC inhibition of the amygdala was intact
Wang et al[74]	18 MDD patients with childhood maltreatment, 20 MDD patients without childhood maltreatment, and 20 controls	Resting-state fMRI	Whole-brain functional connectivity analysis	Both patients group demonstrated weakened connectivity in bilateral ventral medial prefrontal cortex/ventral anterior cingulate cortex; Childhood neglect was associated with decreased connectivity of the prefrontal-limbic-thalamic-cerebellar circuitry

inability to sustain positive affect has been shown to be associated with reduced frontostriatal connectivity.[34] In addition, depressed individuals exhibited lower caudate-dACC connectivity than the controls in response to monetary gains.[35] Win/loss anticipation was mediated through distinct mechanisms in diseased and healthy individuals, with bottom-up striatal-frontal connectivity seen in MDD and frontostriatal top-down connectivity observed in the controls.[36] Furthermore, aberrant activation and connectivity of the reward network have also been shown to be associated with depression-related appetite loss/increase in the patients.[37]

3.3 | Hyperconnectivity of the default mode network and excessive self-focus

The third system involved in the neural substrates of depression is the task-negative default mode network (DMN) (Figure 2, Table 1). The DMN mainly encompasses the precuneus, posterior cingulate cortex (PCC), and medial prefrontal cortex (mPFC), as well as the inferior parietal cortex.[38,39] This network is known as a task-negative network as regions within this network generally demonstrate deactivation during performance of cognitive tasks.[39,40]

Enhanced DMN connectivity is marked in depression. An early study conducted by Greicius et al[41] reported elevated resting-state DMN connectivity in patients with depression. Their findings of increased DMN connectivity have been reproduced by several other studies and our analyses.[16,42-44] In addition, Zhang et al[45] reported increased nodal centralities in DMN regions in the patients. Furthermore, depressed subjects also demonstrated enhanced DMN connectivity while being engaged in externally focused thought,[46] in an emotion identification task,[44] and during self-referential processing.[47] Elevated DMN functional connectivity thus appears to be a robust marker of MDD that is evident even in remitted,[48] and recovered state.[49] Notably, a history of preschool depression in children may also affect the developmental trajectory of the DMN, with increased PCC functional connectivity in the subgenual and anterior cingulate cortices detected in these individuals.[50]

The DMN is associated with self-referential processes,[51,52] which are enhanced in patients with depression. Depressed individuals usually demonstrate maladaptive rumination—the process of repetitively and passively thinking about one's negative feelings, possible causes, and consequences.[48,53] Rumination, the content of which is typically negative, has been shown to predict the onset of depression, prolong the duration, exacerbate negative thinking, and impair problem-solving.[53] Hyperconnectivity of the DMN may represent excessive self-referential processes and maladaptive rumination in the patients.[42,48,54,55] In a study by Berman et al,[42] resting-state functional connectivity, between the posterior cingulate and the subgenual cingulate, correlated positively with rumination scores both in depressed and healthy subjects. In addition, increase in DMN connectivity was seen in the MDD group from unconstrained resting states to induced-ruminative states.[55] Accordingly, stronger DMN connectivity was associated with higher levels of rumination in depression,[54] which was also evident in remitted depressed patients.[48]

3.3.1 | DMN subnetworks in depression

Previous studies have also suggested that the DMN may consist of interacting subnetworks.[56,57] Zhu et al[54] reported elevated functional connectivity in the anterior division of the DMN in MDD patients to be positively correlated with rumination score. Interestingly, they also found attenuated functional connectivity in the posterior division of the DMN in the patients to be negatively correlated with autobiographical memory scores. In our study, using group ICA to investigate resting-state functional connectivity in MDD, we found evidence for two dissociable subnetworks in the DMN: an anterior subnetwork which had the highest amplitude in the mPFC, and a posterior subnetwork, which had the highest amplitude in the precuneus.[43] Unlike Zhu and colleagues, Sambataro et al[58] found increased functional connectivity within posterior, ventral, and core DMN subsystems in patients with MDD. They also reported altered interactions between DMN subsystems in patients.

3.4 | Diminished cognitive control network connectivity and impaired top-down control

In patients with depression, impaired emotion processing is often accompanied by cognitive impairments.[59,60] These impairments can persist even after remission of affective symptoms. Related to these impairments, another brain network has been implicated in the pathophysiology of depression, the so-called cognitive control network (CCN). This network mainly consists of functionally connected brain regions including the dorsolateral prefrontal cortex (DLPFC), the cognitive subdivision of ACC, and the parietal cortex.[61-64] The CCN is thought to be an executive or control system, responsible for regulating thoughts, and actions in accordance with internal goals.[65,66] Neuroimaging studies have identified coactivation of the CCN during performance of different cognitive tasks. A failure of effective cognitive control over emotional processing is one of the central characteristics of depression.[67,68] Neuroimaging studies seeking to elucidate the neural substrates of depression therefore have identified prominent impairments of the CCN in depression (Figure 2, Table 1).

Dysconnectivity of regions involved in the CCN has been reported in patients with depression during performance of tasks involving working memory,[69] executive-control,[70] and affective interference,[71] as well as during rest.[16,72-74] However, the findings have been divergent. Sheline et al,[16] using the bilateral DLPFC as a seed region, reported increased resting-state functional connectivity in the bilateral dorsomedial prefrontal cortex (DMPFC) in depressed subjects. Vasic et al[69] observed increased functional connectivity in the left DLPFC during a working memory task in MDD. However, Stange et al[75] reported attenuated CCN connectivity which was stable over time in remitted MDD. Aizenstein et al[70] reported reduced DLPFC-dACC functional connectivity on an executive-control task in patients with late-life depression (LLD). Children with a parental history of depression are known to be at high risk to develop this disorder. In a recent study, Clasen and the colleagues reported

decreased resting-state functional connectivity within the CCN in depression-naive adolescent females with a parental history of depression. In addition, severity of the parents' depression was associated with deficits in functional connectivity of the CCN in their children.[76] Neuroimaging studies thus support a link between impairments in the CCN and depression vulnerability even in healthy patients.

Evidence over the years suggests that abnormal top-down cortical regulation of the limbic systems may also contribute to inefficient emotion regulation in depressed patients. In an early study, Anand and colleagues found that while regions in the affective network showed increased activation, functional connectivity between the ACC and limbic regions was decreased both at rest and during exposure to different stimuli (neutral, positive, and negative pictures) in depressed subjects. This finding may reflect an ineffective regulatory effect of the ACC on the hyperactivation of the limbic system in the patients.[77] Additionally, reduced functional connectivity between amygdala and the PFC was found in depressed subjects both at rest and in response to fearful faces.[78,79] In a resting-state study of mood regulation in refractory and nonrefractory major depression, Lui et al[80] found decreased functional connectivity in bilateral prefrontal-limbic-thalamic areas in both patient groups. Recently, Song et al[81] also reported reduced resting-state frontal-subcortical connection. These findings appear to further support a poor top-down emotional regulation view of depression.

Studies of directed functional and effective connectivity have further confirmed a diminished top-down cortical control of the limbic systems in depressed patients. Using structural equation modeling, Carballedo et al[82] found lower bilateral effective connectivity from the amygdala to OFC in major depression. A recent study compared activity and effective connectivity in postpartum healthy and depressed mothers, when subjects responded to negative emotional faces.[83] Using Granger causality mapping, the authors studied the top-down regulation of the amygdala by the dorsomedial prefrontal cortex. They found a significant effective connection from the left dorsomedial prefrontal cortex to the left amygdala in healthy controls, but this connection was absent in depressed subjects.[83] In a separate study using PPI analysis, Erk and colleagues observed reduced amygdala-DLPFC connectivity in depressed patients during active emotion regulation.[84] However, a GCM study showed that only MDD subjects with a history of early life trauma (ELT) presented reduced mPFC-amygdala connectivity. In non-ELT exposed patients, mPFC inhibition of the amygdala was intact.[85]

4 | BRAIN CONNECTIVITY AND TREATMENT OF DEPRESSION

In addition to providing a better understanding of the neural substrates of depression, brain connectivity analyses have also helped with the treatment of the disease. fMRI studies have reported partially restored brain connectivity in keeping with improvement in depressive symptoms in the patients after treatment. Notably, pretreatment brain connectivity patterns were shown to be able to predict the outcomes of antidepressant treatment. Responders and nonresponders were characterized by distinct connectivity patterns. Interestingly, although brain stimulation techniques adopted in the treatment of depression targeted a single brain region, the therapeutic effects seem to be mediated by the connections from the target to distributed regions or brain networks. Brain connectivity studies thus allow the identification of the optimal stimulation sites (Figure 3).

4.1 | Normalization of aberrant brain connectivity after antidepressant treatment

An important question of interest to researchers and psychiatrists is whether normalization of aberrant brain connectivity would accompany improvement in depressive symptoms after antidepressant treatment. Studies of depression have reported restored connectivity of the AN,[19,86] RN,[87,88] DMN,[19,89-94] and CCN[95] in the patients following antidepressant treatment. A variety of treatments have targeted the AN and RN in depression. Connectivity of the subcallosal cingulate cortex with limbic regions was reduced after electroconvulsive therapy (ECT) treatment.[86] Even administration of a single dose of ketamine (0.5 mg kg^{-1}) resulted in increased neural responses and connectivity of the right caudate during positive emotion perception in patients with treatment-resistant major depressive disorder.[88] In addition, enhancement of dopaminergic transmission in the reward network through amisulpride potentiated diminished corticostriatal connectivity,[96] while treatment-induced increases in network connectivity were associated with gains in positive affect in depressed patients.[94] Abnormal connectivity of the DMN has also been modulated by antidepressants and transcutaneous vagus nerve stimulation (tVNS).[43,91] Given the central role of the CCN in the neurobiology of depression, its response to antidepressant treatments has been studied frequently, revealing increased post-treatment ACC connectivity.[97,98]

4.2 | Prediction of treatment outcomes

The outcomes of antidepressant treatment vary largely among patients, thereby yielding responders, and nonresponders. Brain connectivity patterns have been shown to be able to predict treatment outcomes with quite high sensitivity and specificity.[99] Baseline degree centrality of the posterior default mode network was associated with changes in depression severity after 2 weeks of medication.[100] Pretreatment connectivity of the OFC, insula, and RN has been shown to predict response to psychotherapy.[101,102] Compared with responders, nonresponders of dorsomedial prefrontal repetitive transcranial magnetic stimulation (rTMS) were characterized by more severe pretreatment anhedonia symptoms and lower connectivity of the RN.[103] Higher baseline sgACC connectivity was associated with greater TMS-induced clinical improvement.[92,104] Furthermore, two resting-state networks centered in the dorsomedial prefrontal cortex and ACC have been found to predict the outcome of ECT in

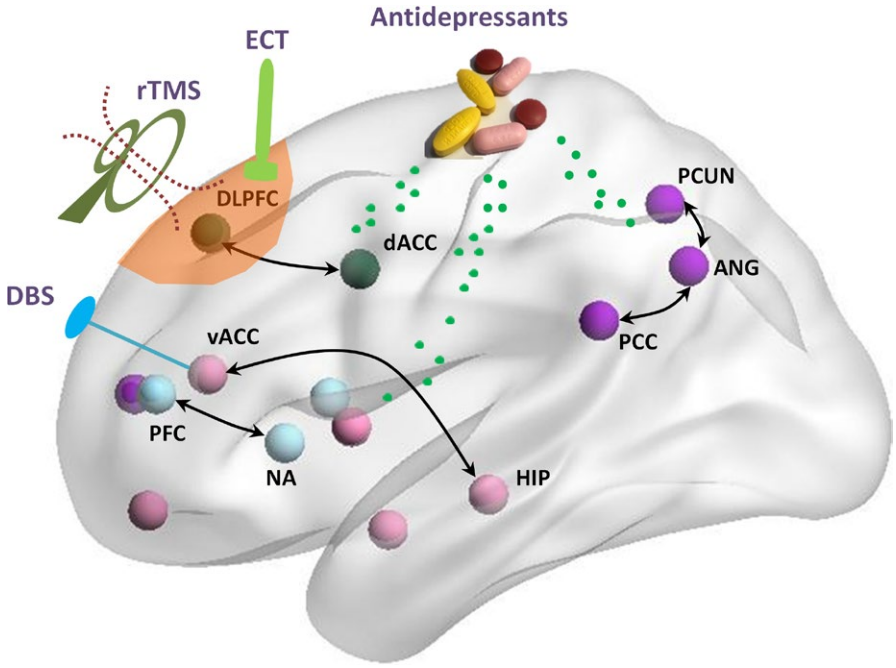

FIGURE 3 Brain effects of antidepressant treatment. A large part of aberrant connections reported in the patients have been shown to be normalized after treatment with antidepressants, psychotherapy, repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and electroconvulsive therapy (ECT). This figure was prepared with the BrainNet Viewer[132]

treatment-resistant patients.[99] In addition, low pretreatment CCN functional connectivity was associated with low remission rate and residual symptoms when patients with late-life depression were treated with escitalopram.[73] Notably, it has been shown recently that resting-state functional connectivity of the subcallosal cingulate cortex with left anterior ventrolateral prefrontal cortex/insula, the dorsal midbrain, and the left ventromedial prefrontal cortex may be capable of guiding treatment choice. Specifically, positive summed connectivity scores for these three regions were associated with remission to CBT, while negative summed connectivity was associated with better treatment outcomes to medication. These findings are of particular importance in the identification of the most effective treatment option that an individual patient is likely to benefit from.

4.3 | Identification of optimal stimulation sites

Brain stimulation techniques such as deep brain stimulation(DBS) and TMS aim to normalize aberrant brain activity in depressed subjects by applying electrical or magnetic stimulation to specific regions. Such therapy alternatives have been shown to be effective in treatment-resistant depression.[105] DBS initially targeted the sgACC to restore hyperactivity of this region observed in the patients, while the first applications of rTMS targeted the DLPFC which demonstrated hypoactivity.[106] However, the clinical efficacy of these traditional protocols still needs to be improved as the response and remission rates are relatively low. Attempts thus have been made to apply rTMS over targets beyond the DLPFC. New advances in neuroimaging studies of depression, MRI-guided rTMS, as well as the introduction of coils with the capacity to stimulate deep structures, have helped improve the identification of optimal stimulation sites. rTMS targeting other core regions whose connectivity has been shown to be disrupted in depression such as the DMPFC,[103,107-109] OFC,[110,111] ACC,[112] has demonstrated apparent therapeutic effectiveness. Although commonly applied to single brain regions, the effects of DBS and TMS are mediated via distributed networks. Notably, the efficacy of the rTMS was associated with the connectivity profile of the targets.[103,104,113] Responders and nonresponders to DMPFC-rTMS had distinct connectivity patterns of the reward network,[103] while DLPFC-rTMS targets that demonstrated stronger anti-correlation with subgenual cingulate cortex were found to be more effective than others.[113] Neuroimaging studies thus not only provide important insights into our understanding of the pathophysiology of depression, but also facilitate the identification of the optimal stimulation sites for the treatment of the disease.

5 | FUTURE STEPS

We review recent studies of functional and effective connectivity in depression. The findings above present an emerging picture of four aberrant networks in depression; namely, abnormal connectivity *within* the AN, RN, DMN, and CCN. However, the interactions *between* different networks may be disrupted as well.[24,47,114,115] Recent meta-analysis studies have revealed increased functional connectivity of the AN (subgenual prefrontal cortex)[115] and the CCN[114,115] with the DMN in MDD. In fact, Sheline et al[16] found a bilateral region in the dorsomedial prefrontal cortex, which they termed the dorsal nexus, consistently

showing increased functional connectivity with the AN, DMN, and CCN in depression. Later, Perrin et al[95] reported reduced connectivity of the dorsal nexus and an improvement in symptoms in depressed patients following treatment with ECT. There is further evidence showing that TMS targeting the DLPFC (a component of the CCN) modulated functional connectivity of the DMN.[92] These findings suggest that depression may not only be associated with abnormal interactions between different brain regions within the same neural circuit, but also abnormal interactions between distributed brain networks. Future studies should aim to integrate these core networks and their contributions toward developing an extended model of depression for improved diagnosis, treatment, and prevention of the disorder.

Recent studies confirmed a structural basis for the altered functional integration seen in depression. Studies using dMRI have demonstrated disrupted white matter integrity and/or structural connectivity in the patients.[116-120] In addition, topological organization of white matter networks was also impaired in the patients.[121,122] Future studies may need to further elucidate how changes in structural changes may relate to functional dysconnectivity in widely distributed networks. Furthermore, the pathophysiology of dysfunctional integration or disconnection in depression may rest on a failure to contextualize interregional coupling; for example, aberrant neuromodulation of synaptic efficacy may be an important etiological factor. One important candidate for this sort of pathophysiology is the neuromodulatory effect of neurotransmitters such as serotonin. Indeed, the imaging literature—using positron emission tomography and radio-ligand binding—points to an abnormality of 5HT neurotransmission, at the level of transporter availability, (5HT1-A) receptor binding, *etc*.[123,124] Furthermore, secondary or complementary changes in metabotropic glutamate receptor function may be intimately involved (or respond) to the synaptic pathophysiology that underlies functional disconnections. This is suggested by imaging studies that show, for example, reduced glutamate receptor 5 (mGluR5) density in major depression and response to antidepressant treatment.[125,126]

It is worth emphasizing that although the interactions among different brain regions have been demonstrated to fluctuate over time,[127-130] the majority of functional and effective connectivity studies on depression have treated the brain as a stationary system and calculated the averaged functional or effective connectivity over the whole session which generally last for 5-10 minutes. Investigating the dynamics of functional interactions among distributed systems may be critically important to concisely delineate the neural mechanisms of the diseases. In a recent study on patients with schizophrenia, the authors reported that transient states of dysconnectivity could only be captured by dynamic connectivity analyses, but not traditional static functional network connectivity analyses.[131] Future studies on depression utilizing dynamic functional or even effective connectivity analyses may provide a better understanding of the etiology of depression.

6 | CONCLUSION

In conclusion, we have reviewed an overwhelming amount of evidence based upon studies of functional and effective connectivity that implicate key modes or intrinsic brain networks in depression. The functional anatomy of these modes fits comfortably with the psychopathology of depression; namely, depressive rumination, a failure of emotion regulation, and difficulties with top-down or executive control. The fact that the implicit functional disconnection shows systematic changes with therapeutic interventions lends further support to the notion that depression is linked to a functional disintegration or disconnection within and between intrinsic brain networks.

ACKNOWLEDGMENTS

We acknowledge the support of the National Natural Science Foundation of China (81301199, 61420106001, 81630032, 81230035), National Key Technologies R & D Program of China (2015BAI13B00, 2015BAI13B01), National Clinical Research Center on Mental Disorders(2015BAI13B02), NLM Family Foundation and Wellcome Trust Principal Research Fellowship (Ref: 088130/Z/09/Z).

DISCLOSURES

This manuscript has not been published nor is it being considered for publication elsewhere. The authors report no biomedical financial interests or potential conflict of interests.

ORCID

Bao-Juan Li http://orcid.org/0000-0002-2916-9948

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How to cite this article: Li B-J, Friston K, Mody M, Wang H-N, Lu H-B, Hu D-W. A brain network model for depression: From symptom understanding to disease intervention. *CNS Neurosci Ther*. 2018;24:1004–1019. https://doi.org/10.1111/cns.12998