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Functional connectomics in depression: insights into therapies

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Abstract

Depression is a common mental disorder characterized by heterogeneous cognitive and behavioral symptoms. The emerging research paradigm of functional connectomics has provided a quantitative theoretical framework and analytic tools for parsing variations in the organization and function of brain networks in depression. In this review, we first discuss recent progress in depression-associated functional connectome variations. We then discuss treatment-specific brain network outcomes in depression and propose a hypothetical model highlighting the advantages and uniqueness of each treatment in relation to the modulation of specific brain network connectivity and symptoms of depression. Finally, we look to the future promise of combining multiple treatment types in clinical practice, using multisite datasets and multimodal neuroimaging approaches, and identifying biological depression subtypes.

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Keywords

depression; antidepressant treatments; resting-state networks; functional magnetic resonance imaging; connectome; therapy-specific network connectivity

Depression and therapies: a brain network perspective

Depression is a prevalent and disabling psychiatric disorder characterized by persistently depressed mood as well as a host of other heterogeneous symptoms, such as loss of pleasure or interest, feelings of guilt and worthlessness, changes in appetite and weight, tiredness and lack of energy, sleep disturbances, and impairments in cognitive function such as attention and memory [1]. In addition, depression is the leading cause of persistent impairment in well-being and quality of life and is associated with significant morbidity and mortality [2].

A variety of treatments are available in clinical practice, such as pharmacotherapy [3], psychotherapy [4], neuromodulation [5], and sleep deprivation [6]. Typically, depressed patients are treated with pharmacotherapy using various antidepressant medications or different types of psychotherapy, such as the most frequently used cognitive behavioral therapy (CBT). However, approximately 30% of depressed patients do not respond to pharmacotherapy or psychotherapy [7]. To improve the **treatment response** (see Glossary) and **clinical remission** rates, alternative treatment options are used for patients with **treatment-resistant depression** (TRD [8]) when the full course of pharmacotherapy or psychotherapy is completed without sufficient improvement. Specifically, neuromodulation approaches, such as transcranial magnetic stimulation (TMS) [9], electroconvulsive therapy (ECT) [10], and deep brain stimulation (DBS) [11,12], have been used to improve depression symptoms by modulating neuronal activity in the brain.

Critically, when combined with imaging, treatments can help uncover the causal circuit-based mechanisms of symptoms improvement [13]. Approaches that elicit fast-acting antidepressant effects such as ketamine and sleep deprivation are especially appealing, as they offer experimentally tractable opportunities to investigate how fast brain changes could induce rapid remission from depression [6,14]. However, these interventions are not yet optimal due to low response/remission rates and high relapse rates [3,4,6,9,11,15], and there is an urgent need to identify the neurobiological mechanisms of depression and effective therapies, as this holds promise for the development of novel interventions and the identification of novel personalized treatment targets.

Understanding the functional connectivity and topological organization of the human brain, commonly referred to as the functional connectome, is crucial for comprehending normal brain functioning [16] and the neurobiological mechanisms of brain disorders [17–20]. Depression, in particular, is increasingly being recognized as a brain network disorder [21–24]. Consequently, there is a growing tendency to conceptualize antidepressant treatments as network therapies that improve depressive symptoms by modulating the functional connectivity of multiple brain subnetworks (for review, see [13,25–27]).

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In this article, we first briefly describe the key concepts and organization of human functional brain networks. In the next two sections, we review the existing empirical data on functional brain network abnormalities and related depressive symptoms in untreated depressed individuals. We then discuss treatment-specific functional network changes in depression. In particular, we highlight the advantages and uniqueness of each treatment in relation to the modulation of specific network connectivity and dimensional symptoms of depression. Next, we propose a hypothetical three-dimensional network model that provides a conceptual framework for understanding the relationships between brain network connectivity changes, specific depressive symptoms, and different treatment effects in depression. Finally, we outline the prospects of the combination of multiple treatment types in clinical practice with the use of multisite datasets and multimodal neuroimaging approaches, and of the identification of biological depression subtypes for addressing disease heterogeneity and developing novel symptom-specific and connectome-guided therapeutic targets. For information on how we identified relevant studies, see Supplementary Materials.

Human functional brain networks

The human brain is a complex network (i.e., **connectome**) consisting of subnetworks and hubs (highly connected brain regions) [16,18,28]. In this review, we focus on functional brain network studies identified using functional magnetic resonance imaging (fMRI) data. Resting-state fMRI (rs-fMRI) studies have identified multiple subnetworks, also called resting-state networks (RSNs; see Box 1 and Figure 1), including the default mode network (DMN), frontoparietal network (FPN), salience network (SAN, also termed as cingulo-opercular network (CON) [29] or ventral attention network (VAN) [30]), limbic network (LIM), dorsal attention network (DAN), somatomotor network (SMN), and visual network (VIS). Each of these RSNs plays an important role in a specific cognitive and/or behavioral domain [31], and their architectures are crucial for maintaining brain function. Importantly, these RSNs are linked by hubs, such as the precuneus, angular gyrus, and ventromedial prefrontal cortex (vmPFC) in the DMN [32] and posterior middle frontal gyrus (pMFG) in the FPN [33]. These hubs facilitate efficient communication and information integration from multiple RSNs [34]. Functional network connectivity estimated from resting-state or task-related fMRI data has shown better behavioral prediction performance than anatomical and diffusion MRI (dMRI) measures, regardless of regression model or behavioral measure [35]. This highlights the significance of investigating functional network abnormalities in the context of depression.

Human functional brain network abnormalities in untreated depression

Many fMRI studies have reported abnormal functional network connectivity in multiple RSNs, including the DMN, FPN, SAN, and LIM, in individuals with unipolar or bipolar depressive disorder compared with controls. These RSNs are involved in a variety of cognitive functioning (Figure 1), such as self-referential thinking (e.g., DMN) [36], executive control (e.g., FPN) [20], detection and integration of emotionally significant internal and external stimuli (e.g., SAN) [37], and emotion and memory processing (e.g., LIM) [38,39]. In particular, depressed individuals have shown hypoconnectivity

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(reduced FC) within the FPN [40,41] and SAN [42,43]. However, a few studies have reported hyperconnectivity (increased FC) in the FPN [44] and SAN [40] in depressed individuals compared with controls. Depressed individuals have also shown hyperconnectivity in the DMN [40,45– 47] and LIM [48]. However, a few studies have reported hypoconnectivity [49] or mixed results [44,50] of the DMN. Some studies have also observed hyperconnectivity within the VIS [40], and hypoconnectivity within the DAN [40,42], SAN [40], and SMN [42] in depression, although these findings are less frequently reported than those for the DMN, FPN, SAN, and LIM.

Inconsistent results are often attributed to genetic, environmental, and clinical heterogeneity of the samples and to variability in analytic methods. The use of multisite data [51–53] could help produce converging and generalizable findings by improving statistical power. Until we are able to identify a unified analytic framework, reliable findings are likely to be generated when tested with different approaches (e.g., brain atlases [51,54], connectivity [51,55], and network [56] metrics, preprocessing methods [57], etc.).

Regarding between-network connectivity, depressed individuals have shown hypoconnectivity between the LIM and some other RSNs, such as the FPN [58,59], DMN [41,60], and SAN [61], hypoconnectivity between the DMN and FPN [58], and hypoconnectivity between the FPN and SAN [43,44]. A few studies have also reported hyperconnectivity between the DMN and FPN [40–42], hyper-[40,46] or hypoconnectivity [42] between the DMN and SAN, and hyper- [40] or hypoconnectivity [41,42] between the FPN and DAN.

Recent research of **connectomics** using graph-theoretical tools has also revealed disrupted **topological organization** of brain networks in depression [23], including disturbed global integrity (quantified by clustering coefficient [62], shortest path length [62–64] and global efficiency [63,64]), modular structure [65], and regional nodal connectivity (characterized by nodal degree [64], betweenness centrality [63,64,66], and local efficiency [63,64]).

Overall, depression has been associated with altered topological organization and functional connectivity of RSNs primarily in the DMN, FPN, SAN, and LIM.

Symptom-specific functional brain network abnormalities in untreated depression

Depressed patients often have heterogeneous symptoms as described above. As specific depressive symptoms might differ in the underlying neurobiology, symptom-specific connectome studies are a promising tool to identify biomarkers [67]. Recent studies have reported a set of symptom-specific functional network abnormalities in depression [68]. Specifically, hyper- [50,69–72] or hypoconnectivity [73] within the DMN was associated with increased rumination. Hyperconnectivity within the DMN was also associated with increased pessimism [74]. Several studies found that patients with higher levels of depressive mood and anxiety showed hypoconnectivity within the SAN [e.g., ventral striatum (VS)-caudate/midcingulate] [75] and between the FPN [e.g., dorsolateral prefrontal cortex (dlPFC)] and SAN [e.g., anterior insula (AI)] [76]. Depressed patients with greater

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anhedonia showed hyperconnectivity within the SAN (e.g., VS-caudate/midcingulate) [75], DMN [e.g., vmPFCdorsomedial prefrontal cortex (dmPFC)], VIS [77], and between the DMN (e.g., vmPFC) and right FPN (e.g., right dlPFC), as well as hypoconnectivity between the FPN [e.g., MFG and dorsal anterior cingulate cortex (dACC)] and SAN (e.g., striatum) [78,79], between the DMN (e.g., vmPFC) and LIM (e.g., ventral tegmental area/striatum), and between the DMN (e.g., vmPFC) and left FPN (e.g., left dlPFC) [80]. In addition, some studies found that patients with higher levels of somatic symptom severity showed lower neural activity in the SAN (e.g., dorsal mid-insula deactivation) [81] and hypoconnectivity between the FPN [e.g., orbitofrontal cortex (OFC)] and SAN (e.g., AI) [82]. Moreover, greater neuroticism in depressed patients was associated with higher within-network connectivity in the SAN, FPN, and SMN, as well as between-network connectivity of SAN-FPN, SAN-SMN, and DMN-LIM [83]. Suicidality was associated with higher connectivity between the FPN [e.g., middle/superior frontal gyrus (MFG/SFG)] and SAN (e.g., VS) [75]. Low flexibility in FPN may be involved in anxiety syndrome while hypoflexibility in DMN may be indicative of hysteresis [84]. In addition, abnormalities in network connectivity have also been found to be associated with depression severity [64,75], illness duration [42,63], number and length of episodes [43,52], and traumatic childhood experiences [40,85].

Taken together, different depressive symptoms were related to the connectivity of different RSNs, such as rumination in relation to DMN connectivity, depressive mood in relation to FPN-involved connectivity, anxiety in relation to SAN- and FPN-involved connectivity, and anhedonia in relation to SAN-, DMN-, VIS-, and FPN-involved connectivity.

Therapy-specific functional brain network changes in depression

As summarized above, depression is associated with impaired functional connectivity in multiple brain networks related to different depression symptoms. Although the therapeutic implications of these findings remain unclear, one possible implication could be that antidepressant interventions improve depressive symptoms by selectively modulating pathological connectivity patterns. Such an explanation has gained crucial support from recent neuroimaging studies (see key studies listed in Table 1; for a complete list, see Table S1 in the Supplementary Materials). In the following sections, we will first discuss treatment-induced connectivity changes and then targeted interventions for depression.

Treatment-induced connectivity changes

Antidepressant medications.—Antidepressants (e.g., SSRIs, SNRIs, and ketamine; Box 2) improve the performance of depressive individuals through modulating FC primarily within and between the FPN, DMN, SAN, and LIM networks (Table 1). Multiple fMRI studies, both during active tasks and in a resting state, have consistently indicated that antidepressants can aid in the restoration of emotional regulation and promote a positive mindset by reducing self-referential thinking. Of note, medication-induced reduction of LIM connectivity (e.g., amygdala, hippocampus, medial thalamus, and nucleus accumbens) [48] and increase of connectivity between FPN/SAN and LIM (e.g., between PFC/ACC and amygdala, hippocampus, medial thalamus, and pallidostriatum) [48,59,60,86–90] might

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reflect antidepressants' role in the suppression of bottom-up emotional hyperarousal and the normalization of abnormal top-down cortical control over subcortical emotional processes in depressed patients.

Several event-related and resting-state fMRI studies have also reported medication-elicited FC increases in frontostriatal reward circuitry (e.g., between ventrolateral prefrontal cortex/ACC and caudate/putamen) [43,91,92], which indicates that the increased connectivity between the FPN and SAN, which leads to the restoration of reward processing, is a crucial factor that contributes to the clinical improvement seen with antidepressant medications. Antidepressants have also been found to modulate the heightened DMN connectivity in depression, and this could be interpreted as a restoration of the capacity to appropriately regulate self-referential activities [48,93,94]. The effects of antidepressants were also associated with FC changes of other RSNs (e.g., DAN, SMN, VIS, and cerebellum-SAN) [43,95–97] or baseline functional connectome characteristics (e.g., connectome gradient, connectome fingerprint, functional connectivity strength) [53,83,98]. For instance, a recent connectome study [99] found reduced DMN connectivity and increased connectivity between the DMN and FPN and between the DMN and SAN one day after applying psilocybin therapy.

Psychotherapy.—As the most frequently used psychotherapy, CBT may be used to improve specific symptoms by modulating brain networks regarding emotional attention control (e.g., the VAN/SAN) and cognitive control (e.g., the FPN) [100]. A longitudinal rs-fMRI study [101] reported symptom-specific connectivity changes in the SAN following 12 weeks of CBT in patients with MDD and posttraumatic stress disorder (PTSD). Specifically, this study found that after 12 weeks of CBT treatment, improvement of depressive symptoms, but not anxious arousal symptoms, was associated with decreased within- and between-network connectivity in the SAN among both MDD and PTSD patients. A task-based CBT-fMRI study [102] confirmed the symptom-specific transdiagnostic brain-symptom association—abnormal task-induced (emotional conflict task) brain activities in the FPN regions (e.g., dlPFC) were related to improved depressive symptoms in both MDD and PTSD after CBT. These findings of common symptom-specific transdiagnostic network changes supports the use of the NIMH **Research Domain Criteria** (RDoC; [103]) for classifying mental disorders based on behavioral dimensions and neurobiological measures.

The efficacy of psychotherapy has also been shown to associate with pre-treatment connectivity between the LIM and FPN/DMN. In an rs-fMRI study [104] of MDD individuals treated with either CBT or antidepressant medication (escitalopram or duloxetine), the summed pre-treatment FC between the subcallosal cingulate cortex (SCC, a component of the LIM) and left ventrolateral prefrontal cortex (vlPFC)/AI, vmPFC, and dorsal midbrain were positively connected in CBT remitters and negative in CBT failures, whereas the inverse was true for antidepressant medication remitters and failures. Moreover, the correlations between the summed FC and percent change in depression severity across all MDD individuals were significant for both treatments, though the strength of the negative correlation was stronger among CBT-treated individuals than the strength of the positive correlation among medication-treated individuals. Findings from this study suggest that abnormal LIM-FPN/DMN connectivity related to emotion dysregulation in MDD

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individuals might be an important predictor of outcomes to differing forms of antidepressant treatment, with higher FC prior to treatment predicting better response to CBT but poorer response to pharmacotherapy.

Sleep deprivation.—Sleep deprivation (SD; [105]) is an effective and rapid antidepressant treatment, which offers immediate relief from depression in 40%−60% of depressed individuals with a single night of total or partial SD [6,106] (Box 3). SD has not been widely used in clinical settings, partially because symptom improvement due to SD is usually short-lived (depressive symptoms relapse after recovery sleep) [106]. A few studies focusing on healthy individuals have shown the effects of SD on brain network connectivity changes [105,107,108] and neurocognitive deficits for example episodic memory deficits due to one night of total SD (TSD) [107]. However, neuroimaging studies of SD in depression are still rare, and it remains unclear how SD could improve depression symptoms by modulating brain network connectivity.

The dorsal nexus (DN), first identified by Sheline et al. [109], is a region in bilateral dorsal medial prefrontal cortex with increased connectivity to DMN, FPN, and affective network (e.g., LIM) in MDD, since implicated in adolescents at risk for depression [110] and in the mechanism of action of ketamine [111]. An rs-fMRI study [112] of partial SD in healthy participants found increased FC of the DN with dlPFC areas and reduced FC of the posterior cingulate cortex (PCC) with ACC. It was indicated that this shift from affective to cognitive network contributions to the DMN could be beneficial in depressed individuals who suffer from excessive ACC and/or impaired dlPFC function. These findings suggest DN-dlPFC connectivity change as a potential explanation of the rapid antidepressant treatment response to SD.

A recent study used TSD as a probe along with rs-fMRI to examine associations between mood changes and changes of the amygdala- and DN-involved connectivity after one night of TSD in both patients with MDD and healthy individuals [113]. This study found that TSD enhanced both amygdala-ACC and DN-dlPFC connectivity in healthy individuals. Amygdala-ACC connectivity increased significantly after TSD in depressed patients with mood improvement but not in depressed patients without mood improvement. Moreover, the enhanced amygdala-ACC connectivity was associated with antidepressant effects of TSD in depressed patients and better mood in healthy individuals. These findings support the key role of the amygdala-ACC circuit in mood regulation in both depressed and healthy populations and suggest that rapid antidepressant treatment may target the enhancement of amygdala-ACC connectivity.

Electroconvulsive therapy.—ECT might alleviate depressive symptoms through modulating FC primarily between the FPN and differing components of the DMN. Several studies have suggested increased FPN-posterior DMN connectivity following ECT being a potential biomarker of recovery from a depressive episode. In particular, two rs-fMRI studies [58,114] reported ECT-elicited FC increases between FPN (e.g., vlPFC, anterolateral PFC, MFG) and posterior DMN (e.g., PCC) at both network and nodal levels, and their associations with depression improvement in MDD patients compared to controls [114]. In line with these findings, an rs-fMRI study in late-life TRD showed normalized

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hypoconnectivity between posterior DMN and FPN (e.g., left dlPFC) after ECT [115], with greater FC increases in ECT remitters but not non-remitters.

There is also evidence that ECT decreased FC between the FPN (e.g., dlPFC) and anterior DMN (e.g., medial frontal cortex and ACC) in depressed patients from an event-related [116] and a resting-state [96] fMRI study, with FC decreases accompanied by significant symptom reductions. Findings from these studies suggest that FC between the FPN and different subnetworks of the DMN might contribute to diverse treatment effects of ECT.

Targeting intervention

Transcranial magnetic stimulation.—TMS is a noninvasive neuromodulation technique that uses magnetic fields to modulate neuronal activity in a specific brain area (Box 4). However, rTMS can effectively relieve symptoms of many but not all (30%−40%) depressed patients, possibly because of the heterogeneity of individual symptoms and brain network organization. For example, there is converging evidence [117–119] that the most effective TMS target is located at the left dlPFC, which shows strong anti-correlation with the subgenual anterior cingulate cortex (sgACC). However, the exact location and connectivity pattern of the left dlPFC varies across individuals, resulting in variability in treatment response. Therefore, identifying personalized rTMS targets may play a key role in optimally treating depressed patients (for review, see [13,120]). Indeed, two fMRI-TMS studies [121,122] have reported consistent association between the proximity to personalized targets estimated by individualized functional connectivity and clinical response to rTMS treatment in MDD patients. Of note, this association disappeared when group-average rTMS targets were used instead, indicating that personalized rTMS targets are perhaps more useful than group-average targets in predicting clinical outcomes. Of note, previous studies [123–126] reported that reliable individual-level functional network connectivity estimated by single-echo fMRI may require a large amount of data collection (e.g., 5 hours of rs-fMRI data), which is challenging for clinical studies. A recent study [127] developed a novel personalized TMS targeting approach by leveraging individualized fMRI-based functional connectome and cortical folding patterns to identify optimized TMS coil placement. This study showed the feasibility of the clinical application of personalized TMS targeting by using 30 minutes of multi-echo fMRI data for each patient [127].

Personalized rTMS could be a promising approach for treating specific depression symptoms by targeting specific brain networks [128–130] (for review, see [25,26]). For example, one study [129] found that dysphoric symptoms, such as sadness, anhedonia, and suicidal thoughts, responded best to stimulation of the circuit involving anterolateral dlPFC sites with anticorrelated FC to the sgACC, while anxiety and somatic symptoms, such as insomnia, decreased libido, and irritability, responded best to stimulation of a different circuit involving FC of posterior dlPFC sites with mPFC. Another study [131] developed a novel approach to identify personalized, symptom-specific TMS targets. Specifically, this study combined each individual’s whole brain resting-state functional connectivity, depression symptom scores, and electric-field modelling to predict symptom changes in anxious misery patients [132]. A generalized research protocol [133] for conducting electric field-optimized, fMRI-based network connectivity-guided, and subject-specific

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TMS targeting has been proposed. This line of research highlighted the importance of identifying symptom-specific brain networks, which might yield new targets for different symptoms, patient subgroups, or treatment personalization [25]. Although brain network-based personalized rTMS is promising, its clinical efficacy needs to be validated by randomized clinical trials.

Of note, many brain network studies [25] have shown that rTMS may not only stimulate the targeted region (e.g., dlPFC), but also a network (e.g., FPN) of regions functionally connected to the target. In addition, single-pulse TMS studies [134,135] have also demonstrated target engagement with networks. These findings shift the focus of rTMS studies from single brain regions to large-scale brain networks for improving spatial TMS targeting for depression.

Targeting dlPFC, findings from rs-fMRI studies converged on a common decrease of dlPFC-sgACC connectivity (e.g., DMN-FPN) relating to therapeutic efficacy of TMS [117,136,137]. Targeting dmPFC, better treatment outcomes were associated with increased FC between dmPFC and thalamic/striatal emotion-related regions (e.g., DMN-LIM) [138,139]. Baseline hyper- [80,137,138,140] or hypoconnectivity [118,119,121,122] between sgACC and multiple areas of the FPN was predictive of greater clinical improvements after TMS. These findings suggest that the action of TMS to the dlPFC might relate to remote suppression of neural activity in the sgACC, whereas TMS to the dmPFC might relate to improved executive control over emotional functions.

Deep brain stimulation.—DBS might improve depressive patients' clinical pathology through modulating FC within and between the FPN, DAN, DMN, and LIM [141]. In support, a recent multimodal study (rs-fMRI combined with structural MRI and/or head CT) leveraging 14 independent datasets [142] found that DBS and TMS stimulation sites that modulate depression were connected to a brain circuit involving the FPN and DAN while anticorrelated with the DMN and LIM, which may represent a refined neurostimulation target for depression.

In a recent rs-fMRI study [143], DBS at the SCC site suppressed activity in corticolimbic regions in patients with MDD, bipolar disorder, or anorexia nervosa. Moreover, SCC-DBS modulated corticolimbic FC through strengthening FC of the three seed regions [e.g., dACC, PCC, and precuneus] with each other, FC of dACC with rostral ACC, mPFC, and frontal pole, FC of PCC with IFG, motor cortical areas, and subcortical structures, and FC of precuneus with insular-opercular cortex, temporal areas, and inferior parietal lobule (IPL). SCC-DBS was also associated with decreased FC between right and left dACC and between right dACC and motor cortical areas. Another rs-fMRI study [144] from the same research group reported increased habenula (a region in the LIM) connectivity with several prefrontal and corticolimbic regions (e.g., mPFC, dlPFC, ACC, PCC) following SCC-DBS in a sub-cohort of patients. Together, SCC-DBS appears to regulate depressive mood by increasing FC between the LIM and DMN/FPN/SAN and between the SAN and DMN, while decreasing FC within the SAN and between the SAN and SMN.

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Besides fMRI, functional connectomics constructed from electrophysiology data [17], in particular intracranial EEG (iEEG), have been used to identify DBS targets. One recent study [145] implemented a novel biomarker-driven closed-loop DBS therapy in a female, who was not responsive to different types of treatment, such as antidepressant medications, ECT, and TMS. Specifically, the authors stimulated and measured neural activity from ten iEEG electrodes implanted in the OFC, amygdala, hippocampus, ventral capsule (VC)/VS, and sgACC [12]. They identified several state-dependent symptom-specific DBS targets and built a directed connectome by estimating effective connectivity between neural signals recorded from the brain areas mentioned above. The right VC/VS in this directed connectome had the highest weighted outdegree and therefore was identified as the DBS target. As a result, when stimulating the VC/VS site, there was a strong evoked response in the amygdala [e.g., increased VC/VS-amygdala connectivity]. The authors used DTI data to identify structural connectivity between the amygdala and VC/VS, providing the evidence that the effective connectivity between the two brain areas was supported by their underlying structural backbone (i.e., axonal fiber tracts; please also see another study [146]). Moreover, decreased amygdala gamma power was related to depression symptom improvement, which could be modulated by the VC/VS stimulation. Therefore, the identified VC/VS-amygdala circuit might serve as a promising personalized symptom-specific biomarker, which was translated into a closed-loop therapy in this study. Findings of this study highlight the importance of integrating multimodal neuroimaging techniques (i.e., dMRI and iEEG) in accurately developing network-guided, symptom-specific personalized DBS targeting.

A hypothetical three-dimensional network-symptom-therapy model

Inspired by the triple network model by Menon [20], we now propose a three-dimensional network model offering a conceptual framework for understanding the relationships between specific depression symptoms and connectivity changes in functional subnetworks (or RSNs), as well as the effects of different therapies (Figure 2). Briefly, Menon's triple network model of psychopathology posits that abnormal functional organization of the SAN, FPN, and DMN and their dynamic cross-network interactions underlie a wide range of psychopathologies, including major depression. Thus, the triple network model is essentially a two-dimensional model, relating brain network changes in three RSNs (network dimension) to multiple psychopathologies (cognitive dysfunction dimension). In this review, we focus on MDD and expand the triple network model by adding a therapy dimension, highlighting the common or distinct effects of different therapies on symptom-specific brain network changes. In addition, as the field evolves, besides the three brain subnetworks (SAN, FPN and DMN) included in the triple network model, recent studies have found additional brain subnetworks as described above, such as the DAN, LIM, and sensory networks (SMN and VIS), that demonstrate abnormal network connectivity in patients with MDD compared with controls. Therefore, we broaden the network dimension from three networks to seven networks.

The main objective of our hypothetical network model is to provide a theoretical framework for hypothesis testing that relates functional connectome changes with specific symptoms and therapies in major depression, which might ultimately facilitate the development of symptom-specific, network-guided treatment targets. For example, studies have found that

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abnormal rumination-related DMN hyperconnectivity could be reduced by antidepressants [68,72,93,94] and TMS [137] (Figure 2). However, patient with recurrent depression showed abnormal DMN hypoconnectivity after using antidepressants [49], suggesting that further decreasing DMN connectivity to abnormal levels might re-induce depressive symptoms. Future studies could use network control tools together with antidepressants or TMS to optimally control the DMN connectivity and therefore maintain the benefits of treatments [147,148]. In the same spirit, other treatments, such as psychotherapy, SD, ECT and DBS, could be used to modulate specific cognitive-related RSNs (Table 1) and improve corresponding depression symptom subtypes, such as depressed mood, anhedonia, anxiety, and somatic symptoms (Figure 2). It should be noted that while we have utilized the existing data to reinforce our model, we acknowledge that certain suggested associations are in the form of hypotheses, rather than established facts. Of course, this framework would need to be validated through empirical research, not only in human studies, but also in animal models, to ensure that it accurately explains the pathophysiology of depression and provides a basis for developing effective treatments.

Concluding remarks and future perspectives

This review has taken a network perspective toward understanding the mechanisms of depression and antidepressant effects to facilitate the development of network-guided personalized targets. Using modern neuroimaging tools and connectome models, depression has been conceptualized as a network disorder with abnormal hypoconnectivity and hyperconnectivity within and between multiple RSNs. Antidepressant treatments modulate specific connectivity among these RSNs that lead to clinical improvement in specific dimensions of depression symptoms. Encouragingly, the modulated network connectivity appears to track with clinical improvement following treatment. Therefore, these RSNs might be convergent substrates for both depression and antidepressant effects, supporting a growing belief that network-level effects might be important in understanding depression pathophysiology and therapeutic mechanisms [142,149,150] and highlights the therapeutic potential of targeted brain network modulation.

Importantly, different therapies tend to modulate symptom-related connectivity changes of distinct RSNs (Figure 1), suggesting different brain-to-behavior effects of these therapies. For example, pharmacotherapy in general appears to modulate FC in distributed brain networks. In contrast, TMS and DBS tend to modulate FC in more specific RSNs. One explanation may come from the different neurobiological mechanisms of different therapies (see Boxes 2–4). For example, neurotransmitter receptors are spread across different brain networks and are thought to respond to pharmacotherapy and others, whereas focal brain stimulation therapies like rTMS and DBS by necessity target a specific region of a brain network. Of note, the effects of rTMS and DBS are not restricted to the stimulated region but will propagate to specific downstream parts of the network. However, due to the lack of studies directly comparing the effects of different therapies (e.g., pharmacotherapy vs. rTMS) to functional brain network changes, we could not exclude the possibility that the different effects of different therapies to network changes might be due to heterogeneity of the studies, such as genetic, environmental, and clinical heterogeneity of the individuals. Nonetheless, we argue that reliable symptom-specific, network-guided targets are likely to

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be identified in individuals with more homogenous genotypes and phenotypes than have hitherto been analyzed. Therefore, to control for the issue of heterogeneity, homogeneous sampling approaches could be considered in future comparable studies [151].

The findings regarding therapy-specific changes of brain subnetworks and related symptoms support the speculation that patients with multiple depression symptoms may benefit from a combination of multiple symptom-specific treatments by simultaneously modulating connectivity in multiple RSNs. A growing literature has shown the efficacy of combining multiple treatments in sustaining clinical gains. For example, augmentation of citalopram with methylphenidate led to higher remission rates compared to either drug alone [152,153]. A combination of treatment types (e.g., antidepressants and psychotherapy) improved remission rates and reduced relapse and recurrence rates of depression [154,155]. SD in patients taking antidepressants is associated with lower rates of relapse [106]. Neuroimaging and connectome techniques could help identify combined treatment plans with symptom-specific and network-guided targeting for depression, eventually facilitating personalized treatment(s) for each individual patient.

Most brain–phenotype modelling studies have assumed that a single brain–phenotype relationship would generalize across all individuals, but models do not work equally well in all participants, especially in participants who defy sample stereotypes [156]. Recent studies [157,158] have uncovered limitations in generalizing population-specific models to other socio-demographic groups. Moreover, individual functional network topology differences [123,126,159,160] have been frequently reported and likely also contribute to difficulty matching networks across studies [161]. Also, there are inconsistent overlaps between what is measured by “depression” scales across studies that may add additional noise [162]. In addition, the results’ inconsistency across studies might be explained by the different sources of variation captured by individual-level and group-level analyses. In particular, individual pathology may get lost in aggregated statistical estimates in group level analysis. For example, one study [163] found that conclusions drawn from aggregated data may be inaccurate, as the variance in individuals is up to four times larger than in group. Therefore, the sample-by-sample group differences in the discussed studies could be real but are weighted by the brain/symptom state of the most abnormal patients in the group at that timepoint. Such failures in group-to-individual generalization have been noted as a particular challenge in research on humans [164]. Future studies focused on developing individualized targets will be promising to overcome the limitations of group-level analysis.

There are likely to be real effects in the neuroimaging literature but there are certainly false positives that cannot be refuted until the use of better-characterized samples (e.g., deep phenotyping [165]) is combined with the use of broader-scale statistical approaches that are less focused on localizing single brain areas [166]. In addition, the test-retest reliability of resting-state connectivity measurements can be improved using multi-echo fMRI [167], which will facilitate longitudinal precision mapping of functional brain networks in clinical populations. Furthermore, recent studies have developed several computational models, such as normative modelling [168] and functional random forest [169], for overcoming the comorbidity and heterogeneity problems [170]. Finally, as noted above, MDD pathology is a multifactorial process that depends on the interactions between clinical and cognitive

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dysfunction, connectome changes, and genetics. Multivariate analytical approaches [171], such as canonical correlation analysis, partial least squares, and structural equation modeling, could be promising tools for integrating the multidimensional data and studying their relationships, although they might require large sample size for ensuring sufficient power and reliability [172,173].

To increase statistical power and generalizability of results, future studies should leverage large-scale multisite datasets, such as the UK Biobank [174], the Enhancing Neuroimaging Genetics Through Meta-Analysis (ENIGMA) consortium [175], and the Adolescent Brain Cognitive Development (ABCD) study [176]. Meanwhile, statistical harmonization methods should be used to minimize confounding effects of site-related differences due to different scanner manufacturers, imaging acquisition protocols, and subject recruitment criteria. For example, the site effects in FC measurements could be successfully removed using the widely used *ComBat* harmonization approach [51,52] and other methods [177,178].

Moving forward, given the heterogeneity of depression, it is unlikely that a single neuroimaging marker can capture all the important features of depression. Multimodal neuroimaging techniques, such as structural, functional, and dMRI, provide complementary but also redundant information in the estimation of individualized connectivity maps. The recently developed multilayer biophysical network models [179,180] can be used to integrate functional and structural network connectivity patterns and study interactions between different network configurations, which may provide more reliable markers to inform diagnostics and identify individualized treatment targets. Moreover, to address the clinical heterogeneity of depression, biological depression subtypes could be identified by using symptom- and treatment-specific large-scale brain network connectivity patterns [27,80,181]. However, current depression biotypes are not yet optimally reproducible. MDD has been classified into different subtypes based on the presence or absence of specific symptoms, age of onset, severity, and other clinical features. It should be noted that reliable biotypes of depression can only be identified if we are able to find distinct biological (e.g., brain network features) and clinical features in major depression. However, due to the biological and clinical heterogeneity of the disease [169,182], it remains a challenge to identify reliable biotypes of depression. In addition, genotypes and environmental factors may also play important roles in the identification of biotypes of major depression [183]. Therefore, we argue that reliable biotypes of major depression are likely to be identified in individuals with more homogenous genotypes and phenotypes than have hitherto been analyzed. Future neuroimaging studies should leverage knowledge of connectomics [16,184], high-quality [185] and large sample-sized neuroimaging data [172,186], and data dimensionality reduction methods [187], as well as proper statistical or machine-learning techniques [188,189] to identify replicable and interpretable connectome-based depression biotypes, which can ultimately be applied in clinical settings [190].

To conclude, emerging evidence suggests that depressive symptoms are likely to be related to abnormal functional network dysconnectivity of multiple brain subnetworks and different therapies might improve specific symptoms through modulating functional connectivity of specific brain subnetworks. The proposed hypothetical three-dimensional network model offers a conceptual framework to synthesize a wide range of studies that examine how

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the effects of various therapies are related to brain connectivity changes across multiple functional subnetworks, as well as specific symptoms of depression. We hope this review and hypothetical network model could facilitate the development of personalized symptom-specific and connectome-guided therapeutic targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

Clinical remission
a HAMD score ≤7 or a MADRS score ≤10 for two consecutive weeks

Connectome
a comprehensive map of neural connections in the brain

Connectomics
the production and study of connectomes. It may range in scale from a detailed map of the full set of neurons and synapses within part or all the nervous system of an organism to a macro scale description of the functional and structural connectivity between all cortical areas and subcortical structures

Research Domain Criteria (RDoC)
an initiative being developed to refine psychiatric nosology. It is a dimensional approach to nosology that characterizes individuals across continuous traits

Topology
the quantification of features of a graph in the context of space defined by the graph itself, without respect to any physical embedding

Treatment response
a >50% reduction in score of the Hamilton Rating Scale for Depression (HAMD) or Montgomery Asberg Depression Rating Scale (MADRS) between the initial and follow-up assessments

Treatment-resistant depression
non-responsiveness to at least two adequate trials with different classes of antidepressants with adequate dosage, duration (a minimum of 6 weeks for each trial), and compliance

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Box 1.

Resting-state networks

The DMN includes mPFC, PCC, precuneus, IPL, and middle temporal lobe [36]. This task-negative network plays an important role in self-referential processes such as evaluating the salience of internal and external cues, remembering the past and planning the future.

The FPN [29], also termed as executive control network [191], is comprised of the dlPFC, OFC, MFG, SFG, rostral ACC, and other brain regions that are active during goal-directed tasks [31]. This task-positive network is implicated in executive control, cognitive reappraisal, and top-down regulation of attentional and emotional processing. It has been suggested that the FPN may contain two separate subnetworks: one connected to the DMN and involved in the regulation of introspective processes; another connected to the DAN and involved in the regulation of visuospatial perceptual attention [192].

There is an anatomical overlap between the limbic network (LIM) identified by fMRI studies and the limbic system defined by the anatomical boundary between the cerebral hemispheres and the brainstem. Specifically, subcortical regions, such as the amygdala, hippocampus, striatum, thalamus, and insula, are central components of the LIM and are involved in memory, reward, and emotional and behavioral processes. [193].

The SAN, consisting of dACC, AI and striatum, is involved in detecting and orienting attention toward salient stimuli, and switching between internal and external thinking [20,37]. In contrast to the FPN, which initiates and adjusts control on a trail-by-trial basis, the SAN provides stable goal-directed control over tasks [194]. The SAN has also been termed as CON [29] or VAN [30]. A recent review study [195] recommended the use of a universal taxonomy to name RSNs, where SAN, CON and VAN were named as ‘midcingulo-insular network’.

There are two sensory orienting attention systems, the VAN (or SAN) and DAN [196]. The VAN is involved in directing attention to stimuli that suddenly appears rather than towards stimuli that are currently the focus of the task at hand. The DAN includes the posterior intraparietal sulcus, frontal eye fields, middle temporal region, ventral premotor cortex, pre- and postcentral gyrus. The DAN is prominently involved in goal-directed and voluntary orienting of visuospatial attention [30].

FMRI and multimodal MRI studies have consistently identified several sensory networks [197,198], such as the SMN, auditory network (AUD) and VIS. The SMN primarily includes the somatosensory (e.g., postcentral gyrus) and motor (e.g., precentral gyrus) regions and extends to the supplementary motor areas. This network plays a major role in the execution of movements of the contralateral side of the body. The AUD is a part of the temporal lobe that processes auditory information. The VIS located in the occipital lobe consists of regions of visual cortex that processes visual information.

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Box 2.

Pharmacotherapy

Pharmacotherapy primarily involves several typical and atypical antidepressants. Typical antidepressants generally include selective serotonin reuptake inhibitors (SSRIs, such as sertraline, fluoxetine, paroxetine, citalopram, and escitalopram), serotonin and norepinephrine reuptake inhibitors (SNRIs, such as venlafaxine, duloxetine, agomelatine, and mirtazapine), tricyclic antidepressants (TCAs), noradrenergic and specific serotonergic antidepressants (NaSSA), and serotonin antagonist and reuptake inhibitors (SARIs). Atypical antidepressants include ketamine, bupropion, amisulpride, among others. Typical antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are usually used as first-line medications for depression [199]. SSRIs exert action by inhibiting the reuptake of serotonin back into the nerve cells that released them, which increases serotonin activity in the brain. Similarly, SNRIs work by blocking the reuptake of serotonin and norepinephrine, thereby increasing the levels of active neurotransmitters. It usually takes at least two to three weeks for SSRIs/SNRIs to achieve symptom relief and three to six months for clinical remission. Among depressed individuals who take SSRIs/SNRIs, approximately 40%−60% of them respond to a single course of treatment, and the remission rate is typically in the range of 30%−49% [3].

Intriguingly, a single subanesthetic dose of ketamine, an ionotropic glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist, produced a rapid antidepressant effect lasting up to 7 days in depression with a response rate of 52.6% and remission rate of 30% [14]. While many antidepressants act on monoamine neurotransmitters (e.g., serotonin, norepinephrine, or dopamine), ketamine triggers the production of glutamate, the most prominent neurotransmitter of the brain. Glutamate receptors are found throughout the brain and spinal cord in neurons and glia.

It is of high interest for future studies to explore if different antidepressants share a common or specific mechanism in modulating brain network changes. For instance, as discussed above, different antidepressants modulate neural transport by increasing or decreasing the levels of specific neurotransmitters in the brain. Of note, recent studies [200] demonstrate that density distributions of receptors across multiple neurotransmitter systems are related to the structural and functional organization of connectomes and disease vulnerability of multiple psychiatric disorders, including major depression. Therefore, it would be interesting for future studies to explore the spatial relationships between functional network connectivity patterns and the receptor densities of specific neurotransmitters targeted by different antidepressants.

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Box 3.

Psychotherapy and sleep deprivation

Several different types of psychotherapies, such as cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT) and problem-solving therapy (PST), are recommended as first-line treatments for depression [4]. As one of the most commonly used psychotherapies, CBT focuses on identifying cognitive distortions that lead to persistent depressive mood and utilizes emotional regulation skills to change the irrational thoughts. IPT is a structured and brief intervention addressing social issues that maintain depression. PST imparts problem solving skills aimed to increase the individual's mastery of the environment and reduce the experience of adversity. As a second-line treatment, behavioral activation therapy for depression (BATD) is developed to define problematic behaviors that maintain depression, thereby ameliorating depressive symptoms (anhedonia symptoms in particular) by promoting rewarding activities and inhibiting avoidance behaviors. Psychotherapies usually require weekly 45- to 90-minite sessions over 10 to 20 weeks. Overall, these psychotherapies have a response rate ranging from 37% to 46%, and a remission rate ranging from 26% to 34% [4].

Sleep Deprivation (SD) has been proven to be a fast-acting (immediate response after a night of sleep loss) and effective treatment for depression with an overall response rate of 45%−50% [6]. SD has not been widely used in clinical practice partly due to its temporary effect on depressive symptoms (e.g., clinical improvement in mood decreases as soon as individuals resume sleeping) [106]. However, the rapidity of onset and offset of clinical improvement is an advantage, as it allows for an ABA study design for investigation of underlying mechanisms of action with greater certainty of causality.

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Box 4.

Neuromodulation: TMS

Transcranial magnetic stimulation (TMS) is a noninvasive technique that uses a rapidly alternating magnetic field to stimulate specific cortical areas of the brain, thereby inducing electrical currents and action potentials in underlying cortical tissue [25]. The biological mechanism of rTMS in treating depression is thought to involve both short-term and long-term changes in synaptic plasticity, which is the ability of neurons to modify their connections in response to experience. In the short-term, rTMS can increase or decrease the excitability of the neurons in the stimulated area, depending on the frequency and intensity of the stimulation. For example, repeated pulses at high frequencies (e.g., 20–50 Hz) are thought to excite cortical activities whereas low-frequency stimulation (e.g., 1 Hz) suppress activity. In the long-term, rTMS is often thought to induce neuroplastic changes in the brain that may be related to the therapeutic effects of the treatment. These changes may include the modulation of neurotransmitter systems (such as dopamine, serotonin, and glutamate), the alteration of synaptic connectivity, and the promotion of neurogenesis (the formation of new neurons). However, the precise mechanisms underlying these effects are still being investigated. TMS changes communication between a cortical stimulation site and any remote target or set of targets, impacting a distributed network of brain regions [13]. Among brain regions that show depression-related abnormalities, the left dlPFC and the sgACC have been most frequently selected as targets of focal brain stimulation [25,117–119]. Other targets include dmPFC [128] and OFC [130], which might affect different neural networks. TMS is typically used for the treatment of medication-resistant depression, and it is usually administered 4 or 5 times weekly for 4 to 6 weeks. The response rate of TMS is typically in the range of 29%−46% and remission rate in the range of 18%−31% [9].

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Box 5.

Neuromodulation: ECT, DBS, and VNS

Electroconvulsive therapy (ECT) is also a noninvasive medical treatment which remains the most effective approach for medication-resistant depression. ECT causes a small amount of electric current to pass through the electrodes to the brain, intentionally triggering a brief seizure that usually lasts less than 60 seconds while the patient is under anesthesia. The ECT stimulus was delivered by electrodes placed either bilaterally or unilaterally at the frontal and/or temporal lobe. ECT is generally administered 2 or 3 times a week over a course of 3 to 4 weeks. The response rate is better for ECT (50%−80%) than for other currently available treatments [10], and the remission rate of ECT generally ranges from 48% to 65% [15].

Deep brain stimulation (DBS) is an invasive neuromodulation technique that employs surgically implanted electrodes into deep neural targets to deliver low-voltage electrical pulses to a specific brain region to modulate brain activity [12]. Several target sites for stimulation have been proposed for the treatment of refractory depression, such as the subcallosal cingulate (SCC), VC/VS, and medial forebrain bundle (MFB). It usually takes 4 to 6 months for the DBS to work. The response and remission rates were 56% (ranging from 43% to 69%) and 35% (ranging from 27% to 44%), respectively [11].

Vagus nerve stimulation (VNS; [201,202]) is also a U.S. Food and Drug Administration (FDA) approved neuromodulation treatment for chronic depression that remains unresponsive to at least two different types of antidepressants. Currently, due to limited available fMRI-based connectome studies conducted in conjunction with VNS, here we provide a brief overview of the biological mechanism of VNS for completeness. Briefly, VNS uses a device to stimulate the vagus nerve (a long nerve that extends from the brainstem through the neck and down into the abdomen) with electrical impulses. The device sends electrical signals to the vagus nerve, which then travels to the brain, where it can affect mood, appetite, and other physiological processes. To our knowledge, there is only one fMRI study [203] reported that transcutaneous VNS could improve depressive symptoms by modulating DMN-involved functional connectivity.

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Outstanding questions

1. How can we develop new brain stimulation techniques and machine learning tools to accurately map symptoms onto brain networks? It remains unclear if different depression symptoms are associated with specific connectivity changes of different brain networks.
2. How do different treatments (i.e., TMS vs. medications) interact and in which way they could collaboratively treat patients with multiple symptoms? What would be a feasible temporal ordering to apply different treatments for patients with heterogeneous symptoms?
3. How can we accurately extract and integrate unique neural information from each neuroimaging modality? Different neuroimaging approaches could provide complementary but also redundant neuronal information.
4. How can we identify replicable and interpretable connectome-based, symptom- and treatment-specific depression biotypes? Current depression biological subtypes identified by neuroimaging-based machine learning models are often not generalizable.
5. Which spatial and temporal scales of the connectome are most valuable in identifying connectome-guided and symptom-specific targeting? Currently, human connectome analysis, structural or functional, are conducted at different spatial and temporal scales, which leads to high variability and low reproducibility of findings.

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Highlights

1. Depressed patients often have cognitive and behavioral deficits, characterized by heterogeneous symptoms, the neurobiological mechanism of which remains unknown.
2. There are different treatment types for depression. However, the response and remission rates remain low, and the neurobiological basis of treatment effects is unclear.
3. Functional connectomics has provided useful tools to characterize depression as a brain network disorder and guide treatment decision-making.
4. Recent work suggests that multi-dimensional depression symptoms are linked with abnormalities of functional connectivity and network organization in different brain networks. Each treatment type tends to improve specific symptoms by modulating specific networks, suggesting the need of combining different treatments.
5. Identifying network-guided, symptom-specific personalized treatment targets is the key for addressing heterogeneity in depression and treatment response.
6. We proposed a hypothetical model offering a theoretical framework for hypothesis testing that relates functional connectome changes with specific symptoms and therapies in major depression.

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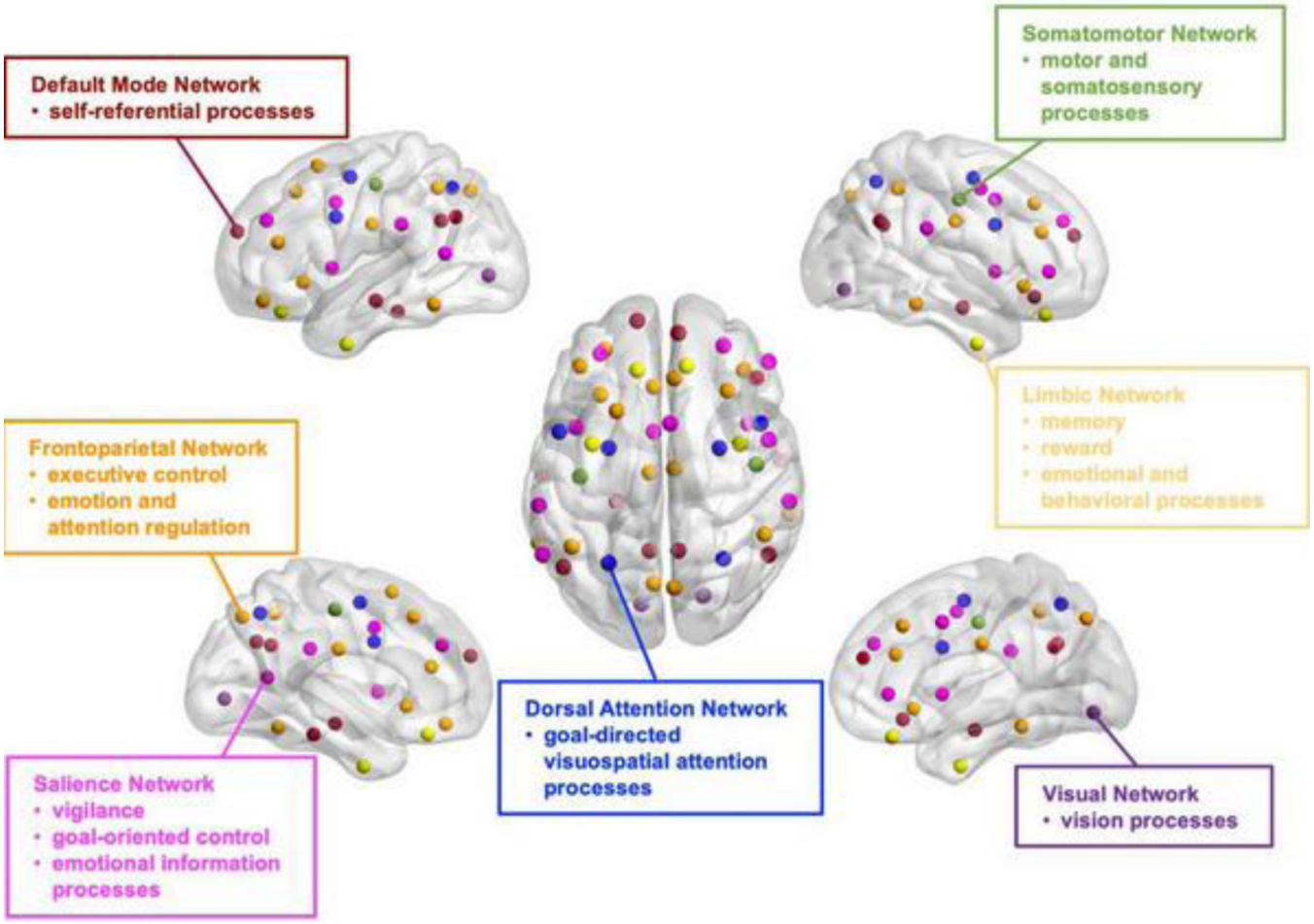

Figure 1. Cognition related resting-state networks (RSNs).

Each RSN has been suggested to play an important role in specific cognitive and/or behavioral domain(s): DMN, self-referential processes; LIM, memory, reward, emotional and behavioral processes; FPN, executive control, emotion and attention regulation; SAN, vigilance, goal-oriented control, and emotional information processes; DAN, goal-directed visuospatial attention processes; SMN, motor and somatosensory processes; VIS, vision processes (for details, see Box 1). The color-coded nodes depicts seven RSNs defined by the Yeo parcellation [208]. RSNs, resting-state networks; DMN, default mode network; LIM, limbic network; FPN, frontoparietal network; SAN, salience network; DAN, dorsal attention network; SMN, somatomotor network; VIS, visual network. The brain mapping for RSNs were plotted by BrainNet Viewer.

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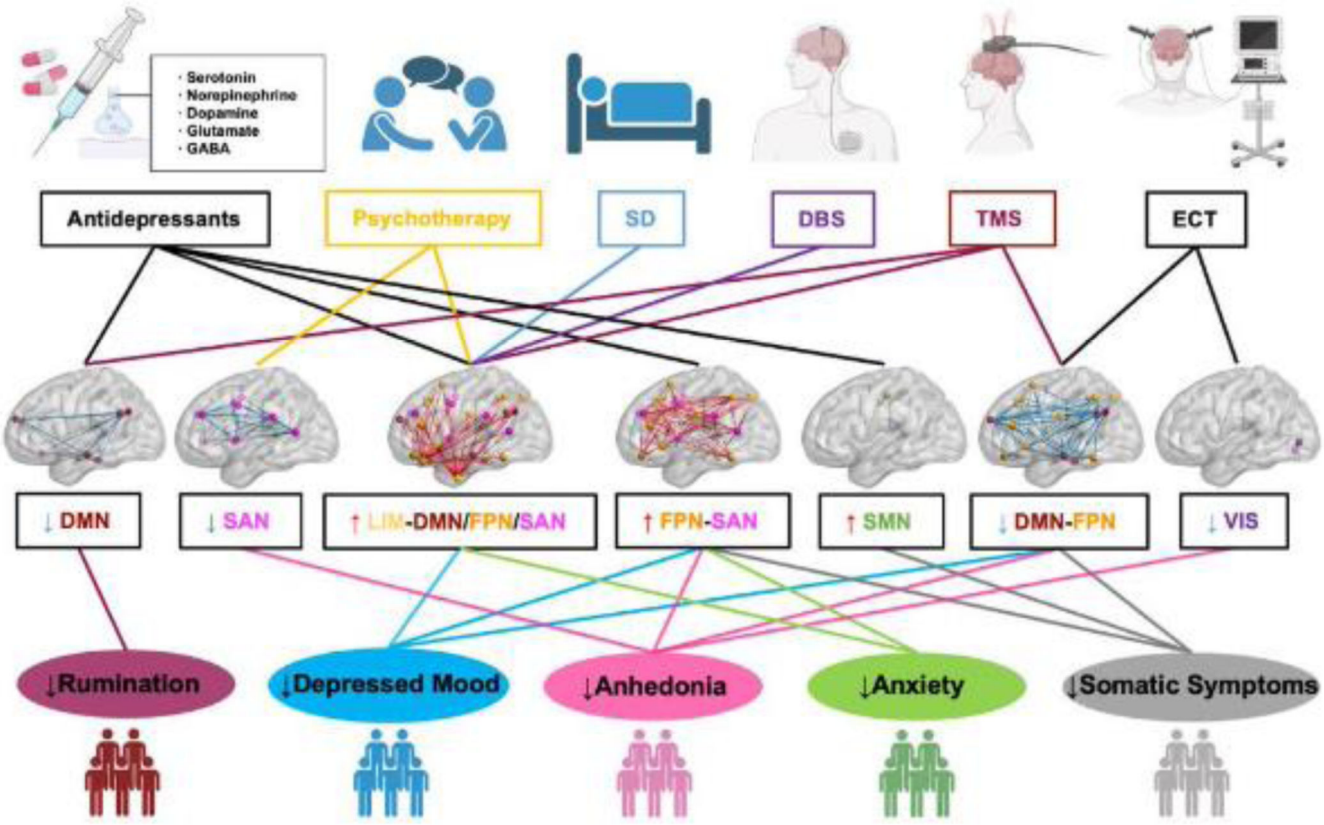

Figure 2. Hypothetical model of symptom-specific, network-guided treatments.

The model was created by a summary of key studies (Table 1) from an emerging literature describing associations between six treatments, brain network abnormalities involving seven RSNs, and five depressive symptoms. Abnormal functional connectivity has been found in multiple RSNs in depressed patients with heterogeneous symptoms. The abnormal connectivity shown in each RSN tend to be associated with its cognitive domain-related symptoms of depression. Of note, different types of treatments are likely to modulate the abnormal connectivity within and/or between common or distinct cognitive-related RSNs, which might improve specific subtypes of depression symptoms, such as rumination, depressed mood, anhedonia, anxiety, somatic symptoms, etc. Specifically, the levels of rumination in depressed patients could be reduced by modulating DMN connectivity using antidepressants and TMS. Antidepressants, TMS and ECT could modulate FPN- and SMN-involved connectivity and reduce the levels of somatic symptoms. All the six treatments could be used to reduce the levels of depressed mood by modulating the connectivity between the FPN and other RSNs, except the two sensory networks, SMN and VIS. Changes of SAN-, FPN-, and VIS-involved connectivity induced by different treatment types (except SD and DBS) are related to the reduction of anhedonia levels. Multiple treatments (except ECT) are used to modulate the FPN- and SAN-involved between network connectivity, which can decrease the levels of anxiety. SD, sleep deprivation; DBS, deep brain stimulation; TMS, transcranial magnetic stimulation; ECT, electroconvulsive therapy. The illustrations of treatments and symptom subtypes were adapted from BioRender.com.

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Table 1.

Treatment-induced network connectivity changes

	Pharmacotherapy	Psychotherapy	Sleep Deprivation	Electroconvulsive Therapy	Transcranial Magnetic Stimulation	Deep Brain Stimulation
DMN	↓ DMN [48,93,94]				↓ DMN [137]	↓ DMN [142]
FPN	↑ FPN-SAN [43,91,92]; ↑ FPN-DMN [99]	↑ FPN [102]		↑ FPN-posterior DMN [58,114,115]; ↓ FPN-anterior DMN [96,116]	↓ FPN-DMN [117,136,137]	↑ FPN [142]
SAN	↓ SAN-cerebellum [95]; ↑ SAN-DMN [99]	↓ SAN [101]				↓ SAN [143]; ↑ SAN-DMN [143]
LIM	↓ LIM [48]; ↑ LIM-FPN/SAN [48,59,60,86–90]	↑ LIM-FPN/DMN [61,104,204–207]	↑ LIM-SAN [113]		↑ LIM-DMN [138,139]	↓ LIM [142]; ↑ LIM-DMN/FPN/SAN [144,145]
DAN						↑ DAN [142]
SMN	↑ SMN [95]; ↓ SMN-FPN/SAN [43]					↓ SMN-SAN [143]
VIS				↑ VIS [96]; ↑ VIS-FPN [96]; ↓ VIS-posterior DMN [96]		