

The Clinical Applicability of Functional Connectivity in Depression: Pathways Toward More Targeted Intervention

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ABSTRACT

Resting-state functional magnetic resonance imaging provides a noninvasive method to rapidly map large-scale brain networks affected in depression and other psychiatric disorders. Dysfunctional connectivity in large-scale brain networks has been consistently implicated in major depressive disorder (MDD). Although advances have been made in identifying neural circuitry implicated in MDD, this information has yet to be translated into improved diagnostic or treatment interventions. In the first section of this review, we discuss dysfunctional connectivity in affective salience, cognitive control, and default mode networks observed in MDD in association with characteristic symptoms of the disorder. In the second section, we address neurostimulation focusing on transcranial magnetic stimulation and evidence that this approach may directly modulate circuit abnormalities. Finally, we discuss possible avenues of future research to develop more precise diagnoses and targeted interventions within the heterogeneous diagnostic category of MDD as well as the methodological limitations to clinical implementation. We conclude by proposing, with cautious optimism, the future incorporation of neuroimaging into clinical practice as a tool to aid in more targeted diagnosis and treatment guided by circuit-level connectivity dysfunction in patients with depression.

Keywords: Affective salience network, Cognitive control network, Default mode network, Functional connectivity, Major depressive disorder, Transcranial magnetic stimulation

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Depression affects up to 20% of people over the course of their lives, making it the leading cause of disability worldwide and the third leading cause of death in adolescents and young adults (1). Despite significant advances in neuroscience over the past several decades, the translational application of research findings into the clinical practice of psychiatry continues to lag behind the rest of medicine. Psychiatrists rely on the classification of symptoms into clusters defined by DSM and lack objective tools, such as neuroimaging scans or serum assays, to assist in the diagnosis, treatment selection, and measurement of treatment response in major depressive disorder (MDD). Although available treatments for depression can be effective, they are based on the ad hoc selection of medication and psychotherapy, and often weeks to months are required to determine efficacy. Just as obtaining a magnetic resonance imaging scan or electroencephalography study is the standard of care for diagnosing dementia or epilepsy, respectively, resting-state functional magnetic resonance imaging (fMRI) has the potential to aid in more precise diagnosis in depression. Psychiatric disorders can be considered as the consequence of disruption or dysrhythmia within interconnected brain circuits that underlie brain functions, including attention, memory, and emotion. As such, a tool optimally suited for understanding circuit dynamics has the potential to bring important insights into understanding and

diagnosing pathophysiology as well as guiding the development of circuit-targeting treatments.

The prospect of applying resting-state fMRI to clinical psychiatry has gained increasing attention in recent years. Resting-state fMRI provides a rapid and noninvasive means of investigating functional connectivity across multiple brain regions (2–4). It detects direct anatomic pathways as well as functional connectivity between regions linked by multisynaptic projections (5,6). This technique is also able to detect short-term and long-term plasticity within networks (7–9) and avoids task-related confounds, such as performance level, ceiling and floor effects, effort, and selection of task strategy (3,10–12). Despite notable strengths, functional neuroimaging is an indirect measure of brain activity. Changes in voxel signal do not solely reflect alterations in neuronal activity, but rather a heterogeneous tissue sample consisting of neurons, glial cells, capillaries, and extracellular matrix. Although sophisticated tools have been developed to minimize spurious correlations in resting-state networks, head movement and other artifacts remain potential confounds when interpreting fMRI data (13). Additional notes of caution addressed by Weinberger and Radulescu (14) include potential alterations in magnetic resonance imaging signal induced by blood perfusion (15), psychiatric medications (16), psychotropic drugs (17), exercise (18), body mass index, and insulin sensitivity (19).

Significant progress has been made with respect to detecting functional connectivity abnormalities associated with characteristic symptoms of depression, including anhedonia, depressed mood (20), deficits in emotion processing (21), cognitive impairment (7,22), negative self-rumination (i.e., feelings of guilt and worthlessness) (23), and neurovegetative symptoms (24). However, these findings have yet to translate into robust diagnostic or treatment biomarkers. The diagnosis of MDD remains a clinical one, based on clinical observation and self-report of depressive symptoms in accordance with DSM criteria. Transitioning resting-state fMRI from a group-based analytic research tool to a clinical biomarker on the single subject level has the potential to provide more precise diagnosis and treatment approaches for patients with depression. Through detecting deficits within neural circuitry that map onto specific symptoms, resting-state fMRI may assist in developing a more accurate subclassification system under the umbrella of “depression”—one that better maps onto the underlying circuit impairment—and thus more targeted therapies. From a treatment perspective, specific symptoms could be targeted by modulating their corresponding connectivity abnormalities.

In the present review, we examine the existing literature on abnormalities within brain networks implicated in the pathophysiology of depression. We summarize their associations with specific symptoms of depression as well as the effects of selective serotonin reuptake inhibitors (SSRIs) and electroconvulsive therapy (ECT) on altering resting-state functional connectivity within these networks. We then discuss circuit-based neuroimaging findings following standard and novel therapeutic interventions, focusing on transcranial magnetic stimulation (TMS) in depression. We conclude by addressing methodological considerations, limitations, and avenues of future research that could aid in the integration of neuroimaging into the clinical practice of psychiatry.

DYSFUNCTIONAL LARGE-SCALE NETWORKS IN DEPRESSION

Functional connectivity studies of patients with MDD have implicated an affective salience network, cognitive control network, and default mode network (DMN). Connectivity differences between cortical and subcortical components within these large-scale neural networks have been associated with characteristic symptoms of depression (25,26). Although we summarize the most robust findings in this section, discrepant findings are prevalent in the literature and likely reflect pathophysiologic heterogeneity. Moreover, the networks described do not operate independently of one another.

Affective Salience Network

When functioning normally, an interconnected mesocortico-limbic network guides motivation and behavior through processing of affective and salient stimuli (27,28). Meta-analyses of both task-based (29,30) and resting-state (31) fMRI paradigms have implicated the amygdala, ventral striatum, dorsal anterior cingulate cortex (dACC), and insula as central hubs within this circuit (24,32,33). In the present review, we refer to this

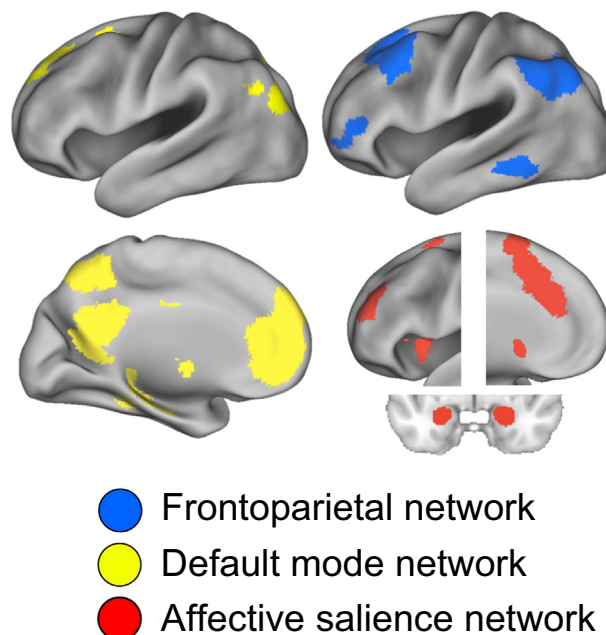


Figure 1. Large-scale neural networks implicated in the pathophysiology of depression. The frontoparietal “task positive” cognitive control network comprises the medial and superior frontal cortex, including the dorsolateral prefrontal cortex, and other brain regions that are active during externally focused attention and goal-oriented task performance. The default mode network consists of brain regions preferentially active in the absence of external stimuli (the so-called resting state). The affective salience network is an interconnected network centered around the amygdala, ventral striatum, insula, and dorsal anterior cingulate cortex that is centrally involved in guiding behavior through processing motivationally salient stimuli.

interconnected large-scale brain network as the affective salience network (Figure 1).

The amygdala is a critical node within this network involved in processing of motivationally salient stimuli (34,35). One of the most robust neuroimaging findings in MDD is abnormally increased connectivity and heightened activation of the amygdala (36,37), although the direction of observed effects has been mixed (33,38). Dysfunctional connectivity between the amygdala, supragenual anterior cingulate cortex (sgACC), and insula and disrupted top-down prefrontal cortical control have been strongly implicated in salience and emotion processing abnormalities found in patients with depression (21,24) and adolescents at risk for MDD (39). Similarly, heightened amygdala and insula activity was found in task-based paradigms when processing negative stimuli (33), which significantly correlated with disease duration and symptom severity (40,41).

Conversely, patients with depression demonstrate attenuated connectivity between the ventral striatum and other regions involved in reward processing, including the dACC, insula, and thalamus (42,43). Reward circuit hypoconnectivity is consistent with underresponsive reward system activation in MDD, supported by a wealth of animal and human neuroimaging data (20,44,45). Functional connectivity of the ventral striatum shows a robust inverse relationship with anhedonia (42) and overall depression severity (43), providing further

support that this network subserves core aspects of MDD, including anhedonia, amotivation, and depressed mood.

The dACC is a prominent cortical node within the affective salience network that serves to assess and integrate emotionally relevant stimuli with regulatory top-down control (46). Reciprocal connections with subcortical components also moderate sympathetic and autonomic effects underlying psychomotor disturbances characteristic of depression (47). Increased activation within the dACC in response to negative stimuli in patients with MDD appears to play a critical role in potentiating negatively biased information processing (33). Regions of this circuit also project to the hypothalamus and autonomic brainstem nuclei, which may contribute to the manifestation of neurovegetative symptoms of depression, including alterations in sleep, decreased energy, and change in appetite (24).

DMN Dysfunction in Depression

The DMN (Figure 1) comprises brain regions that are preferentially active in the absence of external stimuli (the resting state) and become suppressed during experiences that focus one's attention toward the external environment (48,49). Core regions of the DMN include the medial prefrontal cortex (mPFC), posterior cingulate cortex, precuneus, and lateral and inferior parietal cortices (48). The DMN mediates spontaneous, internally generated thought and emotion (3,50,51). Consequently, this network is thought to underlie self-referential processes, such as introspection, formation of beliefs and emotions, and engaging in mental simulations of future events (52).

Abnormalities within the DMN underlie self-ruminative patterns of thought characteristic of MDD (i.e., an exaggerated focus on internal thought at the expense of engaging with the environment) (26,37). An increasing number of studies and several meta-analyses have provided evidence of DMN hyperconnectivity in MDD (53–55). DMN hyperconnectivity strongly correlates with measures of self-rumination (23,56), as well as with disease severity and duration (57). Moreover, hyperconnectivity between the DMN and the sgACC has been proposed to mediate the interaction with the affective salience network via “affective-laden behavioral withdrawal” integrating self-referential DMN-mediated processes with behavioral manifestations of depression (58).

Also, DMN hyperconnectivity likely contributes to impaired concentration, often found in depressed patients and thought to result from attention difficulties (7). Normally, when attention shifts from internally directed mentation to external stimuli, DMN activity is suppressed, and the frontoparietal network (FPN) (Figure 1) is activated (2). The dynamic interaction and functional coupling between these two networks is disrupted in depression (7,26). This disruption could explain the misallocation of attentional resources in depression, with a tendency toward DMN-mediated self-rumination at the expense of allocating attentional resources toward the external world.

Cognitive Control Network Dysfunction

The frontoparietal “task positive” cognitive control network (FPN) (Figure 1) comprises the medial and superior frontal cortex, including the dorsolateral prefrontal cortex (DLPFC),

inferior parietal cortex, and other brain regions that are active during externally focused attention and goal-oriented task performance (2). Deficits in concentration are a defining symptom of MDD (59), and cognitive theories of depression propose that hypoconnectivity of this network results in impaired top-down regulation of aberrant emotional processing, perpetuating a bias toward negative affect and depressed mood (38,60). Widespread connectivity reductions have been detected in frontoparietal regions implicated in executive control and performance monitoring (22,61). In a recent meta-analysis, Kaiser *et al.* (38) found that FPN hypoconnectivity, especially of the DLPFC, was directly associated with goal-directed attention deficits in depression. Decreased connectivity within this network has been found at rest and in response to negative, but not positive, stimuli, implicating this region as contributing to inappropriate cognitive appraisal of negative events (37,44).

Reduced connectivity of lateral prefrontal cortical regions, involved in both cognitive processing and affect regulation, may also contribute to emotion dysregulation and cognitive biases in depression, which have been detected in medication-naïve (62), medicated (63), and treatment-resistant patients with MDD (64). While depression severity correlates with amygdala and sgACC hyperconnectivity, it inversely correlates with lateral orbital prefrontal cortical activity (65). This suggests that cortical regions may have a compensatory or regulatory role with respect to modulation of the affective salience network. In a connectome-wide study of medication-free patients, reduced DLPFC-amygdala connectivity was associated with severity of depressive symptoms (66). Psychotherapy has been found to increase activity within the ventrolateral prefrontal cortex (67).

In summary, resting-state fMRI has provided insight into underlying functional networks implicated in the pathophysiology of depression. Dysfunctional connectivity of the affective salience, cognitive control, and default mode networks appears to underlie characteristic symptoms of depression, including depressed mood, anhedonia, self-rumination, and impaired concentration. Discrepant findings are prevalent in the literature and likely reflect pathophysiologic heterogeneity; this is not surprising given the marked clinical heterogeneity with respect to symptom variation of patients meeting criteria for MDD based on available diagnostic assessments. Resting-state fMRI has helped characterize impairment within specific networks that map onto symptom manifestations of depression. As such, it has the potential for use as a clinical biomarker that both refines diagnostic criteria addressing patient-specific symptoms and guides more targeted treatment interventions for depression.

NEUROSTIMULATION TARGETED MODULATION OF DYSFUNCTIONAL NETWORKS IN DEPRESSION

Effects of Antidepressants and ECT on Functional Connectivity in Depression

Although antidepressants, psychotherapy, and ECT have been available for decades, we are just beginning to shed light on network changes elicited by these treatments. In healthy volunteers, decreased connectivity between the mPFC and

the hippocampus follows SSRI administration (68). In patients with MDD, SSRIs have been shown to reduce DMN hyperactivity (69,70); normalize hypoconnected thalamus-to-dACC connectivity (71); and increase connectivity between the hypothalamus and DLPFC, orbitofrontal cortex, anterior cingulate cortex, insula, putamen, and caudate, while decreasing connectivity between the hypothalamus, frontal gyrus, precuneus, thalamus, and cerebellum (72). In addition, several groups have identified possible biomarkers for predicting treatment outcome of SSRI administration but with inconsistent results. Positive prediction tools for SSRI treatment response include weaker dACC-DLPFC connectivity (73), stronger sgACC anticorrelations, and weaker thalamocortical connectivity (63). To date, however, we lack evidence demonstrating a link between SSRI-driven normalization of abnormal connectivity and improvement in clinical symptoms. There has also been variability regarding whether these changes relate to short-term SSRI administration (single dose or subacute dosing) or acute treatment courses, and studies investigating long-term effects are lacking.

Even fewer studies have evaluated the effect of ECT on brain networks. Studies have demonstrated reduced hippocampal functional connectivity before treatment that increased after treatment (74); increased homotopic connectivity in the superior frontal, middle, and angular gyrus (75); and increased connectivity within the DLPFC and posterior cingulate cortex (76). Some of these neuroimaging findings correlated with clinical improvement (74), whereas others did not (75). In a larger study examining connectivity biomarkers of ECT response, van Waarde *et al.* (77) found a positive correlation between pretreatment connectivity and clinical outcome for networks centered in the dorsal mPFC and anterior cingulate cortex. Overall, these studies suggest that ECT appears to increase functional connectivity in various widespread networks and that response to ECT may be predicted by baseline connectivity. However, the relationship between network localization and clinical response remains unclear.

Modulating Dysfunctional Brain Networks in Depression

Although SSRIs and psychotherapy have been the mainstay therapies for depression, 50% of treated patients fail to achieve remission after 1 year (78). Additionally, ECT, although effective, induces a generalized seizure, requires anesthesia, and can cause retrograde amnesia. In the past decade, deep brain stimulation and TMS have attempted to fill a crucial interventional role in the treatment of depression. Deep brain stimulation involves the implantation of intracranial electrodes that provide high-frequency electrical pulses to modulate the activity of specific brain regions. Although there is no clear consensus regarding the optimal region(s) to stimulate for depression, proposed regions include the subcallosal cingulate gyrus to target mood (79), the ventral capsule/striatum to target perseverative thinking (80), and the medial forebrain bundle to target anhedonia (81). Nonetheless, deep brain stimulation is an invasive procedure, and recent trials have failed to demonstrate clinical benefit (80–83).

TMS is a noninvasive method of targeted network modulation that uses brief time-varying magnetic field pulses to

induce electrical currents on the cortical surface. These currents elicit action potentials, which propagate to downstream brain regions. Hence, TMS is a tool that can probe and modulate neural networks in a targeted fashion. Application of a single pulse (single-pulse TMS) has been used to map the interconnectivity between cortical regions (84), whereas application of pulses in a repetitive manner (repetitive TMS [rTMS]) is thought to elicit plasticity at the stimulation site and downstream regions.

Randomized clinical trials applying 10-Hz rTMS to the left DLPFC for treatment of medication-resistant depression have demonstrated clinical benefit (85–87). However, remission rates for depression treated with rTMS are suboptimal at <50%, which may be due to the inability to accurately localize the DLPFC (88) or the fact that stimulation parameters are not optimized for plasticity induction in particular networks. By developing a mechanistic understanding at the brain circuit level of the effects of rTMS in depression, we can critically evaluate the hypothesis that normalizing dysfunctional network connectivity will alleviate clinical symptoms. As such, TMS may advance treatment of depression, while providing a more thorough and mechanistic understanding of the disorder, including at the individual patient level.

Despite the functionality and popularity of rTMS, few studies have performed neuroimaging scans on patients to test network changes after a single session or daily treatment of >5-Hz left DLPFC rTMS, and no imaging study of clinical rTMS has employed a control intervention arm. Speer *et al.* (89) observed increased regional cerebral blood flow over the left DLPFC, cingulate, amygdala, hippocampus, and thalamus after 2 weeks of daily sessions of 20-Hz left DLPFC rTMS. By contrast, 1-Hz left DLPFC rTMS decreased regional cerebral blood flow over the right DLPFC, left temporal lobe, and amygdala, with no change at the target site. Liston *et al.* (90) reported resting-state fMRI changes following 5 weeks of daily >5-Hz rTMS to the left DLPFC. Their findings showed that rTMS decreased DMN hyperconnectivity and normalized FPN-DMN anticorrelations, but did not alter pretreatment FPN hypoconnectivity. Chen *et al.* (91) directly tested FPN-DMN connectivity and found that single-pulse TMS to the FPN induced negative blood oxygen level-dependent responses (which have been linked to inhibitory processes) in the DMN, suggesting that the FPN negatively regulates the DMN.

Although only a few studies have directly evaluated network changes after rTMS in depression, multiple groups have evaluated possible biomarkers to predict response to therapy. Kimbrell *et al.* (92) conducted a crossover randomized trial by applying 2 weeks of daily left DLPFC rTMS at 1 or 20 Hz followed by 2 weeks of treatment with rTMS at the other frequency. They demonstrated a negative correlation between antidepressant response and the frequency of stimulation. Furthermore, responsiveness was predicted by baseline DLPFC hypometabolism in the 20-Hz rTMS group and hypermetabolism in the 1-Hz rTMS group. Liston *et al.* (90) reported that better clinical outcome was predicted by subgenual-DMN functional connectivity. Consistent with this finding, Salomons *et al.* (93) found that higher baseline sgACC-mPFC and sgACC-DLPFC connectivity and lower corticothalamic, corticostriatal, and corticolimbic connectivity were associated with greater reduction of symptoms. More recently, connectivity

analyses in healthy and depressed subjects showed that these DLPFC sites are also associated with stronger DLPFC-sgACC anticorrelation, although no subject actually received rTMS (94). Multiple biomarkers, including local metabolic activity and within-network as well as between-network connectivity, appear to predict clinical outcome after rTMS. However, as these studies exhibit heterogeneity with respect to the biomarker type and effect, we currently lack a single or set of biomarkers that consistently predicts treatment outcome across studies.

rTMS-Induced Plasticity Within Brain Networks

Behavioral studies after >5-Hz left DLPFC rTMS in healthy subjects have shown variable results, eliciting faster reaction times in some subjects (95) and no effect on behavior in other subjects (96). Although behavioral tasks enhance our understanding of the cognitive changes elicited, brain-derived measures from neuroimaging provide important insight into the neurophysiologic basis of plasticity induction after stimulation. If the “excitatory rTMS” plasticity effect consistently observed in M1 applies to other cortical regions, it should follow that rTMS should modulate both local and downstream connections. Wang *et al.* (97) demonstrated that daily 20-Hz parietal rTMS enhanced memory and increased resting-state fMRI between the parietal cortex (target site) and the functionally connected hippocampus. Halko *et al.* (98) applied 10-Hz rTMS to the lateral and medial cerebellum, which before the stimulation exhibited strong functional connectivity with nodes of the DMN and dorsal attention network, respectively. Stimulation to the lateral cerebellar DMN increased functional connectivity within the DMN, whereas medial cerebellar stimulation did not change functional connectivity within the dorsal attention network. Thus, >5-Hz rTMS appears to elicit functional connectivity changes that outlast the time of stimulation; however, the direction of modulation within the stimulated network is inconsistent. Indeed, >5-Hz rTMS to a node within a network may enhance (97,98), weaken, or provide no change to (98) the within-network connectivity, depending on the network targeted and the frequency of stimulation (99).

Several resting electroencephalography studies have evaluated network changes after DLPFC rTMS (100). Studies applying stimulation to the DLPFC found increased delta (101,102) and theta (101) power local and unilateral to the DLPFC stimulation site, whereas beta and gamma power at the DLPFC decreased bilaterally. These changes typically did not last longer than 10 minutes after rTMS. Continuous theta burst stimulation, a relatively new protocol thought to be more effective than typical >5-Hz rTMS, was applied to the DLPFC in healthy subjects, and changes were observed in the alpha band that persisted for 50 minutes after rTMS (103).

In addition to power modulation, rTMS may alter either the synchronicity (or coherence) between brain regions or aspects of the sleep/wake cycle that relate to the pathophysiology of depression. Jing and Takigawa (104) measured electroencephalography coherence in a group of healthy subjects calculated before and after 10-Hz left DLPFC rTMS. After stimulation, directed but not ordinary coherence increased globally between the stimulation site and other brain regions.

Although consistent results have been observed with rTMS applied to motor cortex in healthy individuals, rTMS applied to the DLPFC and other cortical regions has shown conflicting results. Mixed results regarding behavioral outcomes seem to be provided by rTMS >5 Hz at the DLPFC. There is relatively consistent evidence that rTMS enhances resting-state fMRI functional connectivity between the stimulation site and within network nodes for most networks probed and promising but sparse evidence that rTMS may increase TMS-evoked potentials after stimulation (100).

PATHWAYS TOWARD MORE TARGETED INTERVENTION

Functional connectivity is promising as a means of improving clinical subtyping that more precisely maps onto dysfunction within neural networks. In the present review, we summarized connectivity abnormalities in large-scale networks found in depression as well as the changes evoked by TMS (Figure 2). Obtaining patient-specific functional connectivity maps and using resting-state fMRI to characterize abnormalities in brain networks may provide an image-guided tool for neurostimulation and other targeted interventions. Although TMS has largely targeted cognitive network impairment in depression (through stimulation of the FPN), it has the potential to also modulate networks implicated in the pathophysiology of other characteristic symptoms of depression, such as anhedonia and rumination, by targeting abnormalities in the affective salience network and DMN, respectively.

A primary “limitation” to address within the functional connectivity neuroimaging literature is the heterogeneity of reported findings, which has been considered a limitation in most studies of depression. Given the symptom heterogeneity encompassed within clinical diagnostic criteria of MDD, it not surprising that there are mixed findings with respect to functional connectivity abnormalities reported in this patient population. If we were to capitalize on heterogeneity to identify depression subtypes based on symptom clusters that map onto underlying connectivity differences, we could instead apply this information to develop a more refined diagnostic system and treatment approach.

Integrating neuroimaging biomarkers with vulnerability genes (i.e., genetic and epigenetic determinants) as well as environmental components of risk and resilience endophenotypes will further assist in the development of improved diagnostic and treatment interventions for depression. Depression-related susceptibility genes, such as the risk S allele of the serotonin transporter gene, have shown an association with differences in functional connectivity in affective salience (105) and DMN circuitry (62,106,107). Early life stress has also been found to alter network connectivity, leading to functional alterations in amygdala, insula, and dACC activity during emotion regulation (108) and cognitive processing (109). Up until now, the focus of depression treatment has been on correcting symptoms associated with deficiencies within brain circuits. A critical, and yet to date unexplored, area of investigation is assessing whether prospective strengthening of intact circuitry can augment resilience in at-risk patients and prevent or reduce severity of depression. We are gaining a better understanding of the underlying plasticity

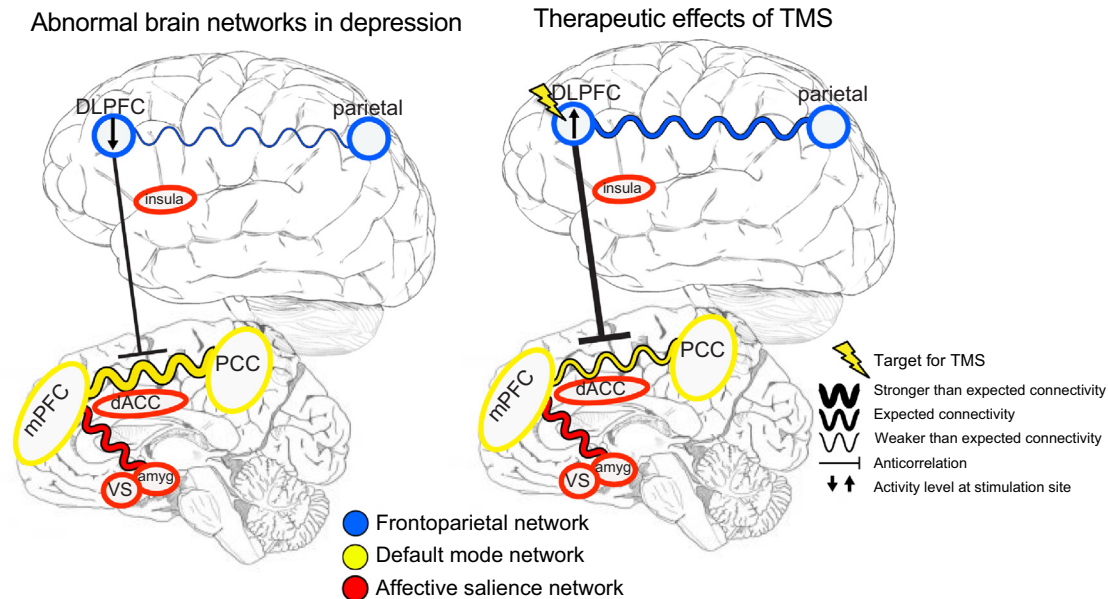


Figure 2. Summary of network connectivity abnormalities in depression and changes following transcranial magnetic stimulation modulation. (Left) Abnormal brain networks observed with resting-state functional magnetic resonance imaging, including amygdala hyperconnectivity within the affective salience network (36,37); hypoconnectivity of reward circuitry, centered around the ventral striatum (43); hypoconnectivity of the frontoparietal network (38); and hyperconnectivity of the default mode network (53). (Right) Effect of targeted neuromodulation on abnormal brain networks. Transcranial magnetic stimulation to the dorsolateral prefrontal cortex increases regional blood flow locally (89) and normalizes a hyperconnected default mode network and hypoconnected frontoparietal network (90). amygd, amygdala; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; TMS, transcranial magnetic stimulation; VS, ventral striatum.

of neural networks and differential genetic expression underlying experience-dependent plasticity (110). A recent study investigating risk and resilience in patients at high familial risk for depression detected significant connectivity differences between regions of the DMN, affective salience network, and cognitive control network in risk and resilient endophenotypes (111). Shifting the focus toward at-risk individuals and strengthening network connectivity underlying resilience through interventions such as mindfulness, psychotherapy, and possibly TMS, instead of targeting pathologic connectivity, may allow for a primary prevention approach to treating depression.

With the relatively recent availability of large-scale functional connectivity imaging data sets and advanced analytic methods, characterization of individual-level circuitry and targeting of neuromodulation may be more feasible than previously thought (112). For example, a method has been recently published for reliable individualized parcellation of cortex based on a template connectivity atlas (113). Similarly, subject-specific patterns of resting connectivity can serve as a “fingerprint” that uniquely identify that individual and predict their cognitive functioning (114). The network that is most variable and underlies both the individualization of network parcellation and the subject-specific fingerprint is the FPN, making this a prime target for personalization of TMS intervention. As resting-state fMRI can detect short-term and long-term plasticity within networks (7–9), it can also be used as a metric to index whether the targeted circuit-level change was achieved. In sum, the study of connectivity and understanding of depression as well as development of

network-modulatory interventions has matured to the point where we can now address the critical challenges facing our field rather than pointing to them as future goals.

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