A Systematic Approach to Neuropsychiatric Intervention: Functional Neuroanatomy Underlying Symptom Domains as Targets for Treatment

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An ever-growing population experiences a wide range of psychopathologies, and there is now more than ever a need for clear differential diagnoses between disorders. Furthering this need is the fact that many psychological, psychiatric, and neurological disorders have overlapping features. Functional neuroimaging has been shown to differentiate not only between the function of different brain structures but also between the roles of these structures in functional networks. The aim of this article is to aid in the goal of parsing out disorders on the basis of specific symptom domains by utilizing the most recent literature on functional networks. Current literature on the role of brain networks in relation to different psychopathological symptom domains is examined and corresponding circuit-based therapies that have been or may be used to treat them are discussed. Research on depression, obsession and compulsions, addiction, anxiety, and psychosis is reviewed. An understanding of networks and their specific dysfunctions opens the possibility of a new form of psychopathological treatment.

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Over the past several decades, many advancements have occurred in the field of clinical neuroscience, particularly in the ability of functional neuroimaging to relate psychopathology to corresponding brain areas. As the field has progressed, however, it has become more evident that simply mapping complex psychological syndromes onto individual brain areas is insufficient. Rather, the future of cognitive neuroscience may lie in the examination of specific symptom domains and modulation of corresponding brain areas in relation to their role in functional networks (1).

Since its inception in 1990, functional magnetic resonance imaging (fMRI) has been used primarily to examine signals from brain regions that show blood oxygen level-dependent changes in response to a given cognitive task (2). As a clinical tool, fMRI is frequently utilized in mapping of language and motor areas prior to resective surgery. However, focus has recently shifted toward examining how multiple brain areas can be functionally connected. The most crucial of these functionally connected brain areas have been termed "networks," and a few of these networks have been determined to be of vital importance to proper neuropsychological functioning. The most commonly discussed networks are the default mode network (DMN), salience network (SN), and central executive network (CEN). These three specific networks have been previously termed the "triple network model," because the dynamic interactions between them make up much of cognitive processing abilities (3).

Currently marketed psychiatric therapies are effective, on average, in approximately half the patients who use them. The arbitrary clustering of various symptoms with different pathophysiological pathways into one illness may be one cause for this low response rate. The transition from one-size-fits-all therapy to targeted, circuit-based therapy may improve the benefit-risk ratio for patients by improving the mechanistic understanding of disease and matching the correct therapies to the right individuals (4). It could also aid with mental illness differential diagnosis and reclassification of heterogeneous subgroups within the same disorder (e.g., depression syndrome into agitated versus apathetic versus anhedonic symptoms or the autism spectrum into Research Domain Criteria [RDoC] symptom-based domains). Many existing mental diseases may thus be regarded as misclassified rather than as heterogeneous in this sense (5). This was the impetus for the National Institute of Mental Health's RDoC Initiative: to parse syndromes into levels (genetic, systems) of specificity (genes, symptoms), allowing for more precise characterization of the underpinnings that lead to and constitute mental illness. For the purposes of this article, we address the system (neural network) and psychiatric symptom domains.

This understanding of networks and their specific dysfunctions opens the possibility of a new form of psychopathological treatment. In this review, we examine the current literature on the role of brain networks in relation to different psychopathological symptom domains and discuss the corresponding circuit-based therapies that have been or may be used to treat them.

SYNDROMES

Depression

Because of the overlap in clinical features, distinguishing between primary symptom domains of "depression" can be challenging. Use of fMRI may offer information on the neurobiology and changes in neurocircuitry involved in the mediation of mood and motivational deficits among elderly persons (6).

Apathy. One explanation for the differences in therapeutic responses between depression and apathy is that depression occurs when paralimbic neurotransmitter function is disrupted, resulting in excessive negative emotion, whereas apathy occurs when the cortex is functionally disconnected from relevant paralimbic input (7). Accordingly, apathy is defined as diminished motivation, without decreased levels of consciousness or emotional distress.

A clinical example that demonstrates the need for treatment of apathy as a symptom independent of "depression" is in patients with neurodegenerative diseases—e.g., Alzheimer's disease (AD), Parkinson's disease (PD), and frontotemporal dementia. Depression is a commonly diagnosed co-occurring disorder in patients diagnosed as having neurodegenerative diseases. However, in studies comparing the two groups, patients with AD exhibited high apathy and low depression ratings, whereas patients with major depressive disorder had high depression and low apathy scores (8). Because apathy was once considered part of depression and has been teased apart as a distinct symptom, particularly in the context of neurodegenerative disease, this study suggests that it may be a distinguishable clinical construct that necessitates a different treatment approach in some patients. In AD patients specifically, it has been shown that apathy and other behavioral issues have a greater influence on everyday function than do the cognitive symptoms, particularly early in the disease process (9).

The need for nonpharmacological treatment of apathy stems from studies that have demonstrated the inefficacy of typical selective serotonin reuptake inhibitor (SSRI) antidepressants in the treatment of apathetic symptoms—and in some cases, these agents worsen such symptoms (10). Low dopamine production has been hypothesized as one cause of apathy, and some success has been observed using amphetamine methylphenidate as a treatment modality; however, this treatment is contraindicated by cardiovascular dysfunction (11) and frequently insufficient to counteract the apathy that is common in PD.

Inability to redirect attentional processes to goal direction has been shown in PD patients, suggesting that connectivity between the executive and emotional networks may be a key factor in initiating motivated behavior (12). Neuroimaging studies have indicated that in patients with apathy, functional connectivity of frontostriatal circuits was diminished, particularly between medial frontal brain areas and linked striatal areas (13). Furthermore, atrophy and functional hypoactivity of the lateral prefrontal cortex have been associated with higher reported apathy scores (14). The dorsolateral prefrontal cortex (dlPFC), in particular, has been shown to be involved with the initiation of motivated behavior, an action that is reported to be of higher difficulty for patients struggling with apathetic affect (15).

Previous studies have demonstrated that frontal-striatal stimulation could restore motivated behavior in schizophrenia patients by normalizing dopamine synthesis in emotion regulation networks (16). In light of this finding, a study of the treatment of apathy investigated the effects of repetitive transcranial magnetic stimulation (rTMS) on the left dlPFC in AD patients. Results showed significant score improvement on scales measuring apathy, activities of daily living, and mental state (17). This suggests that the dlPFC may be a potential stimulation target for the treatment of apathy. Additionally, the network topology of the anterior cingulate cortex (ACC) has been shown to successfully differentiate apathy from depression (characterized more broadly), such that apathy represents a downregulation in salience-related processing by the ACC network, whereas depression represents an increased processing of negative-valence, emotionally salient information (18).

Anhedonia. Anhedonia, or the lack of responsiveness to pleasurable stimuli, has emerged as one of the most promising endophenotypes of depression and is a primary symptom and trait marker of major depressive disorder (19). Anhedonia has, in part, been conceptualized as a lack of emotional reactivity to anticipated reward. This framework has been applied to several neuroimaging studies, associating multiple brain regions with this process.

The ventral striatum—specifically, the nucleus accumbens (NAc)—has been implicated in assigning stimuli with incentive-related properties. Importantly, an fMRI study conducted in 2008 demonstrated that the ventral striatum was more active during reward anticipation than in reward consumption (20). Although the ventral striatum has been implicated in reward anticipation, the orbitofrontal cortex (OFC) has been implicated in stimulus reinforcement and updating stimulus-outcome representations (21). These findings imply that anhedonic phenotypes may be caused by a variety of distinct psychological processes and brain abnormalities. Thus the OFC is a frequent "add-on" treatment target for anhedonic depression treatment-focused rTMS.

Perhaps because of these varying anhedonic phenotypes, traditional SSRI antidepressants have been shown to be unreliable—and, in some cases, ineffective—for depressed patients with anhedonia (22). For this reason, nonpharmacological interventions may be considered.

Deep brain stimulation (DBS) is the stereotaxic placement of a neurostimulator, as well as electrodes, into a specific brain area to electrically stimulate that region (23). In 2004, some success in alleviating depression was shown in a preliminary study after electrodes were implanted in the

white matter tracts near the NAc (24). In light of this finding, a later double-blind study in which electrodes were implanted directly into the NAc was able to show immediate and lasting alleviation of anhedonic/reward-dysfunction symptoms (25). DBS to the NAc may thus be a strategy for refractory severe depression with anhedonic symptoms, according to these preliminary data. As such, research investigating the clinical utility of other neuromodulation or intervention targeting the NAc, or ventral striatum more broadly, may be warranted.

Obsessions and Compulsions

Obsessions are characterized by recurrent intrusive thoughts, images, or impulses that lead to an increase in anxiety or distress, and compulsions are characterized by repetitive behaviors that downregulate the anxiety and distress caused by the obsessions. However, heterogeneity issues have arisen as a result of the current absence of a clear and objective basis for these symptom domains. Traditionally, the presence of these symptoms, when sufficient to cause functional impairment, results in a diagnosis of obsessive-compulsive disorder (OCD). OCD is a mental disorder with a prevalence rate of 2%−3%. It is described as the presence of time-consuming, stressful, or disabling obsessions or compulsions or both (26).

Considering that approximately 40% of OCD patients do not respond to traditional pharmacological treatments (27), multiple methods of neuromodulation have been examined in the search for a nonpharmacological intervention for OCD. DBS has been used in multiple experiments to some notable success. One study implanting electrodes in the ventral capsule and ventral striatum showed significantly decreased symptoms of OCD, anxiety, and depression scores after 36 months, in eight of ten patients treated (28). Another DBS study in which electrodes were implanted in the same brain areas showed similar improvement, including in obsessions and compulsions, after 12 months in four of six patients treated (29). However, DBS is at the same time very cumbersome, expensive, and risky and can at times be insufficiently effective.

Noninvasive neuromodulation techniques have also been explored for the treatment of OCD. A recent study used high-frequency, transcranial alternating current stimulation targeting the OFC and found that it was able to modulate reward-guided behavior and that application over a 5-day period reduced obsessive-compulsive behavior for 3 months (30). Similar effects have also been seen in the use of rTMS treatment, targeted at either the OFC or the supplementary motor area. A review of 12 rTMS studies observed similar efficacy across all experiments, and findings suggested that further improvements could be made by way of neuronavigational targeting (31).

Obsession. To treat OCD on a symptom level, the distinct physiology underlying both obsessions and compulsions must be understood. Obsessions have proven more difficult to characterize than compulsions, which can be easily linked to RDoC dimensions (32). It is possible that a deeper physiological understanding of obsessions will explain their relationship to existing RDoC categories. A recent study based on the RDoC that examined 96 patients diagnosed as having OCD found that obsession specifically was associated with the supplementary motor area, superior parietal lobule, and precentral gyrus (5). Obsession in relation to the triple network model was also examined, and Lee et al. (5) found that higher obsession severity was associated with decreased internetwork connectivity between the dorsal attention network (DAN) and the CEN, as well as decreased connectivity between the DAN and ventral attention network.

Neurostimulation treatments directly targeting the symptom domain of obsession are limited, but the above studies indicate potential networks that could be explored in future studies.

Compulsion. Compulsions are defined by the *DSM-5* as stereotyped actions that are carried out according to strict rules in order to downregulate the distress caused by obsessions or to lessen or avoid otherwise unpleasant consequences. Although commonly ascribed to OCD, compulsive behaviors are also seen in a wide range of psychiatric conditions, especially those involving poor impulse control, such as addiction (33). For the purposes of characterization, compulsive behaviors have been linked to the RDoC component "habit." Habits are defined as automatic, sequential motor or cognitive acts that may be completed without ongoing conscious effort once established and activated by cues. Habits are functionally the inverse of goal-directed activities, which are conducted consciously and are affected by the value of the outcome (34). On an anatomical level, the cortico-striatal circuitry dysfunction often associated with OCD has also been associated with maladaptive habit formation and execution (35). Specifically, neuroimaging studies in patients with OCD have shown that the dorsal striatum plays a large role in the formation and execution of habits (33) and that the putamen of OCD patients is larger and more activated, compared with those of controls (36, 37).

Because the parsing of compulsion into its own symptom domain for treatment in the context of the RDoC is a relatively new concept, neuromodulation studies are limited. However, in 2013, an experiment using compulsive-behavior rat models was completed that targeted the lateral OFC and its terminals in the striatum by using focused optogenetic stimulation (38). The results showed restored compulsive-behavioral inhibition and normalized regulation of striatal projection neuron activity. Further neuromodulation studies in humans are thus warranted.

Addiction

Substance use disorder is a chronically relapsing disorder marked by compulsive substance seeking and a lack of control over intake (39). As previously noted, symptoms of addictive craving have been shown to manifest neural

circuitry dysfunction similar to those of compulsion (33). This is characterized by a hypoactivation of frontal regions associated with decision making and behavioral inhibition and a hyperactivation of striatal regions associated with implicit learning, self-reflection, and rumination. The triple network model has been examined in relation to addictive craving, and resting-state functional connectivity (RSFC) studies have shown decreased activation of the anterior component of the DMN, as well as increased activation of the posterior component (40). Furthermore, this aberrant within-network DMN connectivity has been linked to disrupted internetwork connectivity with the CEN (41). Disrupted DMN-CEN connection may make it difficult for patients to detach attention from internal rumination and cravings, making it harder for them to recruit attention and cognitive resources for external stimuli processing (40). A study examining heroin-dependent individuals showed that, on average, the left dlPFC had decreased connectivity with the rest of the CEN and that this decreased connectivity was associated with higher rates of relapse (42).

This decreased connectivity of the dlPFC has been consistently noted in the literature, leading researchers to consider it a key target for neuromodulation treatments. A recent study hypothesized that applying transcranial direct current stimulation (tDCS) would be able to modulate subjective craving in methamphetamine users via stimulation of the dlPFC (43). Results showed a significant decrease in subjective craving scores, as well as significant modulation of the DMN, CEN, and SN after tDCS. This proposed addiction network with multiple nodes also highlights the potential importance of interventions that are capable of modulating multiple brain regions either simultaneously or in rapid succession.

Anxiety

Anxiety disorders are the most frequent mental illnesses worldwide. In the United States specifically, anxiety affects roughly 29% of people at some point in their lives (44). Anxiety is also a common symptom of several psychiatric diseases, such as OCD, posttraumatic stress disorder (PTSD), substance abuse, addiction, and depression (45, 46). Despite the high incidence of anxiety among patients, current treatments have poor remission rates, with roughly 40% of treated individuals still experiencing symptoms. To improve the treatment of anxiety disorders, a conceptual framework based on empirical evidence is required.

In 2013, Bystritsky et al. (47) proposed a circuit-based model of anxiety called the alarm, belief, and coping (ABC) model. The ABC model of anxiety is used to describe the functional interaction of brain structures in space/time, constructed as follows: alarms (A), detection of dangerous stimuli; beliefs (B), appraisal of threat and selection of response based on prior experiences; and coping (C), active mitigation of threat via learned behaviors executed immediately and/or more delayed via a complex sequence of actions.

Recently, a meta-analysis was published by Bystritsky et al. (48) that utilized Neurosynth (an open-access meta-analytic imaging database) to examine whether the postulates of the ABC model could be appropriately associated with the current functional imaging data. Regions of functional connectivity were analyzed in relation to a search term (i.e., bilateral amygdala activation was associated with the term "anxiety"). The data suggested the following: terms related to alarms were associated most significantly with amygdalar activity, terms related to beliefs were associated most significantly with bilateral temporal pole activity, and terms related to coping were associated most significantly with activation of the bilateral anterolateral frontal cortex, as well as the supplemental motor area (48, 49).

The amygdala has often been examined in relation to anxiety, as it is implicated in perceptual processing and bottom-up emotional control (50). Because of its primary role in the cascading sequence of anxiety (i.e., the initial "alarm" phase), the amygdala is a brain area often studied in relation to other brain networks. Although the amygdala is responsible for the initiation of the fear response, the prefrontal cortex's inhibitory inputs control the activity of the amygdala, which mediates anxiety response. Specifically, the dlPFC has been often cited as playing a key role in the pathophysiology of anxiety disorders (51), and reregulation of this network has been posited as one of the predominant neural network changes underlying the positive benefits of meditation (52).

Less often examined is the functional relationship between the temporal pole and the amygdala. In regard to the sequence of anxiety, the temporal cortex and temporal pole are thought to play a top-down modulatory role in integrating sensory stimuli with conceptual knowledge (i.e., the "belief" phase) (53, 54). A study of 20 patients with generalized anxiety disorder (GAD) examined the RSFC of the amygdala with the dlPFC and of the amygdala with the temporal pole (55). The results showed that in GAD patients, there was disrupted functional connectivity between the amygdala and dlPFC and increased functional connectivity between the left amygdala and the temporal pole, compared with healthy controls.

First, the decreased functional connectivity between the dlPFC and the amygdala supports the theory that anxiety is in part a disorder of impaired ability to mediate the anxiety response, via lack of inhibition from the dlPFC. Second, the increased connectivity between the temporal pole and the amygdala in GAD sufferers may explain why stimuli elicit anxiety more easily in these individuals, as stimuli become more likely to be attributed with negative valence. These findings suggest that the amygdala, the dlPFC, and the temporal pole may serve as potential targets for treatment via neuromodulation.

Multiple neuromodulation technologies have been explored to treat the symptoms of anxiety, to varying degrees of success. A small study (N=10) using rTMS targeting the right dlPFC in GAD patients demonstrated a

significant improvement in scores on the Hamilton Anxiety Rating Scale and in anxiety symptoms in more than half (60%) the participants (49). A 2019 meta-analysis of 520 repetitive transcranial magnetic stimulation (rTMS) studies supported these results and showed similar efficacy in GAD patients treated with the right dlPFC as a target (56). rTMS is the most widely studied neurostimulation treatment for anxiety, and although others (DBS, tDCS, and focused ultrasound) have been studied, there are currently no significant results for these treatments; therefore, further studies are warranted (57).

PTSD

According to the *DSM-5,* intrusive and disturbing memories, increased alertness, mood changes, cognitive deficits, and subsequent avoidance of trauma-related stimuli are all core symptoms of PTSD (58). PTSD, like many other mental diseases, is presently diagnosed by using a variety of clinical symptoms. As a result of this syndrome-based diagnostic approach, the PTSD diagnosis has a great deal of clinical heterogeneity—innumerable potential symptom combinations from which to choose. For this reason, recent studies have explored the neurocircuitry of PTSD symptoms to determine potential targets for neurostimulation. Reduced top-down control over neural circuits (i.e., the amygdala, prefrontal cortex [PFC], and hippocampus) is hypothesized to be a primary cause of PTSD symptoms. Dysfunction in these networks is thought to lead to disordered memory processing and an overgeneralized fear response (59).

With the development of the RDoC in recent years, a few PTSD subtypes based on the above symptom domains have been hypothesized.

Hypervigilance. Hypervigilance (or heightened reactivity) is one of the hallmark symptoms of PTSD and, as with symptoms of anxiety, has long been associated with amygdala hyperactivity (60). Studies of combat veterans with PTSD examining reactivity to combat sounds versus neutral sounds have shown significantly increased amygdalar activation in response to the trauma-related stimuli (61, 62). This increased amygdalar activity in PTSD patients versus controls has also been observed in resting-state studies (63). In trauma-exposed individuals, the ability to habituate to threat-relevant information, which would allow them to differentiate between novel and familiar stimuli, is hindered. This indiscriminate amygdala response pattern could be associated with persistent hypervigilance; therefore, neuromodulation aiming to downregulate activity of the amygdala would be a potential therapy for this symptom in PTSD patients.

One example of neuromodulation is a case study in which DBS was used with a treatment-resistant PTSD patient exhibiting hypervigilant symptoms (64). Electrodes were placed in the basolateral nucleus of the amygdala, and after 8 months, the patient showed decreased amygdala activity via PET scan, as well as significantly reduced scores on the Clinician Administered PTSD Scale (CAPS). Although these results are currently limited to a single patient, the significant improvement in symptoms of hypervigilance warrants further investigation in neuromodulation of the amygdala.

An alternative target for neurostimulation could be the ventromedial prefrontal cortex (vmPFC), because it is thought to play a key role in the hypervigilant subtype of PTSD. The vmPFC has been shown to exert a modulatory effect on the amygdala, and hypoactivity of this region has consequently been associated with unchecked hyperactivation of the amygdala. Furthermore, patients reporting high levels of hypervigilance have exhibited abnormally low activity in the vmPFC (65). A DBS study in PTSD rat-models demonstrated that electrodes stimulating the vmPFC resulted in a reduction of amygdalar activity, as well as a reduction in hyperreactive behaviors (66).

Considering the above studies, future neurostimulation treatment for hypervigilant subtypes could be aimed at either decreasing activity of the amygdala or increasing the modulatory effects of the vmPFC.

Intrusion. Symptoms of intrusion are commonly reported in patients with PTSD and are characterized as a reexperiencing of the given traumatic event. This reexperiencing can manifest as flashbacks, dreams, intrusive memories, and physiological reactivity (58). Intrusion symptoms appear to be anatomically similar to symptoms of hypervigilance, as they are also thought to be linked to an inability of the cortical regions to inhibit hyperactivity of the limbic system (67). A recent machine learning analysis was able to predict the occurrence of intrusive recollections by using multiple neural networks as predictors (68). The predominant network accounting for the largest majority of variance included the lingual gyrus, left hippocampus, middle temporal gyri, supramarginal gyrus, left thalamus, precuneus, inferior and superior frontal gyri, and posterior cingulate cortex (PCC). Networks within these regions constitute the cognition-memory-explicit network, the cognition-language-semantic network, and the cognition-language-phonology network. Each of these networks likely plays a meaningful role in the onset and presentation of intrusive recollections. Indeed, the strong relationship between the amygdala and hippocampus as the foundation for the emotional enhancement of memory serves a major role in the initial formation and subsequent reexperiencing of emotionally salient memories (69, 70). Although neuromodulation studies have yet to be conducted in real time, a recent study of fMRI-based neurofeedback training targeted to this amygdala-hippocampus network found a clinically significant, 38% reduction in CAPS score (71).

Dissociation. Dissociative symptoms are observed in many mental disorders, including dissociative identity disorder, borderline personality disorder, schizophrenia, and PTSD. The *DSM-5* has defined dissociation as "disruption of and/

or discontinuity in the normal, subjective integration of one or more aspects of psychological functioning, including—but not limited to—memory, identity, consciousness, perception, and motor control" (72). The *DSM-5* has recognized dissociative PTSD as a subtype of the broader disorder, neurobiologically separate from nondissociative PTSD.

In contrast to hypervigilant subtypes, neuroimaging studies of dissociative PTSD have demonstrated overmodulation of the emotional networks by cortical regions, with hyperactivation of the vmPFC and dorsal anterior cingulate cortex (dACC) (67). The dACC has been implicated in the appraisal of negative emotion, and hyperactivity of this region may play a part in the vmPFC's increased modulation of the amygdala.

Dissociation can thus be conceptualized as a defense mechanism, overactivating the modulatory regions in an effort to prevent the emotional states triggered by a given traumatic event. These patterns of brain activity have been explored in those with high versus low levels of dissociative symptoms, in studies that used symptom provocation paradigms in patients with PTSD (73). Participants with low levels of dissociation reported symptoms associated with hyperarousal during exposure, whereas those with high levels of dissociation reported entering a state of detachment and numbness. These reported symptoms were consistent with the hypothesized neural activity, as the participants with low dissociation showed a hypoactive vmPFC/hyperactive amygdala, whereas the participants with high dissociation showed a hypoactive amygdala/hyperactive dACC and vmPFC (73, 74).

Neurostimulation studies specifically for the treatment of dissociative PTSD are currently scarce; however, a case report using rTMS has shown positive effects. A 29-year-old combat veteran presented with PTSD, exhibiting strong dissociative symptoms (75). Neuroimaging indicated significant hyperactivity of the ACC. rTMS was prescribed with the cingulate as the primary target, and after 36 treatments, the patient showed significant reductions in mood inventories and a positive improvement on the Global Rating of Change. Because these results are limited to a single individual, the results are not yet generalizable; however, they do warrant further studies exploring the neuromodulatory capability of rTMS and other technologies for dissociative PTSD.

Psychosis

Schizophrenia, which affects 1% of the population, is a syndrome characterized by psychotic symptoms that lead to persistent deterioration (5). Schizophrenia has remained a heterogeneous disorder, with diverse clinical manifestations. The symptoms of schizophrenia are typically separated between "positive psychotic symptoms" (the presence of unusual experiences, such as delusions), and "negative psychotic symptoms" (the absence of normal experiences, such as in anhedonia or apathy).

Although persons more heavily afflicted with negative psychotic symptoms are sometimes able to find relief in mood-stabilizing medications or therapies, these medications remain ineffective for those experiencing positive psychotic symptoms (i.e., delusions and hallucinations) (76). Antipsychotics are frequently prescribed to those with positive psychotic symptoms, but not all antipsychotics are created the same (77). For example, compared with patients using first-generation antipsychotics, patients using quetiapine and those not using any antipsychotics at event time were at an increased risk of mental health events (hazard ratio [HR]=1.38, 95% confidence interval [CI]=1.24–1.54, $p<0.0001$; and HR=1.54, 95% CI=1.44–1.65, $p<0.0001$, respectively) (78). Therefore, investigation into neuromodulation therapies targeting various psychotic symptoms is warranted.

Delusions are characterized as a clearly false belief that suggests a dysfunction in the affected person's thought process; specifically, the key feature that indicates a delusion is how convinced the affected person is that the false belief is true (79). In addition to presenting in schizophrenia, delusions present in bipolar disorder, major depressive disorder with psychotic features, dementia, and other clinical disorders. This heterogeneity is indicative of the need for a clearer understanding of the neural mechanisms that present in a patient afflicted with delusions.

A study by Lee et al. (5) investigated the distinct neural networks associated with delusion. This team compared the RSFC of 75 patients with schizophrenia-related delusions to that of 65 healthy controls. The P1 dimension of the Positive and Negative Syndrome Scale (PANSS) was assessed to determine delusion severity of each patient. The results implicated the degree of precuneus hyperactivity as playing a pivotal role in delusion severity. This is consistent with the literature that suggests that the precuneus—and, in effect, the DMN—is crucial for self-awareness, and dysregulation of this network has been shown to affect one's beliefs about one's self.

In light of these findings, the hyperactivity of the DMN has been shown to be due in part to an inability of the SN to shift from the internal/self-referential processing network (DMN) to the CEN (80). In essence, this model has been hypothesized as "dreaming-while-awake" and suggests that the positive symptoms of psychosis (i.e., delusions) are a result of the fantasizing and daydreaming properties of the DMN bleeding into the conscious awareness system of the CEN via lack of modulation by the SN (81). Therefore, neuromodulation targeting nodes of the SN (anterior cingulate, anterior insula) could be a potential therapy for patients with positive psychotic symptoms, such as delusions.

A recent study examined the efficacy of DBS of either the NAc or the subgenual ACC in patients with severe scores on the positive psychotic symptom dimensions of the PANSS (82). After 24 weeks, two of three patients with NAc electrodes and two of four patients with ACC electrodes showed significant (>25%) improvement in the PANSS total score. Although the sample size was limited, this study suggests that DBS in patients with treatment-resistant delusions

may be a feasible alternative and suggests target brain regions for future intervention studies.

DISCUSSION AND CONCLUSIONS

The DMN has received much attention in the past decade as a target to link intrinsic activity to cognition and to examine how intrinsic signal changes may be altered in dysfunction (i.e., traumatic brain injury, depression, anxiety, psychosis, and PTSD) (83). The DMN seems to be active during states of daydreaming, "wakeful rest," retrospective simulation (remembering the past), prospective simulation (imagining the future), social cognition (imagining what others are thinking), and self-relevant tasks (84). Anatomically, the network is typically thought to consist of the medial prefrontal cortex, PCC, and inferior parietal lobule, as well as the lateral temporal poles (85).

The CEN (also referred to as the "frontoparietal network") has been shown to be anticorrelated with the DMN, because it appears to be most active during states of top-down cognitive control functions, such as decision making, attentional control, working memory, and cognitive flexibility (86, 87). The areas that typically constitute the CEN are the dlPFC and the posterior parietal cortex. These two networks (CEN and DMN) may be easily identified by examining the profile of activation and inactivation generally observed during cognitive tasks—where the CEN typically displays increases in activation, the DMN typically shows declines (88). However, recent studies have shown interest in uncovering the psychopathology that underlies the inability of the brain to properly transition between these two states of network activation; notably, this process of transition has been shown to be mediated by the SN (89).

The SN (also referred to as the "ventral attention network") is highly implicated with marking events in time and space with the appropriate relevance and, when properly functioning, assists the other brain networks in generating appropriate behavioral responses to salient stimuli. According to this concept, the insula facilitates bottom-up access to the brain's attentional and working memory resources. This is largely because the network is composed of the anterior insula, as well as the ACC. Evidence from network analysis suggests that the core function of the insula is to mark salient events for additional processing and initiate the appropriate control signals (90). This marking of salient events seems to be critical in the overall network model, because further studies have shown that the anterior insula mediates the dynamic activity of the DMN and ECN, allowing for flexible attention to internal or external events (91, 92).

As the major networks have become more commonly identified, it is becoming clear that a critical part of individual psychopathological dysfunction may lie in the characterization of the SN and its functional and temporal connections with the DMN and CEN, as well as other to-be-defined networks underlying specific neuropsychiatric symptoms. The majority of significant psychopathologies are being shown to entail failure of multiple complex networks that integrate several cognitive and emotion-regulating systems that rely on many lobes and scattered brain regions. Furthermore, the ability of the brain to rapidly switch between these networks has been shown to be a major discriminatory factor in healthy cognitive function. In a Human Connectome Project study examining the fMRI connectivity in 1,003 healthy adults, data showed that network switching speed was predictive of intersubject variation in working memory, planning, reasoning, and amount of sleep (93). Furthermore, in a recent review, Bystritsky and colleagues (48) looked at neurocircuitry underlying the multiple facets of anxiety and its presentations. More work along these lines using large metanalytic fMRI is needed to better separate the networks that underlie psychiatric illness.

In addition, many psychiatric diseases have symptom domains that may overlap with other disorders. For example, individuals with PTSD have severe anxiety, much like patients with OCD or GAD have anxiety. This makes it difficult to tease apart what is the primary dysfunctional network that leads to irregularity and maladaptive function in secondary networks. Future studies may look at these comorbid network dysfunctions to find what is common among persons presenting with a specific symptom domain.

By beginning to approach psychopathology in this fashion, the developing technologies of multimodal MRI and functional connectivity can be utilized to their fullest extent. To treat patients in a more effective, individualized manner, therapies must be further parsed to specific presenting symptoms. Currently, diagnosis and treatment at the syndrome level leave many patients suffering and symptomatic. Considering this, as well as the research into symptom domains that has been done by groups such as the RDoC, it is clear that the future of neuropsychological/psychiatric treatment lies in discovery of and research into respective networks and symptom presentations. If these aberrant networks can be further identified and treated (as suggested by the research presented in this review), a new era of noninvasive, precision, personalized, and MRI-based treatment may be possible.

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REFERENCES

1. Cortese S, Kelly C, Chabernaud C, et al: Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am J Psychiatry 2012; 169:1038–1055
2. Calhoun VD, Eichele T, Pearlson G: Functional brain networks in schizophrenia: a review. Front Hum Neurosci 2009; 3:17

3. Menon V: Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 2011; 15:483–506
4. Wong EHF, Yocca F, Smith MA, et al: Challenges and opportunities for drug discovery in psychiatric disorders: the drug hunters' perspective. Int J Neuropsychopharmacol 2010; 13:1269–1284
5. Lee TY, Jung WH, Kwak YB, et al: Distinct neural networks associated with obsession and delusion: a connectome-wide association study. Psychol Med 2020; 51:1–9
6. Lavretsky H, Zheng L, Weiner MW, et al: The MRI brain correlates of depressed mood, anhedonia, apathy, and anergia in older adults with and without cognitive impairment or dementia. Int J Geriatr Psychiatry 2008; 23:1040–1050
7. Levy ML, Cummings JL, Fairbanks LA, et al: Apathy is not depression. J Neuropsychiatry Clin Neurosci 1998; 10:314–319
8. Marin RS, Firinciogullari S, Biedrzycki RC: Group differences in the relationship between apathy and depression. J Nerv Ment Dis 1994; 182:235–239
9. Rog LA, Park LQ, Harvey DJ, et al: The independent contributions of cognitive impairment and neuropsychiatric symptoms to everyday function in older adults. Clin Neuropsychol 2014; 28: 215–236
10. Padala PR, Padala KP, Monga V, et al: Reversal of SSRI-associated apathy syndrome by discontinuation of therapy. Ann Pharmacother 2012; 46:e8
11. Scherer RW, Drye L, Mintzer J, et al: The Apathy in Dementia Methylphenidate Trial 2 (ADMET 2): study protocol for a randomized controlled trial. Trials 2018; 19:46
12. van Eimeren T, Ballanger B, Pellecchia G, et al: Dopamine agonists diminish value sensitivity of the orbitofrontal cortex: a trigger for pathological gambling in Parkinson's disease? Neuropsychopharmacology 2009; 34:2758–2766
13. Baggio HC, Segura B, Garrido-Millan JL, et al: Resting-state frontostriatal functional connectivity in Parkinson's disease-related apathy. Mov Disord 2015; 30:671–679
14. Ducharme S, Price BH, Dickerson BC: Apathy: a neurocircuitry model based on frontotemporal dementia. J Neurol Neurosurg Psychiatry 2018; 89:389–396
15. Ballard IC, Murty VP, Carter RM, et al: Dorsolateral prefrontal cortex drives mesolimbic dopaminergic regions to initiate motivated behavior. J Neurosci 2011; 31:10340–10346
16. Lavallé L, Aleman A: rTMS for treatment of negative symptoms in schizophrenia: clinical effects and neural basis. Encephale 2019; 45(suppl 2):S50–S51
17. Padala PR, Boozer EM, Lensing SY, et al: Neuromodulation for apathy in Alzheimer's disease: a double-blind, randomized, sham-controlled pilot study. J Alzheimers Dis 2020; 77:1483–1493
18. Onoda K, Yamaguchi S: Dissociative contributions of the anterior cingulate cortex to apathy and depression: topological evidence from resting-state functional MRI. Neuropsychologia 2015; 77: 10–18
19. Fletcher K, Parker G, Paterson A, et al: Anhedonia in melancholic and non-melancholic depressive disorders. J Affect Disord 2015; 184:81–88
20. Dillon DG, Holmes AJ, Jahn AL, et al: Dissociation of neural regions associated with anticipatory versus consummatory phases of incentive processing. Psychophysiology 2008; 45:36–49
21. O'Doherty JP: Reward representations and reward-related learning in the human brain: insights from neuroimaging. Curr Opin Neurobiol 2004; 14:769–776
22. Yee A, Chin SC, Hashim AH, et al: Anhedonia in depressed patients on treatment with selective serotonin reuptake inhibitor anti-depressant: a two-centered study in Malaysia. Int J Psychiatry Clin Pract 2015; 19:182–187
23. Schlaepfer T, Kosel M: Novel physical treatments for major depression: vagus nerve stimulation, transcranial magnetic stimulation and magnetic seizure therapy. Curr Opin Psychiatry 2004; 17:15–20
24. Mayberg HS, Lozano AM, Voon V, et al: Deep brain stimulation for treatment-resistant depression. Neuron 2005; 45:651–660
25. Schlaepfer TE, Cohen MX, Frick C, et al: Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology 2008; 33:368–377
26. Gillan CM, Fineberg NA, Robbins TW: A trans-diagnostic perspective on obsessive-compulsive disorder. Psychol Med 2017; 47:1528–1548
27. Fineberg NA, Day GA, de Koenigswarter N, et al: The neuropsychology of obsessive-compulsive personality disorder: a new analysis. CNS Spectr 2015; 20:490–499
28. Greenberg BD, Malone DA, Friehs GM, et al: Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology 2006; 31:2384–2393
29. Goodman WK, Foote KD, Greenberg BD, et al: Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. Biol Psychiatry 2010; 67: 535–542
30. Grover S, Nguyen JA, Viswanathan V, et al: High-frequency neuromodulation improves obsessive-compulsive behavior. Nat Med 2021; 27:232–238
31. Jaafari N, Rachid F, Rotge J-Y, et al: Safety and efficacy of repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder: a review. World J Biol Psychiatry 2012; 13:164–177
32. Kalanthroff E, Anholt GE, Simpson HB: Research Domain Criteria and OCD: an oxymoron? in Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Edited by Pittenger C. Oxford, United Kingdom, Oxford University Press, 2017
33. Fineberg NA, Apergis-Schoute AM, Vaghi MM, et al: Mapping compulsivity in the DSM-5 obsessive compulsive and related disorders: cognitive domains, neural circuitry, and treatment. Int J Neuropsychopharmacol 2018; 21:42–58
34. Gillan CM, Robbins TW: Goal-directed learning and obsessive-compulsive disorder. Philos Trans R Soc Lond B Biol Sci 2014; 369:20130475
35. Pittenger C, Pushkarskaya H, Gruner P: Animal models of OCD-relevant processes: an RDoC perspective. J Obsessive Compuls Relat Disord 2019; 23:100433
36. de Wit SJ, Alonso P, Schweren L, et al: Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder. Am J Psychiatry 2014; 171:340–349
37. Reghunandanan S, Fineberg NA, Stein DJ: Obsessive-Compulsive and Related Disorders, 2nd ed. Oxford, United Kingdom, Oxford University Press, 2015
38. Burguière E, Monteiro P, Feng G, et al: Optogenetic stimulation of lateral orbitofronto-striatal pathway suppresses compulsive behaviors. Science 2013; 340:1243–1246
39. Koob GF, Volkow ND: Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 2016; 3:760–773
40. Zhang R, Volkow ND: Brain default-mode network dysfunction in addiction. Neuroimage 2019; 200:313–331
41. Liang Y, Wang L, Yuan TF: Targeting withdrawal symptoms in men addicted to methamphetamine with transcranial magnetic stimulation: a randomized clinical trial. JAMA Psychiatry 2018; 75:1199–1201
42. Li Q, Liu J, Wang W, et al: Disrupted coupling of large-scale networks is associated with relapse behaviour in heroin-dependent men. J Psychiatry Neurosci 2018; 43:48–57
43. Shahbabaie A, Ebrahimpoor M, Hariri A, et al: Transcranial DC stimulation modifies functional connectivity of large-scale brain

networks in abstinent methamphetamine users. Brain Behav 2018; 8:e00922
44. Kessler RC, Berglund P, Demler O, et al: Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62: 593–602
45. Martins SS, Gorelick DA: Conditional substance abuse and dependence by diagnosis of mood or anxiety disorder or schizophrenia in the US population. Drug Alcohol Depend 2011; 119: 28–36
46. Devane CL, Chiao E, Franklin M, et al: Anxiety disorders in the 21st century: status, challenges, opportunities, and comorbidity with depression. Am J Manag Care 2005; 11(suppl):S344–S353
47. Bystritsky A, Khalsa SS, Cameron ME, et al: Current diagnosis and treatment of anxiety disorders. PT 2013; 38:30–57
48. Bystritsky A, Spivak NM, Dang BH, et al: Brain circuitry underlying the ABC model of anxiety. J Psychiatr Res 2021; 138:3–14
49. Bystritsky A, Kaplan JT, Feusner JD, et al: A preliminary study of fMRI-guided rTMS in the treatment of generalized anxiety disorder. J Clin Psychiatry 2008; 69:1092–1098
50. Phelps EA: Emotion and cognition: insights from studies of the human amygdala. Annu Rev Psychol 2006; 57:27–53
51. Sehlmeyer C, Dannlowski U, Schöning S, et al: Neural correlates of trait anxiety in fear extinction. Psychol Med 2011; 41:789–798
52. Tang YY, Hölzel BK, Posner MI: The neuroscience of mindfulness meditation. Nat Rev Neurosci 2015; 16:213–225
53. Carota F, Kriegeskorte N, Nili H, et al: Representational similarity mapping of distributional semantics in left inferior frontal, middle temporal, and motor cortex. Cereb Cortex 2017; 27:294–309
54. Pehrs C, Zaki J, Schlochtermeier LH, et al: The temporal pole top-down modulates the ventral visual stream during social cognition. Cereb Cortex 2017; 27:777–792
55. Li W, Cui H, Zhu Z, et al: Aberrant functional connectivity between the amygdala and the temporal pole in drug-free generalized anxiety disorder. Front Hum Neurosci 2016; 10:549
56. Cirillo P, Gold AK, Nardi AE, et al: Transcranial magnetic stimulation in anxiety and trauma-related disorders: a systematic review and meta-analysis. Brain Behav 2019; 9:e01284
57. Kar SK, Sarkar S: Neuro-stimulation techniques for the management of anxiety disorders: an update. Clin Psychopharmacol Neurosci 2016; 14:330–337
58. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA, American Psychiatric Association, 2013
59. Besnard A, Sahay A: Adult hippocampal neurogenesis, fear generalization, and stress. Neuropsychopharmacology 2016; 41:24–44
60. Rauch SL, van der Kolk BA, Fisler RE, et al: A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. Arch Gen Psychiatry 1996; 53:380–387
61. Liberzon I, Taylor SF, Amdur R, et al: Brain activation in PTSD in response to trauma-related stimuli. Biol Psychiatry 1999; 45: 817–826
62. Pissiota A, Frans O, Fernandez M, et al: Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study. Eur Arch Psychiatry Clin Neurosci 2002; 252:68–75
63. Chung YA, Kim SH, Chung SK, et al: Alterations in cerebral perfusion in posttraumatic stress disorder patients without re-exposure to accident-related stimuli. Clin Neurophysiol 2006; 117:637–642
64. Langevin J-P, Koek RJ, Schwartz HN, et al: Deep brain stimulation of the basolateral amygdala for treatment-refractory posttraumatic stress disorder. Biol Psychiatry 2016; 79:e82–e84
65. Lanius RA, Bluhm R, Lanius U, et al: A review of neuroimaging studies in PTSD: heterogeneity of response to symptom provocation. J Psychiatr Res 2006; 40:709–729
66. Reznikov R, Bambico FR, Diwan M, et al: Prefrontal cortex deep brain stimulation improves fear and anxiety-like behavior and reduces basolateral amygdala activity in a preclinical model of posttraumatic stress disorder. Neuropsychopharmacology 2018; 43:1099–1106
67. Lanius RA, Vermetten E, Loewenstein RJ, et al: Emotion modulation in PTSD: clinical and neurobiological evidence for a dissociative subtype. Am J Psychiatry 2010; 167:640–647
68. Clark IA, Niehaus KE, Duff EP, et al: First steps in using machine learning on fMRI data to predict intrusive memories of traumatic film footage. Behav Res Ther 2014; 62:37–46
69. Murty VP, Labar KS, Adcock RA: Threat of punishment motivates memory encoding via amygdala, not midbrain, interactions with the medial temporal lobe. J Neurosci 2012; 32:8969–8976
70. Brown VM, Morey RA: Neural systems for cognitive and emotional processing in posttraumatic stress disorder. Front Psychol 2012; 3:449
71. Zotev V, Phillips R, Misaki M, et al: Real-time fMRI neurofeedback training of the amygdala activity with simultaneous EEG in veterans with combat-related PTSD. Neuroimage Clin 2018; 19:106–121
72. Spiegel D, Loewenstein RJ, Lewis-Fernández R, et al: Dissociative disorders in DSM-5. Depress Anxiety 2011; 28:E17–E45
73. Pitman RK, Orr SP, Forgue DF, et al: Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. Arch Gen Psychiatry 1987; 44:970–975
74. Fenster RJ, Lebois LAM, Ressler KJ, et al: Brain circuit dysfunction in post-traumatic stress disorder: from mouse to man. Nat Rev Neurosci 2018; 19:535–551
75. Blades R, Jordan S, Becerra S, et al: Treating dissociative posttraumatic stress disorder presenting as a functional movement disorder with transcranial magnetic stimulation targeting the cingulate gyrus. Neurol Sci 2020; 41:2275–2280
76. Dokucu ME: Neuromodulation treatments for schizophrenia. Curr Treat Options Psychiatry 2015; 2:339–348
77. Harrison G, Hopper K, Craig T, et al: Recovery from psychotic illness: a 15- and 25-year international follow-up study. Br J Psychiatry 2001; 178:506–517
78. Vanasse A, Blais L, Courteau J, et al: Comparative effectiveness and safety of antipsychotic drugs in schizophrenia treatment: a real-world observational study. Acta Psychiatr Scand 2016; 134: 374–384
79. Kiran C, Chaudhury S: Understanding delusions. Ind Psychiatry J 2009; 18:3–18
80. Looijestijn J, Blom JD, Aleman A, et al: An integrated network model of psychotic symptoms. Neurosci Biobehav Rev 2015; 59: 238–250
81. Manoliu A, Riedl V, Zherdin A, et al: Aberrant dependence of default mode/central executive network interactions on anterior insular salience network activity in schizophrenia. Schizophr Bull 2014; 40:428–437
82. Corripio I, Roldán A, Sarró S, et al: Deep brain stimulation in treatment resistant schizophrenia: a pilot randomized cross-over clinical trial. EBioMedicine 2020; 51:102568
83. Fransson P, Marrelec G: The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: evidence from a partial correlation network analysis. Neuroimage 2008; 42:1178–1184
84. Buckner RL, Andrews-Hanna JR, Schacter DL: The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008; 1124:1–38
85. Spreng RN, Stevens WD, Chamberlain JP, et al: Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. Neuroimage 2010; 53:303–317
86. Cole MW, Reynolds JR, Power JD, et al: Multi-task connectivity reveals flexible hubs for adaptive task control. Nat Neurosci 2013; 16:1348–1355

87. Seeley WW, Menon V, Schatzberg AF, et al: Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007; 27:2349–2356
88. Greicius MD, Krasnow B, Reiss AL, et al: Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 2003; 100:253–258
89. Bolton TA, Wotruba D, Buechler R, et al: Triple network model dynamically revisited: lower salience network state switching in pre-psychosis. Front Psychol 2020; 11:66
90. Craig AD: How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci 2009; 10:59–70
91. Fedota JR, Ding X, Matous AL, et al: Nicotine abstinence influences the calculation of salience in discrete insular circuits. Biol Psychiatry Cogn Neurosci Neuroimaging 2018; 3: 150–159
92. Sridharan D, Levitin DJ, Menon V: A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci USA 2008; 105: 12569–12574
93. Pedersen M, Zalesky A, Omidvarnia A, et al: Multilayer network switching rate predicts brain performance. Proc Natl Acad Sci USA 2018; 115:13376–13381