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REVIEW

Noninvasive brain stimulation treatments for addiction and major depression

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Major depressive disorder (MDD) and substance use disorders (SUDs) are prevalent, disabling, and challenging illnesses for which new treatment options are needed, particularly in comorbid cases. Neuroimaging studies of the functional architecture of the brain suggest common neural substrates underlying MDD and SUDs. Intrinsic brain activity is organized into a set of functional networks, of which two are particularly relevant to psychiatry. The salience network (SN) is crucial for cognitive control and response inhibition, and deficits in SN function are implicated across a wide variety of psychiatric disorders, including MDD and SUDs. The ventromedial network (VMN) corresponds to the classic reward circuit, and pathological VMN activity for drug cues/negative stimuli is seen in SUDs/MDD. Noninvasive brain stimulation (NIBS) techniques, including rTMS and tDCS, have been used to enhance cortico–striatal–thalamic activity through the core SN nodes in the dorsal anterior cingulate cortex, dorsolateral prefrontal cortex, and anterior insula. Improvements in both MDD and SUD symptoms ensue, including in comorbid cases, via enhanced cognitive control. Inhibition of the VMN also appears promising in preclinical studies for quenching the pathological incentive salience underlying SUDs and MDD. Evolving techniques may further enhance the efficacy of NIBS for MDD and SUD cases that are unresponsive to conventional treatments.

Keywords: addiction; depression; fMRI; rTMS; tDCS

Introduction

Major depressive disorder (MDD) and substance use disorders (SUDs) are challenging illnesses that produce significant burdens on patients and the healthcare system. Mental illness and SUDs are the leading worldwide cause of years lived with a disability (YLD),[1] and MDD is the second leading psychiatric cause of YLD.[2] The societal burden of MDD and SUDs have also dramatically increased over the last 20 years,[2] emphasizing the importance of access to care and effective treatment options.

For MDD, the mainstays of conventional treatment are pharmacotherapy and psychotherapy. Studies of real-world effectiveness suggest that about one-third of patients will remit on an initial trial of antidepressant medication, while another one-third will remit after 1–3 additional medication trials.[3,4] The remaining one-third of patients are labeled as having treatment-resistant depression (TRD), with a low likelihood of remission (10–15%) on further trials.[4] TRD affects approximately 2% of the general population.[5] To address the challenge of treating TRD, combination therapies (antidepressant + antipsychotic, or antidepressant + anticonvulsant)[6–9] and electroconvulsive therapy (ECT)[10] have yielded promising clinical results. Even for TRD, however, these intensive interventions achieve varied remission rates between approximately 30%[11] and 50%,[6–8] and the relapse rate following ECT is 50% by 2 years.[12]

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As with MDD, in SUD patients the mainstays of conventional treatment are pharmacotherapy and psychotherapy. Lifetime rates of drug use are 92% for alcohol, 74% for tobacco, 42% for cannabis, and 16% for cocaine, in the United States.[13] The lifetime prevalence of alcohol dependence is 13%, and up to 3% for illicit substances.[14–16] The most common psychotherapeutic approach to substance dependence is cognitive behavioral therapy.[17,18] A meta-analysis of 34 randomized controlled trials on cognitive behavioral therapy for SUDs demonstrated that the average effect size was moderate ($d = 0.45$), with the highest effects for cannabis, cocaine, and opioid treatment.[19] A form of behavioral therapy known as contingency management appears to be a particularly potent tool for multiple classes of SUD patients.[20,21] Contingency management, however, requires that an individual is able to regulate/control their drug intake in order to get an alternative non-drug reinforcer. This may be difficult for many patients, as disruptions in response inhibition and in the neural circuitry required for response inhibition are hallmarks of addiction.[22]

From a pharmacotherapy perspective, the therapeutic approach varies with the substance being abused. Pharmacotherapy may complement behavioral approaches by replacing the abused substance with a less harmful substitute[23,24] and thereby reduce the social and personal harm associated with the drug. However, dependences on several classes of drugs, including cocaine, have no approved pharmacotherapy, and relapse rates in the first 6 months after an outpatient treatment program are often higher than 75%.[25] Some evidence also suggests that pharmacotherapy that interacts with neurotransmitter systems related to reward learning may enhance impulse control itself.[26]

High rates of treatment resistance and relapse represent a common challenge for MDD or SUDs. However, effective MDD and SUD treatment response is frequently hampered even further by the comorbidity of the two conditions. Among individuals with MDD, approximately 25–40% have a comorbid SUD. Conversely, MDD is among the common psychiatric disorders that have high comorbidity with all types of SUDs.[27,28] These patients report poorer response rates compared to their singly diagnosed counterparts from a 12-step program,[29] from single-medication trials,[30–32] and from cognitive behavioral therapy.[33] Likewise, MDD patients with nicotine dependence also have increased difficulty with smoking cessation, with antidepressants having little influence on abstinence, and these patients are more likely to develop an episode of depression post–smoking cessation.[34–37] Hence, treatment strategies should ideally accommodate the frequent comorbidity of these illnesses.

Treatment strategies for MDD and SUDs are traditionally approached separately and sequentially. Such an approach implicitly assumes that if the primary diagnosis is addressed, secondary diagnoses may resolve on their own.[38] However, limited success rates for conventional approaches to MDD and SUDs raise several fundamental questions. Is it helpful to identify one of the disorders—MDD or SUD—as the primary disorder? Does the underlying pathophysiology of MDD and SUDs support separate treatment strategies in comorbid cases? Finally, can the neurobiology of SUDs and MDD suggest new treatment strategies that might address the problem of comorbidity, while improving remission and relapse rates for both disorders?

To answer these questions, we can take advantage of recent advances described in the neuroimaging literature on human brain function. These include an increasingly robust model of the functional neuroanatomy and network architecture of the brain, a vast body of neuroimaging literature on the pathophysiology of SUDs and MDD in humans, and, finally, a set of automated, quantitative meta-analytic software that renders this enormous literature more tractable. Such tools allow us to detect consistent and statistically robust patterns by combining scans in thousands of patients and healthy individuals.

Of course, advances in the functional neuroanatomy of SUDs and MDD are of limited immediate clinical interest unless they can translate into anatomically specific therapeutic interventions. While it is difficult to aim conventional treatments at specific brain circuits, noninvasive brain stimulation (NIBS) is an emerging treatment modality that exerts neuroanatomically specific effects. There are two particular NIBS technologies that are quickly translating from research into clinical practice: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Repetitive TMS has held regulatory approval for MDD in many jurisdictions for several

years and is being explored for SUDs in clinical trials. Transcranial DCS is a few years behind rTMS in translational progress but is likewise being explored with encouraging results in both MDD and SUDs. Unlike medications or therapy, the success of NIBS depends critically on the choice of target circuit and the type of stimulation (inhibitory or excitatory) applied to that circuit.[39–41]

This review is intended to serve four purposes. First, it will summarize key advances in our understanding of the functional architecture of the brain. Second, it will review how this emerging model of brain function relates to the pathophysiology behind SUDs and MDD. Third, it will review NIBS for the treatment of SUDs and MDD, particularly in cases where conventional treatments fail. Finally, it will review a number of promising areas for future research on NIBS in SUDs and MDD.

Functional architecture of the human brain

Functional networks of intrinsic brain activity

One of the key advances in the neuroimaging literature over the last 20 years is the demonstration that brain regions organize their activity into coherent functional networks.[42] On functional magnetic resonance imaging (fMRI), these networks appear as correlations of the low-frequency fluctuations in blood oxygenation level–dependent (BOLD) signal between brain regions.[43] Many networks were originally identified through data-driven methods for analyzing brain activity at rest and are termed *resting-state networks*. However, these networks reliably appear in ongoing brain activity during tasks as well,[44] and meta-analyses of task-based activation also reveal consistent *functional networks* similar to those identified at rest.[45]

The precise number of functional networks and the functional role of each network are still being studied. An emerging consensus has been identified between 7 and 20 distinct functional networks.[43] One recent resting-state fMRI analysis in 1000 healthy individuals found a stable seven-network parcellation; these networks were further subdivided into a stable 17-network parcellation (Fig. 1).[46] Many of these cortical networks also have correlated counterparts in the striatum[47] and cerebellum,[48] thus hinting that they may represent integrated, whole-brain functional circuits.

The default-mode network (DMN)[49] is the best known and most studied of these functional networks. The DMN contains subcomponents that serve various introspective functions ranging from mind wandering,[50] recollection and prospection,[51] rumination,[52] and self-reflection.[51] Other networks act in opposition to the DMN and activate during behaviorally regulated task performance and externally focused cognition. These networks include frontoparietal networks (FPNs) and related areas sometimes known as the dorsal (DAN) and ventral attention networks (VAN).[46] Other networks include lower-level sensory and motor cortices and ventromedial limbic networks that encompass the temporal pole and the orbitofrontal cortex (OFC)[46] (Fig. 1).

Relevance of functional networks to MDD and SUDs

Several functional networks have been studied extensively in MDD and SUDs, particularly the DMN. However, there are two functional networks that are of particular interest in both SUDs and MDD, and it is worthwhile to briefly characterize these networks.

The first network of interest is the anterior cinguloinsular network (aCIN), or salience network (SN).[46] Figure 2 visualizes the SN on the basis of a quantitative meta-analysis of SN neuroimaging studies analyzed using Neurosynth.[45] The SN activates for salient sensory events,[53,54] transitions from introspection to task performance,[55] and during task initiation and switching.[56] A remarkable recent study highlighted the central importance of the SN as a common neural substrate across psychiatric illness categories.[57] The authors performed a meta-analysis of structural abnormalities across six psychiatric disorder categories, including MDD and SUDs, and found that all of them showed gray matter volume reductions in the dorsal anterior cingulate cortex (dACC) and anterior insula. Further analyses demonstrated that these areas belonged to a common functional network in healthy controls, both at rest and during task performance.[57] This network corresponded almost exactly to the SN.[45,46] Thus, of the 7–17 networks previously discussed, the SN merits particular attention for its role in MDD, SUDs, and other psychiatric pathophysiology.

The second network of interest is the ventromedial network (VMN), encompassing the nucleus accumbens (NAcc), medial OFC (mOFC), and

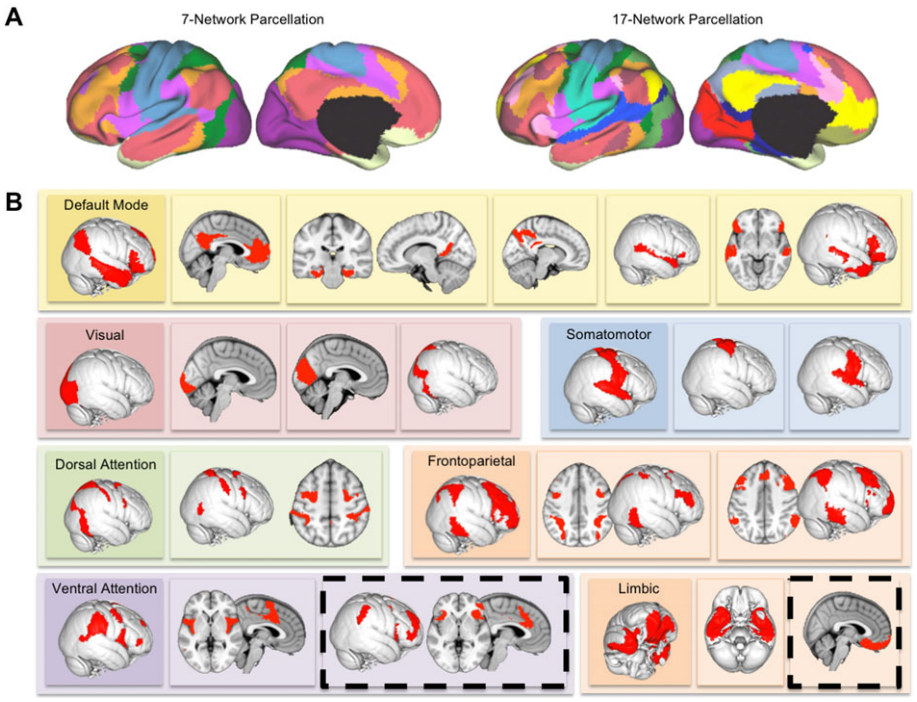

Figure 1. Functional networks in the intrinsic activity of the brain. (A) The intrinsic ongoing activity of the brain at rest or during task performance can be decomposed into sets or networks of brain regions that show correlated patterns of activation and deactivation over time. A set of at least seven distinct functional networks has been identified as consistently appearing in large datasets of up to 1000 individuals. However, these seven networks contain smaller sub-networks. A 17-network parcellation has been identified as stable across individuals. (B) The 17 resting-state networks identified by Yeo *et al.*[46] include low-level visual and somatosensory cortical areas, higher-level networks involving premotor and sensory association areas, and larger frontoparietal networks involved in attention, cognition, and executive control. However, two networks (highlighted in dashed black lines) are of particular interest in MDD and SUDs: the more anterior of the two subnetworks of the ventral attention network and the ventromedial subnetwork of the limbic network. Adapted from Yeo *et al.*[46]

ventromedial prefrontal cortex (VMPFC) (Fig. 3, created using Neurosynth[33]). This circuit is best known as the reward pathway and also includes components of the mediodorsal thalamus and midbrain dopaminergic structures. The VMN activates not only for rewards, but also for stimuli of other incentive value, including losses.[58] The role of the VMN in SUDs is well documented,[59,60] particularly for mediating abnormal incentive salience of drug cues, which is proposed to drive craving and relapse.[61] VMN dysfunction is linked to anhedonia in MDD[62] and activates paradoxically for negative stimuli, suggesting that negative cues have abnormal incentive salience in MDD, analogous to drug cues in SUDs.[63]

The opposed functions of the SN and VMN

The SN is critical for "switching" brain activity between the introspective DMN and the externally focused FPNs.[64] It is also active during performance-related errors and task initiation.[56,65] The functions of the SN map rather well on to the Research Domain Criteria (RDoC) construct of cognitive control: specifically, the subdomain of response inhibition/response selection. A quantitative fMRI meta-analysis using Neurosynth[45] revealed a network closely matching the SN (Fig. 2). This function stands in opposition to the functions of the VMN in mediating reward, incentive salience, and value assignment in similar meta-analyses using Neurosynth[45] (Fig. 3). These two circuits have been proposed to play opposing roles in behavioral regulation: the VMN as a "drive network" mediating craving and urge, and the SN as a "gatekeeper network" mediating response selection and inhibition.[66]

If the roles of these networks are indeed opposed, we might predict one to be active when the other

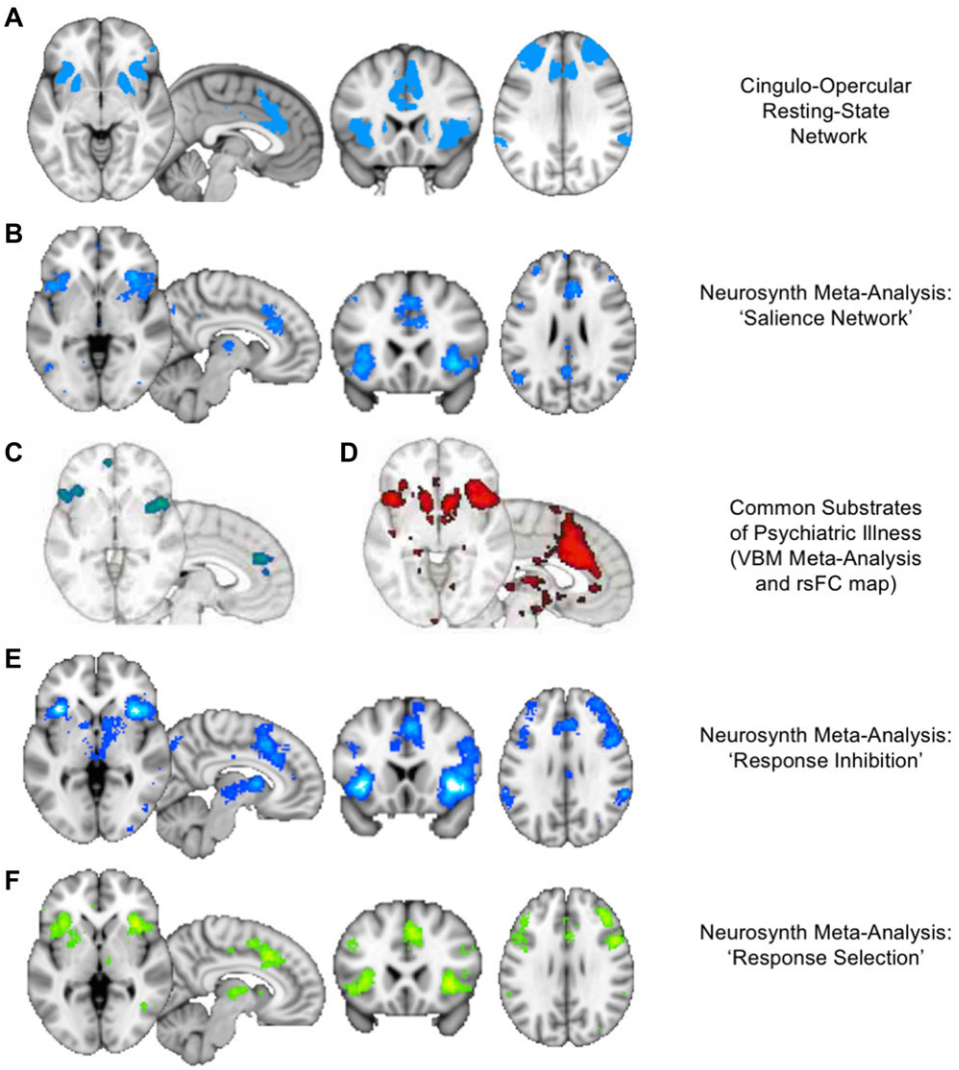

Figure 2. The salience network (SN). The reader is encouraged to replicate and explore the depicted networks in the Neurosynth tool.[45] (A) The cingulo–opercular network from the parcellation of Figure 1 includes prominent nodes in the dorsal anterior cingulate cortex (dACC), anterior insula, dorsolateral prefrontal cortex (DLPFC), and inferior parietal lobule, as well as the dorsal anterior caudate nucleus. (B) A Neurosynth meta-analysis[45] using the term "salience network" reveals the close correspondence of this network to the cingulo–opercular network identified above. Note that the mediodorsal thalamus can also be seen in the network in this analysis. (C) The areas identified as common sites of gray matter loss across MDD, SUDs, and several other categories of psychiatric disorders in a meta-analysis of 193 voxel-based morphometry studies[57] correspond closely to SN nodes in the dACC and anterior insula. (D) Resting-state functional connectivity maps seeding from the nodes in C reveal a network that corresponds closely to the rest of the SN, as seen in A and B.[45] (E, F) Neurosynth meta-analyses using the terms "response inhibition" and "response selection" yield maps of activation that correspond closely to the SN, thus highlighting the role of the SN as a neural substrate for cognitive control.[57]

is not, and vice versa.[67] In fact, this is precisely the case. For many of the functional networks previously discussed, there also exists a map of corresponding negatively correlated regions: the anti-network.[68] The anti-network for the VMN, shown by qualitative meta-analysis, consists of the SN and corresponding striatothalamic partners. Conversely, the anti-network for the SN is the VMN, as evident in functional connectivity data[45] (Fig. 4). Thus, the SN and VMN may play

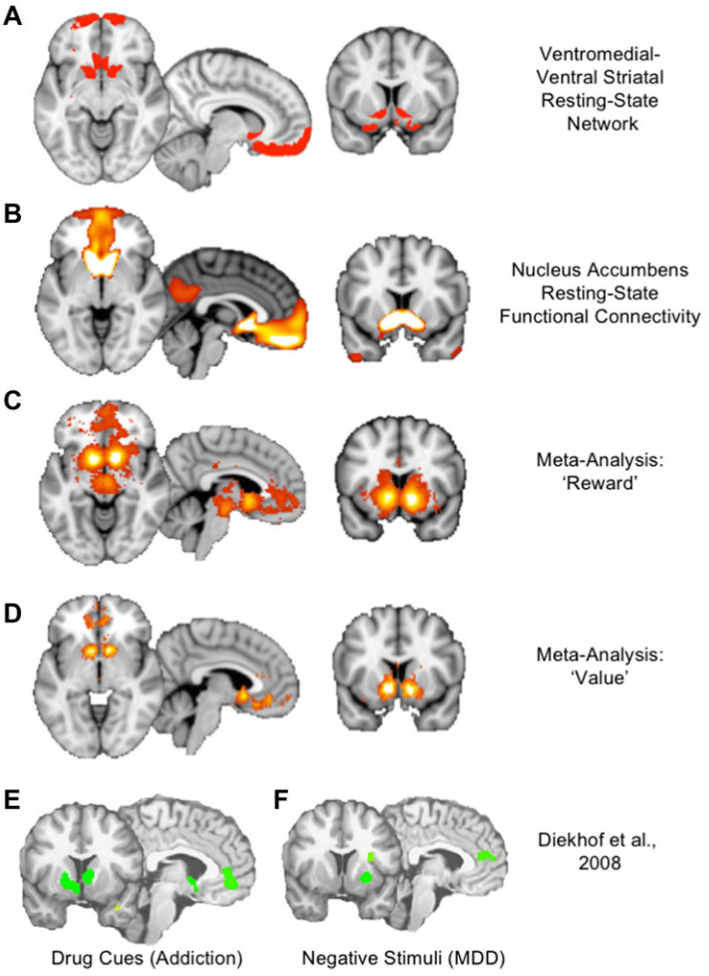

Figure 3. The ventromedial network (VMN). The reader is encouraged to replicate and explore the depicted networks in the Neurosynth tool.[45] (A) The VMN consists of the cortical and striatal nodes of the ventral striatal–ventromedial prefrontal network from the parcellation of Figure 1. (B) A resting-state functional connectivity map seeded from the nucleus accumbens illustrates the strong connection to the ventromedial prefrontal cortex (VMPFC) and frontal pole.[45] (C) A Neurosynth meta-analysis using the term "reward" reveals the classic reward circuit, including mesolimbic dopaminergic structures in the ventral tegmental area (VTA) and substantia nigra (SN), the ventral striatum, and a specific subregion of the VMPFC slightly posterior to the medial frontal pole.[45] (D) A Neurosynth meta-analysis using the term "value" reveals the striatal and cortical components of the VMN, suggesting a broader role beyond reward to include valuation of incentives.[45] (E) A meta-analysis of regions activated by drug cues in patients with addiction reveals a circuit corresponding closely to the VMN, illustrating the pathological distortion of reward value for drug cues in addiction.[63] (F) A meta-analysis of regions activated by negative emotional stimuli in MDD reveals a similar signature of pathological activation of reward-related areas for negative rather than positive cues, illustrating a common pathophysiology of distorted incentive salience in the VMN across SUDs and MDD.[63]

reciprocal roles as each other's anti-networks, with opposing patterns of activity even in the resting brain. This functional architecture might explain the tendency for highly salient stimuli to reduce inhibitory control or, conversely, for cognitively demanding activities to attenuate urges, cravings, or emotions.

Coordination among the functional networks

Modeling the brain as a network can allow us to map information flow among its regions. Approaches to the study of the brain using graph theory, a set of mathematical techniques allowing formal analysis of network structures, consider individual brain regions as "nodes" and functional

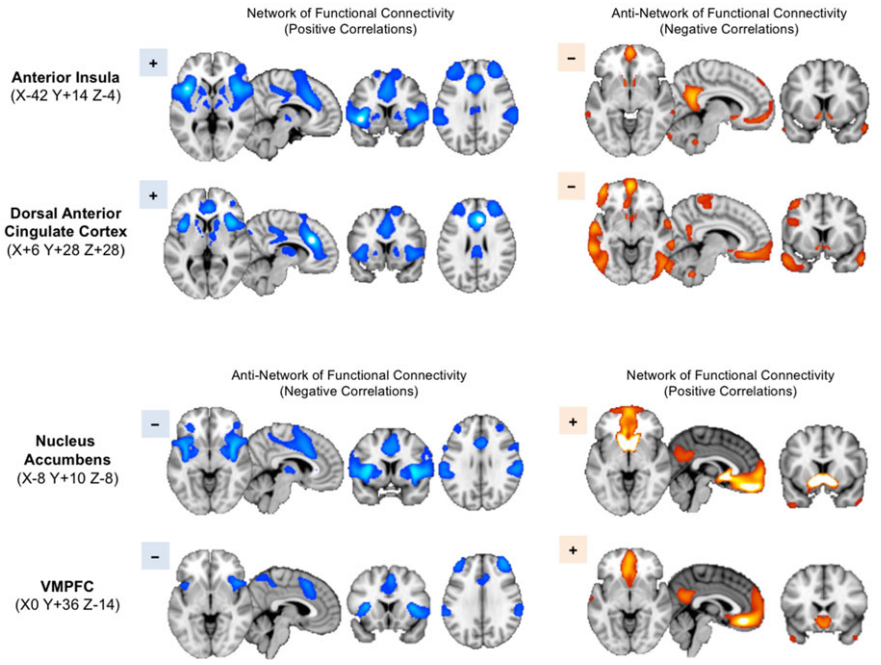

Figure 4. Reciprocal relationship of SN and VMN activity. The reader is encouraged to replicate and explore the depicted networks in the Neurosynth tool. Resting-state functional connectivity maps are generated using the Neurosynth tool[45] from the seed coordinates indicated at left. Seeds in the anterior insula and dACC reveal a network of positively correlated regions throughout the other nodes of the SN, as expected (upper left). Notably, the anti-network of these SN seeds (i.e., regions showing negative rather than positive correlations) includes the key VMN nodes in the ventral striatum, VMPFC, and temporal poles (upper right), as may be seen by comparison with Figure 3. Conversely, seeds in the nucleus accumbens and VMPFC reveal a network of positively correlated regions corresponding to the VMN (lower right). The anti-network of these seeds corresponds well to the SN (lower left). In order to highlight the correspondence of the networks and anti-networks, blue colors are used for the SN networks and the VMN anti-networks, while orange colors are used for the VMN networks and SN anti-networks.

connections between correlated regions/nodes as "edges." Such analyses identify clique-like "communities" of nodes and "hubs" that bridge together different communities within a larger network.[69] This means that graph theoretical approaches can characterize the structural and functional interactions between networks and nodes.[70]

Reassuringly, graph theoretical analyses of the brain extract 10–12 communities that correspond to the same data-driven functional networks[70] and also show how these communities connect to one another (Fig. 5A). Generally, sensory and motor networks lie on the functional outskirts of the brain, as isolated functional units with few connections outside of their network. This makes sense given their roles as pathways for processing elementary sensory input and motor output.

What about other prominent networks, such as the DMN itself? The intuitive expectation is that the DMN should be situated centrally, in a crossroads position linking the other networks together. Instead, the DMN appears as a peripheral, close-knit module much like the visual cortex, but taking feedback from the VMN rather than the retina. The DMN's position is not that of an integrative controller, but rather another specialized "think tank," linking the incentive functions of the VMN to the high-level executive and cognitive functions of the FPNs, but not in close communication with most other networks (Fig. 5B).

Does another functional network hold the crossroads position? One recent study using graph theoretical methods identified nodes standing in critical hub positions between many networks. These nodes lay not in the DMN but in the SN itself.[71] Close inspection of the whole-brain graph showed that the SN is in a gatekeeper position between the deliberative functions of the DMN and FPN and the behavioral output of the somatomotor cortex (Fig. 5B).

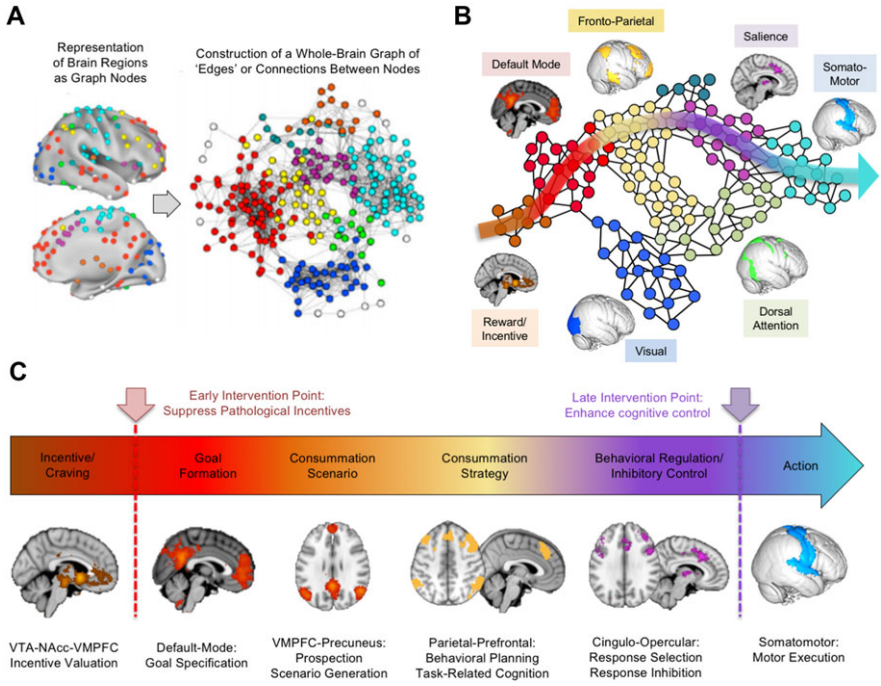

Figure 5. Network architecture of the brain from incentive formation to behavioral execution. (A) The network architecture of the brain can be derived by placing nodes to cover the entire cerebrum and then extracting the intrinsic activity of these nodes over time. By connecting the well-correlated nodes with "edges," a graph of the network architecture of the brain can be constructed. Within this architecture, the functional networks illustrated in Figure 1 appear as clusters of cliques, and the larger relationship between the networks can be seen.[70] (B) A schematic derived from A illustrates a trajectory of information flow for behavioral control. This trajectory begins in the reward circuitry of the VMN, passing through the default-mode and frontoparietal networks and then the SN, before exiting the cerebrum via the nodes of the sensorimotor cortex to direct bodily movements. (C) This pathway of connections passes from one brain region to the next and allows the mapping of basic drives into specific incentives or cravings via the VMPFC and then the elaboration of these incentives into specific goals and scenarios via the default-mode network, followed by the refinement of these scenarios into specific strategies or plans for consummation of the goal. However, before these strategies can be executed as motor actions in the sensorimotor cortex, they must pass through the nodes of the SN, which thus sits in a gatekeeper position for response selection and behavioral inhibition. This functional architecture suggests that two points of intervention may be possible in SUDs and MDD: suppressing the pathological incentives early in this pathway at the VMPFC and/or strengthening the gatekeeper functions of response selection late in the pathway, via excitatory stimulation of the SN.

This overall functional architecture provides a framework for understanding the roles of the VMN, DMN, FPN, SN, and motor cortex in behavioral control (Fig. 5C). The trajectory of information flow originates within the basic drives of midbrain dopaminergic regions, which are elaborated into specific incentives or urges via the VMN and elaborated further into goals and mapped onto relevant scenarios via the DMN. The FPNs then develop these goals and scenarios into consummatory strategies, which are broken down into cognitions and behaviors that can be either inhibited or selected via the gatekeeper-like SN. If selected, responses finally map to the action-control systems of the somatomotor cortex to initiate overt behavior.

This urges-to-actions trajectory through the brain offers early and late points for pathology to arise in MDD or SUDs. Early pathology at the VMN–DMN interface would drive priorities away from core survival needs, assigning inappropriately high incentive salience to drug cues (in the setting of SUDs) or negative emotional cues (in the setting of MDD). Late pathology near the SN would interfere with response selection and inhibitory control, producing a pattern of chronic emotional liability, intrusive thinking, and impulsive behavior. These more elementary dysfunctions may cut across the diagnostic entities of MDD and SUDs, and may also shed light on MDD and SUD comorbidity as arriving from more fundamental disruptions in

network architecture. Importantly, the neural overlap between MDD and SUDs may be an opportunity, rather than an obstacle, for interventions that can address both illnesses concurrently by targeting the underlying circuitry of the SN and VMN using NIBS.

Functional architecture in psychiatric disorders

Neural circuit disruptions in SUDs

It is challenging to concisely summarize the neural circuits that are involved in all SUDs, since each substance has a unique pharmacologic profile and addiction involves multiple temporal phases, including regular controlled use, regular uncontrolled/habitual use, abstinence, and relapse. However, there appear to be common neurobiological pathways operating across substances of abuse, involving dysfunction of both the VMN and its anti-network, the SN.

Although patients with SUDs can become dependent on a variety of drugs that have diverse initial pharmacologic actions, nearly all drugs of abuse have a common final pathway in which they modulate reward circuitry in the ventral striatum–ventral tegmental area (VTA) pathway.[72] For example, cocaine modulates this pathway directly by increasing dopamine transmission, while nicotine also has direct actions on the VTA via nicotinic receptors. Opiates and alcohol, however, modulate the ventral striatum and VTA indirectly via GABAergic disinhibition. While the majority of basic science research in addiction has focused on this subcortical reward pathway, recent work has demonstrated that many cortical and subcortical regions interact with this mesolimbic dopamine pathway, especially the VMN and its anti-network, the SN, as described below.

First, the SN is hypoactive in SUDs. Specifically, in SUD patients, the dACC and insula display hypoactivity to a variety of executive tasks, including the Stroop task,[73,74] response inhibition[75,76] (although this finding is mixed[77]), and emotion regulation.[78] The dACC also displays abnormal connectivity on resting-state and graph theoretical measures in SUDs.[79] The abnormal network activation in the dACC may relate to the aberrant salience of substance-specific cues.[80] SUD patients display lowered structural and functional integrity in both the dACC and insula.[81,82] Although the role of the insula is still under debate, insular lesions have been reported to be associated with improved abstinence, possibly because disease-relevant cues are less salient.[83,84] There is also an increase in dACC activation and an improvement in self-control behavior following abstinence, suggesting a causal role in SUD psychopathology.[85]

The anti-network of the SN, the VMN, is involved in limbic arousal in SUDs. Functional MRI studies have demonstrated that cue reactivity and craving are associated with elevated activity in the VMN, particularly in the ventral striatum, vmPFC, and OFC.[86–88] Hyperactivation from the OFC is also seen during reward evaluation,[89–91] risky decision making, personal relevance,[92–95] and goal-driven processes associated with the ventral striatum. This abnormal VMN activity normalizes in smokers and cocaine users following treatment with varenicline/buproprion[96–98] and methylphenidate,[99] respectively. As in MDD, SUD patients also show VMN hypoactivation for natural rewards, compared to healthy controls.[100]

Connectivity between the VMN and SN is also impaired in SUDs, with SUD patients showing reduced corticostriatal VMN and SN resting-state functional connectivity.[101,102] Furthermore, altered ACC corticocortical and corticostriatal connectivity between these circuits are related to SUD severity,[101] high-risk behavior, and genetic polymorphisms associated with SUDs.[103]

Neural circuit disruptions in MDD

As with SUDs, MDD has been linked to a pattern of SN hypoactivity and VMN hyperactivity[104] in a wide variety of network-based descriptions of the illness over the last decade.[105,106] Ventral prefrontal activation in MDD predicted dorsal inactivation, in keeping with the framework of opposed SN and VMN activity.[107] Inhibition of SN control mechanisms by pathological salience signals from the VMN may create a self-perpetuating imbalance, resulting in the persistent low mood of MDD rather than the transient low mood of normal sadness.

MDD patients display a similar disruption of incentive salience for primary rewards[108,109] and instead become attuned to disease-specific stimuli. For example, the rostral ACC and ventral striatum are hypoactive during reward feedback[110–112] and hyperactive during self-referential negative processing.[113,114] MDD patients also show an absence of ventral striatal and VMPFC/OFC inactivation

for pleasant sights and tastes but heightened activation in the caudate in response to viewing aversive images.[115] Altered responses from the subgenual cingulate and OFC are also found in MDD during rumination and negative self-focus.[116]

As in SUDs, MDD patients show reduced activation in SN regions at rest. Reflecting this deficiency, MDD patients exhibit task-related hyperactivation from the dACC on many cognitive control tasks, including the Stroop[117,118] and n-back tasks.[119] The DMPFC is also inappropriately activated during positive affect processing in MDD, which normalizes after successful treatment.[120] Additionally, the anterior insula and DMPFC are inappropriately active during negative affect.[121] Increased activation after treatment also results in improved resting-state activity in the cingulate in MDD.[122] On structural imaging, TRD patients tend to show volumetric alterations in regions of the SN and cognitive deficits relative to their treated counterparts.[123]

Neural similarities in MDD/SUDs

As noted earlier, voxel-based morphometry studies of MDD and SUDs reveal a common neural substrate of decreased gray matter affecting the dACC and anterior insula—both key nodes of the SN.[57] One interpretation of this neural overlap is that both SUDs and MDD feature deficits in self-regulation of impulses, cognition, emotion, and behavior—or in RDoC terms, response inhibition/selection. SUDs and MDD also share a common feature of inappropriate VMN activation as shown by fMRI. In SUDs, the VMN's reward circuit activates in response to drug cues, despite their lack of primary survival value. In MDD, the VMN activates in response to negative rather than positive affective stimuli. One interpretation is that, for MDD, negative emotional stimuli acquire aberrant incentive salience, as with drug cues in SUDs. If so, both SUD and MDD patients also share an underlying pathology of distorted incentive salience.[63]

The shared neural substrates of SUDs and MDD may help to account for the high prevalence of MDD/SUD comorbidity. From a therapeutic standpoint, the shared neural circuitry between SUDs and MDD may also present an opportunity to address both disorders concurrently, using NIBS interventions. On this view, NIBS treatments should not be regarded as antidepressant or anti-substance use. Rather, they should be considered to offer two more nuanced approaches to treatment, cutting across diagnostic categories: enhancing cognitive control by targeting the nodes of the SN or relieving the distorted incentive salience of substance/negative cues by inhibiting the VMN.

One prediction of this framework is that any NIBS interventions that target SN nodes (i.e., DLPFC, DMPFC, or anterior insula) with excitatory stimulation should exert a therapeutic effect across both MDD and SUDs, by enhancing cortico–striatal–thalamic connectivity through the SN on fMRI and by enhancing capacity for response selection/inhibition. Another prediction is that any NIBS interventions that target the VMN (by stimulating the frontal pole or VMPFC) should also exert a therapeutic effect across both MDD and SUDs by reduced cortico–striatal–thalamic connectivity through the VMN on fMRI, and by reducing incentive salience of drug cues/negative affective stimuli.

NIBS as a treatment for MDD/SUDs

Repetitive TMS overview

Repetitive TMS applies powerful, focused, magnetic field pulses to target regions of the brain via a handheld induction coil placed against the scalp. By applying trains of pulses over several minutes, rTMS increases or decreases target brain region activity. While experimental applications of rTMS usually involve 1–3 sessions on a single day, therapeutic applications of rTMS typically require 20–30 daily sessions.[124,125]

Repetitive TMS appears to act through the mechanisms of synaptic plasticity: long-term potentiation and depression, although there is conflict among the effects of genetic polymorphisms, such as brain-derived neurotrophic factor, on these functions.[126,127] Generally, the direction of the effect depends on the intensity, duration, and stimulation pattern.[128,129] High-frequency stimulation (5–20 Hz) is classically considered excitatory, while low-frequency stimulation (1 Hz) is inhibitory.[130,131] Some recent rTMS studies use stimulation patterns that mimic theta electroencephalography (EEG) rhythms, thought to be especially efficient for inducing plasticity.[132,133] For example, two advantages of theta-burst stimulation (TBS)—classified as intermittent TBS (iTBS), which is generally excitatory, or continuous TBS (cTBS), which is generally inhibitory—are that the time required for a session of stimulation is rather brief and that it is as

potent as conventional stimulation, both in model systems such as the motor cortex[133] and in clinical applications.[134,135]

One current drawback to all forms of rTMS concerns the variability of effect: a certain percentage of individuals show neutral or inhibitory effects from excitatory stimulation and, conversely, some individuals show excitatory effects from inhibitory stimulation.[128,136] This variability is observed both in model systems such as the motor cortex during single sessions and in therapeutic applications of rTMS over multiple sessions.[137,138]

Therapeutic effects of rTMS in neuropsychiatric disease may ensue through changes in cortico–striatal–thalamic circuits stemming from SN and VMN nodes. Positron emission tomography (PET) studies of rTMS reveal changes in striatal dopamine receptor occupancy following rTMS, with the changes localized to the specific region of the striatum that serves the cortical target (DMPFC and DLPFC) of stimulation.[139,140] In keeping with this observation, dopamine agonists and antagonists can potentiate or block the effects of rTMS.[141] Baseline cortico–striatal–thalamic functional connectivity on resting-state fMRI predicts treatment outcome across multiple conditions, including MDD,[142] eating disorders,[138] OCD,[143] and movement disorders.[144] Pre–post treatment changes in this measure also track outcomes across all of these disorders. Thus, rTMS is posited to exert therapeutic effects by enhancing or suppressing cortico–striatal–thalamic circuit integrity from the SN and/or VMN.

Transcranial DCS overview

Transcranial DCS applies lower-energy stimulation to the brain, using a montage of over two scalp electrodes, each typically 3–7 cm across. Constant-current stimulation is applied through the electrodes at intensities of just 1–2 mA. A tDCS session typically lasts 5–30 min, and a therapeutic course typically involves daily stimulation over 10–30 days.[145]

Transcranial DCS seeks to modulate the synaptic activity of target brain regions, rather than directly eliciting action potentials, as does rTMS.[146] Anodal stimulation is classically considered to increase cortical excitability in the underlying brain region, while cathodal stimulation is considered to be inhibitory. However, as with rTMS, some individuals show the opposite pattern of effect, and variability remains a problematic issue.[147] Newer patterns of stimulation include transcranial random noise stimulation (tRNS), as well as transcranial alternating current stimulation (tACS). The latter approach is considered promising, since stimulation can be tuned to match specific EEG frequency bands for more potent or more selective effects.[148] In one notable recent example, investigators were able to induce lucid dreaming in healthy subjects during rapid eye movement (REM) sleep by applying tACS at 20–40 Hz, but not at 2–12 Hz.[149]

The mechanisms of tDCS/tACS are still under investigation.[150] However, the technique does appear to modulate the activity of resting-state networks on fMRI[151] and may also modulate cortico–striatal functional connectivity.[152] In these respects, its mechanisms may resemble those of rTMS to some degree, and, for therapeutic purposes, both techniques have been used to target similar brain regions in similar illnesses. However, at the physiological level, there are likely to be important mechanistic differences between the two approaches, the details of which require further study.[146]

Transcranial DCS is likely capable of stimulating many of the same regions as rTMS, although, once again, focal stimulation becomes more difficult for deeper structures. Electrical field simulations suggest that the direct effects of tDCS on neural activity are most prominent near superficial brain regions directly under the electrode, although deeper effects may be possible.[153] Preclinical studies indicate that tDCS can modulate the excitability of the motor cortex and DLPFC,[154] as well as deeper structures of the medial wall, such as the motor cortex of the lower limb,[155] supplementary motor area,[156] and DMPFC.[157] There are also suggestions that tDCS may be capable of modulating the reward value of stimuli during task performance, suggesting engagement of deeper VMN nodes, such as the VMPFC and even the midbrain.[158] Thus, many of the areas of interest for NIBS in MDD and SUDs are likely to be accessible to both tDCS and rTMS.

NIBS as a treatment for MDD

MDD is the original and best-studied therapeutic indication for rTMS. To date, dozens of large-scale randomized controlled trials have confirmed efficacy for rTMS in MDD, as summarized in recent meta-analyses.[159,160] Response and remission rates in the most recent large studies are approximately

50–55% and 30–35%, respectively;[161,162] real-world effectiveness studies report similar outcomes.[159,160] Course lengths of 26–28 sessions are required for maximum effect;[124] the poorer outcomes of early trials may be attributable in part to inadequate course lengths of 5–10 sessions.[160]

The most widely used rTMS protocol in MDD is high-frequency left DLPFC stimulation. Some studies alternatively used low-frequency right DLPFC rTMS,[161] or both.[162] Meta-analyses have not found marked outcome differences between these approaches,[160] and no one stimulation pattern appears markedly superior.[162] Few NIBS studies have sought targeted non-DLPFC nodes of the SN or VMN in MDD.[163] One exception is the DMPFC,[164] which was recently targeted with rTMS in a sham-controlled study and in several open-label case series,[142,165,166] with promising results. However, no rTMS trials have targeted the anterior insula or the VMPFC in MDD; these remain theoretically promising targets for intervention.

Mechanistic studies show that DLPFC or DMPFC stimulation may enhance cognitive control in healthy subjects and MDD patients. DLPFC or DMPFC excitatory rTMS in healthy subjects can enhance impulse control via delay-discounting tasks;[167] likewise, rTMS of the presupplementary motor area, just posterior to the DMPFC, improves stop-signal task performance.[168] Neurally, rTMS may enhance impulse control via strengthened DLPFC and DMPFC frontal–striatal–cortical circuit integrity on fMRI,[138] and, on PET, rTMS changes dopamine receptor occupancy in these same striatal regions.[169] In MDD, cortico–striatal–thalamic connectivity on fMRI predicts and correlates with treatment outcomes.[142] These findings suggest that rTMS could be relieving MDD by enhancing cortico–striatal–thalamic circuit integrity in the nodes of the SN, thereby enhancing cognitive control over negative cognition and affect.

The literature on tDCS in MDD is more nascent. To date, 10 randomized controlled trials have been completed, with a recent meta-analysis supporting tDCS efficacy in MDD.[145] Outcomes appeared comparable to antidepressant medication in one comparative trial.[170] Again, 20–30 sessions may be required for maximal efficacy;[171] the shorter, 10-session courses and relatively small sample sizes used in many tDCS trials may imply an underestimate of the true efficacy of the technique.[145]

To date, all tDCS trials in MDD have targeted the left DLPFC, using anodal, excitatory stimulation over the F3 EEG site; the inhibitory cathode has been variously applied to either the right DLPFC via the F4 EEG site or to the neighboring right supraorbital area near Fp2/F8. Mechanistically, anodal tDCS over the left DLPFC enhances cognitive control in healthy participants on a working memory task with negative emotional distracters.[172] In a more direct demonstration, anodal DLPFC tDCS abolished the effect of negative emotional distractors on a working memory task in MDD patients,[173] suggesting that the mechanisms of effect may likewise involve enhanced cognitive control. The functional anatomy of the SN suggests that similar effects might also be achieved via excitatory tDCS of the right DLPFC, the DMPFC, and the anterior insula. Frontopolar tDCS is also of interest for the anhedonic symptoms of MDD, since anodal stimulation of this site engages the VMPFC and VTA on fMRI, and enhances perceived attractiveness of faces.[158] These regions are therefore important candidate targets for future tDCS trials in MDD.

NIBS as a treatment for SUDs and comorbid SUD/MDD

NIBS is attracting increasing interest as a novel therapeutic intervention in SUDs. To date, approximately 25 original research reports have been published on the efficacy of rTMS as a tool to decrease craving, along with at least six reviews on rTMS in addiction.[174] The types of SUDs, the targets of stimulation, and the patterns of stimulation have varied across these studies. However, as in MDD, most so far have sought to enhance cognitive control mechanisms by targeting the nodes of the SN.[174] The alternative approach, of attenuating craving and incentive salience via the VMN, is also beginning to be explored.[175]

For alcohol cravings, most studies have targeted the left or right DLPFC. In sham-controlled studies of rTMS, low-frequency right DLPFC stimulation reduced alcohol craving in some reports[176] but not others,[177,178] and high-frequency left DLPFC stimulation reduced attention to alcohol cues but did not reduce cravings.[179] In open-label case reports, bilateral high-frequency rTMS reduced alcohol cravings in three patients,[180] and low-frequency dACC rTMS likewise reduced refractory cravings in one patient; however, this patient eventually

relapsed following rTMS.[181] For DLPFC tDCS, left anodal/right cathodal stimulation reduced alcohol cravings in initial studies;[182,183] however, relapse rates improved with this montage.[184] Reversing the polarity to left cathodal/right anodal DLPFC tDCS yielded superior abstinence rates at 6 months, despite no differences in craving.[185] Such findings are consistent with a model in which SN stimulation exerts therapeutic effects by enhancing cognitive control rather than reducing cravings.

For stimulants (cocaine and methamphetamine), one open-label study reported reduced spontaneous craving with rTMS of the left DLPFC at high frequencies,[186] while another found effects for right low-frequency, but not left high-frequency, DLPFC rTMS.[187] Of note, rTMS of the left DLPFC at low frequencies has increased cue-induced craving,[188] and anodal tDCS of the left DLPFC has increased risky decision making in cocaine users,[189] once again suggesting that the stimulation parameters may be important in determining whether cognitive control is enhanced or diminished. A recent study of tDCS in crack cocaine dependence accordingly reversed the polarity of stimulation to left cathodal/right anodal DLPFC tDCS, reporting a reduction in craving with five sessions of active but not sham stimulation.[190]

For nicotine, a slightly wider variety of targets have been studied across the SN, including the DLPFC and anterior insula. Left DLPFC rTMS, using low- or high-frequency stimulation, has reduced cravings in experimental studies.[191,192] One clinical trial of high-frequency DLPFC rTMS reported reductions in the number of cigarettes smoked, even in the absence of changes in craving.[193] A more recent trial targeted the anterior insula, as well as the DLPFC, bilaterally with a helmet-shaped deep rTMS coil, in a large sample of 115 patients.[194] Thirteen sessions of high- but not low-frequency or sham rTMS reduced cigarette consumption and increased abstinence rates, with stronger effects when the patients were exposed to smoking cues during stimulation. However, there were no significant effects on craving despite the reduction in use, once again suggesting a mechanism of cognitive control enhancement rather than craving reduction per se.

With respect to tDCS in nicotine dependence, a preliminary study found that one session of active but not sham anodal bilateral DLPFC tDCS reduced cigarette cravings.[195] Another preliminary study[196] found a significant reduction in cigarettes smoked for active but not sham DLPFC stimulation using the left anodal/right cathodal polarity that had proven useful in alcohol and crack cocaine use, as above. A more recent study using the same type of tDCS[197] found a reduction in cigarettes smoked after 5 days of active but not sham stimulation. Furthermore, the active group showed signs of enhanced cognitive control, in the form of a greater propensity to reject offers of cigarettes (but not money) in a decision-making task known as the Ultimatum game. On an important side note, at least one report has noted that nicotine patches abolish the effects of both anodal and cathodal tDCS in healthy volunteers,[198] potentially posing a challenge to the therapeutic use of tDCS in tobacco cessation.

One final point concerns the potential of rTMS for treating comorbid MDD/SUDs in tandem, by addressing their common deficits in cognitive control. A recent study[199] used high-frequency bilateral DLPFC rTMS via a deep helmet coil, and compared outcomes in patients with MDD versus MDD and alcohol dependence. One major difference between deep TMS and conventional rTMS is the coil geometry; deep TMS coils employ complex helmet-shaped windings that are able to reach deeper cortical structures.[200] Depression scores improved 55% and 62% in the two groups, while scores on the Clinical Global Impression scale improved 67% and 78%. Improvement was actually significantly greater in the comorbid MDD/alcohol dependence patients than in the patients with MDD alone. It is also worth noting that a recent meta-analysis found that deep TMS appears to achieve antidepressant effects over multiple sessions.[201] The suggestion is that the presence of SUDs may not interfere with the outcomes of rTMS for MDD and indeed that the presence of comorbid SUDs might be an indicator of broader underlying deficits in cognitive control that render DLPFC rTMS more likely to be successful. This possibility warrants future investigation.

Future directions for NIBS in MDD and SUDs

Enhancing cognitive control

Cognitive control, and specifically response selection/inhibition, is presented in this review as one

of the key transdiagnostic deficits across MDD and SUDs. Its associated functional network, the SN, maps closely onto a set of areas affected across multiple categories of psychiatric illness. Of its core cortical nodes, investigations have relied heavily on the DLPFC for NIBS in MDD and SUDs. The dACC and anterior insula, however, actually appear more prominently and consistently in the network than the DLPFC.[57] Hence, it may be productive to pursue studies of dACC or anterior insula excitatory NIBS, under the hypothesis that these targets will surpass the DLPFC for enhancing cognitive control and thus achieve superior clinical outcomes in MDD and SUDs.

For the dACC, early evidence supports this hypothesis. In healthy controls, excitatory dorsomedial rTMS can reduce impulsivity on a delay-discounting task,[167] and there is a growing literature supporting clinical efficacy for DMPFC rTMS across multiple disorders.[142,165,166] DMPFC rTMS also shows initial promise for treating acute and chronic craving.[202] Dorsal ACC activity is higher in response to addiction cues,[93,203] especially when personally relevant,[92,93,95] and during other tasks involving cognitive control and response inhibition.[73,75,204]

Reducing incentive salience

Reward circuitry pathology, and specifically distorted incentive salience, is also presented in this review as a common feature of MDD and SUDs. The associated network, VMN, is a candidate target for NIBS treatments. At present, rTMS and tDCS are unlikely to be able to stimulate the ventral striatum directly because of the depth of this structure. However, the cortical nodes of the VMN are not markedly deeper than the dACC or anterior insula. At least one deep rTMS coil has been designed to target the VMPFC,[205] although it has not yet been used in MDD or SUDs. Likewise, at least one tDCS study has successfully modulated the VMPFC, along with the VMN circuit into the midbrain, enhancing perceived attractiveness of faces.[158] In SUD patients, one study recently targeted the frontopolar cortex[206] and found that high-frequency rTMS increased cue-induced cigarette craving, as would be expected for excitatory stimulation of this incentive pathway. Thus, stimulation of the VMN appears feasible and may exert effects on disease-relevant reward function.

Could inhibitory TMS to the VMPFC be beneficial for SUD patients?

While the majority of rTMS studies to date have focused on the DLPFC and its downstream targets in the dorsal striatum, a recent study demonstrated that it is also possible to activate the VMPFC and its targets in the ventral striatum with TMS. Using integrated TMS/MRI scanning, they demonstrated that it is possible to differentially activate the frontal–striatal systems that govern executive control from those that govern limbic arousal by applying single-pulse TMS to the DLPFC and the VMPFC/frontal pole, respectively.[66] TMS pulses applied to the frontal pole (EEG coordinate: FP1) led to elevated BOLD signal in the VMPFC, ventral striatum, and OFC—core regions of the VMN involved in limbic arousal and craving. TMS pulses applied to the DLPFC in healthy individuals at rest (EEG coordinate: F3) led to elevated BOLD signal in the DLPFC and dorsal striatum—core regions of the SN involved in executive control (Fig. 6A). Additionally, elevated DLPFC activity was accompanied by a reciprocal decrease in VMPFC activity, highlighting the reciprocal activity of these two networks.

Having demonstrated that it was possible to modulate activity in the VMPFC and ventral striatum, the authors performed a study in cocaine users[175] in which they applied an inhibitory form of TMS (continuous theta burst stimulation) to the medial PFC (FP1) while the participants were engaged in a craving-induction task. Specifically, patients underwent a functional MRI scan immediately before and after a single session of real or sham cTBS. Immediately before the cTBS session, participants were asked to describe the last time that they used cocaine, using standardized techniques from exposure therapy. They were then primed and asked to think about this event while the cTBS was administered. It was demonstrated that, relative to sham, active stimulation significantly decreased stimulus-evoked BOLD signal in the VMPFC and the ventral striatum—critical brain regions for craving (Fig. 6B). Additionally, these data revealed a significant correlation between the TMS pulse intensity and the effect on these neural circuits (Fig. 6C). Thus, inhibitory rTMS to the frontal pole appears to be a successful strategy for engaging and attenuating the VMN target, especially when an inhibitory dose of rTMS is

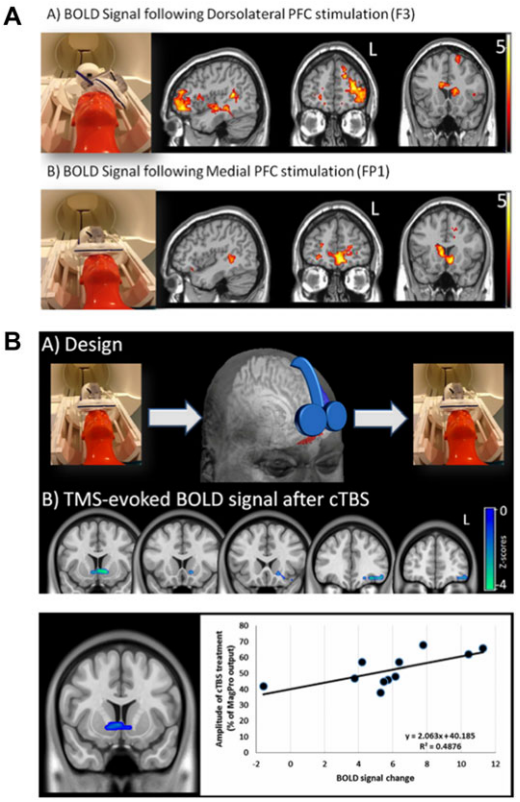

Figure 6. Preclinical evidence for targeting the VMN in SUDs. (A) TMS–fMRI studies reveal that stimulation of the DLPFC elicits activation in the corresponding corticostriatal circuit through the dorsal caudate nucleus, as well as other nodes of the SN. Stimulation over the frontal pole, in contrast, elicits activation in VMN nodes, including the VMPFC and ventral striatum.[66] (B) Applying an inhibitory pattern of rTMS to the frontal pole (two trains of 1800 pulses of cTBS, 60 s apart) causes a reduction in TMS-evoked activation in the VMN and other limbic-network regions, including the ventral striatum and orbitofrontal cortex (OFC). The degree of inhibition is proportional to the intensity of stimulation. This evidence suggests that inhibitory stimulation of the frontal pole may successfully reduce activation in the cortical and striatal nodes of the VMN, which could have therapeutic value for reducing cravings in SUDs and the incentive salience of negative emotional cues in MDD.

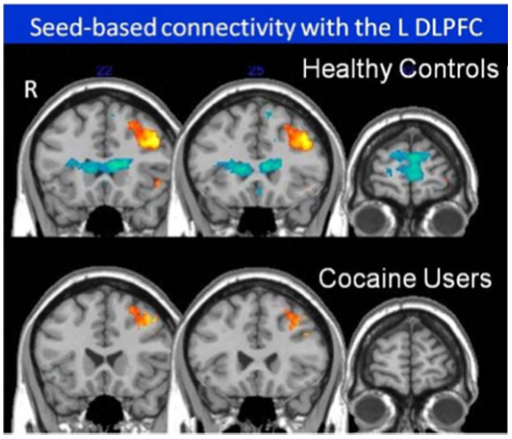

Figure 7. Aberrant functional connectivity of the SN and VMN in cocaine users versus MDD patients.[207] TMS of the DLPFC (F3 EEG site) during fMRI elicits local activation of the DLPFC itself, and reciprocal deactivation of the striatum and VMPFC, highlighting the reciprocal relationship of the SN and VMN in healthy controls. In cocaine users, however, TMS of the DLPFC elicited only local activation, suggesting a possible absence of the usual reciprocal relationship between SN and VMN may contribute to the pathophysiology of SUDs. If so, SN excitation alone may fail to inhibit the VMN and therefore may not exert the same degree of therapeutic effect in such cases. Instead, direct intervention to inhibit the VMN may be required.

applied to a neural circuit that is in a primed state (e.g., thinking about drug cues).

There are hints that this strategy may be more useful than SN excitatory stimulation in at least some patients with SUDs. Although the SN and VMN show reciprocal activity in healthy subjects, this may not be true in all individuals. In cocaine users, a recent MRI–TMS study showed that DLPFC rTMS did not elicit the usual pattern of reciprocal deactivation of the VMN[207] (Fig. 7). Thus, although some individuals may be able to achieve the desired suppression of the VMN indirectly during excitatory stimulation of the SN, other patients may require the VMN to be targeted directly. Investigating this hypothesis in MDD and SUD patients with neuroimaging methods will be an important area for future study.

Controlling the cognitive state during treatment

Few NIBS trials to date have controlled patients' cognitive state during treatment. Brain activity during stimulation is known to have an important influence on the effects of rTMS,[208–210] as evident even in the difference between resting and active motor threshold during motor cortex stimulation.

Repetitive TMS of the SN for nicotine addiction is more effective in the presence of smoking cues.[194] Conversely, in MDD, negative stimuli exposure during rTMS may disrupt the beneficial effects of treatment.[209] With frontopolar stimulation, the effects of rTMS on cigarette craving were different, depending on whether the patient was presented with smoking or neutral cues during stimulation.[206]

Thus, future efforts to improve outcomes for NIBS in MDD/SUDs will likely benefit from more rigorous manipulation of the cognitive state during treatment.

Optimizing the treatment protocol

Available evidence concurs with clinical experience in suggesting that maximal effects of rTMS in MDD require 20–30 sessions of treatment, regardless of site or protocol.[161,162,166] The limited evidence for tDCS likewise suggests that benefits continue to accumulate over 30 sessions in MDD.[171] For this reason, early literature may underestimate the therapeutic potential of NIBS, and longer courses are required for future studies to establish the true effect size.

Long courses of treatment may negatively affect treatment adherence, as well as the scalability of NIBS as a treatment in the larger population. SUD patients respond better to briefer treatment interventions than to extended ones.[211] However, more sessions need not require more days of treatment. Recent rTMS studies have begun to explore the use of multiple daily sessions separated by short intervals. These protocols are safe and tolerable, and have reduced the treatment course to 10 days with 2x daily stimulation,[212] 5 days with 4x daily stimulation,[213] and, in one small case series, 2 days with 15 sessions.[214] The optimal session number and interval have not been systematically investigated under randomized conditions, and this is an important area for future study. Accelerated regimens may be facilitated by cTBS and iTBS, which achieve similar effects as longer conventional protocols despite requiring only 1–3 min for delivery.[134,166] Other products that have the potential to be clinically impactful include deep TMS[201] and external trigeminal nerve stimulation.[215]

Reducing the variability of effect for NIBS

Although different NIBS protocols are classically considered to be excitatory or inhibitory, many individuals display effects opposite to the usual direction, or no effect at all. For 1-Hz rTMS, approximately 50% of individuals show excitation rather than inhibition;[128,136] likewise, for 10-Hz rTMS, a similarly large proportion show inhibition rather than excitation.[128] Variability is also problematic for cTBS and iTBS.[216] Likewise, for tDCS, one study found that only 36% showed the classic pattern of excitatory effects for anodal and inhibitory for cathodal stimulation, and the opposite was true in 21%.[147] The variability is not confined to the motor cortex: fMRI studies reveal similarly inconsistent effects of 1-Hz parietal rTMS on resting-state functional connectivity.[136]

This variability of effect likely impedes successful treatment outcome. Currently, there is no known reliable biological or neuroimaging marker to predict a priori which individuals will respond best to a particular stimulation target or stimulation protocol. However, group-level differences between responders and non-responders to treatment may help to elucidate these markers. For example, recent studies have found that 30 sessions of 10-Hz DMPFC rTMS strengthens cortico–striatal–thalamic resting-state connectivity in patients (responders) with low baseline connectivity, but weakens it in those with high baseline connectivity (non-responders).[138] Thus, variability of NIBS effects must be addressed in future studies to improve treatment outcomes.

Better methods to control patient brain activity during stimulation may ameliorate some of the interindividual variability. For example, 20-Hz rTMS and newer forms of cTBS more consistently show effects both in the motor cortex[128] and on resting-state functional connectivity.[136] Quadripulse stimulation (QPS) uses 4-pulse bursts of stimulation that can be excitatory or inhibitory depending on the inter-pulse interval,[217] and effects are longer lasting and appear consistent across greater than 85–90% of individuals. Unfortunately, most rTMS devices cannot perform QPS without significant hardware modification, and QPS protocols may require 30 min of stimulation for optimal effects.[218] Nonetheless, studies of novel rTMS protocols should be pursued to achieve better consistency in the effects.

Selecting and phenotyping patients

Important considerations in SUD trials are the type of substance dependence and the selection of SUD patients that are seeking treatment. Studies often do not disclose patient treatment-seeking status or whether patients are active substance users during NIBS treatments. Generally, patients are not abstinent for tobacco- or alcohol-related NIBS trials, while for illicit drug trials patients have completed detoxification. The active use of certain substances may influence the effect of

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NIBS. For example, tobacco use in healthy controls can reduce NIBS-induced inhibition of the motor cortex.[198] In cigarette smokers, NIBS-induced facilitation was found to be abolished during nicotine withdrawal.[219] Future studies should take into account these sources of heterogeneity, as they may alter clinical outcomes.

Diagnostic criteria are another important source of heterogeneity. MDD and SUDs are increasingly recognized to encompass a wide variety of subtypes, or endophenotypes. In MDD, for example, distinct endophenotypes have recently been proposed for patients with prominent memory impairment, neuroticism, cognitive control, and anhedonia.[220] The latter three have recently been linked to VMN disconnectivity and, consequently, poor response to DMPFC rTMS.[165] The presence of neutrally distinctive endophenotypes suggests that treatment targeted to individual pathology may improve success rates. For example, patients without cognitive control deficits, but with poor reward sensitivity, may be poor candidates for standard SN rTMS and might instead be better suited to stimulation of the VMN. Conversely, patients with mood liability, cognitive-control deficits, and multiple comorbidities, such as SUDs, might be identified as particularly good responders to SN NIBS.

A common practice in clinical trials of NIBS is to attempt to limit patient heterogeneity by excluding MDD patients with comorbid SUDs or active substance dependence. However, given that SN pathology may give rise to multiple comorbidities, this practice may be counterproductive in that it excludes good treatment candidates. A more productive approach may be to adopt generous inclusion criteria and to carefully characterize each patient before treatment.

Conclusions

Neuroimaging has revealed two functional networks playing key roles in MDD and SUD pathophysiology. The SN mediates cognitive control, and its hypofunction is a common feature across multiple psychiatric illnesses. The SN's anti-network, the VMN, plays a key role in reward and incentive salience. Distorted incentive salience is a common feature of both MDD and SUDs. MDD/SUD comorbidity, and the tendency for symptoms of one disorder to exacerbate the other, can therefore be understood as reflecting a shared set of reciprocal neural substrates: inappropriate VMN activation, resulting in pathological incentives, and/or insufficient SN activation, resulting in an inability to exert cognitive control over those incentives. NIBS targeting the SN may enhance cognitive control, thereby relieving a deficit common to MDD and SUDs. NIBS targeting the VMN is less well explored, but may attenuate pathological incentive salience, thereby reducing craving in SUDs and negative affect in MDD.

In conclusion, NIBS offers a promising new approach to treat MDD and SUDs. By strengthening cognitive control and quelling pathological incentive salience, NIBS may address underlying deficits common to both disorders, and may be particularly well suited to comorbid cases. Given the high prevalence and social impact of MDD and SUDs and high nonresponse rates, new treatment options will be a welcome development for clinicians and patients alike.

Conflicts of interest

The authors declare no conflicts of interest.

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