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Network-Guided Transcranial Magnetic Stimulation for Depression

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Abstract

Purpose of Review—First, we will identify candidate predictive biomarkers of antidepressant response of TMS based on the neuroimaging literature. Next, we will review the effects of TMS on networks involved in depression. Finally, we will discuss ways in which our current understanding of network engagement by TMS may be used to optimize its antidepressant effect.

Recent findings—The past few years has seen significant interest in the antidepressant mechanisms of TMS. Studies using functional neuroimaging and neurochemical imaging have demonstrated engagement of networks known to be important in depression. Current evidence supports a model whereby TMS normalizes network function gradually over the course of several treatments. This may, in turn, mediate its antidepressant effect.

Summary—One strategy to optimize the antidepressant effect of TMS is to more precisely target networks relevant in depression. We propose methods to achieve this using functional and neurochemical imaging.

Keywords

Depression; TMS; transcranial magnetic stimulation; Neuroimaging; Neuronavigation; Network; GABA; Biomarker

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Compliance with Ethics Guidelines

Conflict of Interest

Dr. Conor Liston, Dr. Michael A. Avissar, Dr. Irena Ilieva, and Dr. Faith M. Gunning declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Traditionally, transcranial magnetic stimulation (TMS) has been used for treatment of major depression via focal stimulation of the frontal lobes [1]. A hypofrontality model of depression, as supported by hypoperfusion of the left DLPFC on PET-imaging of depressed patients [2, 3] and post-stroke depression [4] provided the initial impetus for targeting the left DLPFC with TMS. Early case reports that TMS to the left DLPFC was efficacious in treating depression [5, 6] were followed by verification of the efficacy of TMS to the left DLPFC in both open label studies and rigorous sham controlled trials [7-9]. Antidepressant effects of TMS have been supported by several meta-analyses [10-13].

Early neuroimaging studies of the antidepressant mechanisms of TMS provided evidence that baseline frontal lobe perfusion predicted TMS response. In turn, TMS treatment modulated the abnormal frontal lobe perfusion often observed in depressed patients [14-17]. As neuroimaging technology, acquisition, and analytic techniques have advanced, studies of the antidepressant mechanisms of TMS increasingly focus on network-based mechanisms associated with the clinical expression of the depressive illness (e.g. emotional regulation, reward processing, anhedonia and psychomotor slowing).

This review will highlight how advances in magnetic resonance imaging (MRI) techniques (see [18, 19]) have been used to understand antidepressant mechanisms of TMS. The objectives of this review are threefold: 1. To identify neural predictors of antidepressant response; 2. To examine the effects of TMS on brain regions and networks involved in major depression, and 3. To use neural networks to inform the optimization of the antidepressant effects of TMS. To identify gaps in knowledge and to guide directions for future research, this review is restricted to major depressive disorder and focuses on two MRI modalities: resting state fMRI and neurochemical Imaging.

Resting state fMRI

Baseline predictors of TMS response

One highly replicated biomarker of the depressed state is elevated functional connectivity of the default mode network (DMN) [20-22]. The DMN comprises the medial prefrontal cortex (MPFC), posterior cingulate cortices, precuneus, inferior lateral parietal lobes, and parts of the medial temporal lobe. The BOLD signal of the DMN is most active when the subject is at rest and deactivates during periods of effortful behavior [23]. The DMN plays a key role in self-referential processing [24, 25], a process necessary for adaptive functioning which entails making sense of one's internal reality and one's role in the external environment. Negative self-referential processing is a hallmark feature of major depression and is expressed via cognitive symptoms including a negativity bias, rumination, pessimism, and hopelessness. The degree of increased functional connectivity (“hyperconnectivity”) of the DMN during the depressed state has been correlated with rumination [26] and persistent pessimism following antidepressant treatment [27]. Hyperconnectivity of the DMN normalizes following treatment with electroconvulsive therapy (ECT) [28] and serotonin-norepinephrine reuptake inhibitors [29].

A primary goal of personalized medicine is to discover measurements that can reliably predict the likelihood that a patient will respond to each one of a variety of prospective treatments [30]. In the quest for such predictive biomarkers of TMS treatment for depression, several investigators have evaluated differences in baseline, pre-TMS resting state functional connectivity of the DMN in patients who subsequently either responded or did not respond to a course of high-frequency (≥10Hz) TMS. Three studies in individuals with TRD produced convergent findings. First, TMS targeting the dorsomedial prefrontal cortex (DMPFC) produced better antidepressant response in patients with higher baseline functional connectivity between the DMPFC and sgACC and between the sgACC and DLPFC and lower baseline functional connectivity of cortico-thalamic, cortico-striatal and cortico-limbic projections [31]. Second, using a left DLPFC target [32] our group observed that higher FC between the sgACC and DLPFC, DMPFC, VMPFC, mOFC and bilateral posterior parietal cortex was associated with better antidepressant response. Another group replicated the predictive value of sgACC-DLPFC hyperconnectivity for response to 10Hz TMS over the left DLPFC [33]. The sgACC is a structure repeatedly found to be overactive and hypermetabolic in depression [34, 35]. These studies all highlight the potential for functional connectivity with the sgACC node of the default mode network to be a candidate predictive biomarker for response to TMS.

Several lines of research lend more direct support to the potential role of sgACC-DLPFC functional connectivity as a predictor of TMS-driven antidepressant response. In retrospective analyses, Fox and colleagues compared treatment efficacy of previously published studies on TMS for depression that used different methods of left DLPFC target identification. Relative to a set of normative resting state functional connectivity data, the best antidepressant response across studies was associated with increasing functional connectivity between the DLPFC target location and the left sgACC [36]. These results were then replicated and extended in a prospective study of a sample of depressed patients. First, the authors showed that it was feasible to identify a region within left DLPFC that was maximally functionally connected to the sgACC. Furthermore, this region of maximal functional connectivity remained stable across subsequent days.[37]. Additionally, the DLPFC TMS target producing the greatest antidepressant response was most strongly functionally connected to the sgACC. Of note, open label studies have provided evidence that sgACC is an effective target for deep brain stimulation for depression [38] providing a link between targets of noninvasive and deep brain stimulation which has held true for several neuropsychiatric disorders [39].

One obstacle to identifying a strong predictive biomarker of TMS response is that most studies average measurements of functional connectivity across groups of patients. Thus, it is difficult to make inferences about the relationship between functional connectivity and an individual patient's antidepressant response. Accordingly, Fox and colleagues [36] have demonstrated that the use of baseline functional connectivity of the individual patient can meaningfully predict subsequent antidepressant response to TMS. Similar studies of this type, which base targeting on network-based measurements from individual patients, show promise for optimizing antidepressant response from TMS.

Change in functional connectivity from pre- to post-TMS: Evidence for TMS-induced neuroplasticity

Converging evidence demonstrates that TMS normalizes the functional connectivity of cortical circuits characterized by abnormal pre-TMS functional connectivity during the depressed state. Studies from our lab showed that daily 10Hz TMS over the left DLPFC for 25 days normalized functional connectivity between the sgACC and several nodes of the DMN and the cognitive executive network (CEN) [32], though there were no functional connectivity changes between the left DLPFC and other nodes of the CEN. Another study using the same left DLPFC stimulation site and parameters was associated with similar changes in functional connectivity, although the normalization of functional connectivity was specific to treatment responders [33].

Targeting the DMPFC has also been associated with normalization of functional connectivity with the sgACC. Specifically, in a sample of 25 patients on stable medication treated with a 4-week course of 10Hz TMS, functional connectivity of the sgACC was reduced following TMS. The reduction of sgACC functional connectivity to the mid-cingulate, caudate, and insula was correlated with antidepressant response. Additionally, increases in DMPFC-thalamus functional connectivity correlated with improvement in depression [31].

In summary, studies using similar methods of open-label TMS in depressed cohorts, provide convergent evidence that effective TMS treatment is associated with normalization of specific nodes of the DMN, a network involved in the negative self-referential processing typical of depression. Two of the three studies also demonstrate (to different degrees) that the cognitive executive network (CEN) and the interactions of the CEN and DMN also normalize with TMS. Resting state fMRI is easy to acquire and thus may be particularly suitable as a biomarker for predicting and tracking treatment response.

Functional connectivity is constrained, in part, by structural connectivity of white matter connections between neural regions [40, 41]. Abnormalities in white matter structure may underlie circuit dysfunction that may impede signal propagation beyond the stimulation site to more distributed networks. For example, the effects that occur “at a distance” in the sgACC with DLPFC stimulation and in downstream networks depend on the integrity of axonal pathways. Indeed, preliminary data from our lab suggests that abnormalities in the structural connectome, as measured by diffusion tensor imaging predict treatment response to TMS [42]. How white matter abnormalities affect the response to TMS is an important, but relatively neglected area of investigation.

Neurochemistry – Monoamine Neurotransmitters

Studies in both animals and humans implicate neurotransmitter systems in the antidepressant mechanism of TMS. These include both monoamine neurotransmitter systems, including dopamine and serotonin, as well as the amino acid transmitter systems GABA and glutamate.

Dopamine depletion is known to correlate with depression [43, 44] and dopamine reuptake inhibitors may produce their antidepressant effects by increasing the availability of dopamine at striatal synapses [45]. Studies in healthy human subjects [46] and in subjects with depression [47, 48] using radioligands with affinity for D2 receptors show that TMS to the left DLPFC stimulates striatal dopamine release (but see also [49-51]). This effect has also been observed in the rat dorsolateral striatum and nucleus accumbens [52, 53]. As dopamine signaling in the striatum is important for reward processing, which is compromised in anhedonia, and for motor control, which is impaired in psychomotor symptoms of depression [54, 55], it is possible that this mechanism of dopamine enhancement may play a role in the antidepressant mechanism of TMS. Our findings from resting state fMRI suggest that functional connectivity from target to the striatum may be necessary for treatment response [56].

Both animal and human studies demonstrate that TMS modulates serotonin release. In healthy volunteers TMS over the left DLPFC at 10Hz modulates serotonin release throughout the limbic system, including in the cingulate gyrus, cuneus, parahippocampal gyrus and insula [57]. TMS over prefrontal targets in rats is associated with increases in serotonin release in hippocampus suggesting that TMS and monoamine reuptake inhibitors could share a final common pathway of antidepressant mechanism [58, 59]. However, serotonin modulation by TMS has yet to be demonstrated for individuals with depression.

If serotonin and dopamine release prove to be integral to the antidepressant mechanism of TMS, as could be investigated with PET to test whether neurotransmitter release correlates with treatment response, this would raise a host of questions about overlapping mechanisms between TMS and medication treatments. For example, is treatment resistance due to different mechanisms of monoamine release? Does TMS enhance monoamine release through direct neuronal stimulation instead of reuptake inhibition or monoamine oxidase inhibition? Such PET findings would also open up another avenue to target TMS by choosing a site that maximizes downstream monoamine release.

Neurochemistry – Amino Acid Neurotransmitters

Several lines of evidence implicate GABA, the primary inhibitory neurotransmitter in the brain, in the pathophysiology of depression. MR-Spectroscopy reveals low GABA levels in the limbic system in severe depression in both adults [60, 61] and adolescents. In the sgACC, GABA levels have correlated inversely with anhedonia symptoms in adolescents [62]. Glutamate decarboxylase (GAD) enzymes, which synthesize GABA, are low in post-mortem brains of individuals who suffered depression [63] as are GABAergic interneuron counts [64]. Single and paired pulse TMS-based assays of cortical inhibition have also been used to probe $GABA_A$ and $GABA_B$ receptor activity and have found that depression severity correlates with level of GABA signaling deficit [65]. GABA has also been implicated in animal models of learned hopelessness suggesting depression may result from an inhibitory/excitatory imbalance [66].

GABA homeostasis may be related to other biomarkers of depression. For example, GABA in the medial PFC has been found to correlate with reductions in functional connectivity of

the default mode network [67], raising the question that these two biomarkers of depression may be causally related [68, 69]. Additionally, multiple antidepressant treatments have been shown to elevate (or normalize) GABA levels, including ECT [70] and SSRIs [71]. More recent MR-spectroscopy results from ketamine studies add to the evidence that GABA modulation seems to be a final common pathway of psychopharmacological and neuromodulation treatments of depression [72]. An intriguing possibility is that GABAergic mechanisms modulate abnormal circuit functional connectivity in depression.

TMS targeting the left DLPFC at 10Hz has been shown to increase GABA in the MPFC in treatment-resistant depression in adults [73]. The effect was limited to treatment responders. Glutamate and glutamine metabolism is also dysregulated in depression [74] although this has been more difficult to study, given technical limitations of MR spectroscopy of separating the resonances of these two neurotransmitters. TMS has been found to increase glutamate concentration in the MPFC in healthy individuals [75]. However, results after TMS for depression have been less conclusive. One study showed a lack of effect on glutamate in the MPFC in depressed adults [73]. Another found elevation in the glutamine/glutamate ratio immediately after a course of TMS and again at 6 month follow up in both DLPFC and MPFC [76], an effect in which the Gln/Glu ratio change was correlated with symptomatic improvement.

In summary, there is evidence that TMS over the left DLPFC modulates the GABA and glutamate systems and this modulation has been correlated with response to treatment for depression. Studies in this area have been limited by lack of blinding, use of standard rather than image-guided targeting, and the coarse region-of-interest approach necessary for MR-Spectroscopy. Future studies could benefit from addressing these shortcomings, as well as using correlation with neurophysiological measures in the same patients [77]. Larger studies may be able to determine the predictive value of neurotransmitter levels for treatment response. Finally, co-localization of neurochemical maps (e.g. GABA level maps) with functional or structural connectivity maps could help determine if targeting lateral-convexity regions that project to GABA-deficient regions optimizes treatment response.

Conclusions and Future Directions

The Search for Biomarkers of Antidepressant Response

There have been a number of advances in the search for biomarkers of the TMS antidepressant response, but the utility of these markers awaits prospective TMS trials in which depressed subjects are selected for the presence or absence of the biomarker. This approach has distinct advantages. First, it can provide more robust evidence that TMS engages a circuit known to be abnormal. Second, it will help determine if personalizing treatment by pairing individuals who have the “appropriate predictive biomarker with the appropriate target” leads to a better response rate.

Using MRI to Optimize TMS for Depression

MRI can be used to optimize the spatial targeting of the stimulus so as to most effectively change abnormally functioning neural circuits. One approach has been to design magnetic

coils that penetrate to deeper neural structures; for example, the H-Coil, which can penetrate to 5cm and directly stimulate at that depth [78]. However, this coil does so at the expense of focality, which may explain why it is not more clinically effective for depression than current superficial TMS using a standard treatment protocol [79].

An alternative approach is to personalize targeting of superficial TMS based on the functional connectivity of an individual's different prefrontal projections. For example, DLPFC targets that we know are optimally connected to the sgACC could be studied in sham-controlled and head-to-head studies with currently-accepted targets. A treatment protocol would start with a resting state fMRI, which would be immediately analyzed online for functional connectivity to the sgACC (the striatum could be another candidate “deep target’). Resting state fMRI in an individual patient may reveal that sgACC-DLPFC functional connectivity is normal, or even lower than normal, which is a poor predictor of response according to the preliminary studies [32, 33]. However, if functional connectivity between the DMPFC and sgACC is abnormally high, it would indicate that this patient would have a higher likelihood of response to TMS targeting the DMPFC [31] and that this target should be chosen.

Conclusions and Future Directions

Although fMRI provides some mechanistic insight into the effects of TMS on neuroplasticity, the BOLD signal used in fMRI is based on blood oxygenation, while the physiologic underpinnings are at the neuronal signaling level [80]. Cerebral blood flow change and functional connectivity have been found to correlate with power in the alpha band of the EEG and quantitative EEG methods have been developed to study functional connectivity [81]. In turn, TMS may also be optimized if delivered at a frequency that can create resonance with baseline oscillatory activity of neural networks [82-86]. Future studies of mechanism of action that incorporate pre/post EEG with fMRI BOLD can leverage the high temporal resolution of EEG to better understand the response of intrinsic connectivity networks to TMS therapy.

Current evidence suggests that functional connectivity of networks important in depression has the potential to predict antidepressant response to TMS. TMS, in turn, can induce plasticity in these same networks and this may contribute to its antidepressant mechanism. Targeting TMS to achieve network engagement has shown promise in optimizing TMS response. Additional research is needed to fully exploit the neuromodulatory properties of TMS to normalize networks in individual depressed patients.

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