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Imaging TMS: Antidepressant mechanisms and treatment optimization

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Abstract

With the antidepressant efficacy of Transcranial Magnetic Stimulation well-established by several meta-analyses, there is growing interest in its mechanism of action.

TMS has been shown to engage, and in some cases, normalize functional connectivity and neurotransmitter levels within networks dysfunctional in the depressed state.

In this review, I will suggest candidate biomarkers, based on neuroimaging, that may be predictive of response to TMS. I will then review the effects of TMS on networks and neurotransmitter systems involved in depression. Throughout, I will also discuss how our current understanding of response prediction and network engagement may be used to personalize treatment and optimize its efficacy.

Keywords

Depression; TMS; Neuroimaging; Functional connectivity; Neuronavigation; Biomarker

Introduction

Since its first use for the treatment of major depression, transcranial magnetic stimulation (TMS) has targeted frontal lobe dysfunction (George & Wassermann, 1994). Choosing to stimulate the left dorsolateral prefrontal cortex (DLPFC) came from the theory of hypofrontality in depression, which was supported by evidence from PET-imaging (Buchsbaum et al., 1986; Martinot et al., 1990) and post-stroke depression (Starkstein & Robinson, 1989). Indeed, early case reports found that stimulating this target was effective for treating depression (George et al., 1995; Pascual-Leone, Rubio, Pallardó, & Catalá, 1996), leading to verification in open label studies and rigorous sham controlled trials (George et al., 2010; 1997; O'Reardon et al., 2007). Meta-analyses have well-established the efficacy of TMS targeting this region (Schutter, 2009; Slotema, Blom, Hoek, & Sommer, 2010).

Early studies into the antidepressant mechanisms of TMS demonstrated patterns of frontal lobe perfusion at baseline that correlated with TMS response and that TMS modulated

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frontal perfusion (Speer et al., 2009; 2000; Teneback et al., 1999). More recent work has focused on circuit-based mechanisms of emotional regulation, reward processing, anhedonia and psychomotor behavior in depression. Although biomarkers have been found, and to some extent replicated, the utility of these markers awaits prospective TMS trials in which depressed subjects are selected for the presence or absence of the biomarker. First, this will provide more robust evidence TMS engages a circuit known to be abnormal. Second, over time, it will help us determine if personalizing treatment by pairing individuals who have the “appropriate predictive biomarker with the appropriate target” leads to better response rates.

This review will highlight some of the advances in using neuroimaging to understand antidepressant mechanisms of TMS. This will not be a comprehensive review of those advances as excellent reviews have already been published (Noda et al., 2015; Silverstein et al., 2015). I will try to provide a critical review of studies using resting state fMRI and neurochemical imaging modalities, to identify gaps in understanding and to identify directions and hypotheses for future research. Although bipolar depression and depression associated with dual diagnosis are clinically important areas with high morbidity and in which TMS may play an important role, I will limit this review to major depressive disorder.

Baseline functional connectivity

The depressed state is characterized by elevated functional connectivity of the default mode network (DMN), a collection of midline frontal and parietal areas as well as lateral parietal structures. This network becomes active and oscillates at 0.1Hz when the subject is doing nothing and becomes inactive during periods of purposeful behavior (Fox & Raichle, 2007). The network can be assayed using functional MRI (fMRI) and the strength of active connections between areas determined. In depression, this “functional connectivity” is elevated (Greicius et al., 2007; Sheline et al., 2009; Sheline, Price, Yan, & Mintun, 2010), the degree to which has been correlated with rumination scores (Zhu et al., 2012). This “hyperconnectivity”, has been highly replicated across studies (Northoff, 2016a). Hyperconnectivity of the DMN has been shown to improve after electroconvulsive therapy (ECT) (Perrin et al., 2012) and with serotonin-norepinephrine reuptake inhibitors (van Wingen et al., 2014).

Personalized medicine aims to discover reliable measurements, which can be taken from individual patients, that will be able to predict the likelihood that a patient will respond to a variety of prospective treatments (Kapur, Phillips, & Insel, 2012). In the quest for such predictive biomarkers of TMS for depression, several investigators have evaluated differences in baseline, pre-TMS resting state fMRIs of patients who subsequently either responded or did not respond to a course of TMS. Three studies in individuals with TRD had convergent findings. Stimulation targeting the dorsomedial prefrontal cortex (DMPFC) led to better response in patients with higher baseline functional connectivity between DMPFC and sgACC and between sgACC and DLPFC and lower baseline functional connectivity of cortico-thalamic, cortico-striatal and cortico-limbic projections (Salomons et al., 2013). A second study demonstrated similar findings using a left DLPFC target (Liston et al., 2014). This study found that higher functional connectivity between the sgACC and DLPFC, DMPFC, VMPFC, mOFC and bilateral posterior parietal cortex was associated with

treatment response. A third group replicated the predictive value of sgACC-DLPFC hyperconnectivity for response to 10Hz TMS over the left DLPFC (Baeken et al., 2014).

The strength of functional connectivity of the sgACC, a structure repeatedly found to be overactive and hypermetabolic in depression (Fu, Steiner, & Costafreda, 2013; Mayberg et al., 1997), to dorsomedial and dorsolateral prefrontal cortex, is a candidate predictive biomarker for response to TMS (Baeken et al., 2014; Liston et al., 2014; Salomons et al., 2013). These studies average measurements of functional connectivity across groups of patients, while being able to say less about the individual patient. However, the case toward using baseline functional connectivity of the individual patient as a predictive biomarker was strengthened by a pair of studies by Fox and colleagues. In the first, this group compared treatment efficacy of previously published studies of TMS for depression that used left DLPFC targets that were localized using different methods. Using a set of normative resting state functional connectivity data, the group found that the best antidepressant response across studies was associated with increasing functional connectivity between the target location and the left sgACC (Fox, Buckner, White, Greicius, & Pascual-Leone, 2012). These results were then reproduced in a small sample of depressed patients. In the second study, the group showed the feasibility of targeting the region within the left DLPFC with maximal functional connectivity to the sgACC by demonstrating that functional connectivity between these two regions was stable between subsequent days (Fox, Liu, & Pascual-Leone, 2013). Additionally, the optimal TMS target for depression was strongly functionally connected to the sgACC stimulation site for deep brain stimulation (Mayberg et al., 2005). This relationship between targets of noninvasive and deep brain stimulation held true for several neuropsychiatric disorders (Fox et al., 2014).

Plasticity of functional connectivity

Several studies, including those introduced in the previous section, have demonstrated that TMS normalizes cortical circuits with abnormal baseline functional connectivity in depression. Studies from our lab showed that daily 10Hz TMS over the left DLPFC for 25 days normalized connectivity between the sgACC and several nodes of the DMN and the cognitive executive network (CEN) (Liston et al., 2014). There were no connectivity changes between the left DLPFC and the CEN. Although there was no correlation demonstrated between the size of the change in connectivity and the degree of improvement of depressive symptoms, this study was not powered to test for this. A second study using the same left DLPFC stimulation site and parameters led to similar changes in functional connectivity. However, change in connectivity was specific to treatment responders (Baeken et al., 2014). Responder-specific findings in the latter study may have been attributable to the medication washout required in the Baeken study which may have made subjects more sensitive to both clinical and neurophysiological effects of TMS.

The study by Salomons et al used a different stimulation site, the dmPFC, a similar sample size of 25 patients, on stable medication and a 4 week course of 10Hz TMS. As in the previous two studies, connectivity of the sgACC was reduced after TMS. Reduction of sgACC connectivity to the mid-cingulate, caudate, and insula was correlated with treatment response. Additionally, increases in dmPFC-thalamus connectivity correlated with

improvement in depression. The authors suggest that TMS may be normalizing deficits in cognitive control, although this clinical outcome was not measured explicitly (Salomons et al., 2013).

The studies using similar methods of open label TMS in depressed cohorts, provide convergent evidence that TMS treatment is associated with normalization of the DMN, a self-monitoring network involved in the negative ruminative state of depression. Two of the 3 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. However, future research should also address how changes in specific cognitive domains may be mediating the antidepressant effects of TMS by employing RDoC (Insel et al., 2010) and capturing behavioral change within these domains during a course of TMS.

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 (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). 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 connectivity (Leuchter, Cook, Hunter, Cai, & Horvath, 2012). It has been suggested that the changes in functional connectivity observed with BOLD may be generated by “entraining” cortico-cortical and cortical-subcortical networks to a frequency which helps to “reset” the oscillation frequency of the network and restore its normal function (Leuchter, Cook, Jin, & Phillips, 2013; Leuchter, Hunter, Krantz, & Cook, 2015b). Future studies of the mechanism of action should incorporate pre/post EEG to correlate BOLD findings with frequency entrainment. Attempts have been made to “personalize” the stimulus to the patient’s individual alpha frequency, with mixed results (Leuchter et al., 2015a).

Functional connectivity is, in part, determined by structural connectivity between neural regions (Anderson, Hoy, Daskalakis, & Fitzgerald, 2016; Gong & He, 2015). Abnormalities in white matter structure may disrupt 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 physical, axonal pathways. Preliminary data from my lab suggests that abnormalities in the structural connectome, as measured by graph-theoretic nodal degree and clustering coefficient predict response of depression to TMS (Deng et al., 2016).

Monoamine systems

As in the case of psychopharmacology, studies in both animals and humans implicate neurotransmitter systems in the antidepressant mechanisms of TMS. These include the monoamine neurotransmitter systems, dopamine and serotonin, as well as the amino acid neurotransmitter systems, GABA and glutamate.

Dopamine depletion is known to correlate with depression (Hamon & Blier, 2013; Savitz & Drevets, 2013) and dopamine reuptake inhibitors may produce their antidepressant effects by increasing the availability of dopamine at striatal synapses (Argyelán et al., 2005). Studies in healthy human subjects (Strafella, Paus, Barrett, & Dagher, 2001) and in subjects with depression (Pogarell et al., 2006; 2007) using radiotracers to the D2 receptor show that TMS stimulating the left DLPFC results in increased dopamine release in the striatum. This effect has also been observed in the rat dorsolateral striatum and nucleus accumbens (Kanno, Matsumoto, Togashi, Yoshioka, & Mano, 2004; Zangen & Hyodo, 2002). 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 (Grace, 2016; L. K. Tremblay et al., 2005), it is possible that this mechanism of dopamine enhancement may play a role in the antidepressant mechanism of TMS. Work on whether functional connectivity between the frontal stimulation site and the striatum is predictive of antidepressant response is mixed, with one study using DMPFC as the target showing decreased connectivity predictive of response (Salomons et al., 2013), while another using DLPFC as the target showing increased connectivity predictive of response (Avissar, Powell, Casey, Liston, & Dubin, 2015), suggesting “access” to the striatum may be necessary for treatment response.

Similarly, TMS over the left DLPFC at 10Hz modulates serotonin release in healthy volunteers throughout the limbic system, including in the cingulate gyrus and cuneus, parahippocampal gyrus and insula (Sibon et al., 2007). TMS over prefrontal targets in rat led to increases in serotonin release in hippocampus suggesting there is some overlap in mechanism between TMS and monoamine reuptake inhibitors (Juckel, Mendlin, & Jacobs, 1999; Levkovitz, Grisaru, & Segal, 2001). However, serotonin modulation by TMS has yet to be demonstrated for individuals with depression.

If monoamine neurotransmitters are demonstrated to play an important role in the antidepressant mechanism of TMS, this would raise several 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 another avenue to target TMS by choosing a site that maximizes downstream dopamine release.

GABA and Glutamate systems

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 (Croarkin, Levinson, & Daskalakis, 2011; Sanacora, Mason GF, Rothman DL, et al, 1999) and adolescents. In the sgACC, GABA levels have correlated inversely with anhedonia symptoms in adolescents (Gabbay et al., 2012). Levels of glutamate decarboxylase (GAD) enzymes, which synthesize GABA, are low in post-mortem brains of individuals who suffered depression (Hasler et al., 2007) as are GABAergic interneuron counts (Maciag et al., 2010). 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 (Levinson et al., 2010). GABA has also been implicated in animal models of learned helplessness suggesting depression may result from an inhibitory/excitatory imbalance (Yizhar et al., 2011).

GABA homeostasis may be related to other biomarkers of depression. For example, GABA levels in the medial PFC have been found to correlate with reductions in functional connectivity of the default mode network (Northoff et al., 2007), raising the question that these two biomarkers of depression may be causally related (Northoff, 2016b; Northoff & Sibille, 2014). Additionally, multiple antidepressant treatments have been shown to elevate (or normalize) GABA levels, including ECT (Sanacora et al., 2003) and SSRIs (Sanacora, Mason, Rothman, & Krystal, 2002). 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 (Milak et al., 2015). Further, GABA's intermediate mechanism of action may be to modulate abnormal circuit 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 (Dubin et al., 2016). Although TMS in this study was open label, the effect was limited to treatment responders. Although baseline GABA level was not predictive of treatment response, this study was not powered to test this hypothesis. Glutamate and glutamine metabolism is also dysregulated in depression (Sanacora, Treccani, & Popoli, 2012) 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 normals (Michael et al., 2003). However, results after TMS for depression have been less conclusive, with one study showing a lack of effect on glutamate in the MPFC in depressed adults (Dubin et al., 2016) and another showing elevation in the glutamine/glutamate ratio immediately after a course of TMS and again at 6 month follow up in both DLPFC and MPFC (Croarkin et al., 2016), 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 being open-label, by using the standard treatment protocol and by using MR spectroscopy with its necessary selection of specific a priori regions of interest. Future studies could benefit from addressing these shortcomings, as well as using correlation with TMS-based neurophysiological measures, in the same patients (S. Tremblay et al., 2013). Larger studies may be able to determine the predictive value of neurotransmitter levels for treatment response. Finally, maps of neurotransmitter levels (for example, GABA levels) may be coupled with functional or structural connectivity maps to determine if targeting surface-convexity regions that project to regions of GABA deficit optimizes treatment response.

Second-Generation Targeting Strategies

How can we apply our current understanding of the aspects of neural structure and function that predict outcome of TMS to optimize and personalize treatment for depression? One treatment optimization strategy is to focus on the temporal domain, including number of sessions, length and spacing of individual sessions and temporal structure of the stimulus, including frequency and inter-stimulus train intervals. Another strategy is 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 (Levkovitz et al., 2009). However, this coil does so at the expense of focality, which may explain why it is not more clinically effective for depression than superficially stimulating TMS (Levkovitz et al., 2015). This suggests that taking a “surgical” approach to engaging the appropriate circuits instead of a “shotgun” approach, is important for treatment response.

Refining this targeted approach will be an iterative process as more is learned about how best to access downstream circuits from the cortical surface. However, as reviewed here, enough is currently known to hypothesize and test potential targets. 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 connectivity to the sgACC (the striatum could be another candidate “deep target”). Resting state fMRI in this patient may reveal that sgACC-DLPFC connectivity is normal, or even lower than normal, which is a poor predictor of response according to published studies (Baeken et al., 2014; Liston et al., 2014). However, connectivity between the DMPFC and sgACC may be abnormally high in this patient, which would indicate that this patient may have a higher likelihood of response to TMS targeting the DMPFC (Salomons et al., 2013).

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References

- Anderson RJ, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Repetitive transcranial magnetic stimulation for treatment resistant depression: Re-establishing connections. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*. 2016; 127(11):3394–3405. [PubMed: 27672727]
- Argyelán M, Szabó Z, Kanyó B, Tanács A, Kovács Z, Janka Z, Pávics L. Dopamine transporter availability in medication free and in bupropion treated depression: a 99mTc-TRODAT-1 SPECT study. *Journal of Affective Disorders*. 2005; 89(1–3):115–123. [PubMed: 16213028]
- Avißar M, Powell F, Casey BJ, Liston C, Dubin M. TMS Over the Left Dorsolateral Prefrontal Cortex Modulates Frontostriatal Connectivity in Depression. *Journal of ECT* June 2014. 2015; 31(3):E33–E33.

- Baeken C, Marinazzo D, Wu GR, Van Schuerbeek P, De Mey J, Marchetti I, et al. Accelerated HF-rTMS in treatment-resistant unipolar depression: Insights from subgenual anterior cingulate functional connectivity. *The World Journal of Biological Psychiatry*. 2014; 15(4):286–297. [PubMed: 24447053]
- Buchsbaum MS, Wu J, DeLisi LE, Holcomb H, Kessler R, Johnson J, et al. Frontal cortex and basal ganglia metabolic rates assessed by positron emission tomography with [18F]2-deoxyglucose in affective illness. *Journal of Affective Disorders*. 1986; 10(2):137–152. [PubMed: 2941470]
- Croarkin PE, Levinson AJ, Daskalakis ZJ. Evidence for GABAergic inhibitory deficits in major depressive disorder. *Neuroscience & Biobehavioral Reviews*. 2011; 35(3):818–825. [PubMed: 20946914]
- Croarkin PE, Nakonezny PA, Wall CA, Murphy LL, Sampson SM, Frye MA, Port JD. Transcranial magnetic stimulation potentiates glutamatergic neurotransmission in depressed adolescents. *Psychiatry Research: Neuroimaging*. 2016; 247:25–33. [PubMed: 26651598]
- Deng, Z-D., Davis, S., Asturias, G., Glidewell, M., Liston, C., Dubin, MJ. Effect of Repetitive Transcranial Magnetic Stimulation on the Structural Connectome in Patients with Major Depression. Presented at the 6th International Conference on Transcranial Brain Stimulation; Gottingen, Germany. 2016.
- Dubin MJ, Mao X, Banerjee S, Goodman Z, Lapidus KAB, Kang G, et al. Elevated prefrontal cortex GABA in patients with major depressive disorder after TMS treatment measured with proton magnetic resonance spectroscopy. *Journal of Psychiatry & Neuroscience*. 2016; 41(2):E37–E45. [PubMed: 26900793]
- Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*. 2007; 8(9):700–711. [PubMed: 17704812]
- Fox MD, Buckner RL, Liu H, Chakravarty MM, Lozano AM, Pascual-Leone A. Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. *Proceedings of the National Academy of Sciences of the United States of America*. 2014; 111(41):E4367–75. [PubMed: 25267639]
- Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biological Psychiatry*. 2012; 72(7):595–603. [PubMed: 22658708]
- Fox MD, Liu H, Pascual-Leone Á. Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. *NeuroImage*. 2013; 66:1–10. [PubMed: 23063446]
- Fu CHY, Steiner H, Costafreda SG. Predictive neural biomarkers of clinical response in depression: A meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. *Neurobiology of Disease*. 2013; 52(C):75–83. [PubMed: 22659303]
- Gabbay V, Mao X, Klein RG, Ely BA, Babb JS, Panzer AM, et al. Anterior cingulate cortex γ -aminobutyric acid in depressed adolescents: relationship to anhedonia. *Archives of General Psychiatry*. 2012; 69(2):139–149. [PubMed: 21969419]
- George MS, Wassermann EM. Rapid-rate transcranial magnetic stimulation and ECT. *Convulsive Therapy*. 1994; 10(4):251–4. discussion 255–8. [PubMed: 7850394]
- George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Archives of General Psychiatry*. 2010; 67(5):507–516. [PubMed: 20439832]
- George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *American Journal of Psychiatry*. 1997; 154:1752–1756. [PubMed: 9396958]
- George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport*. 1995; 6(14):1853–1856. [PubMed: 8547583]
- Gong Q, He Y. Depression, neuroimaging and connectomics: a selective overview. *Biological Psychiatry*. 2015; 77(3):223–235. [PubMed: 25444171]

- Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nature Reviews Neuroscience*. 2016; 17:524–532. [PubMed: 27256556]
- Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, et al. Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. *Biological Psychiatry*. 2007; 62(5):429–437. [PubMed: 17210143]
- Hamon M, Blier P. Monoamine neurocircuitry in depression and strategies for new treatments. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2013; 45:54–63. [PubMed: 23602950]
- Hasler G, van der Veen JW, Tumonis T, Meyers N, Shen J, Drevets WC. Reduced prefrontal glutamate/ glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Archives of General Psychiatry*. 2007; 64(2):193–200. [PubMed: 17283286]
- Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*. 2010; 167(7):748–751. [PubMed: 20595427]
- Juckel G, Mendlin A, Jacobs BL. Electrical stimulation of rat medial prefrontal cortex enhances forebrain serotonin output: implications for electroconvulsive therapy and transcranial magnetic stimulation in depression. *Neuropsychopharmacology*. 1999; 21(3):391–398. [PubMed: 10457536]
- Kanno M, Matsumoto M, Togashi H, Yoshioka M, Mano Y. Effects of acute repetitive transcranial magnetic stimulation on dopamine release in the rat dorsolateral striatum. *Journal of the Neurological Sciences*. 2004; 217(1):73–81. [PubMed: 14675613]
- Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Molecular Psychiatry*. 2012; 17(12):1174–1179. [PubMed: 22869033]
- Leuchter AF, Cook IA, Feifel D, Goethe JW, Husain M, Carpenter LL, et al. Efficacy and Safety of Low-field Synchronized Transcranial Magnetic Stimulation (sTMS) for Treatment of Major Depression. *Brain Stimulation*. 2015a; 8(4):787–794. [PubMed: 26143022]
- Leuchter AF, Cook IA, Hunter AM, Cai C, Horvath S. Resting-State Quantitative Electroencephalography Reveals Increased Neurophysiologic Connectivity in Depression. *PLoS ONE*. 2012; 7(2):e32508. [PubMed: 22384265]
- Leuchter AF, Cook IA, Jin Y, Phillips B. The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. *Frontiers in Human Neuroscience*. 2013; 7:37. [PubMed: 23550274]
- Leuchter AF, Hunter AM, Krantz DE, Cook IA. Rhythms and blues: modulation of oscillatory synchrony and the mechanism of action of antidepressant treatments. *Annals of the New York Academy of Sciences*. 2015b; 1344(1):78–91. [PubMed: 25809789]
- Levinson AJ, Fitzgerald PB, Favalli G, Blumberger DM, Daigle M, Daskalakis ZJ. Evidence of Cortical Inhibitory Deficits in Major Depressive Disorder. *Biological Psychiatry*. 2010; 67(5):458–464. [PubMed: 19922906]
- Levkovitz Y, Grisaru N, Segal M. Transcranial magnetic stimulation and antidepressive drugs share similar cellular effects in rat hippocampus. *Neuropsychopharmacology*. 2001; 24(6):608–616. [PubMed: 11331140]
- Levkovitz Y, Harel EV, Roth Y, Braw Y, Most D, Katz LN, et al. Deep transcranial magnetic stimulation over the prefrontal cortex: Evaluation of antidepressant and cognitive effects in depressive patients. *Brain Stimulation*. 2009; 2(4):188–200. [PubMed: 20633419]
- Levkovitz Y, Isserles M, Padberg F, Lisanby SH, Bystritsky A, Xia G, et al. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World Psychiatry*. 2015; 14(1):64–73. [PubMed: 25655160]
- Liston C, Chen AC, Zebly BD, Drysdale AT, Gordon R, Leuchter B, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biological Psychiatry*. 2014; 76(7):517–526. [PubMed: 24629537]
- Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. *Nature*. 2001; 412(6843):150–157. [PubMed: 11449264]

- Maciag D, Hughes J, O'Dwyer G, Pride Y, Stockmeier CA, Sanacora G, Rajkowska G. Reduced Density of Calbindin Immunoreactive GABAergic Neurons in the Occipital Cortex in Major Depression: Relevance to Neuroimaging Studies. *Biological Psychiatry*. 2010; 67(5):465–470. [PubMed: 20004363]
- Martinot JL, Hardy P, Feline A, Huret JD, Mazoyer B, Attar-Levy D, et al. Left prefrontal glucose hypometabolism in the depressed state: a confirmation. *American Journal of Psychiatry*. 1990; 147(10):1313–1317. [PubMed: 2399999]
- Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, et al. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport*. 1997; 8(4):1057–1061. [PubMed: 9141092]
- Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005; 45(5):651–660. [PubMed: 15748841]
- Michael N, Gosling M, Reutemann M, Kersting A, Heindel W, Arolt V, Pfeleiderer B. Metabolic changes after repetitive transcranial magnetic stimulation (rTMS) of the left prefrontal cortex: a sham-controlled proton magnetic resonance spectroscopy (1H MRS) study of healthy brain. *European Journal of Neuroscience*. 2003; 17(11):2462–2468. [PubMed: 12814378]
- Milak MS, Proper CJ, Mulhern ST, Parter AL, Kegeles LS, Ogden RT, et al. A pilot in vivo proton magnetic resonance spectroscopy study of amino acid neurotransmitter response to ketamine treatment of major depressive disorder. *Molecular Psychiatry*. 2015; 21:320–327. [PubMed: 26283639]
- Noda Y, Silverstein WK, Barr MS, Vila-Rodriguez F, Downar J, Rajji TK, et al. Neurobiological mechanisms of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex in depression: a systematic review. *Psychological Medicine*. 2015; 45(16):3411–3432. [PubMed: 26349810]
- Northoff G. How do resting state changes in depression translate into psychopathological symptoms? From 'Spatiotemporal correspondence' to 'Spatiotemporal Psychopathology'. *Current Opinion in Psychiatry*. 2016a; 29(1):18–24. [PubMed: 26651006]
- Northoff G. How do resting state changes in depression translate into psychopathological symptoms? From 'Spatiotemporal correspondence' to 'Spatiotemporal Psychopathology'. *Current Opinion in Psychiatry*. 2016b; 29(1):18–24. [PubMed: 26651006]
- Northoff G, Sibille E. Why are cortical GABA neurons relevant to internal focus in depression? A cross-level model linking cellular, biochemical and neural network findings. *Molecular Psychiatry*. 2014; 19(9):966–977. [PubMed: 25048001]
- Northoff G, Walter M, Schulte RF, Beck J, Dydak U, Henning A, et al. GABA concentrations in the human anterior cingulate cortex predict negative BOLD responses in fMRI. *Nature Neuroscience*. 2007; 10(12):1515–1517. [PubMed: 17982452]
- O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial. *Biological Psychiatry*. 2007; 62(11):1208–1216. [PubMed: 17573044]
- Pascual-Leone A, Rubio B, Pallardó F, Catalá MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *The Lancet*. 1996; 348(9022):233–237.
- Perrin JS, Merz S, Bennett DM, Currie J, Steele DJ, Reid IC, Schwarzbauer C. Electroconvulsive therapy reduces frontal cortical connectivity in severe depressive disorder. *Proceedings of the National Academy of Sciences*. 2012; 109(14):5464–5468.
- Pogarell O, Koch W, Popperl G, Tatsch K, Jakob F, Zwanzger P, et al. Striatal dopamine release after prefrontal repetitive transcranial magnetic stimulation in major depression: Preliminary results of a dynamic [123I] IBZM SPECT study. *Journal of Psychiatric Research*. 2006; 40(4):307–314. [PubMed: 16259998]
- Pogarell O, Koch W, Popperl G, Tatsch K, Jakob F, Mulert C, et al. Acute prefrontal rTMS increases striatal dopamine to a similar degree as d-amphetamine. *Psychiatry Research: Neuroimaging*. 2007; 156(3):251–255. [PubMed: 17993266]

- Salomons TV, Dunlop K, Kennedy SH, Flint A, Geraci J, Giacobbe P, Downar J. Resting-State Cortico-Thalamic-Striatal Connectivity Predicts Response to Dorsomedial Prefrontal rTMS in Major Depressive Disorder. *Neuropsychopharmacology*. 2013; 39(2):1–11.
- Sanacora G, Mason GF, Rothman DL, et al. Reduced cortical γ -aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. *Archives of General Psychiatry*. 1999; 56(11):1043–1047. [PubMed: 10565505]
- Sanacora G, Mason GF, Rothman DL, Krystal JH. Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. *American Journal of Psychiatry*. 2002; 159(4):663–665. [PubMed: 11925309]
- Sanacora G, Mason GF, Rothman DL, Hyder F, Ciarcia JJ, Ostroff RB, et al. Increased cortical GABA concentrations in depressed patients receiving ECT. *American Journal of Psychiatry*. 2003; 160(3): 577–579. [PubMed: 12611844]
- Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression. *Neuropharmacology*. 2012; 62(1):63–77. [PubMed: 21827775]
- Savitz JB, Drevets WC. Neuroreceptor imaging in depression. *Neurobiology of Disease*. 2013; 52:49–65. [PubMed: 22691454]
- Schutter DJLG. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychological Medicine*. 2009; 39(1):65–75. [PubMed: 18447962]
- Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, et al. The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106(6):1942–1947. [PubMed: 19171889]
- Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107(24):11020–11025. [PubMed: 20534464]
- Sibon I, Strafella AP, Gravel P, Ko JH, Boij L, Soucy JP, et al. Acute prefrontal cortex TMS in healthy volunteers: Effects on brain 11C- α Mtp trapping. *NeuroImage*. 2007; 34(4):1658–1664. [PubMed: 17188517]
- Silverstein WK, Noda Y, Barr MS, Vila-Rodriguez F, Rajji TK, Fitzgerald PB, et al. Neurobiological predictors of response to dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation in depression: a systematic review. *Depression and Anxiety*. 2015; 32(12):871–891. [PubMed: 26382227]
- Slotema CW, Blom JD, Hoek HW, Sommer IEC. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *The Journal of Clinical Psychiatry*. 2010; 71(7):873–884. [PubMed: 20361902]
- Speer AM, Benson BE, Kimbrell TK, Wassermann EM, Willis MW, Herscovitch P, Post RM. Opposite effects of high and low frequency rTMS on mood in depressed patients: Relationship to baseline cerebral activity on PET. *Journal of Affective Disorders*. 2009; 115(3):386–394. [PubMed: 19027962]
- Speer AM, Kimbrell TA, Wassermann EM, Repella DJ, Willis MW, Herscovitch P, Post RM. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Bps*. 2000; 48(12):1133–1141.
- Starkstein SE, Robinson RG. Affective disorders and cerebral vascular disease. *The British Journal of Psychiatry: the Journal of Mental Science*. 1989; 154:170–182. [PubMed: 2673474]
- Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci*. 2001; 21(15):1–4.
- Teneback CC, Nahas Z, Speer AM, Molloy M, Stallings LE, Spicer KM, et al. Changes in prefrontal cortex and paralimbic activity in depression following two weeks of daily left prefrontal TMS. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 1999; 11(4):426–435. [PubMed: 10570754]
- Tremblay LK, Naranjo CA, Graham SJ, Herrmann N, Mayberg HS, Hevenor S, Busto UE. Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a

- dopaminergic probe. *Archives of General Psychiatry*. 2005; 62(11):1228–1236. [PubMed: 16275810]
- Tremblay S, Beaulé V, Proulx S, de Beaumont L, Marjanska M, Doyon J, et al. Relationship between transcranial magnetic stimulation measures of intracortical inhibition and spectroscopy measures of GABA and glutamate+glutamine. *Journal of Neurophysiology*. 2013; 109(5):1343–1349. [PubMed: 23221412]
- van Wingen GA, Tendolkar I, Uner M, van Marle HJ, Denys D, Verkes RJ, Fernández G. Short-term antidepressant administration reduces default mode and task-positive network connectivity in healthy individuals during rest. *NeuroImage*. 2014; 88:47–53. [PubMed: 24269575]
- Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*. 2011; 477(7363):171–178. [PubMed: 21796121]
- Zangen A, Hyodo K. Transcranial magnetic stimulation induces increases in extracellular levels of dopamine and glutamate in the nucleus accumbens. *Neuroreport*. 2002; 13(18):2401–2405. [PubMed: 12499837]
- Zhu X, Wang X, Xiao J, Liao J, Zhong M, Wang W, Yao S. Evidence of a Dissociation Pattern in Resting-State Default Mode Network Connectivity in First-Episode, Treatment-Naive Major Depression Patients. *Biological Psychiatry*. 2012; 71(7):611–617. [PubMed: 22177602]