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Testing Causal Relationships Between Emotion Processing Circuitry and Behavior Using Noninvasive Brain Stimulation

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Two systems interact to facilitate attention to and regulation of emotional stimuli: a stimulus-driven system associated with limbic regions, particularly the amygdala, that is involved in the rapid deployment of attentional resources to potential threatening/emotionally salient information in the environment, and a frontal-cingulo-parietal domain-general cognitive control system. These two systems are thought to interact during the processing of emotional stimuli and the regulation of one's own emotional state, predominantly via top-down regulation of the stimulus-driven limbic system, mediated by the dorsolateral prefrontal cortex (DLPFC) (1). The myriad emotion processing impairments and associated symptomatology observed across psychiatric disorders are theorized (at least in part) to be a product of abnormalities in one or both systems. This theoretical model has predominantly been based on neuroimaging studies examining the associations between neural activation and behavioral responses during emotion processing tasks. However, the increased feasibility of using noninvasive brain stimulation (NIBS) in the laboratory setting has enabled researchers to begin to directly test causal links between neural states and behavior via the in vivo manipulation of regional and network activity. This approach is a necessary precursor to the development of NIBS therapeutics and reflects a particular advantage of experimental designs that combine neuroimaging with NIBS over traditional neuroimaging studies, which are limited to correlational interpretations of brain-behavior relationships and can suffer from the problem of reverse inference (2). By disrupting a circuit or causing a temporary lesion, NIBS can be used to directly test a putative causal relationship between activity in a particular region/circuit and a measurable behavior. Alternately, NIBS can be used to test competing hypotheses by applying both excitatory and inhibitory stimulation to the same region, in the same experimental design, assisting with the reconciliation of seemingly contradictory findings in the literature.

In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Notzon *et al.* (3) provide an example of this approach using transcranial magnetic stimulation (TMS). The authors combined data from two separate studies in an effort to resolve a perplexing contradiction in the literature regarding the role of the right DLPFC in the processing and regulation of negative affect and the relative beneficial effects of add-on inhibitory TMS to the right DLPFC in the treatment of depression. Excitatory TMS to the

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left DLPFC is already approved by the U.S. Food and Drug Administration for treatment-refractory depression in adults and is believed to normalize the left DLPFC hypoactivity that is consistently observed in individuals with depression. Although not approved by the U.S. Food and Drug Administration, some TMS protocols also include inhibitory TMS to the right DLPFC, motivated by the valence lateralization hypothesis, which posits that hypoactivation of the left DLPFC is thought to reflect depression-related positive attenuation (i.e., impaired ability to upregulate positive stimuli), whereas hyperactivation in the right DLPFC is thought to reflect depression-related attentional biases to negative stimuli (4). However, Notzon *et al.* (3) rightly point out that, given that the extant neuroimaging literature indicates that depression is predominantly characterized by bilateral DLPFC hypoactivation associated with reduced downregulation of negative stimuli, inhibitory TMS to the right DLPFC seems counterintuitive. The head scratcher is that a recent meta-analysis of TMS in depression indicates beneficial therapeutic effects for combined excitatory and inhibitory TMS to the left and right DLPFC, respectively (5).

In an effort to reconcile these contradictory findings, Notzon *et al.* (3) combined magnetoencephalography (MEG) and behavioral methods in healthy individuals to directly test the effect of excitatory ($n = 20$) or inhibitory ($n = 20$) TMS to the right DLPFC on the processing of fearful (vs. neutral) faces. The MEG results demonstrated a facial expression by stimulation type interaction in two spatially extended clusters in the right occipital and right temporal regions, such that excitatory TMS to right DLPFC was associated with reduced differentiation of activity associated with the passive viewing of fearful versus neutral faces in these regions, whereas inhibitory TMS showed the opposite. These findings were accompanied by complementary behavioral findings; participants demonstrated reduced reaction times and reduced arousal ratings in response to fearful faces after excitatory TMS, and the converse after inhibitory TMS. These results indicate that top-down regulation of stimulus-driven attention to negative stimuli can be modulated by means of excitatory or inhibitory TMS to the right DLPFC. The authors posit that excitatory stimulation enhances the regulatory role of the right DLPFC to reduce visual processing of fear relative to neutral faces. Conversely, they posit that temporary lesioning of the right DLPFC via inhibitory TMS disrupts top-down regulation to produce more stimulus-driven processing of emotional stimuli, resulting in negative attentional biases similar to those observed in depression. While there are limitations to the study (e.g., its between-subjects design and the fact that behavioral responses to faces were gathered independently of MEG), Notzon *et al.* (3) present important insights into how emotion processing circuits can be modulated using NIBS and how these circuits may be disrupted in psychiatric disorders that are characterized by emotion processing biases.

Given these findings, why then might combined excitatory TMS to the left DLPFC and inhibitory TMS to the right DLPFC have beneficial effects for individuals with depression? To date, the literature is unclear. One possibility, consistent with the authors' interpretations, is that inhibitory TMS to the right DLPFC reduces top-down regulation of stimulus-driven processing of emotional stimuli in general (rather than negative stimuli specifically) (4), resulting in increased stimulus-driven processing of positive emotional stimuli and/or increased approach-related activity in response to rewarding stimuli (6), thereby improving depression-related positive attenuation. This seems counterintuitive, however, particularly in

light of data demonstrating that the impaired ability to sustain positive emotion in depression is associated with reduced frontostriatal connectivity (7), which one might reasonably hypothesize would be further negatively impacted by inhibitory stimulation and result in more severe symptoms of anhedonia. Future work could directly examine this with a series of fully crossed experimental designs that test the effect of excitatory/inhibitory TMS on neural and behavioral responses to both positive and negative (vs. neutral) stimuli, in both the left and right DLPFC. It would also be prudent to distinguish between passive emotional processing [as implemented in Notzon *et al.* (3)] and explicit regulation of emotional stimuli, because there are some data to suggest task-specific abnormalities in frontolimbic networks in depression (8). Finally, it is worth noting that positively valenced stimuli have received limited attention in the emotion processing literature (relative to negative stimuli, and in the context of fully crossed designs). This may partly be due to trade-offs in experimental design decisions—the inclusion of positive stimuli in emotion processing paradigms significantly increases the number of trials required for a well-powered task, and consequently, increases the length of the task to impractical levels. However, delineating causal relationships between modulation of neural and behavioral responses to both negative and positive stimuli is a necessary step in furthering our understanding of common emotional disturbances observed in psychiatric disorders, and NIBS presents an elegant methodology to achieve this.

Despite the clear strengths of NIBS as a method of testing causal relationships, the status of understanding regarding the remote effects of stimulating a particular region limits interpretations. As illustrated by Notzon *et al.* (3), stimulating a particular region does not necessarily lead to activity changes in that region itself—why does stimulation of the right DLPFC result in activation changes in temporal and occipital regions during face processing? The inherent limitations of MEG in terms of spatial localization and connectivity limit the authors' ability to make inferences on this topic. The inclusion of multimodal neuroimaging approaches and dual focus on both regional activation and connectivity could help answer this question. For example, it may be that stimulation to the right DLPFC leads to changes in fronto-amygdala-occipital-temporal functional connectivity and, consequently, changes in stimulus-driven sensory visual processing of fearful faces. Combined functional magnetic resonance imaging and electroencephalography/MEG data along with the use of dynamic causal modeling approaches could begin to address how NIBS to a specific region might affect dynamic changes in one neuronal population that in turn cause dynamic changes in another (9). In addition, individual differences in cortical folding patterns and gross neural structure can alter current distribution in nontrivial ways, resulting in within- and between-subject heterogeneity that may confound results. One way to address this is to calculate individual-level realistic electric field calculations using approaches such as the finite element method (10). Although computationally heavy and time-consuming, this can assist with predictions regarding induced current magnitude, focality, and penetration depth, and informs our understanding of the spatial pattern and neural effects of NIBS.

Notzon *et al.* (3) provide an example of how NIBS can be used to directly test competing hypotheses to untangle seemingly contradictory findings in the literature. Although there remains much we do not understand about the remote stimulation effects of NIBS,

particularly in the context of individual differences in current distribution, it provides an elegant method for testing causal relationships between brain states and behavior that will likely have a significant impact on our understanding of neural mechanisms underlying cognition–emotion interactions and how these relate to psychiatric disorders.

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