The Causal Role of the Dorsolateral Prefrontal Cortex in the Modification of Attentional Bias: Evidence from Transcranial Direct Current Stimulation

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Background: A pattern of attentional bias for threatening information is thought to be involved in the etiology of anxiety. Consistent with this idea, cognitive training techniques directly targeting such patterns of biased attention have been shown to reduce symptoms of anxiety. Research seeking to establish the neurologic underpinnings of change in the attentional bias for threat have implicated, but not confirmed, the role of lateral prefrontal regions.

Methods: The current study sought to confirm experimentally the causal role of lateral prefrontal areas in the modification of attentional bias by delivering targeted cortical stimulation during attention bias modification training to assess the consequent effects on attentional bias change. While completing either an "attend threat" or "avoid threat" attention bias modification task, 77 volunteers (17–22 per group) received either active transcranial direct current stimulation of the left dorsolateral prefrontal cortex or a sham stimulation control condition.

Results: Participants receiving active stimulation showed greater evidence of attentional bias acquisition in the targeted direction (toward or away from threat) compared with participants in the sham stimulation condition.

Conclusions: Our findings provide the first experimental evidence that increasing activity in the dorsolateral prefrontal cortex leads to greater evidence of attention bias modification. This evidence confirms the role of these areas in facilitating change in the allocation of attention to threat. We believe this study provides a critical step in the translation of neuroimaging findings to novel neuromodulatory interventions capable of enhancing the treatment of emotional pathology.

Key Words: Anxiety, attentional bias, cognitive bias, cognitive bias modification, cognitive training, tDCS

Anxious individuals are prone to having their attention drawn to mildly threatening information in the environment (1). This pattern of biased attention to threat has been reliably observed across a range of anxiety and mood disorders (2,3) as well as among normal individuals with high levels of anxiety (4,5). Cognitive and neurological models of anxiety implicate attentional bias to threat in the development, maintenance, and remediation of anxiety pathology (6–8). Consistent with a causal relationship between attentional bias and anxiety, it has been observed that a reduction in attentional bias to threat accompanies successful psychological (9) or pharmacological treatment (10,11). However, the most convincing evidence that biased attention for threat is not simply an epiphenomenon of heightened emotional vulnerability comes from research that has sought to directly modify patterns of selective attention using cognitive training tasks. Using such attention bias modification (ABM) techniques, numerous studies have shown that the induction of attentional bias for threatening information in healthy controls leads to elevated anxiety vulnerability (12,13). Of more clinical relevance, it has also been demonstrated that reducing attentional bias to threat in anxious patients leads to a consequent reduction in anxious symptoms (14), suggesting considerable promise of ABM in the treatment of anxiety pathology. Although the cognitive tasks used in ABM have not always succeeded in modifying biased attention to threat as intended (15,16), it has been consistently demonstrated that when a change in attentional bias is achieved, emotional benefits follow (17). Findings from a meta-analysis indicate that the degree of change in attentional bias achieved using ABM tasks predicts the degree of emotional benefit subsequently observed (14). Thus, identifying, how to maximize the change in attentional bias to threat is central to realizing the therapeutic potential of ABM.

A detailed understanding of the neurocognitive processes that underpin biased attention is critical to facilitating change in these patterns of cognition. Neural models of anxiety (7,18) consistently emphasize two systems in the allocation of attention to emotional information. A stimulus-driven system associated with limbic areas (particularly the amygdala) is believed to be responsible for the rapid deployment of attention to potential threatening information in the environment. In contrast, the second system is implicated in the inhibitory control of attention and is linked with areas in the lateral prefrontal cortex (lPFC). This system is known to be associated with the top-down maintenance of attention via the inhibition of task-irrelevant information, including the inhibition of attentional deployment to low-level threatening information (19,20). Mounting evidence from neuroimaging research suggests that the lPFC, and in particular the dorsolateral prefrontal cortex (dlPFC), plays a regulatory role in attentional deployment (21). Biased attention to threat is thought to be the product of an imbalance between these two systems. Specifically, greater activation of the amygdala or deficient attentional inhibition through reduced activity in the lPFC, or the combination of both, is believed to result in biased attention for threatening information (20).

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Received Jan 28, 2014; revised Feb 25, 2014; accepted Mar 1, 2014.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2014.03.003

Because both systems contribute to attentional vigilance for threat, psychotherapeutic interventions may modify attentional bias (and consequently emotional vulnerability) either by increasing inhibitory control for threat through enhanced activity in prefrontal areas, or by reducing amygdala activation to such stimuli. Because ABM is designed to encourage attentional avoidance of one class of stimulus (i.e., threat) in favor of another (neutral/positive), it strongly implicates inhibitory control of attention via activity in the lPFC. In a novel examination of the role of the lPFC in ABM, Browning *et al.* (22) delivered two versions of a computerized ABM task designed to encourage an attentional bias either toward or away from threatening information to a group of healthy individuals. Neurological changes were inferred by performing functional magnetic resonance imaging after the ABM task. The study found that participants had increased activation in the lPFC when presented with the type of stimulus that the ABM task trained them to attend away from. Specifically, increased activation in the lPFC was observed when neutral stimuli were presented to subjects trained to attend away from neutral (toward threat) and when threat stimuli were presented to subjects trained to attend away from threat (toward neutral). This pattern of findings is entirely consistent with the role of the lPFC in mediating change in attentional bias through the selective inhibition of specific stimuli (threat or neutral) in line with the ABM training condition.

Although this finding is consistent with the role of the lPFC in ABM, it falls short of providing conclusive evidence for such a causal relationship. First, Browning *et al.* (22) did not compare activation before and after training, with group differences being examined after training only. Also, as acknowledged by the authors (22), change in cortical activity in the lPFC could represent a consequence of ABM, rather than a causal mediator of this process. To directly assess the causal status of this relationship, it is necessary to manipulate cortical activity in the lPFC and assess the impact on the acquisition of attentional bias in response to ABM; this represents the central aim of the current study. We sought to manipulate cortical excitability in targeted lateral prefrontal areas via transcranial direct current stimulation (tDCS) and to assess the impact of this on the acquisition of attentional bias in response to an ABM training procedure. This study represents both the extension of the neuroimaging study by Browning *et al.* and a critical step in translational research toward establishing potential therapeutic benefits of enhancing change in attentional bias via cortical stimulation. We predicted that if the lPFC does indeed causally mediate the acquisition of attentional bias, subjects receiving active anodal tDCS should exhibit greater evidence of attentional bias acquisition in line with the ABM training compared with subjects who do not receive tDCS (sham stimulation condition).

Methods and Materials

Participants

To decrease the likelihood that persons recruited for the study already possessed a strong attentional bias either toward or away from threat, we sought to recruit participants with midlevel trait anxiety. Participant selection was guided by prescreening of 1132 individuals from the University of Western Australia School of Psychology research participant pool on the trait version of the State–Trait Anxiety Inventory—Trait (STAI-T) (23). Persons whose STAI-T scores fell within the middle quartiles of the distribution of scores (STAI-T 34–48, $n = 624$) were considered eligible for recruitment and were invited to sign up for the study. Of the 79 individuals who accepted this invitation, 2 demonstrated significant increases in STAI-T scores since screening (had increased >50) and were deemed ineligible to participate. The remaining 77 individuals were considered eligible for inclusion in that their average reaction times reflected consistent rapid responding as instructed (indicated by mean reaction times within 2 SD of the group mean at the pre- and posttraining attentional assessment) and their accuracy on the attentional probe assessment tasks was >75%. The final 77 participants were a representative sample of the undergraduate population from which they were drawn, showing highly similar STAI-T scores to the larger sample (mean = 39.57, SD = 3.36, and mean = 40.47, SD = 4.10, respectively). Participants were randomly assigned to one of the four experimental conditions derived from the two experimental factors of ABM condition (attend threat vs. avoid threat training) and tDCS condition (active vs. sham).

Questionnaire Measures

Participants completed questionnaire assessments of current and general anxious mood at the beginning of the experimental session via the state and trait subscales of the STAI (23). The STAI has been shown to have fair reliability and adequate internal consistency (24). Participants did not receive any additional screening or clinical assessment.

ABM Task

Because the goal of the current study was to assess whether tDCS would yield greater evidence of ABM either toward or away from threat, we included two alternative ABM tasks [as per Browning *et al.* (22)]. We sought to incorporate ABM task parameters that would maximize the magnitude of the original effect. The design of the ABM task (Figure 1) was therefore guided by the findings of Hakamata *et al.* (14) in their meta-analysis. These findings indicated that tasks using vertically aligned stimuli tended to yield larger effect sizes compared with a horizontal formation ($d = .79$ vs. $d = .21$), and word stimuli typically generated larger effect sizes than face stimuli ($d = 1.29$ vs. $d = .37$). Figure 1 provides details on the precise format, timing, and stimuli adopted in the task. The task is designed to encourage an attentional bias toward or away from threat depending on the experimental condition. For the avoid threat condition, probe targets consistently replaced the neutral member of the stimulus pair, encouraging an attentional bias away from threat. Conversely, for the attend threat condition, probes consistently replaced the threat member of the stimulus pair to encourage an attentional bias toward threat. No information was provided to alert participants to these alternative conditions. Participants were provided a brief break at the midpoint of the ABM task.

Attentional Bias Assessment Task

To assess the impact of the ABM training task, participants completed 96 attentional bias assessment trials immediately before and after the ABM task. These trials were identical in structure to the ABM trials with the exception that target probes replaced threatening and neutral words with equal frequency. These trials are capable of indexing the relative attentional distribution between the competing threatening and neutral stimuli by comparing latencies to identify probes in either word location. Word stimuli used in the assessment trials were different from stimuli used in the ABM training trials to ensure that training effects were related to the emotional valence of the stimuli and not the specific stimuli themselves.