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

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Abstract

Background: A pattern of attentional bias for threatening information is thought to be involved in the aetiology of anxiety pathology. Consistent with this, cognitive training techniques directly targeting such patterns of biased attention have been shown to reduce anxiety symptomatology. Research seeking to establish the neurological 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 experimentally confirm the causal role of lateral prefrontal areas in the modification of attentional bias by delivering targeted cortical stimulation during attentional bias modification training to assess the consequent effects on attentional bias change. A total of 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 while completing either an “attend threat” or “avoid threat” attention bias modification task.

Results: Participants receiving active stimulation showed greater evidence of attentional bias acquisition in the targeted direction (toward or away from threat) as compared to those 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 serves to confirm the role of these areas in facilitating change in the allocation of attention 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.

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), and amongst high anxious members of the normal population (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 consistently 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, a number of studies have now 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 symptomatology (14), suggesting considerable promise of ABM in the treatment of anxiety pathology. While 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). Indeed, meta-analytic findings 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 maximise the change in attentional bias to threat is central to realising 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 emphasise 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. The second system in contrast 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 and/or deficient attentional inhibition through reduced activity in the LPFC is believed to result in biased attention for threatening information (20).

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 favour 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 computerised ABM task designed to encourage either an attentional bias toward, or away from threatening information to a group of healthy individuals. Neurological changes were inferred using functional magnetic resonance imaging (fMRI) following 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 those trained to attend away from neutral (toward threat), and when threat stimuli were presented to those 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.

While this finding is consistent with the role of the LPFC in attentional bias modification, it falls short of providing conclusive evidence for such a causal relationship. Firstly, Browning et al. (22) did not compare activation before and after training, with group differences being examined at post-training only. Also, as acknowledged by the authors (22), change in cortical activity in the LPFC could represent a consequence of attentional bias modification, rather than a causal mediator of this process. In order to directly assess the causal status of this relationship it is instead necessary to manipulate cortical activity in the LPFC and assess the impact on the acquisition of attentional bias in response to ABM. Accordingly, 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 assess the impact of this on the acquisition of attentional bias in response to an ABM training procedure. This study therefore represents both the extension of Browning et al's neuroimaging study and also 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, then those receiving active anodal tDCS stimulation should exhibit greater evidence of attentional bias acquisition in line with the ABM training, compared to those who do not receive tDCS (sham stimulation condition).

Methods and Materials

Participants

To decrease the likelihood that those recruited for the study already possessed a strong attentional bias either toward or away from threat, we sought to recruit those with mid-level trait anxiety. Participant selection was therefore guided by pre-screening of 1132 individuals from the University of Western Australia School of Psychology research participant pool on the trait version of the Spielberger State-Trait Anxiety Inventory (STAI-T) (23). Those whose STAI-T scores fell within the middle quartiles of the distribution of scores (STAI-T between 34-48, $n = 624$) were considered eligible for recruitment and were extended an invitation to sign up for the study. Of the 79 individuals to accept this invitation, two demonstrated significant increases in their STAI-T scores since screening (had increased above 50) and were therefore deemed ineligible to participate. The remaining 77 were considered eligible for inclusion in that their average reaction times reflected consistent rapid responding as instructed (indicated by mean reaction times within two standard deviations of the group mean at the pre and post attentional assessment), and their accuracy on the attentional probe assessment tasks was above 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 ($M = 39.57$, $SD = 3.36$, and $M = 40.47$, $SD = 4.10$ respectively). Participants were randomly allocated 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 Spielberger State-Trait Anxiety Inventory (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.

Attention Bias Modification Task

As the goal of the current study was to assess whether tDCS stimulation would yield greater evidence of attention bias modification either toward or away from threat, we included two alternative attention bias modification tasks (as per Browning et al. (22)). We sought to incorporate ABM task parameters that would maximise the magnitude of the original effect. The design of the ABM task (see Figure 1) was therefore guided by the meta-analytic findings of Hakamata et al. (14). This has indicated that tasks using vertically aligned stimuli have tended to yield larger effect sizes compared to a horizontal formation ($d = 0.79$ vs. $d = 0.21$ respectively), and word stimuli have also typically generated larger effect sizes than face stimuli ($d = 1.29$ vs. $d = 0.37$ respectively). 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 mid-point of the ABM task.

Attention Bias Assessment Task

To assess the impact of the ABM training task, participants completed 96 attentional bias assessment trials immediately before and after the attention bias modification 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 therefore

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 those 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.

Transcranial Direct Current Stimulation

We employed a battery-powered, current controlled iontophoresis device (25) for tDCS delivery. Direct current was transferred via two 4 cm x 6 cm conductive silicone electrodes (anodal and cathodal) each within a saline soaked sponge pouch. The positioning of the anodal electrode was guided by past findings that specifically implicate the left dorsolateral prefrontal cortex (dlPFC) in inhibitory control and attentional selection of salient information (26, 27). The anodal electrode was therefore positioned on F3 using the 10/20 international system, consistent with the protocol outlined by DaSilva et al. (28). Cathodal tDCS did not target a cortical region. This reference electrode was placed on the left superior region of the trapezius muscle near the base of the participant's neck (see Figure 2 for illustration of electrode placement). The tDCS dose was fixed at 1 mA/min with a 30s ramp up/down time. The duration of the dose was manipulated according to the experimental condition. The experimenter delivering the tDCS was necessarily aware of condition allocation. Experimental protocols were identical across the two conditions with all participants led to believe that they were receiving active tDCS. Those who were in the active tDCS condition received stimulation from the time they initiated the attentional probe practice trials until the break at the mid-point of the ABM task. This equated to a mean stimulation duration of 17min 13s ($SD = 1\text{min } 24\text{s}$, Min = 14min 32s, Max = 19min 30s). Alternatively, those in the sham tDCS condition received 1 min of tDCS stimulation initiated at the commencement of the attentional probe practice trials. This sham condition has been

used successfully in previous studies to provide the initial sensation of stimulation without the subsequent effects on cortical excitability (29). Figure 3 provides a timeline of tDCS delivery, attention bias modification, and attentional bias assessment tasks.

Data Analysis

Questionnaire Data. Baseline measures of state and trait anxiety in addition to demographic characteristics (age, gender) were compared across the tDCS and ABM conditions using 2×2 ANOVAs for continuous data, and chi-square tests for categorical data.

Attentional Bias Data. The effect of cortical excitation of the dlPFC on attention bias modification was assessed via reaction time data derived from the attentional probe assessment tasks. To minimise the influence of outlying data, reaction times faster than 200ms and longer than 2000ms were initially removed. Response latencies falling three SD from each participant's own mean reaction time were then excluded. An index of attentional bias was computed for both the pre and post-training assessments by taking mean response latencies to detect probes appearing in the location of threat words from the mean response latencies to detect probes appearing in the location of neutral words. The resulting attentional bias indices for the pre and post-training assessments provide a measure of the relative attention to threat, with higher scores representing greater attention to threatening over neutral stimuli. These data were subjected to a $(2 \times 2 \times 2)$ mixed-model repeated measures ANOVA with the two between-group factors of tDCS condition (active vs. sham) and ABM condition (attend threat vs. avoid threat) and the repeated measures factor of assessment point (pre-training vs. post-training).

Results

Baseline Characteristics

There were no significant group differences on baseline measures, suggesting that randomisation was successful. Examination of questionnaire measures and age using 2×2 ANOVAs revealed no significant main effects of either ABM group, tDCS group, and no interactions between these (all $p > .13$). Similarly, no differences in gender ratios were observed across conditions ($p > .19$). Table 1 displays gender ratios and group averages for these measures.

Attentional Bias Data

Consistent with the causal role of the dlPFC in the modification of attentional bias, tDCS stimulation produced greater evidence of attentional bias modification in the targeted direction. This was demonstrated in a significant, 3-way tDCS group $\times$ ABM group $\times$ assessment point interaction, $F(1, 73) = 7.06, p = .01, \eta^2 = .10$. No other significant main effects or interactions emerged from this analysis (all other $p > .17$). The component two-way interactions for each tDCS group revealed a significant ABM condition $\times$ assessment point interaction for those in the active tDCS condition only, $F(1, 35) = 5.91, p = .02, \eta^2 = .15$, with the equivalent interaction not approaching significance for those in the sham tDCS condition, $F(1, 38) = 1.70, p = .20, \eta^2 = .05^1$. As depicted in Figure 4, the nature of the significant two-way interaction for the active tDCS condition was entirely consistent with the acquisition of an attentional bias in the targeted direction of the ABM training. Those in the attend threat condition showed an increase in the index of attentional bias to threat from pre- to post-training while those in the avoid threat condition showed the reverse pattern. Examination of the component one-way effects for pre vs. post-training in this active condition revealed that participants did not differ on attentional bias at pre-training, $F(1, 35) = 0.68, p = .42, \eta^2 = .031$, however, at post-training they showed a significant difference in line with the assigned

¹ Separate follow up analyses for the 3-way tDCS group $\times$ ABM group $\times$ assessment point interaction, and for the component two-way interactions for each tDCS group were conducted in which age, gender, STAI-T score, and STAI-S score were entered as covariates. In none of these analyses did the addition of these covariates influence the significance or the pattern of the effects in either the active or sham tDCS conditions.

ABM condition $F(1, 35) = 6.84, p = .01, \eta^2 = .12$. This confirms that while no baseline differences in attentional bias were present, delivery of the alternative ABM tasks produced a relative difference in attentional bias in the targeted direction. The component within-subject one-way effects for the active tDCS condition revealed that those who received the attend neutral ABM showed a significant change in attentional bias away from threat from pre to post-training, $F(1, 19) = 4.33, p = .05, \eta^2 = .28$, while those in the attend threat condition showed an increase in attentional bias to threat from pre to post that did not approach significance $F(1, 16) = 1.93, p = .18, \eta^2 = .08$.

Discussion

The current study provides the first empirical evidence showing that cortical stimulation of the dlPFC causally contributes to the modification of attentional bias. Specifically, these findings demonstrate that anodal tDCS targeting the left dlPFC produced greater evidence of attention bias modification. This was demonstrated by a significant change in patterns of selective attention in line with the assigned training task in the active tDCS condition relative to the sham condition. These findings provide robust experimental support for the hypothesis that increased activity in the IPFC is not simply a consequence of acquired attentional bias, but directly contributes to the modification of attention bias. This is consistent with the implications of Browning et al.'s (22) neuroimaging research which demonstrated greater activity in the IPFC following ABM. These findings therefore provide support for neuroimaging data implicating the IPFC in inhibitory control of attention in relation to threatening information (30), and further highlight its role in modifying patterns of attentional bias for threatening information.

The present study represents an important step in a broader neurocognitive translational research program. The original fMRI research of Browning et al (22) served to identify the

neural regions putatively involved in producing change in selective attention, the current study has now provided experimental confirmation that dlPFC stimulation leads to increased evidence of ABM. This paves the way for further investigation into the applied value of such a combined intervention in clinical populations. Thus, not only does this research represent a critical step in the development of a novel neurocognitive intervention approach, but it also represents a model of the manner in which neuroimaging can potentially lead to tangible improvements in patient treatment by identifying appropriate targets for neuromodulatory interventions.

As with Browning et al (22), the current study intentionally utilised a non-clinical sample to experimentally determine the impact of neurostimulation on ABM in the absence significant emotional pathology. While deliberate, the use of a non-clinical sample limits the degree to which the current findings can be generalised. The obvious next stage of this research should be to pilot tDCS potentiation of ABM in clinical groups to assess the degree of emotional benefit experienced under these conditions relative to ABM alone. Anxiety disorders represent an obvious candidate for empirical scrutiny. ABM has been shown to reduce anxiety symptomatology (31, 32), with meta-analytic findings indicating that the magnitude of change in attentional bias is directly related to the degree of emotional benefit attained (14). Given this, any enhancement of ABM is likely to also enhance emotional benefits for those who suffer anxiety disorders. Furthermore, anxiety pathology has also been consistently linked to deficits in inhibitory control (7) as well as attentional bias to threat (8). As such, an intervention approach which has the capacity to ameliorate problematic patterns of attention, and achieves this through increased stimulation of cortical structures that improve inhibitory control, could provide an ideal treatment for conditions that implicate specific dysfunction in both these neurocognitive processes.

While these findings clearly suggest that stimulation of the dlPFC led to greater evidence of attention bias modification, it was also the case that we did not find evidence of attentional bias change for those in the sham tDCS condition. This does not appear to have been an issue of power as the direction of the means following training was not in line with the assigned ABM condition. As there was no trend towards significance in the sham tDCS condition, the appropriate conclusion must be that this condition provided no evidence of training. For the current study we sought to achieve the best chance of obtaining the attentional change by adopting an ABM regimen informed by past meta-analytic findings. It is entirely possible, however, that an alternative ABM regimen may have yielded potentially larger training effects. For example, a recent study by Browning et al. (33) examining the impact of ABM in preventing relapse for depression found that the greatest emotional benefits were observed for those who received face-based training. We would therefore strongly encourage future research into alternative ABM tasks in combination with tDCS.

Although the current study ceased tDCS stimulation at the mid-point of ABM training, it is known that the application of direct current will continue to potentiate cortical activity for some time following the cessation of stimulation (34). It is therefore worth considering whether latent activation could have impacted the attentional effects observed in the active tDCS condition. While possible, the between-subjects design ensures that any generic effect of stimulation will be present in both the attend threat and attend neutral ABM conditions. Our present findings show that there was no evidence of a generic effect of tDCS but more specific evidence of attentional bias modification in each direction across the different training conditions. An interesting, though perhaps less likely possibility is that the effects of tDCS could potentially increase the likelihood of detecting an ABM effect. This would suggest that attention bias modification may have been achieved in both the active and sham tDCS conditions, but was only detected in the active condition. This question could be readily

addressed in future research either by moving the assessment task to a later point in time when there is unlikely to be any effect of latent stimulation, or, by manipulating the timing of tDCS across groups to deliver stimulation either during training or after training and before assessment.

Our decision to target the dlPFC in the current study was guided both by the previous research findings of Browning, et al. (22), and neural/imaging models of attention suggesting that this area is involved in the regulation of attentional deployment to salient information (18). However, other neural models place greater emphasis on the ventrolateral prefrontal cortex (vlPFC) in mediating the control of attentional deployment to threat (35). This is partly due to research suggesting that the dlPFC has few direct anatomical projections to the amygdala (36). These alternative models therefore suggest that the impact of the dlPFC on attentional deployment to threat may not be direct, but could instead be mediated by the vlPFC (21, 37). It is apparent that the pattern of findings in the current study could be amenable to the action of the vlPFC rather than the dlPFC. Specifically, while electrode placement was designed to target stimulation of the dlPFC, it is possible that the observed effect could be due to activation of the vlPFC via excitatory projections from the dlPFC to the vlPFC. Thus, while the present findings clearly support the position that targeted stimulation of the dlPFC leads to increased evidence of attention bias modification, they do not preclude the potential involvement of the vlPFC. Future research could therefore usefully serve to differentiate whether stimulation targeting vlPFC or the dlPFC is likely to produce greater change in attentional bias.

As with Browning et al. (22), the present study included two alternative attention bias modification conditions. While this permits conclusions about the overall impact of changes in attentional bias, a limitation with this design is that we cannot determine whether tDCS increased the ability to train attention away from threat, increased attentional training towards

threat, or both. To say with certainty where the training effect was most evident it would be necessary to also include a non-ABM control condition. The inclusion of such an additional condition could address this question and would also help to inform potential therapeutic applications of combined tDCS and ABM.

While our study clearly invites further research into the neurocognitive underpinnings and potential therapeutic implications of ABM, we can gain encouragement from the present findings which clearly demonstrate that active tDCS leads to greater evidence of modifying a known therapeutic mechanism. Our findings present the first empirical evidence that increasing cortical activation in the dlPFC causally contributes to the modification of attentional bias. This provides the necessary precursor to future applied research that should seek to establish the efficacy of combined tDCS and ABM in attenuating symptoms of emotional pathology within clinical populations.

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Tables**Table 1.** Demographic details for participants across experimental conditions

	Active tDCS		Sham tDCS	
	Attend threat	Avoid threat	Attend threat	Avoid threat
	ABM	ABM	ABM	ABM
Total per group	17	20	22	18
Female:Male	10:7	14:6	15:7	10:8
Age	19.64 (4.00)	19.60 (3.06)	20.64 (10.04)	19.94 (19.94)
STAI-Trait	35.41 (37.86)	36.05 (5.44)	37.86 (4.05)	36.94 (4.63)
STAI-State	30.76 (5.88)	32.25 (6.23)	29.50 (4.79)	31.61 (7.37)

All continuous measures reported as group means (SD).

STAI, Spielberger state-trait anxiety inventory.

Figure captions

Figure 1. Example trials from the attention bias modification task. On each trial an initial fixation screen is followed by two vertically aligned words are presented in the centre of the monitor 3 cm apart, one threatening and one neutral. After 500 ms the word-pair are replaced by a single probe appearing in the location of one of the words. Participants are instructed to discriminate the probe identity (horizontally or vertically aligned dots) as quickly as possible without compromising accuracy by pressing the corresponding left or right mouse key. Word pairs were identical to those used by MacLeod et al. (12). Across the two ABM conditions, the position of the probe in relation to the threat word was fixed. For those in the avoid threat condition, probes consistently appeared in the location of the neutral word, while for those in the attend threat condition probes consistently appeared in the location of the threat word. Participants completed a total of 576 trials of the ABM task (six blocks of 96 randomised trials). The figure depicts example trials from the attend threat (left) and avoid threat (right) training conditions.

Figure 2. Electrode placement for transcranial direct current stimulation showing the target location of the anodal electrode (F3; left) and the positioning of both anodal and cathodal electrodes (right; securing headbands not shown for illustrative purposes).

Figure 3. Timeline of tDCS delivery, attention bias modification and attentional bias assessment tasks.

Figure 4. Three-way interaction between tDCS condition, attention bias modification condition, and attentional bias assessment point (error bars = SEM). Higher scores represent greater attentional bias toward threatening over neutral words.