Neuroplastic changes in anterior cingulate cortex gray matter volume and functional connectivity following attention bias modification in high trait anxious individuals

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Abstract

Attention bias modification (ABM) was developed to alleviate anxious symptoms by way of a reduction in anxiety-linked attentional bias to threat. Central to the rational of ABM is a learning-related reconfiguration of attentional biases. Yet, the neuroplastic changes in brain structure that underlie this learning are unresolved. The amygdala, anterior cingulate cortex, and lateral prefrontal cortex are part of a system linked to attentional bias to threat and its modification with ABM. We assessed the extent to which ABM modulates gray matter volume and resting-state functional connectivity. Sixty-one individuals selected for attentional bias to threat and heightened trait anxiety completed a 6-week multi-session ABM protocol with 7200 total training trials. Participants were assigned to either an ABM (*n* = 30) or a control (*n* = 31) condition. We found that participants' levels of attentional bias and anxiety did not differ following ABM and control training interventions. However, the ABM group displayed greater levels of anterior cingulate cortex gray matter volume as well as greater superior frontal gyrus resting-state functional connectivity with the anterior cingulate cortex and insula. Changes in anterior cingulate cortex gray matter volume were linked to reduced anxious symptoms in the ABM, but not control, group. These findings suggest that ABM distinctively impacts structural and functional neural mechanisms associated with emotion reactivity and cognitive control processes.

Introduction

Anxiety disorders are highly prevalent with a lifetime diagnosis rate of approximately 30% in the United States (Hirschfeld, 2001). Elevated attentional bias to threat is not only a cardinal symptom of anxiety (Fox, 2002; MacLeod & Mathews, 1988; MacLeod et al., 1986; Mogg & Bradley, 2002; Mogg et al., 1995), but theorized to be a causal mechanism in the development and maintenance of anxiety (MacLeod et al., 2002; Mathews & MacLeod, 2002). Attentional bias refers to the prioritization of threating information for more elaborative processing at the expense of non-threatening information (Desimone & Duncan, 1995), which is adaptive and pervasive within the general population (Ohman & Mineka, 2001; Vuilleumier, 2005). For individuals with anxiety, however, this adaptive process is exaggerated and can become maladaptive (Bar-Haim et al., 2007).

Given that attentional bias to threat may lead to anxious symptoms (MacLeod et al., 2002), researchers have trained participants to focus their attention on non-threatening stimuli to reduce attentional bias to threat, and in turn anxiety. Initial research utilizing this approach, called attention bias modification (ABM), generally reported training-related decreases in attentional bias and anxiety (Bar-Haim, 2010; Beard, 2011; Beard et al., 2012; Browning, Holmes, & Harmer, 2010; Hakamata et al., 2010; Hallion & Ruscio, 2011; Hertel & Mathews, 2011; MacLeod & Mathews, 2012; Mogoase et al., 2014). However, more recent research indicates that ABM is not universally effective (Heeren, Mogoase, et al., 2015; Kuckertz & Amir, 2015; Mogg et al., 2017). Rather, ABM seems to be effective in some individuals, but not in others. Considering the central rationale of ABM is that learning-related reductions in attention bias reduce anxiety,

identifying the neuroplastic changes in brain structure underling this learning may provide insight into who benefits from ABM and why.

Theoretical models (Bishop, 2008; Cisler & Koster, 2010; Dolcos et al., 2020; Pourtois et al., 2013; Vuilleumier, 2005) and empirical evidence (Armony & Dolan, 2002; Bush et al., 2000; Carlson et al., 2009; Fu et al., 2015; Monk et al., 2008; Price et al., 2014; White et al., 2016) implicate the amygdala, anterior cingulate cortex (ACC), and lateral prefrontal cortex (LPFC) as core neural mechanisms underlying attentional bias to threat. Evidence from patients with amygdala damage indicates that the amygdala is necessary for initial threat detection and attention allocation (Anderson & Phelps, 2001; Bach et al., 2014; Framorando et al., 2021; Vuilleumier et al., 2004). The ACC is thought to detect and resolve conflict between threat signals and ongoing tasks/goals; whereas LPFC exerts attentional control to regulate threat-related signals and maintain focus on goal-relevant information (Bishop, 2008).

Neuroimaging research suggests that ABM training alters activity in the amygdala–PFC circuitry. Specifically, ABM leads to attenuated activity in the ACC (Hilland et al., 2020; Taylor et al., 2014) and enhanced activity in LPFC (Browning, Holmes, Murphy, et al., 2010; Liu et al., 2018; Mansson et al., 2013; Taylor et al., 2014). Increases in PFC activity have been linked to reductions in attentional bias and anxious symptoms (Taylor et al., 2014). However, this association is not consistently tested/observed. ABM-related changes in amygdala activity have been inconsistent with both decreases (Hilland et al., 2020; Liu et al., 2018; Taylor et al., 2014) and increases (Britton et al., 2015; Mansson et al., 2013) being reported. Additional evidence suggests that event-related potentials localized to the ACC are modulated by ABM (Carlson, 2021) and that neuromodulation of the dorsal LPFC (DLPFC) increases the effectiveness of ABM

(Clarke et al., 2014; Heeren, Baeken, et al., 2015). Thus, there is converging evidence implicating the amygdala–PFC circuit in ABM (Wiers & Wiers, 2017). It should be noted that the majority of (task-based) ABM neuroimaging studies in adults had small sample sizes (i.e., 4/5 studies had group *ns* ≤ 15) and did not select for preexisting bias, which moderates ABM efficacy (Amir et al., 2011; Heeren, Philippot, et al., 2015; Kuckertz, Gildebrant, et al., 2014; Mogoase et al., 2014). These factors may contribute to inconsistent findings across studies. Furthermore, the extent to which ABM produces structural-level changes within the amygdala–PFC circuit, or elsewhere in the brain, remains unresolved.

Identifying the neuroplastic changes in brain structure that accompany ABM is important for understanding the mechanisms underlying the efficacy of ABM training. Only two previous studies assessed structural changes following multi-session ABM (Abend et al., 2019; Hakamata et al., 2018). These studies had small sample sizes (group *ns* = 14-18) (Parsons, 2020), did not focus on (or observe) structural changes in the amygdala-PFC circuitry, and did not screen for pre-existing attentional bias. Prior research indicates that greater ACC gray mater volume (GMV) is related to heightened attentional bias to threat (Carlson et al., 2012). Given this, it has been hypothesized that changes in ACC (and extended amygdala) GMV underlie the effects of ABM and individual-level reductions in attentional bias and anxiety (Aday & Carlson, 2017). Here, we directly tested these hypotheses in a sample of individuals selected for elevated levels of anxiety and attentional bias to threat. Participants' structural MRIs and resting-state fMRIs (rsfMRI) were collected before and after completing a 6-week cellphone administered ABM (or control) training protocol. It was hypothesized, that ABM would result in reduced anxiety, attentional bias, and GMV in the ACC and extended amygdala, which would

relate to symptom changes. We further hypothesized that ABM training would alter the strength of resting-state functional connectivity (rsFC) within the amygdala–PFC circuit.

Method

Participants

The final sample included sixty-one (female = 42) right-handed adults aged 18-38 (*M* = 21.92, *SD* = 5.10; see Figure 1 for CONSORT flow diagram). As shown in Table 1, the ABM (*n* = 30) and control (*n* = 31) groups did not differ in age, sex, pre-training anxiety, or pre-training attention bias. We performed a sensitivity analysis using G*Power (version 3.1.9.2) with α = .001, power = .80, and total sample size = 61, indicating that our study was powered to detect medium to large effect sizes of f ≥ 0.28 for the training time x training group (2 x 2) interaction. Participants provided written informed consent and received monetary compensation for their participation. The study was approved by the Northern Michigan University Institutional Review Board and preregistered on clinicaltrials.gov (NCT03092609).

Research suggests that ABM is most effective in highly anxious individuals with a pre-existing attentional bias to threat (Amir et al., 2011; Heeren, Philippot, et al., 2015; Kuckertz, Gildebrant, et al., 2014; Mogoase et al., 2014). For this reason, we screened participants to have high levels of anxiety (STAI-T scores ≥ 40) and some level of attentional bias (dot-probe task incongruent – congruent bias scores ≥ 7ms). Additionally, to be included in the study, participants were screened to meet the following criteria (1) right-handed, (2) 18–42 years old[1], (3) normal (or corrected to normal) vision, (4) no current psychological treatment, (5) no recent history of

[1] The age range was expanded from the initial age range of 18-37 to allow for broader participation.

head injury or loss of consciousness, (6) no current psychoactive medications, (7) not claustrophobic, (8) not pregnant, and (9) no metal in the body or other MRI contraindications.

General Procedure

Enrollment began in Feb 2018 and continued on a rolling basis until Feb 2020. The study used a 50:50 parallel assignment design. The general procedure consisted of pre- and post-training sessions separated by 6 weeks of offsite ABM training. Pre and post-training measures included: (1) dot-probe task, (2) anxiety questionnaire, as well as (3) structural MRI and rsfMRI[2]. The dot-probe task and questionnaires were collected in a controlled laboratory setting. MRI data were collected at the Upper Peninsula Health System-Marquette Hospital. Dot-probe task attention bias scores were the primary outcome measure, STAI-T anxiety was the secondary outcome, and MRI measures were collected as additional outcomes. Participants and MRI technicians were blind to training condition.

State-Trait Anxiety Inventory

The Spielberger State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970) was used to measure state and trait anxiety. The STAI-S measures how anxious one *currently* feels or state anxiety. The STAI-T measures how anxious one *generally* feels or trait anxiety. Each subscale contains 20 items with scores that range from 20 – 80. A score of 40 or greater has been linked to clinical levels of anxiety in adults and was used as a cutoff for inclusion in this study (Emons et al., 2019; Julian, 2011; Spielberger et al., 1970). Prior to training, STAI-T levels ranged from 40-71 (M = 52.85, SD = 7.88).

Dot-Probe Task

[2] EEG data was also collected in the Flanker task.

E-Prime2 (Psychology Software Tools, Pittsburg, PA) was used to program the dot-probe task (MacLeod & Mathews, 1988). Participants were seated 59 cm from a 60 Hz 16" LCD monitor. Stimuli consisted of 20 fearful and neutral grayscale faces of 10 different actors from two databases[3] (half female; from Gur et al., 2002; Lundqvist et al., 1998). Facial stimuli were cropped to exclude extraneous features. A separate sample (N = 85) rated fearful faces as more negative (M = 3.83, SD = .30) than the neutral faces (M = 4.45, SD = .52), t (18) = 3.23, p = .005 (Carlson & Fang, 2020). The methodology for the dot-probe task used here has been previously described (Carlson & Fang, 2020; Carlson & Fang, 2021; Carlson et al., 2021; Strand et al., 2021) and is summarized in Figure 2.

Attention Bias Modification Training

Given that convenience is an advantage of ABM treatment and research has shown that ABM can be self-administered remotely (Kuckertz, Amir, et al., 2014; MacLeod et al., 2007; See et al., 2009; Teng et al., 2019), we used a cellphone app-based version of ABM training[4]. Participants were randomly assigned in an alternating order to complete ABM or control training using their personal smart phone device. The app was programmed such that even numbered participants were assigned to one condition and odd numbered participants to the other condition. ABM sessions included a modified dot-probe task that *only contained incongruent trials* (i.e., target-dot – neutral stimulus 100% pairing). In contrast, control sessions, included a standard dot-probe task (i.e., target-dot – neutral/threat stimulus 50% pairing).

[3] Fearful and Neutral face stimuli were from actors: 207, 208, 213, and 217) as well as AF14, AF19, AF22, AM10, AM22, AM34.

[4] This approach is also consistent with NIMH's focus on Technology in its Strategic Plan for Research.

During each session, a 'Prepare for Trial' screen instructed participants to 1) set their phone to 'Do Not Disturb', 2) turn the brightness to highest level, and 3) find a quiet distraction-free environment to complete the session. After this initial screen, participants completed the 10-item short-form Positive and Negative Affective Schedule (PANAS) (Thompson, 2007; Watson et al., 1988). Participants were asked to 'Indicate to what extend you CURRENTLY feel this way' on a scale ranging from 1 ('Not at all') to 5 ('Extremely'). After the PANAS, participants saw the following prompt: "Please try your best to concentrate on the task. Your performance may be compared anonymously with other participants' performance at a later time." Participants then proceeded to their respective training session.

Based on the dot-probe task, each training trial started with a white fixation cue (+) centered on a black background. Two valenced stimuli were then simultaneously presented to the left and right of fixation. A target dot appeared in the location formerly occupied by one of the two stimuli using the pairing percentages described above for ABM and control conditions. Responses were recorded using touch screen technology. Stimuli included grayscale fearful and neutral faces from standardized databases (Gur et al., 2002; Lundqvist et al., 1998) as well as threatening and non-threatening word stimuli (Bradley & Lang, 1999). Threatening and non-threatening word pairs (30 pairs) were matched based on word length and frequency. Participants completed a total of 36 training sessions (each session contained 200 trials) over the course of 6 weeks (7200 total trials) with each week containing 6 training sessions (no more than 3 in a single day). First week of training started with face stimuli and from the second week on face and word stimuli appeared alternatively every other session. The difficulty of training also changed, stimuli were presented for 500 ms in weeks 1-2 and 300 ms in the following weeks.

Weeks 4-6 included distractor targets (i.e., other shapes) with one distractor in week 4, three in week 5, and five in week 6. In order to track changes in attention bias, each training session included an additional 30 standard dot-probe trials (50% congruent and 50% incongruent). During each session, participants were able to monitor their (1) progress via a trial counter at the top right of the screen and (2) percent correct on the top left of the screen.

A website was used to track participant progress. If participants' accuracy for a session was below 75%, contact was made to determine if their phone was functioning properly or if they had questions about the training procedure. If participants had 1-2 days of non-usage, the following message was sent: "To complete the required 6 sessions per week, you will need to complete X sessions in the next Y days." If participants had 3 days of non-usage, the following message was sent: "You are in danger of not meeting the study requirements and being excluded from further participation. To complete the required 6 sessions per week, you will need to complete X sessions in the next Y days. Please contact the lab, if you will not be able to complete these sessions." If a participant fell behind in their sessions by more than a week, the participant was considered to be non-compliant and was excluded from further participation.

MRI Data Acquisition and Analysis

Structural and functional MRI data were collected with a 1.5 Tesla General Electric whole-body scanner within 1-2 weeks following laboratory sessions. High-resolution 3D fast spoiled gradient echo (FSPGR) T1-weighted images were obtained using the following acquisition parameters: TR = 5.6ms, TE = 2.1ms, TI = 450ms, flip angle = 9°, FOV = 250, matrix = 256 × 256, voxel size = 0.98 × 0.98 x 1.2mm. In addition, 240 functional volumes were collected in a 10-minute resting-state protocol using the following T2*-weighted echo planar imaging gradient

echo pulse sequence: TR = 2500 ms, TE = 35 ms, flip angle = 90°, FOV = 220, matrix = 64 × 64, voxel size = 3.4 × 3.4 x 5 mm, gap = 0.

Voxel based morphometry (VBM) is an automated user-independent voxel-wise measurement approach (2000). We used standard VBM processing procedures to assess how ABM affects regional brain volumes. Three-dimensional T1-weighted MRIs were visually examined for artifacts or abnormalities and manually adjusted to a common origin at the anterior commissure. Using SPM12 (http://www.fil.ion.ucl.ac.uk/spm), pre and post images were first realigned and resliced to their mean image. Realigned images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) tissue types. Images were normalized to Montreal Neurological Institute (MNI) space using a modulation step to permit voxel-wise information about local tissue. Images were visually inspected following normalization and smoothed using an 8mm full width at half-maximum (FWHM) Gaussian kernel. Measures of intracranial volume (ICV) were obtained from summed global signals of segmented GM, WM, and CSF images. The Image Calculator process was run in SPM12 to create difference maps for GMV (ΔGMV; Post-training – Pre-training).

Within SPM12, a general linear model (GLM) t-test was conducted to assess group (ABM vs. control) differences in ΔGMV. Age, ICV, and scanner[5] were included as covariates to control for their potential confounding effects (Ge et al., 2002; Peelle et al., 2012; Tisserand et al., 2004). Global normalization was applied with ANCOVA to assess regional differences in ΔGMV controlling for total GMV (Peelle et al., 2012). The initial whole brain threshold was set to

[5] Due to the hospital moving to a new location, MRI data were collected on two identical scanners (scanner 1 *n* = 50 & scanner 2 *n* = 11). All participants' pre and post scans were collected at the same scanner site.

$p_{\text{uncorrected}} < .001$. A family-wise error (FWE) small volume correction (SVC) at $p_{FWE} < .05$ was applied to an ACC region of interest (ROI) using a 12mm sphere centered on: xyz = ±8,36,16 and an extended amygdala ROI at xyz = ±12,2,2 (Aday & Carlson, 2017).

Resting-state fMRI data were preprocessed using the standard preprocessing pipeline (Whitfield-Gabrieli & Nieto-Castanon, 2012) through the functional connectivity (CONN) toolbox (http://www.nitrc.org/projects/conn) in MATLAB (Math Works, Natick, MA). Images were realigned to correct for head movement and then resliced to match the timing of the first image. Subject motion was calculated and removed in CONN's artifact detection step (subject-motion threshold = 0.2 mm, global-signal z-value threshold = 5). 10 participants (8 ABM and 2 control) were removed due to having < 50% valid scans. The six motion parameters and their first-order derivatives were included in the GLM analyses to control head movement. Images were normalized to MNI space, smoothed with an 8-mm FWHM Gaussian kernel, and band-pass filtered to frequencies between 0.008 and 0.09 Hz. First-level GLM analyses were performed using Pearson's correlation coefficients for the time course of the seed region and that of all voxels across the brain for each participant. These correlation coefficients were then Fisher transformed to Z scores for use in the second-level analysis. Age and mean motion were included as covariates in second-level models. Our seed-to-voxel analysis utilized regions linked to attentional bias and ABM (i.e., ACC, amygdala, and LPFC regions) using CONN's default atlas defined ROIs from Harvard-Oxford Atlas (Desikan et al., 2006; Frazier et al., 2005; Makris et al., 2006) and Automated Anatomoical Labeling Atlas (Tzourio-Mazoyer et al., 2002) as well as the ACC cluster implicated in our VBM analyses. Results were initially thresholded at $p_{\text{uncorrected}} < .001$ and then cluster-level $p_{FWE} < .05$.

Results

Effects of ABM on Behavioral Measures

Data were filtered to include correct responses between 150-750 ms post-target onset (92.46% included) (Torrence et al., 2017). A 2 × 2 mixed factors analysis of variance (ANOVA) was conducted to assess the effects of training (pre vs post) and group (ABM vs control) on attention bias scores (incongruent – congruent reaction time (RT) difference in ms). There was a main effect of training, $F(1, 59) = 29.68$, $p < .001$, $\eta_p^2 = .35$, such that post-training attention bias ($M = 6.75$, $SD = 9.14$) was lower than pre-training attention bias ($M = 16.49$, $SD = 10.18$). However, group did not influence this general training effect $F(1, 59) = 0.59$, $p = .45$, $\eta_p^2 = .01$. Attention bias decreased in both the ABM (Pre: $M = 14.97$, $SD = 8.95$; Post: $M = 6.62$, $SD = 8.98$) and control groups (Pre: $M = 17.96$, $SD = 11.19$; Post: $M = 6.86$, $SD = 9.44$).

A 2 × 2 mixed factors ANOVA was conducted to assess the effects of training (pre vs post) and group (ABM vs control) on trait anxiety levels. There was neither a main effect of training, $F(1, 59) = 0.30$, $p = .59$, $\eta_p^2 = .01$, nor a training × group interaction, $F(1, 59) = 0.04$, $p = .85$, $\eta_p^2 = .001$.

Week-to-week tracking of attention bias and PANAS data are reported in **Supplementary Material**.

Effects of ABM on Neuroimaging Measures

ABM (relative to control) training increased GMV in the dorsal ACC (dACC) ROI, $t(54) = 3.89$, $p_{FWE} < .05$, $k = 30$, xyz = 6,42,23. At $p_{uncorrected} < .001$ (Figure 3). This same pattern was

observed in the amygdala, temporal parietal junction, and superior temporal gyrus, whereas the reverse pattern was observed in the posterior cingulate (Table 2).

For seed-to-voxel analysis, (*N* = 45 participants; 20 ABM vs. 25 control, Figure 1) relative to control, ABM training resulted in increased connectivity between the right SFG (see **Supplementary Material** for seed) and bilateral dACC (xyz = 0,-8,32), $t(41) = 5.61$, $p_{FWE} < .01$, $k = 273$, and between the rSFG and right insula (xyz = 40,-10,-8), $t(41) = 5.90$, $p_{FWE} < .01$, $k = 264$ (post > pre; Figure 4). No associations were significant for the amygdala and dACC seeds at $p_{FWE} < .05$.

Associations between Neuroimaging and Behavioral Measures

In partial correlations controlling for ICV, age, and scanner, ΔACC GMV correlated with ΔAnxiety (post – pre) in the ABM group such that greater increases in ACC GMV were accompanied by greater reductions in anxiety, $r = -.42$, $p = .03$. There was no association between ΔACC GMV and ΔAnxiety in the control group, $r = .06$, $p = .76$. In a GLM with covariates controlling for ICV, age, and scanner, the training group × ΔACC GMV interaction significantly predicted ΔAnxiety, $F(1, 54) = 5.33$, $p = .025$, $\eta_p^2 = .09$, confirming that the association between ΔACC GMV and ΔAnxiety was moderated by training group. ΔACC GMV did not correlate with ΔAttention bias (post – pre) in either group, $rs \leq .28$, $ps \geq .15$.

We also examined whether training-related increases in ΔrsFC (i.e., rSFG–ACC and rSFG–insula) were associated with ΔAnxiety and ΔAttention bias. However, no significant associations were found, $rs \leq .11$, $ps \geq .47$.

Discussion

We aimed to measure neuroplastic changes in brain structure and function following ABM in a sample of high trait anxious individuals characterized by attentional bias to threat. Our results provide novel evidence that ABM training increases dACC GMV as well as SFG rsFC with the dACC and insula. Although ABM training did not lead to reductions in anxious symptoms across all individuals, we found that reductions in anxiety were proportionally linked to increases in dACC GMV following ABM, but not control training.

Contrary to our hypotheses, both ABM *and* control training resulted in reductions in behavioral measures of attention bias, but not anxiety. Reductions in attentional bias have been documented following home-delivered ABM and active control, but not waitlist, training (Teng et al., 2019). Whereas ABM is thought to reduce an implicit threat bias, control training is thought to more generally increase top-down cognitive control (Badura-Brack et al., 2015; Mogg et al., 2017). Therefore, it is possible that ABM and control training reduced attentional bias through different neurocognitive mechanisms. Alternatively, given that we selected for individuals with an attentional bias and these RT measures are unreliable (Schmukle, 2005), the reduction in attentional bias across groups could simply be attributable to regression to the mean.

ABM increased dACC GMV and this change in GMV was linked to anxiety reduction in the ABM group. This is contrary to our hypotheses, which were based on previous research indicating that greater dACC GMV is linked to heightened attentional bias (Aday & Carlson, 2017; Carlson et al., 2012)[6]. Recent research utilizing animal models indicates that learning-related changes in VBM measures of GMV are specifically linked to increases in dendritic spine

[6] Note that pilot data reported in this reference found both increases and decreases in ACC GMV.

density (Keifer et al., 2015). Changes in dendritic spine density are closely related to fear learning and thought to represent the strengthening/weakening of synapses (Heinrichs et al., 2013; Pignataro et al., 2013; Restivo et al., 2009). That is, afferent inputs into a neuron or region. Given this, the interpretation of learning-related GMV changes may depend on the source(s) of input. We speculate that our findings may indicate that increased dACC GMV—and associated anxiolytic effects—following ABM are primarily attributable to increased regulatory input to dACC, rather than decreased input from regions that initiate the threat response. Yet, further research is needed to determine the validity of this speculation. We did not observe GMV changes in our extended amygdala ROI following ABM. However, at an uncorrected level we did observed changes in amygdala GMV, which may be related to fear/extinction learning processes dependent on the amygdala (Knight et al., 2005; LaBar et al., 1998; LeDoux, 2007). Future research is needed to verify this preliminary finding.

Resting-state connectivity represents correlated (or anticorrelated) regions of the brain during non-task states. Brain regions with correlated activity during rest are thought to reflect a functional network of structures that are directly or indirectly connected and involved in shared cognitive processes (Deco et al., 2011). We found increased SFG—dACC and SFG—insula rsFC following ABM. The dACC and insula are two primary nodes in a resting-state network known as the salience network, thought to be involved in detecting emotional (and otherwise salient) stimuli (Seeley et al., 2007). The SFG within the DLPFC is part of an executive control network (Seeley et al., 2007). Therefore, our findings can generally be interpreted as increased rsFC between cognitive control and emotional reactivity regions. This is consistent with previous research in major depressive disorder where ABM leads to increased DLPFC—dACC rsFC

(Beevers et al., 2015). Other research has also found ABM-related changes in salience network rsFC (Hakamata et al., 2018; Hilland et al., 2018; Li et al., 2016).

Two general neurocognitive mechanisms are thought to contribute to successful ABM: an early threat detection system linked to the amygdala and a later cognitive/attention control system linked to the DLPFC (Heeren et al., 2013; Mogg & Bradley, 2016; Mogg & Bradley, 2018). Within this framework, ABM could be effective by decreasing the sensitivity of the threat detection system, increasing the attention control system, or a combination of these factors. We observed greater DLPFC rsFC with the dACC and insula following ABM. This finding represents increased communication between the attention control system and the threat/salience detection system following ABM—potentially reflective of increased attentional control over automatic attentional biases to threat. Although we found changes in DLPFC rsFC following ABM, the GMV of the DLPFC was unchanged. Conversely, increases in dACC GMV were observed following ABM. The ACC is densely connected with the amygdala and these connections are linked to attentional bias (Amaral & Price, 1984; Carlson et al., 2014; Carlson et al., 2013; Rolls, 2019). The ACC is thought to select among stimuli competing for attention and regulate the duration of attentional engagement by threat (Aday & Carlson, 2017; Bishop, 2008). Thus, our results are suggestive of increased goal-directed cognitive control over a critical structure involved in allocating attentional resources to threat-relevant stimuli.

It should be noted that neuroplastic changes in brain structure and function were not correlated with changes in attentional bias, even though both measures decreased following ABM. This may in part be attributable to the poor reliability of RT-based attention bias measures (Schmukle, 2005). Additionally, although the changes in dACC GMV and rsFC were

proximal, they were spatially distinct and dissociable[7]. Critically, increases in dACC GMV were found to be related to decreased anxiety following ABM, whereas increases in rsFC were unrelated to changes in anxiety. Given this, dACC GMV could be a sensitive biological target to objectively track training-related changes and outcomes. Changes in brain structure, such as GMV, are likely to be more stable and reliable targets than functional measures (Aday & Carlson, 2017). Thus, although ABM training commonly impacts the structure and function of the dACC, structural level changes are uniquely linked to changes in anxiety.

Our ABM training was administered using a convenient remote cellphone-based methodology. Previous research has assessed differences in efficacy between laboratory and remote ABM administration. The results of these studies has been mixed with some studies reporting reductions in attention bias following remote ABM (Kuckertz, Amir, et al., 2014; MacLeod et al., 2007; See et al., 2009; Teng et al., 2019), while other report no change in attention bias following romote ABM (Boettcher et al., 2012; Carlbring et al., 2012; Enock et al., 2014; Neubauer et al., 2013). As mentioned above, we found a non-specific decrease in attention bias across the ABM and control groups. Given the repetitive nature of a typical ABM protocol (Kuckertz et al., 2019), we integrated several game elements in order to increase motivation and engagement (Vermeir et al., 2020). For example, participants received feedback after each trial, a progress bar was presented at the top of the screen, a results graph was accessible in the result tab, a new badge was received upon the completion of each week's training, and a weekly review was provided. According to participant feedback at the end of the

[7] Note that changes in dACC GMV were unrelated to changes in SFG – dACC rsFC in both groups, $rs \leq .08$, $ps \geq .71$. In addition, although we found that ABM increased SFG—dACC rsFC, no changes in dACC seeded connectivity were observed.

study, to some participants the game features were helpful, whereas to other participants these features may not have been as effective as expected. This is consistent with previous research that showed benefits of gamified cognitive training tasks (Vermeir et al., 2020), but also detrimental impacts of gamification on training effect (Boendermaker et al., 2016; Zhang et al., 2018). Since there is increasing interest in including game features into cognitive bias training, research that systematically examines the influence of each game feature on training may be of great value.

Moreover, a relatively high number of participants were lost due to non-compliance. For a multiple-session cognitive bias modification protocol, when a large number of repetitive training sessions is indispensable, the length for each session, the temporal separation of the training sessions, as well as personalized scheduling and feedback for training should be carefully considered and their impact on training effects should be further investigated. For instance, it has been proposed that a large interval between each training session could make the attentional changes last longer (Hertel & Mathews, 2011). According to the feedback from our participants, regular reminders from the training app, personalized feedback and rewards, as well as shorter training sessions could potentially increase engagement and compliance.

Limitations

Although our final sample size was larger than many ABM neuroimaging studies, a significant number of participants were lost to non-compliance (likely due to the length of our protocol). Sensitivity analysis indicates that our final sample was only powered to detect medium to large effects. Our initial findings in high trait anxiety individuals are promising;

however, this was not a clinical sample and future research is needed to replicate and generalize these effects to clinical populations. In addition, VBM measures of GMV are sensitive to contributions from cortical thickness and surface area. Further research will be needed to isolate ABM-related changes in these measures. Given that the assignment of ABM and control training conditions was based on participant number, research assistants collecting the data may not have been fully blind to the training condition. Although training was delivered remotely with limited experimenter interaction, the single blind nature of the study is a limitation. In addition, given the 100% contingency between neutral faces and target dots in the ABM condition, it is possible that participants noticed this pattern. Yet, potential awareness for the training contingency in the ABM group does not appear to have impacted changes in attentional bias as both the ABM and control groups displayed lower levels of attention bias following training.

It should be noted that the null effects of ABM on anxiety symptoms and attention bias is a limitation of the current study. The lack of symptom-based changes may reflect a shortcoming of our cellphone delivered dot-probe task-based approach to ABM. In particular, the small screen size used to administer ABM may have limited the scope in which the allocation of attentional resources could be modified and/or the extent to which such modifications would generalize to the pre and post dot-probe assessments of attentional bias on computer monitors occupying a larger portion of the visual field. These null effects indicate that ABM training was not successful at the behavioral level and therefore the changes in GMV and rsFC observed here should be interpreted with caution. Future research should assess the neural correlates of ABM following more personalized and dynamic attention training

approaches such as eye-gaze contingent attention training (Sanchez-Lopez et al., 2021; Sanchez-Lopez et al., 2019; Sanchez et al., 2016). Beyond these limitations, the study had several strengths including our convenient cellphone delivered ABM protocol, multimodal neuroimaging approach, and relatively large sample size.

Conclusion

In sum, we provide novel evidence that multi-session ABM training in high trait anxious individuals leads to increased dACC GMV. Neuroplastic changes in dACC GMV were linked to reductions in anxiety following ABM, but not control, training. Beyond structural level changes, ABM resulted in increased SFG—dACC and SFG—insula rsFC. Collectively, our results suggest that ABM distinctively impacts structural and functional neural mechanisms associated with emotion reactivity and cognitive control processes.

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Contributions

JMC drafted the manuscript and secured funding for the project. JMC, LF, EHWK, and JAA designed the study. JMC and LF analyzed the data. LF, JAA, HG, KAE, and TRZ collected the data. All authors read the manuscript and provided critical feedback and revisions.

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Tables

Table 1. *Group Comparisons for Age, Sex, Anxiety, and Attention Bias at Baseline*

Measure	ABM Group (*n* = 30)	Control Group (*n* = 31)	Comparison
Age	21.10 (3.72)	22.71 (6.12)	$t(59) = 1.24$, $p = .22$
Sex	*F* = 20, *M* = 10	*F* = 22, *M* = 9	$\chi^2(1) = 0.13$, $p = .72$
(pre) Anxiety	52.30 (6.79)	53.39 (8.89)	$t(59) = 0.54$, $p = .60$
(pre) Attention Bias	14.97 (8.95)	17.96 (11.19)	$t(59) = 1.15$, $p = .26$

Table 2. *Changes in Gray Matter Volume Following Attention Bias Modification (ABM)*

Region	Hemisphere	MNI Coordinates X	Y	Z	Voxels*	Peak *t* value
ABM > Control						
Anterior Cingulate Cortex	R	6	42	23	30	3.89
Temporal Parietal Junction	L	-60	-47	20	24	4.02
Amygdala	L	-20	3	-29	12	3.74
Superior Temporal Gyrus	R	62	-6	-5	17	3.69
ABM < Control						
Posterior Cingulate	R	15	-41	42	45	3.73

* At $p < .001$ uncorrected, $k > 10$.

Figures

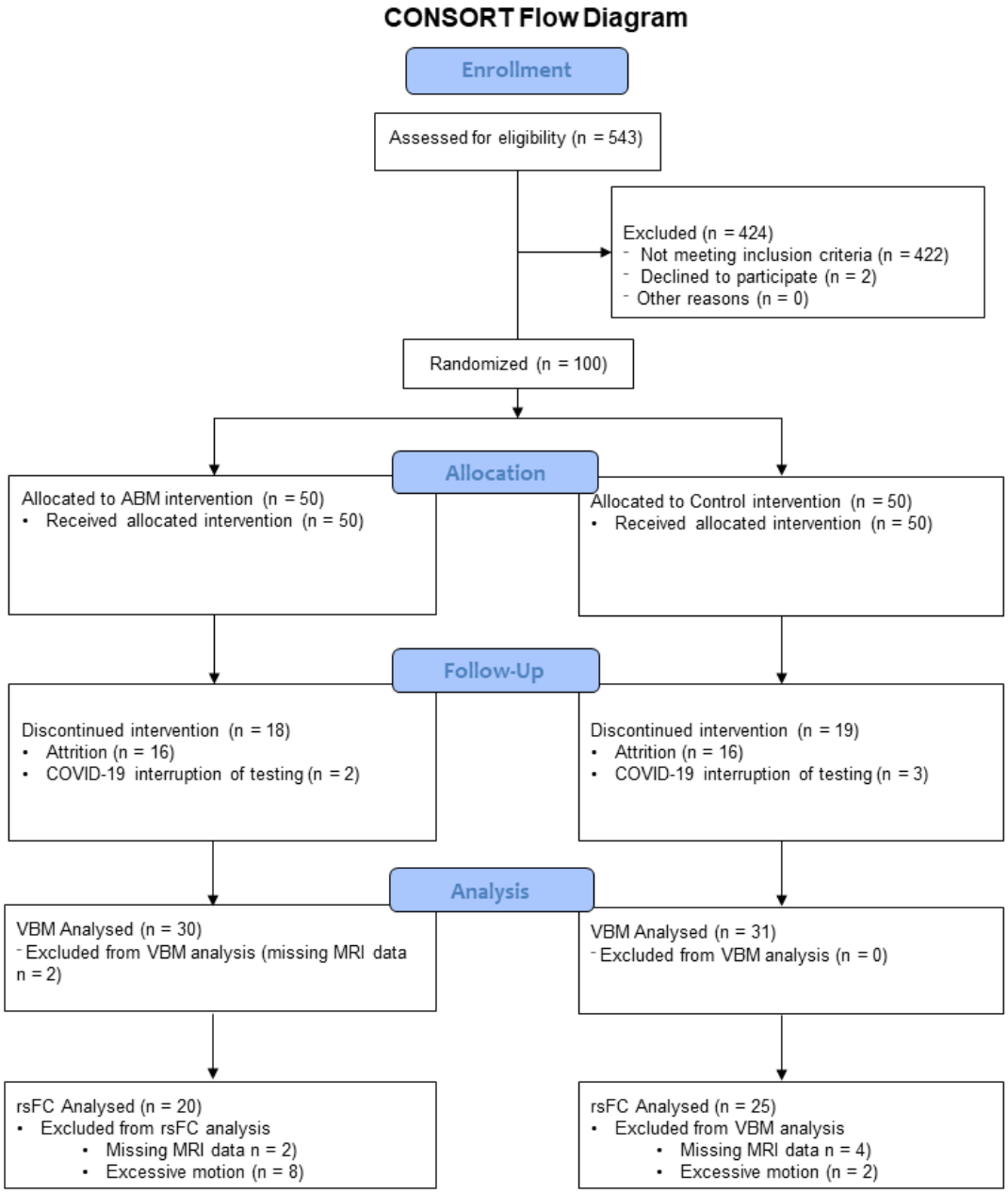

Figure 1. *CONSORT flowchart for participants from enrollment through analysis. Note that a subset of the 100 randomized participants were invited to complete a 3rd MRI session (6 weeks post follow-up) with an additional 19 participants as a part of a another project. VBM = voxel-based morphometry. rsFC – resting-state functional connectivity*

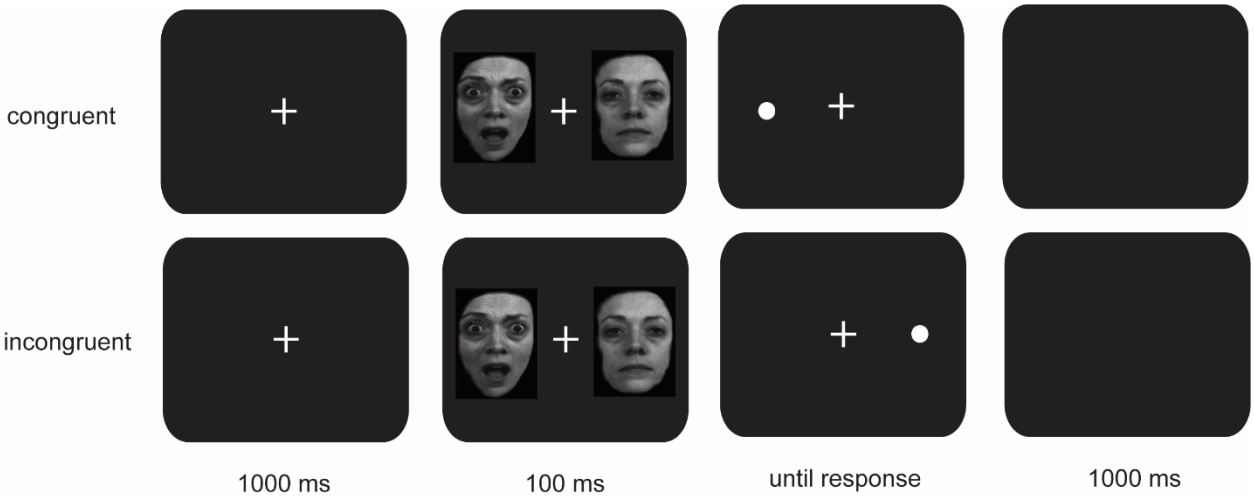

Figure 2. *A white fixation cue (+) was displayed in the center of a black screen for 1000 ms to start each trial. This central fixation remained on the screen throughout the trial and participants were instructed to focus on the fixation cue at all times. Following the initial fixation screen, two faces (5cm × 7cm in size) were presented simultaneously on the horizontal axis for 100 ms in a randomized order. A target dot then appeared at one of the two locations previously occupied by a face and remained until a response. Using a Chronos E-Prime response box, participants pressed the first, leftmost, button with their right index finger for left-sided targets and the second button with their right middle finger for right-sided targets. Participants were instructed to respond to the target dot as quickly and accurately as possible. Following the participant's response, there was a 1000ms intertrial interval. The task included congruent trials (dot on the same side as the emotional face), incongruent trials (dot on the same side as the neutral face), and trials with two neutral faces (neutral-neutral). Attentional bias to threat is measured by faster responses on congruent compared to incongruent trials. The task consisted of five blocks. Each block contained 30 congruent, 30 incongruent, and 30 neutral-neutral trials presented in a random order for a total of with 450 trials. Feedback about overall task accuracy and reaction times was provided after each block to encourage accurate rapid responses. Note that stimuli in the figure are not to scale.*

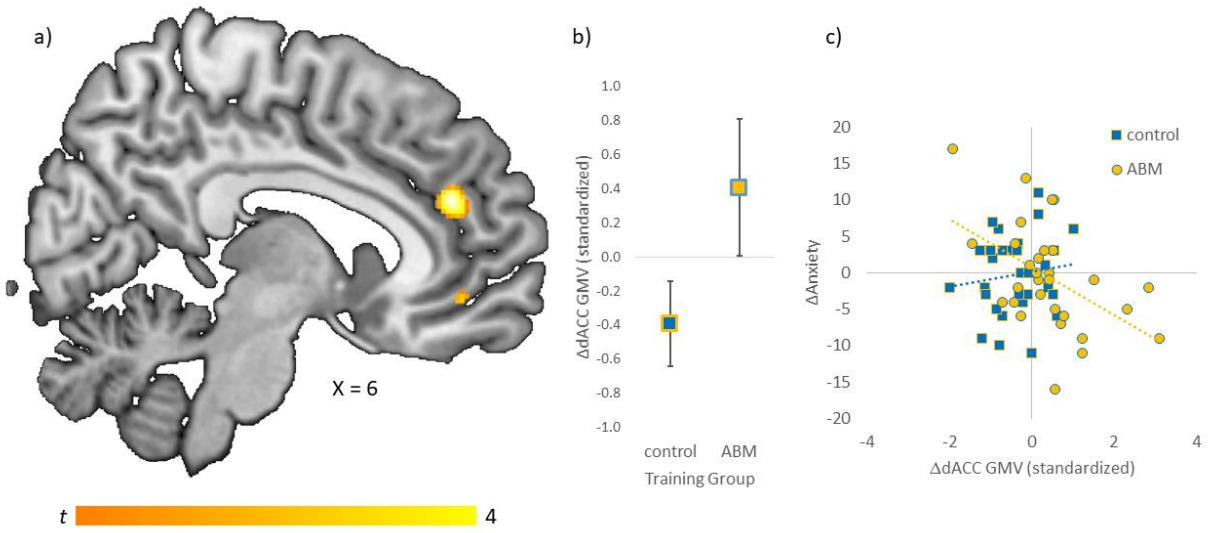

Figure 3. a) *Dorsal anterior cingulate cortex (dACC) region with differences in gray matter volume (GMV).* ***b)*** *Attention bias modification (ABM) resulted in greater GMV in the dACC relative to control training. Error bars represent the 95% confidence interval.* ***c)*** *Increases in GMV in the ABM group were associated with anxiety reduction, whereas there was no association between changes in GMV and anxiety in the control group.*

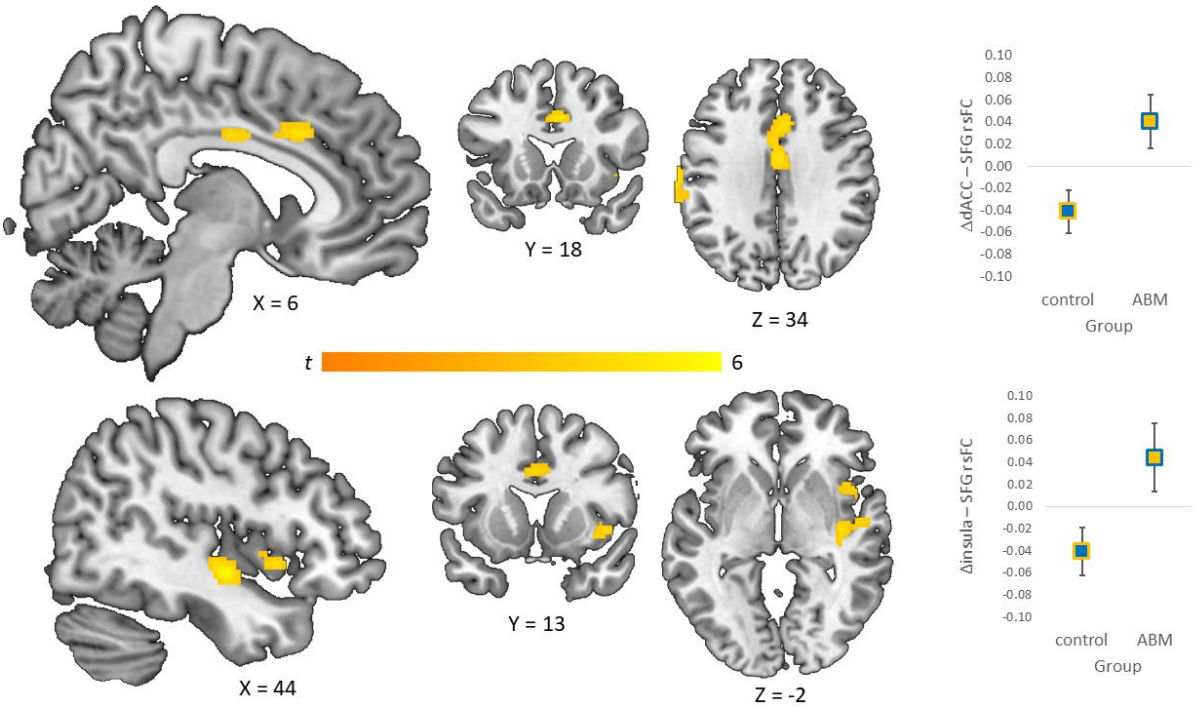

Figure 4. *Attention bias modification (ABM) resulted in greater resting state functional connectivity (rsFC) between the superior frontal gyrus (SFG) and dorsal anterior cingulate cortex (dACC) as well as between the SFG and insula. Error bars represent the 95% confidence interval. Connectivity displayed at p < .001 for visualization purposes.*