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Neural correlates of a computerized attention modification program in anxious subjects

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Computerized attention modification is a relatively new and empirically validated treatment approach for different types of anxiety disorders. However, its neural basis and processes involved are poorly understood. This study examined the effect of a one-time application of an attention modification program (AMP) on neural substrates underlying emotion processing in individuals with high social anxiety. Fourteen individuals with elevated social anxiety symptoms completed an emotional face processing task during functional magnetic resonance imaging before and after AMP, and were subsequently exposed to a laboratory stressor. Results revealed the following: First, there was attenuated activation from pre- to post-AMP in the bilateral amygdala, bilateral insula and subgenual anterior cingulate cortex. Second, post-AMP, individuals exhibited increased activation in several regions of the prefrontal cortex (PFC). Third, those individuals with greater enhancement of ventromedial PFC activation after AMP showed diminished attentional allocation for threat and attenuated anxiety reactivity to the stressor. We conclude that AMP exerts effects that are similar to those previously reported for standard anxiolytics; however, it also appears to foster deployment of top–down brain processes aimed to regulate anxiety.

INTRODUCTION

The tendency to preferentially allocate attention toward threat-relevant information is considered an important mechanism in the pathogenesis and maintenance of anxiety (Mathews and MacLeod, 2005; Bar-Haim *et al.*, 2007). Recently, researchers have used variants of the traditional probe detection task (MacLeod *et al.*, 1986) to modify attention to emotional stimuli (Figure 1) and have demonstrated that experimentally manipulating attentional allocation toward threatening information heightens susceptibility to anxiety when provoked in stressful contexts (e.g. MacLeod *et al.*, 2002; Clarke *et al.*, 2008) whereas decreasing attentional bias for threat attenuates anxiety reactivity in response to laboratory-induced (Amir *et al.*, 2008) as well as naturally occurring stress (See *et al.*, 2009). Moreover, several placebo-controlled randomized clinical trials (RCTs) support the efficacy of multisession attention modification programs (AMPs) in reducing symptoms in individuals meeting diagnostic criteria for an anxiety disorder (Amir *et al.*, 2009a,b; Schmidt *et al.*, 2009) (for recent meta-analyses, see Hakamata *et al.*, 2010; Hallion and Ruscio, 2011). Remarkably, AMPs yielded treatment effects in these RCTs that were medium to large in magnitude (posttreatment placebo-controlled effect size range = 0.57–1.59)—commensurate with established pharmacological and psychosocial interventions for anxiety.

How is it that a simple computerized training procedure can produce such robust anxiolytic effects? As a step toward addressing that issue we combined a validated attentional training procedure (Amir *et al.*, 2008, 2009b; Schmidt *et al.*, 2009) with functional neuroimaging to test the hypothesis that the anxiolytic effects of AMPs are achieved in part through the modulation of activity in brain regions that subserve emotional processing. Neurocognitive models of selective attention to threat (Vuilleumier, 2005; Bishop, 2008, 2009; Shechner *et al.*, 2012) propose that deployment of attention in the presence of emotional stimuli is regulated by two primary neural systems: (i) A bottom–up (stimulus-driven) amygdala-based system that produces a signal reflecting the perceived salience of stimuli (Adolphs *et al.*, 1995; Davis and Whalen, 2001) and directs attention toward salient stimuli, and (ii) a top–down (goal-directed) system comprised of the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) that produces a signal when conflicting demands are made on attention, for example, when two or more stimuli compete for processing resources (MacDonald *et al.*, 2000; Bishop *et al.*, 2004). According to this perspective, heightened risk for anxiety results from greater amygdala response to emotionally salient cues combined with impoverished attentional control mechanisms, i.e. reduced recruitment of regulatory PFC regions.

Considerable evidence supports a link between anxiety and heightened amygdala reactivity to negative emotional processing (see Etkin and Wager, 2007 for a meta-analysis and review). Research also suggests that anxiety may be associated with abnormalities in prefrontal regulatory regions (Etkin and Wager, 2007; Aupperle and Paulus, 2010; Etkin, 2010). Although evidence regarding the direction and specific location of PFC dysfunction in anxiety differs across experimental paradigms (Etkin and Wager, 2007; Simmons and Matthews, 2012), attenuated activity is often revealed in medial and dorsolateral PFC regions under conditions requiring attentional or inhibitory control (Bishop *et al.*, 2004; Bishop, 2009; Goldin *et al.*, 2009). This corpus of evidence has been taken to suggest that anxiety is associated with a diminished propensity to recruit top–down PFC control regions to regulate limbic-generated emotional responses (Aupperle and Paulus, 2010; Etkin, 2010).

Increasing evidence also underscores the role of the insular cortex in anxiety pathophysiology (Etkin, 2010; Paulus and Stein, 2010). The insula is heavily interconnected with the amygdala, anterior cingulate and medial and orbitofronal cortices, and similar to the amygdala, is activated during negative emotional processing (Phan *et al.*, 2002).

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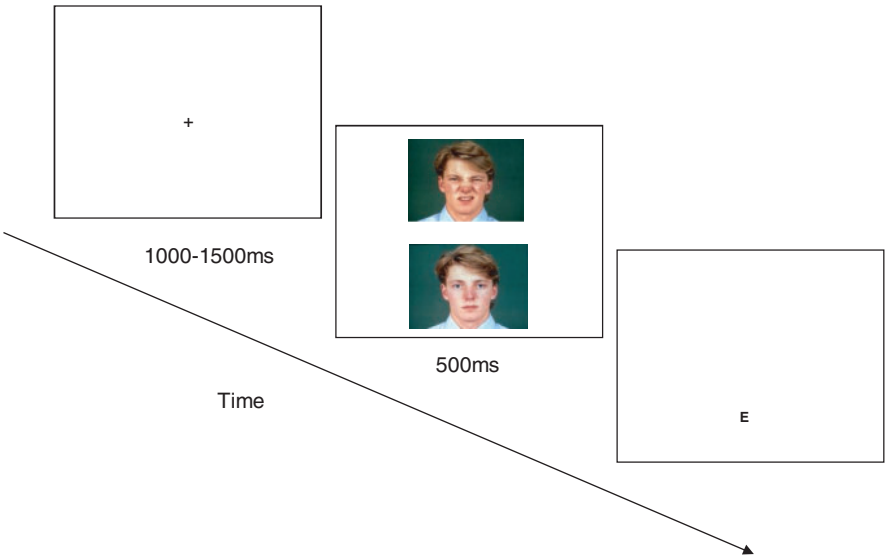

Fig. 1 Sample trial of the AMP. On each trial, participants were presented with a fixation cross '+' in the center of the monitor for 500 ms plus an additional jitter of 500–1000 ms (i.e. total fixation duration range = 1000–1500 ms). Following termination of the fixation cue, two faces of the same individual were presented, one face on top and one on bottom. Face pairs were neutral–threat (80% of trials) or neutral–neutral (20% of trials). After 500 ms, a probe (either the letter 'E' or 'F') appeared in the location of one of the two faces. Participants were instructed to identify whether the letter was an E or an F by pressing the corresponding button (left or right) on the response box. The probe remained on the screen until participants responded, after which the next trial began.

Previous studies reliably find greater insula activity in high anxious samples (Stein *et al.*, 2007) (for a review, see Paulus and Stein, 2010) as well as reduced insula-prefrontal functional connectivity (Klumpp *et al.*, 2012) during the processing of emotional stimuli, suggesting that the insula comprises part of an overactive emotion processing neural circuit characteristic of anxiety (Aupperle and Paulus, 2010; Etkin, 2010).

Taken together, previous studies suggest that experimental procedures that modify attentional allocation in the presence of emotionally salient stimuli may influence functioning of the amygdala, insula and/or prefrontal circuits. Initial evidence suggests that AMPs may primarily modulate activity in prefrontal regions during emotional conflict processing (Browning *et al.*, 2010b). After completing an attentional training procedure designed to induce either a selective processing bias toward (attend-threat) or away from (avoid-threat) threatening stimuli, healthy volunteers displayed greater activation in the lateral PFC and rostral ACC when their attention was oriented to emotional stimuli in the direction opposite to that encouraged by the training task—ostensibly, when the need to exert attentional control was high due to increased conflict demands. These findings converge with research suggesting that efficacious psychosocial (e.g. cognitive behavioral therapy) and some pharmacological interventions (Phan *et al.*, 2013) for anxiety are associated with increased activity in prefrontal circuitry following treatment (Quide *et al.*, 2012).

This study aimed to examine changes in the neural processes during emotion processing that are associated with the anxiolytic effects of attentional training procedures. We recruited a sample of participants with elevated social anxiety symptoms as a first step toward establishing the neural mechanisms of AMPs in an anxious population (cf. Browning *et al.*, 2010b). Participants completed a previously validated emotional face assessment task (Ball *et al.*, 2012) (Figure 2) before and after an attentional training procedure designed to facilitate disengagement from threat-relevant cues (Amir *et al.*, 2008, 2009b). The emotional face assessment paradigm reliably engages the amygdala during emotional face processing (Hariri *et al.*, 2002), reveals greater activation in amygdala and insula regions to emotional faces (irrespective of emotion type) in high anxious compared with low-anxious individuals (Stein *et al.*, 2007; Ball *et al.*, 2012), and is sensitive to revealing the effects of interventions that target brain systems involved in regulating emotional processing [e.g. benzodiazepines (Paulus *et al.*, 2005); selective serotonin reuptake inhibitors (SSRIs) (Arce *et al.*, 2008; Windischberger *et al.*, 2010)]. We predicted that modifying attention away from threat would increase activity in PFC regions implicated in regulatory control over emotional responses [e.g. medial PFC (mPFC; Etkin *et al.*, 2011)] and reduce activation in the amygdala and insula.

To increase the ecological validity of our findings and establish a link with previous AMP research, we also explored whether changes in neural activation on the face processing task following AMP predicted changes in attentional allocation for threat-relevant stimuli as well as anxiety reactivity in response to a laboratory stressor (i.e. impromptu videotaped speech) completed following the MRI scan (Amir *et al.*, 2008). Given the pivotal role of the mPFC and amygdala in neurocognitive models of selective attention to threat, we were primarily interested in testing the hypothesis that greater enhancement of mPFC activation and/or greater attenuation of amygdala activation following AMP would be associated with a larger decrease in attentional bias for threat as well as attenuated anxiety reactivity to the speech challenge.

METHODS AND MATERIALS

Subjects

The current sample comprised 14 individuals (4 men, 10 women) drawn from a pool of undergraduate students at a large university. Participants were selected on the basis of scoring ≥ 40 on the Liebowitz Social Anxiety Scale–Self-Report version [LSAS–SR (Liebowitz, 1987; Fresco *et al.*, 2001); scale range 0–144] completed during a testing session conducted earlier in the semester. Individuals who expressed an interest in the study were contacted via telephone and completed a clinician-administered LSAS and MRI safety-screening interview. Individuals who obtained an LSAS score ≥ 40 and did not evidence contraindications to completing an MRI scan (e.g. metal in their body) were invited to participate. Sixteen individuals were scheduled for the functional magnetic resonance imaging (fMRI) session. However, one individual did not attend the testing session and another participant's data were lost due to a technical error when transferring the data. Thus, the final sample comprised 14 individuals

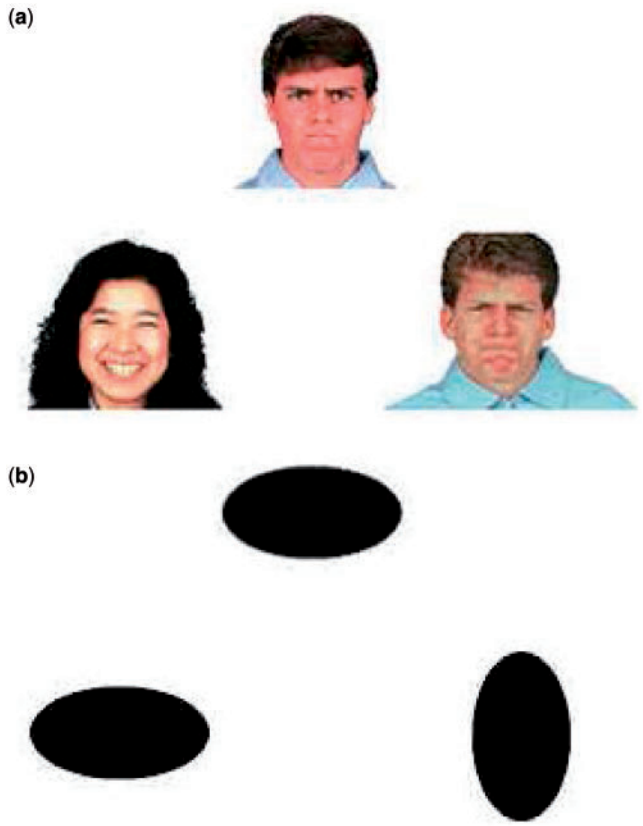

Fig. 2 Emotional Face Processing Task. Sample trials for the face-matching condition (**a**) and shape-matching (control) condition (**b**). During each 5-s trial, participants were instructed to press the left or right key on a button box to indicate which of two response options presented at the bottom of the screen matched the target at the top of the screen.

[mean age = 19.36, $SD = 1.86$; mean years of education = 13.57, $SD = 1.22$; mean LSAS = 79.07, $SD = 22.29$] who completed the testing procedures. The current sample mean LSAS score was comparable to the mean for individuals meeting diagnostic criteria for social anxiety disorder [$M = 74.53$, $SD = 23.31$(Fresco *et al.*, 2001)]. Participants were paid $100 for their participation. The University of California, San Diego Human Research Protection Program approved this study.

Measures

Baseline self-report measures

In addition to the LSAS–SR, subjects completed the Beck Depression Inventory–II (Beck *et al.*, 1996; sample $M = 17.50$, $SD = 10.34$) and the Spielberger State-Trait Anxiety Inventory–Trait version (Spielberger *et al.*, 1983; sample $M = 45.36$, $SD = 13.21$).

Emotional reactivity assessment

The STAI–State subscale (STAI–S; Spielberger *et al.*, 1983) was administered at baseline, immediately following the fMRI scan (i.e. post-AMP), and immediately following the speech task to evaluate changes in participant anxiety following the experimental manipulation as well as in response to the stressor.

Tasks

Dependent Measure–Emotion Face Assessment Task

During fMRI, participants completed a slightly modified (Paulus *et al.*, 2005; Stein *et al.*, 2007) version of the Emotion Face Assessment Task (Hariri *et al.*, 2002) before and after AMP (Figure 2). Each Emotion Face Assessment Task consisted of face and sensorimotor trials. During each 5-s face trial, subjects were presented with a target face (on the top of the computer screen) and two probe faces (on the bottom of the screen) and were instructed to match the probe with the same emotional expression to the target by pressing the left or right key on a button box. A block consisted of six consecutive trials where the target face was angry, fearful or happy. Face stimuli were taken from the NIMSTIM Set of Facial Expressions (Tottenham *et al.*, 2009). During sensorimotor control trials, subjects were presented with 5-s trials of either wide or tall ovals or circles in an analogous configuration and instructed to match the shape of the probe to the target. Each block of faces and of the sensorimotor control trials was presented three times in a pseudorandomized order. A fixation cross lasting 8 s was interspersed between each block presented at the beginning and end of the task (resulting in 14 fixation periods). For each trial, response accuracy and response latency data were obtained. There were 18 trials (three blocks of six trials) for each face set as well as for shapes. The whole task lasted 512 s. Participants completed a second Emotion Face Assessment Task comprising a different face set during the post-AMP run.

Experimental Manipulation–Attention Modification Program (Amir et al., 2008)

Between the two Emotional Face Assessment Tasks, while still in the scanner, participants completed a modified probe detection task (MacLeod *et al.*, 1986) designed to manipulate attentional allocation away from threat-relevant stimuli (see Amir *et al.*, 2008 for details) (Figure 1). Each trial began with a fixation cross '+' presented in the center of the monitor for 500 ms plus an additional jitter of 500–1000 ms (i.e. total fixation duration range = 1000–1500 ms). Following termination of the fixation cue, the computer presented two faces of the same individual against a gray background, one face on top and one on bottom. We used a standardized set of male and female faces portraying disgust and neutral expressions taken from a different stimuli set (Matsumoto and Ekman, 1988) than those used in the Emotion Face Assessment Task. After 500 ms, a probe (either the letter 'E' or 'F') appeared in the location of one of the two faces. Participants were instructed to identify whether the letter was an E or an F by pressing the corresponding button (left or right) on the response box. In each of two runs, participants saw a total of 160 trials: 32 trials included only neutral faces and 128 trials included one neutral face and one disgust face. To modify attentional allocation away from threat-relevant cues, the probe always replaced the neutral face during neutral–disgust trials.

Following prior research (Koster *et al.*, 2004; Salemink *et al.*, 2007; Klumpp and Amir, 2009; Amir *et al.*, 2011), we compared participants' response latencies to correctly identify visual probes following one of two neutral faces (neutral–neutral trials) with response latencies to identify probes following a neutral face when the other face displayed a disgust (threat-relevant) expression (i.e. neutral–threat, or *incongruent* trials). Biased processing of threat is indexed by slower response latencies when responding to a probe following a neutral face in the neutral–threat trials compared to responding to a probe following a neutral face in the neutral–neutral trials (Klumpp and Amir, 2009). Thus, our incongruent *vs* neutral bias index reflects difficulties disengaging attentional allocation from threat-relevant information (Koster *et al.*, 2004; Salemink *et al.*, 2007). We examined the relationship between change in incongruent *vs* neutral bias scores and neural activation during emotion processing following AMP.

Behavioral assessment

To examine the relationship between changes in neural activation following AMP and emotional reactivity to a stressor, participants

completed an impromptu speech following the MRI scan (for details see Amir *et al.*, 2008 and the Supplementary Methods and Materials). One participant declined taking part in the speech task. Thus, $N = 13$ for anxiety reactivity analyses.

Image acquisition

During completion of each Emotion Face Assessment task, one fMRI run sensitive to blood oxygenation level-dependent (BOLD) contrast was collected for each participant using a Signa Excite (GE Healthcare) 3.0T scanner (T2*-weighted echoplanar [EPI] imaging, repetition time = 2000 ms, echo time = 32 ms, flip angle = 90°, field of view- = 240 × 240 mm^2, 64 × 64 matrix, 40 3-mm axial slices, 256 scans for each Emotion Face Assessment run). During the same session, a high resolution T1-weighted image of the whole brain [172 sagitally acquired spoiled gradient recalled (SPGR) 1-mm thick slices, inversion time = 450 ms, repetition time = 8 ms, echo time = 4 ms, field of view = 250 × 250 mm^2, 256 × 256 matrix, flip angle = 12°] was obtained for anatomical reference.

Image processing and analysis pathway

All structural and functional imaging data were preprocessed and analyzed using the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996) and R statistical package (2012) (http://cran.r-project.org). See Supplementary Methods and Materials for preprocessing details. Individual participant time series data were analyzed using AFNI's 3dDeconvolve program. The orthogonal regressors of interest were the angry, fearful, happy and shape blocks. Regressors were convolved with a modified gamma variate function to account for the delay and dispersion of the hemodynamic response of the BOLD–fMRI signal. The time series alignments in the roll, pitch and yaw directions were used to create motion regressors for each participant, which were included in the general linear model as nuisance regressors to account for motion artifacts. Additional regressors were used to model the baseline, linear and quadratic trends in the time series. The regressors were applied to the AFNI program 3dDeconvolve to calculate the estimated voxelwise response amplitude. The resultant regressor coefficients were divided by the baseline (zero-order) regressor to determine the percent signal change (PSC) within each voxel. This PSC was used for all subsequent analyses. To account for individual variation of anatomical landmarks, a Gaussian filter with 4 mm full width at half maximum was applied to the voxelwise PSC data. Data for each subject were normalized to Talairach coordinates using AFNI's auto Talairach program, which was followed by visual inspection of each image.

Following prior work (Paulus *et al.*, 2005; Stein *et al.*, 2007), *a priori* regions of interest [ROIs; defined by the Talairach atlas (Talairach and Tournoux, 1988)] in the bilateral amygdala, insula, and medial PFC (ventromedial PFC; consisting of anterior cingulate, subgenual cingulate, and medial frontal gyrus, corresponding to Brodmann's areas 24, 25 and 32) were used as masks. A threshold adjustment method based on Monte-Carlo simulations (conducted using AFNI's program 3dClustSim) was used to guard against identifying false-positive areas of activation (considering region voxel size, 4 mm smoothness and 0.05 alpha threshold). This resulted in the following minimum cluster volumes to be considered significant: 256 mm^3 amygdala regions, 384 mm^3 for insula regions, 384 mm^3 for mPFC regions and 768 mm^3 for whole-brain analyses. All reported coordinates are peak-voxel Talairach coordinates (x, y, z) and labeled based on visual observation and Talairach Daemon software (Lancaster *et al.*, 2000).

Statistical analysis

Analysis of self-report and behavioral data was carried out with PASW Statistics (Version 17.0). Changes in attentional processing of threat cues and state anxiety were examined using one-way (Time) repeated measures ANOVAs conducted on incongruent *vs* neutral bias scores (first and second AMP runs) and STAI-State scores (baseline, postscan, postspeech), respectively. For the imaging analyses, the main contrast of interest was face blocks *vs* shape blocks. The voxel-wise PSC data were submitted to a linear mixed effects (LMEs) analysis in R (www.cran.org). Task Condition (angry-shape, fearful-shape, happy-shape) and Time (pre, post-AMP) were treated as fixed factors and Subjects as a random factor. *F*- and *P*-values were calculated for the LME output using the ANOVA function with sequential sum of squares.

RESULTS

Behavioral results

Emotion face assessment task

See Supplementary Results and Figure S1.

Attention modification program

Accuracy rates were uniformly high and did not differ across AMP runs, $F(1, 13) = 0.026$, $P = 0.87$ [pre-AMP: $M = 98.75\%$, $SD = 0.85$; post-AMP: $M = 98.71\%$, $SD = 1.04$]. As a group, participants did not differ in their incongruent *vs* neutral bias scores from the first to the second run of AMP, $F(1, 13) = 0.033$, $P = 0.86$ [pre-AMP: $M = -2.00$, $SD = 24.99$; post-AMP: $M = -3.61$, $SD = 22.10$].

Emotional reactivity

Results of a one-way (Time) repeated measures ANOVA conducted on the STAI-State revealed a significant main effect of Time, $F(2, 11) = 12.36$, $P = 0.002$. Although participants did not differ in self-rated anxiety from before to after the MRI scan (post-AMP), [$t(12) = -0.38$, $P = 0.71$], they experienced a significant increase in anxiety from before to after the speech, [$t(12) = -5.15$, $P < 0.001$] (Figure 3).

Functional neuroimaging results

Changes in BOLD-activity on the Emotional Face Processing Assessment following AMP

Results from the ROI analysis revealed, irrespective of face type, significant changes in the amygdala, ventral portions of the medial PFC (vmPFC), insula and subgenual ACC (sgACC) from before to after AMP for contrasts between emotional faces and shapes (Table 1). Consistent with our predictions, activation in the bilateral amygdala and bilateral insula was significantly lower post-AMP relative to pre-AMP whereas activation in the vmPFC and vmPFC/orbitofrontal cortex (OFC) significantly increased from before to after AMP for

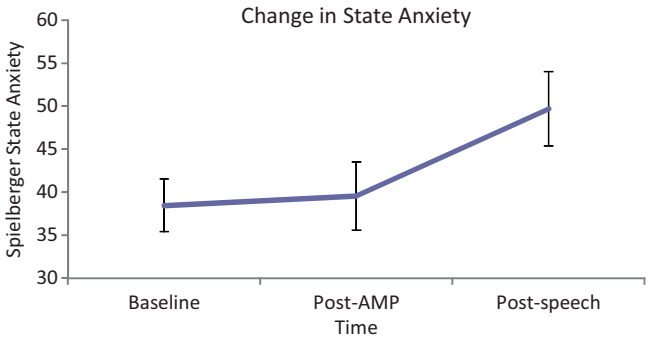

Fig. 3 Change in state anxiety throughout the experimental procedures. Participants did not differ in state anxiety from baseline to post-AMP. However, participants experienced a significant increase in anxiety from post-AMP to postspeech. Error bars represent ±1 SE.

Table 1 ROI analysis showing main effects of time (pre-, post-AMP) for contrasts of emotional faces *vs* shapes

Region	BA	Volume (mm^3)	Center of mass			*F*
			x	*y*	*z*	
Pre > Post						
Right amygdala		576	27	−7	17	13.38
Left amygdala		320	−24	−9	−14	12.15
Subgenual ACC	25	576	6	18	−6	11.08
Right insula	13	448	32	−6	17	9.19
Left insula	13	384	−39	−5	−2	6.90
Post > Pre						
vmPFC	32	896	0	40	−3	13.29
vmPFC/OFC	11, 32	448	−4	29	−11	11.70

Regions in which activation significantly differed from before to after AMP. Results shown from LMEs analysis of Condition (Angry-Shapes, Fear-Shapes, Happy-Shapes) by Time (pre-, post-AMP) on PSC, $P < 0.05$, Monte-Carlo adjusted for ROI volume multiple comparisons. All coordinates are Talairch coordinates (*x,y,z*) based on Talairach Deamon Software (Lancaster *et al.*, 2000). Abbreviations: BA = Brodmann Area.

contrasts between emotional faces and shapes. See Figure 4. We also observed significantly lower activation in the sgACC from before to after AMP. See Figure 4. The interaction between face type (Angry-Shapes, Fear-Shapes, Happy-Shapes) and Time (pre, post-AMP) did not yield any significant clusters of activation. Thus, changes in activation in the amygdala, insula, sgACC and vmPFC from before to after training did not differ significantly across face types (Supplementary Figure 2).

Results from the whole-brain analysis revealed significantly greater increases in activation during emotional face processing from pre- to post-AMP in several prefrontal regions (i.e. left anterior dorsal ACC, left dorsolateral PFC, vmPFC and right ventrolateral PFC) as well as regions implicated in visual processing (i.e. bilateral inferior occipital gyrus, right cuneus and right lingual gyrus). Significant decreases in activation during emotional face processing were observed in the bilateral middle and superior temporal gyrus, right parahippocampal gyrus, left supramarginal gyrus, right postcentral gyrus, right inferior frontal gyrus and left superior frontral gyrus (Table 2).

Brain–behavior relationships

We computed Spearman's rho correlations to test our hypothesis that greater enhancement of mPFC activation and/or greater attenuation of amygdala activation following AMP would be associated with a larger decrease in incongruent *vs* neutral biases as well as attenuated anxiety reactivity to the speech task. Mean PSC for contrasts between emotional faces and shapes was extracted from clusters of activation identified within ROI (coordinates shown in Table 1). Results revealed that larger increases in activation in the vmPFC were associated with significantly greater reductions in incongruent *vs* neutral bias scores, $\text{rho}(14) = -0.622$, $P = 0.018$ as well as less anxiety reactivity to the speech, $\text{rho}(13) = -0.654$, $P = 0.015$ (Figure 5a). Similarly, larger decreases in bilateral amygdala activation following AMP were associated with less anxiety reactivity to the speech, $\text{rho}(13) = 0.604$, $P = 0.029$ (Figure 5b). Changes in amygdala activation following AMP, however, were not significantly associated with change in incongruent *vs* neutral bias scores, $\text{rho}(14) = 0.147$, $P = 0.615$. Although changes in activation in the bilateral insula, sgACC and vmPFC/OFC from pre- to post-AMP were associated with changes in incongruent *vs* neutral bias scores and anxiety in response to the speech challenge in the expected direction, these relationships were not statistically significant (all $P > 0.20$) (Supplementary Table S1).

To establish the unique contribution of changes in amygdala and vmPFC activation following AMP in predicting changes in attentional allocation for threat-relevant stimuli and anxiety response to the stressor, we conducted two linear regression analyses (Table 3). For the analysis predicting change in incongruent *vs* neutral bias scores, results revealed that change in vmPFC activation from before to after AMP ($\beta = -0.615$, $t = -2.65$, $P = 0.023$), but not change in amygdala activation ($\beta = 0.137$, $t = 0.59$, $P = 0.57$) significantly predicted change in attentional allocation for threat *vs* neutral cues. For the anxiety reactivity analysis, change in vmPFC activation from pre- to post-AMP significantly predicted change in anxiety from before to after the speech task ($\beta = -0.532$, $t = -2.45$, $P = 0.034$] and change in amygdala activation was marginally associated with change in anxiety following the speech ($\beta = 0.444$, $t = 2.05$, $P = 0.068$).

Supplementary analyses

In the absence of an experimental control group, it is possible that the observed changes in neural activation from before to after AMP reflected habituation to repeatedly viewing emotional stimuli. To explore that possibility, we examined changes in neural activation during emotion processing in the amygdala, insula and mPFC from the first tertile (early trials) to the third tertile (late trials) of the pre-AMP emotional face assessment run, that is, prior to the implementation of the attentional training procedure. Results revealed significant decreases in activation during processing of emotional faces in the left posterior insula and portions of the subgenual ACC and vmPFC (Supplementary Table S2). Significant increases in activation were not observed in any ROIs. Considered together with the main analysis, only changes in activation in the left insula and subgenual ACC were consistent with the possibility that habituation effects accounted for the observed pattern of findings. These results bolster confidence that decreases in neural activation in the amygdala and increases in activation in the vmPFC from before to after AMP were not merely due to the effects of time or repeated presentation of emotional stimuli.

DISCUSSION

The goal of the current study was to examine the neural mechanisms that account for the anxiolytic effects of AMPs in individuals with elevated social anxiety symptoms. Results revealed that modifying attentional allocation away from threat attenuated activation in the amygdala, insula and sgACC, and increased activation in several regions of the PFC during emotional face processing. Moreover, increases in vmPFC activation following AMP were reliably associated with reductions in incongruent *vs* neutral bias scores and attenuated anxiety reactivity to a laboratory stressor. Previous studies support the efficacy of AMPs in reducing anxiety vulnerability under stress as well as decreasing symptoms in individuals meeting diagnostic criteria for an anxiety disorder (for reviews, see Hakamata *et al.*, 2010; Hallion and Ruscio, 2011). Together, these findings suggest that AMPs may improve the effective engagement of top–down emotion control brain systems to reduce anxiety via neural substrates that have been implicated in pathogenesis and maintenance of anxiety disorders.

Considerable evidence suggests a link between anxiety and increased activation of the amygdala and insula during emotional processing (Etkin and Wager, 2007). Attenuation of amygdala and insula activation has previously been reported for benzodiazepines (Paulus *et al.*, 2005), SSRIs (Harmer *et al.*, 2006; Arce *et al.*, 2008; Windischberger *et al.*, 2010) and psychotherapy (Holzschneider and Mulert, 2011). To our knowledge, the present investigation is the first to demonstrate that a computerized procedure designed to modify attentional allocation in the presence of emotional information similarly alters activity in these regions. We observed significant decreases in activation in the

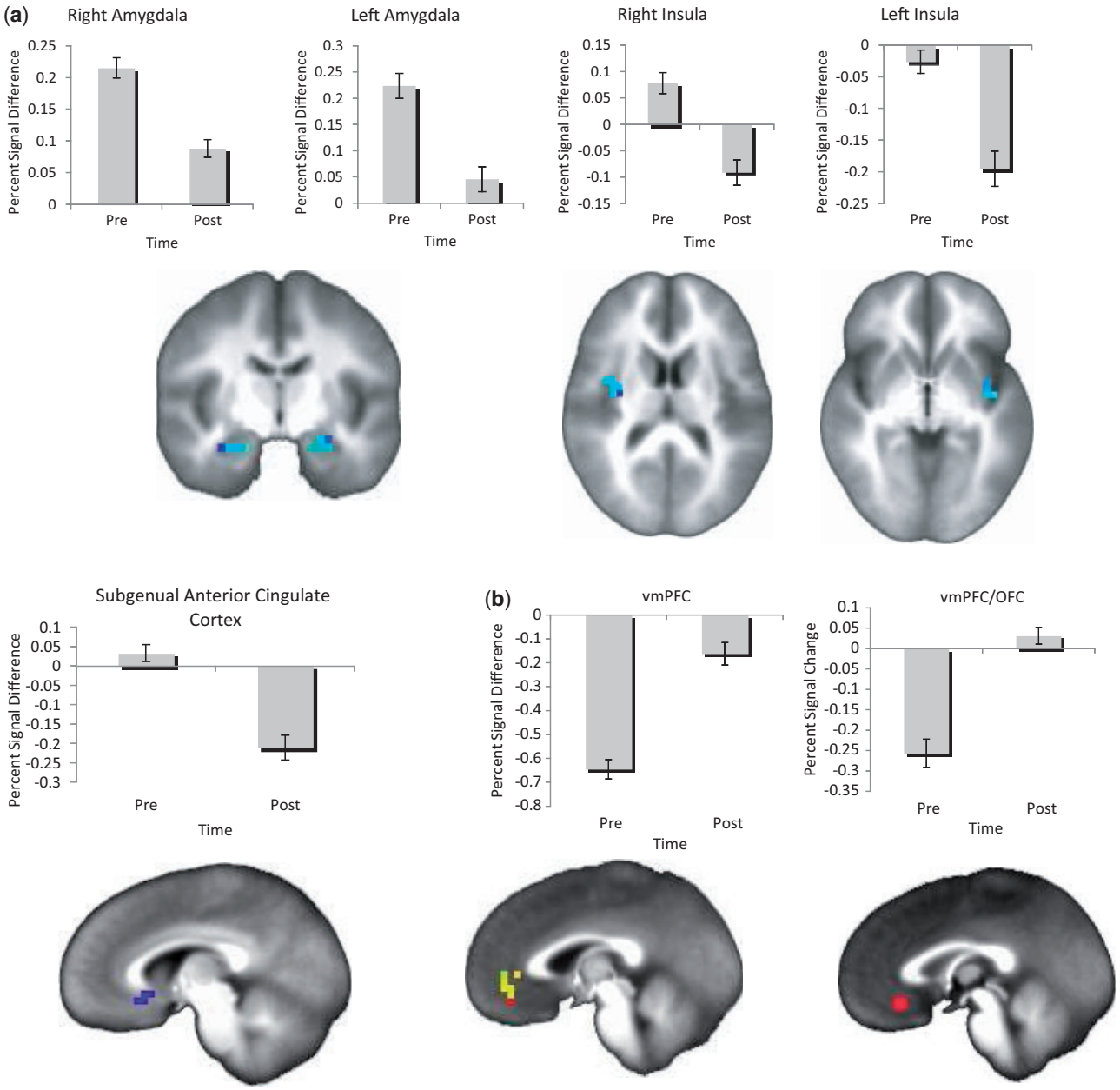

Fig. 4 Change in fMRI–BOLD activation on the Emotion Face Assessment Task from pre- to post-AMP in *a priori* ROI. Attentional training attentuated activation within the bilateral amygdala (shown at $y = -9$), bilateral insula (shown at $z = 16$ for right insula and $z = 0$ for left insula) and sgACC (shown at $x = -6$) (**a**), and increased activation in the vmPFC (shown at $x = -2$) and vmPFC/OFC (shown at $x = -4$) (**b**) for processing of emotional faces relative to shapes. Error bars represent ± 1 SE.

bilateral amygdala and insula during emotional face processing from before to after AMP. Moreover, the magnitude of reduction in amygdala activation was significantly associated with attenuated anxiety reactivity in response to the speech task. To the extent that amygdala activity reflects a bias in the processing of salient, i.e. threat-relevant stimuli (Shechner *et al.*, 2012), reduced amygdala activation following AMP may suggest a raised threshold for threat-detection in the context of the stress-provoking challenge. Although a similar pattern of findings emerged for changes in insula activation and anxiety reactivity, these relationships were not significant. These findings suggest that the previously documented anxiolytic effects of attentional training procedures may operate in part through reduced activation of the amygdala and insula, areas that are important for emotional processing in general, and anxiety in particular.

We also observed changes in the vmPFC from before to after AMP. Individuals who showed greater enhancement of vmPFC activation following AMP displayed larger reductions in incongruent *vs* neutral bias scores and less anxiety reactivity to the laboratory stressor. Several studies have shown that the vmPFC may have a regulatory role with respect to limbic regions involved in generating emotional responses. For example, Etkin *et al.* (2011) reviewed previous studies suggesting that emotional conflict regulation, a controlled top–down process, recruits ventral ACC and mPFC areas to inhibit negative emotional processing in the amygdala. Individuals with elevated levels of anxiety have been shown to evidence diminished activation in prefrontal regions, including the vmPFC (e.g. Bishop *et al.*, 2004; Etkin and Wager, 2007; Bishop, 2009). In the current study, increased activation in the vmPFC from before to after AMP may reflect an enhancement in

Table 2 Whole-brain analysis showing main effects of Time (pre-, post-AMP) for contrasts of emotional faces *vs* shapes

Region	BA	Volume (mm^3)	Center of Mass			*F*
			x	*y*	*z*	
Pre > Post						
Left middle temporal gyrus	21	137 536	−11	−36	7	37.86
Right superior/middle temporal gyrus	21	5056	52	2	−14	18.55
Right middle/superior temporal gyrus	21	4672	32	−6	17	16.70
Right parahippocampal gyrus	35	3392	24	−12	−22	17.16
Left supramarginal gyrus	40	2368	−45	−40	32	9.71
Right postcentral gyrus	3, 2	896	43	−23	41	8.29
Left superior temporal gyrus	38	768	−20	11	−30	15.49
Right inferior frontal gyrus	45	768	52	23	11	14.28
Left superior frontal gyrus	10	768	−24	52	24	10.77
Post > Pre						
Left inferior occipital gyrus	18	3200	−24	−89	−8	17.76
Left anterior dorsal ACC, superior/medial frontal gyrus	32, 8, 6	3072	−14	25	38	25.68
Left dorsolateral PFC	9	2432	−29	35	35	25.59
Ventromedial PFC	11, 32	1600	0	41	−8	13.29
Right cuneus	19, 18	1536	16	−84	22	16.16
Right lingual gyrus	18, 17	1472	4	−91	−3	22.69
Right inferior/middle occipital gyrus	18	1344	37	−83	−5	21.48
Right ventrolateral/medial PFC	10	1280	18	48	−7	13.72
Right dorsolateral PFC	9, 46	1216	43	38	24	13.08
Right medial frontral gyrus, dorsal ACC	24	1216	13	1	48	15.06
Right medial frontal gyrus	6	832	8	−28	63	23.38
Left lingual gyrus, parahippocampal gyrus	19	768	−20	−57	−6	7.36
Right middle occipital gyrus	18	768	30	−83	7	11.64

Regions in which activation significantly differed from before to after AMP Results shown from LMEs analysis of Condition (Angry-Shapes, Fear-Shapes, Happy-Shapes) by Time (pre-, post-AMP) on PSC, $P < 0.05$, Monte-Carlo adjusted for ROI volume multiple comparisons. All coordinates are Talairach coordinates (*x,y,z*) based on Talairach Deamon Software (Lancaster *et al.*, 2000). Abbreviations: BA = Brodmann Area; PHG = Parahippocampal Gyrus.

attentional control mechanisms that regulate emotional processing and affective reactivity. Moreover, results of a whole-brain analysis revealed significantly greater activation during emotional processing following AMP in additional prefrontal regions comprising the anterior dorsal ACC, dorsolateral PFC and ventrolateral PFC. These findings are broadly consistent with those of Browning *et al.* (2010b) who found that an attentional training procedure led to greater activation in the lateral PFC and rostral ACC under task conditions in which participants' attention was oriented in the direction opposite to that encouraged by the training task. Together, current and previous findings converge in suggesting that attentional training procedures may act upon neural regions implicated in attentional control and emotional regulation.

Our ROI analysis also revealed a region of the sgACC that displayed significantly reduced activation from before to after AMP. In the absence of specific *a priori* hypotheses regarding the effects of attentional training on this region, these results should be interpreted cautiously and are in need of replication. Nevertheless, they are consistent with previous studies suggesting a role of the sgACC in emotional processing and anxiety. For example, Ball *et al.* (2012) found a positive relationship between level of social anxiety and BOLD response to emotional faces in the sgACC. Pezawas *et al.* (2005) found that activation in subgenual regions of the ACC was positively correlated with amygdala activity during processing of threatening faces. Thus, decreased activation in the sgACC and amygdala following AMP may reflect overall improvements in functioning of limbic system circuitry during emotional processing. Future research is needed to more clearly delineate the effects of AMP on functioning of the sgACC as well as its connectivity to core limbic regions.

Can the observed changes in neural activation following AMP simply be attributed to changes in the subjective emotional state of the individual as a direct result of training (Browning *et al.*, 2010a)? The current data are not consistent with that explanation. Participants' level of state anxiety did not differ significantly from baseline to after AMP, a finding consistent with previous attentional training studies. Considered in the context of the current study, these findings suggest that changes in neural activation following AMP reflected the direct action of the intervention rather than changes in participants' subjective emotional state. Critically, the observed changes in neural activity following AMP predicted subsequent emotional reactivity to a validated stressor. These findings suggest a link between the neural systems modulated by AMP and subsequent vulnerability toward anxiety.

Limitations and future directions

Several caveats should be noted when drawing conclusions from the current study. First, the present sample comprised undergraduate student volunteers with elevated social anxiety symptoms. Thus, generalizability to community and clinical samples of individuals diagnosed with SAD is needed. Second, the sample size was small and replication in larger samples is needed. Third, we did not include an attentional training control group in which there was no contingency between the location of the probe and the location of the threat-relevant stimuli (i.e. the probe follows threat and neutral faces on 50% of trials, respectively). Thus, we cannot definitively conclude that the observed changes in neural activation are a direct result of the attentional training procedure per se. It is encouraging, however, that we found little evidence for habituation effects in the primary ROIs across the first administration of the emotion face matching task and prior to the implementation of AMP. Moreover, the correlational analyses establishing a link between pre- to post-AMP changes in neuroimaging and behavioral data provide indirect support for a causal relationship between AMP and neural activation changes. Nevertheless, an experimental control group is needed to more conclusively establish causal neural mechanisms of AMP.

Another limitation is that we did not include an independent behavioral assessment of attentional bias for threat from pre- to post-AMP that includes both congruent and incongruent trials. Thus, we were unable to determine participants' baseline attentional bias for threat, or definitively establish at the behavioral level that the training induced the intended attentional bias away from threat stimuli. Rather, our incongruent *vs* neutral bias index was derived from the experimental training trials, which may have provided a less sensitive behavioral measure of change in attentional processes at the group level compared to previously established measures (e.g. Amir *et al.*, 2008). It is also possible that implementing AMP during the MRI scan may have influenced the sensitivity of our behavioral measure of attentional training effects. Future studies should include an independent assessment of attentional bias for threat using stimuli and trials not included as part of the experimental manipulation and conducted outside of the scanning environment.

We did not find evidence of emotion face processing specificity with respect to changes in neural activation from pre- to post-AMP. These findings are consistent with prior studies using the emotion face matching task in which cross-sectional comparisons [high *vs* low anxious groups; (Stein *et al.*, 2007)] and pharmacotherapy intervention studies (Paulus *et al.*, 2005) revealed differences in neural substrate activation to all emotional faces irrespective of valence. Thus, although AMP was designed to modify attentional orientation away from threat-relevant cues, the training manipulation may facilitate more global emotion regulatory effects. One important avenue for future research

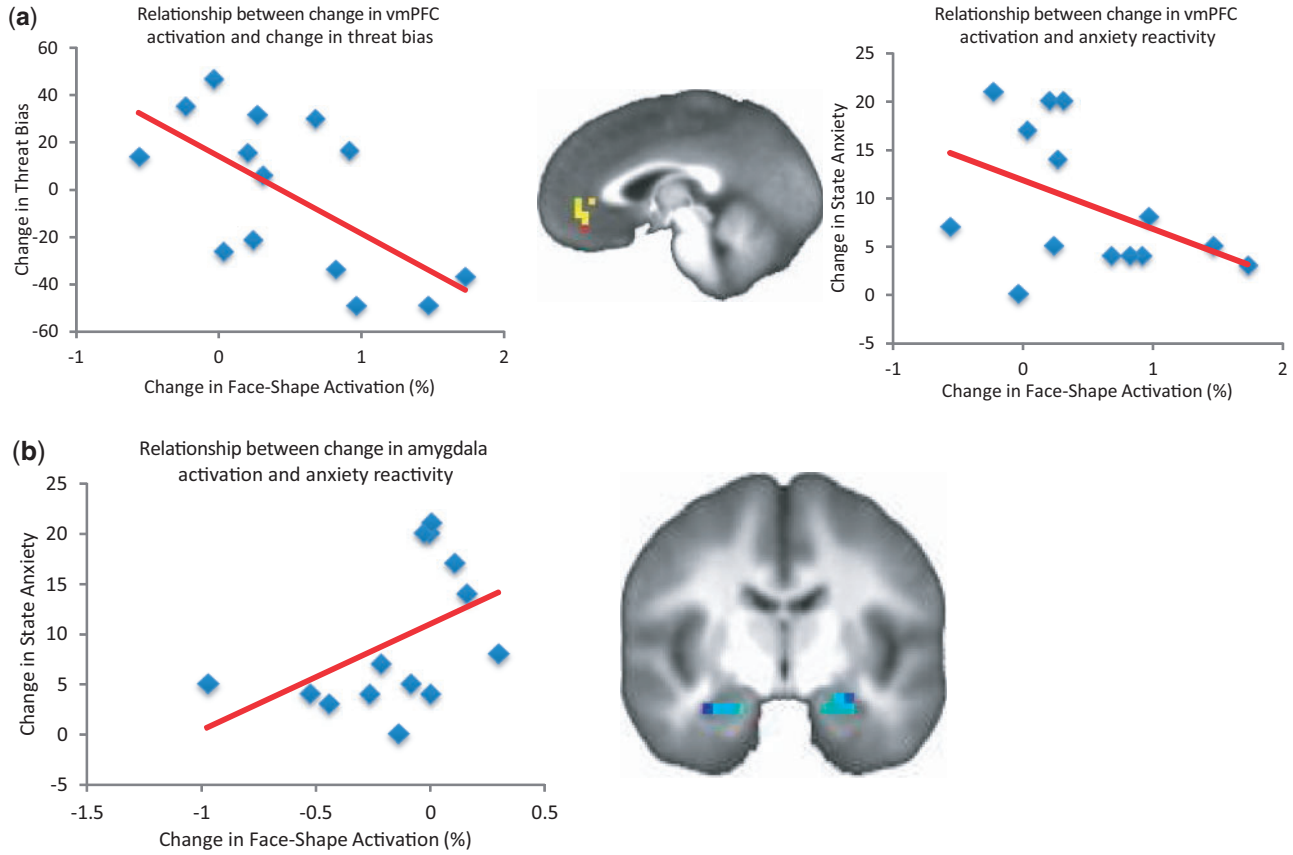

Fig. 5 Brain–behavior relationships. (**a**) The vmPFC ($x = 0$, $y = 40$, $z = -3$) showed significantly greater activation post-AMP relative to pre-AMP during emotional face processing. The difference in extracted PSC (face-shape contrast) in the vmPFC from before to after AMP (post- minus pre-PSC) was negatively associated with change in incongruent *vs* neutral bias scores [postbias minus prebias; rho(14) = −0.622, $P = 0.018$] and anxiety reactivity to the speech challenge (postspeech anxiety ratings minus prespeech anxiety ratings; rho(13) = −0.654, $P = 0.015$). (**b**) The bilateral amygdala (right amygdala; $x = 27$, $y = -7$, $z = 17$ and left amygdala; $x = -24$, $y = -9$, $z = -14$) showed significantly less activation post-AMP relative to pre-AMP during emotional face processing. The difference in extracted PSC (face-shape contrast) in the bilateral amygdala was positively associated with anxiety reactivity to the speech challenge, [rho(13) = 0.604, $P = 0.029$].

Table 3 Linear regression analyses of changes in activation (face-shape contrast) in the vmPFC ($x = 0$, $y = 40$, $z = -3$) and bilateral amygdala (right amygdala; $x = 27$, $y = -7$, $z = 17$ and left amygdala; $x = -24$, $y = -9$, $z = -14$) from pre- to post-AMP predicting change in (A) attentional allocation for threat-relevant stimuli and (B) anxiety reactivity to the speech challenge

Dependent variable	(A) ΔIncongruent *vs* neutral bias				(B) Anxiety reactivity			
	B	*SE B*	*β*	ΔR^2	*B*	*SE B*	*β*	ΔR^2
Model				0.42*				0.54*
ΔvmPFC	−31.93	12.06	−0.62*		−5.81	2.37	−0.53*	
ΔBilateral amygdala	14.08	23.91	0.14		9.34	4.56	0.44†	

Anxiety reactivity = postspeech STAI-State minus prespeech STAI-State (higher scores reflect greater anxiety reactivity); ΔIncongruent *vs* neutral bias = post-AMP bias score minus pre-AMP bias score (lower scores reflect greater reductions in incongruent *vs* neutral bias scores); Change in brain activation (ΔvmPFC/ΔBilateral amygdala) = mean PSC (faces-shapes) post-AMP minus pre-AMP. AMP = Attention Modification Program; STAI = Spielberger State-Trait Anxiety Inventory; †$P < 0.10$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ (two-tailed).

will be to examine whether attentional training procedures that manipulate attentional allocation in the presence of other emotional stimuli [e.g. positive stimuli (Taylor *et al.*, 2011)] produce valence-specific *vs* global emotion processing neural effects. It is also possible that the current sample was too small to detect valence specific emotion face processing effects of AMP. Future studies in larger samples are needed to resolve this issue.

CONCLUSIONS

The results from this study are consistent with the view that AMPs attenuate anxiety by modulating activity in both top–down and bottom up brain regions involved in processing of emotional information. Specifically, the extent of decreasing amygdala, insula and/or sgACC activation and increasing vmPFC activation following training may be a candidate for a biomarker predictive of the anxiolytic effects of AMPs demonstrated in previous laboratory studies and clinical trials. The current findings point to the potential value of combining fMRI with computerized cognitive bias modification procedures to better understand the interface between neurocognitive and clinical science and to identify ways of enhancing the efficacy of AMP and similar interventions through a better understanding of the neural mechanisms that account for treatment effects.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

Conflict of Interest

N.A. has a financial interest in Cognitive Retraining Technologies Incorporated, which has licensed elements of the technology described in this study for commercial purposes.

The authors otherwise report no biomedical financial interests or potential conflicts of interest.

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