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Brain structure changes induced by attention bias modification training

Rany Abend[a,*,1], Ariel Rosenfelder[b,1], Dana Shamai[b,d], Daniel S. Pine[a], Ido Tavor[d,e], Yaniv Assaf[c,d], Yair Bar-Haim[b,d]

[a] Section on Development and Affective Neuroscience, National Institute of Mental Health, 9000 Rockville Pike, Bethesda, MD 20892, USA
[b] School of Psychological Sciences, Tel Aviv University, P.O. Box 39040, Tel Aviv 69978, Israel
[c] Department of Neurobiology, George S. Wise Faculty of Life Sciences, Tel Aviv University, P.O. Box 39040, Tel Aviv 69978, Israel
[d] Sagol School of Neuroscience, Tel Aviv University, P.O. Box 39040, Tel Aviv 69978, Israel
[e] Department of Anatomy and Anthropology, Sackler Faculty of Medicine, Tel Aviv University, P.O. Box 39040, Tel Aviv 69978, Israel

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ABSTRACT

Attention bias modification (ABM) therapy aims to reduce anxiety by changing threat-related attention patterns using computerized training tasks. We examined changes in brain microstructure following ABM training. Thirty-two participants were randomly assigned to one of two training conditions: active ABM training shifting attention away from threat or attention control training involving no attention modification. Participants completed six lab visits, including five training sessions and three diffusion tensor imaging scans: immediately before and after the first training session, and at the end of the training series. Indices of local and global changes in microstructure and connectivity were measured. Significant longitudinal differences in fractional anisotropy (FA) between the active and control training regimens occurred in inferior temporal cortex. Changes in FA occurred across groups within ventromedial prefrontal cortex and middle occipital gyrus. These results indicate specific effects of active ABM on brain structure. Such changes could relate to clinical effects of ABM.

1. Introduction

Attention bias modification (ABM) is a treatment aimed at reducing anxiety by altering threat-related attention patterns through repeated computerized training (Bar-Haim, 2010; MacLeod & Clarke, 2015). Most ABM research focuses only on clinical efficacy; less is known about the neural changes underlying the modification of threat biases, and no information exists regarding ABM-related brain structural changes. Such changes may index the effects of training and inform ABM treatment development. The current study maps short- and cumulative, longer-term changes in brain structure induced by ABM training.

ABM protocols typically involve repeated practice on a task presenting pairs of threatening and neutral stimuli (e.g., disgusted and neutral faces) that are followed by a probe appearing at the neutral-stimulus locations (Bar-Haim, 2010; MacLeod & Clarke, 2015). As subjects implicitly learn the contingency between the locations of the neutral face and subsequent probe, they learn to shift their attention away from threat cues. These shifts manifest in reaction times through both online learning and offline memory consolidation effects (Abend, Karni, Sadeh, Fox, Pine & Bar-Haim, 2013; Abend, Pine, Fox, & Bar-Haim, 2014, Lazarov, Abend, Seidner, Pine, & Bar-Haim, 2017). Moreover, evidence suggests that learning effects accumulate over multi-session training protocols; these cumulative effects then relate to change in symptomatology (Abend, Naim et al., 2019). The few brain imaging studies to examine ABM-induced alterations studied functional activation and connectivity. For example, electroencephalogram event-related potentials studies find that ABM changes components related to early spatial attention, attention control, and emotion processing (Arad, Abend, Pine, & Bar-Haim, 2019; Eldar & Bar-Haim, 2010; O'Toole & Dennis, 2012; Sass, Evans, Xiong, Mirghassemi, & Tran, 2017; Suway et al., 2013), as well as a reduction in error-related negativity (Nelson, Jackson, Amir, & Hajcak, 2015); but see (Osinsky, Wilisz, Kim, Karl, & Hewig, 2014). Other studies use functional magnetic resonance imaging (fMRI) to chart changes in amygdala functional connectivity (Britton et al., 2014) or frontal function (Browning, Holmes, Murphy, Goodwin, & Harmer, 2010; White et al., 2017). No prior work examines changes in brain structure.

The current study compares microstructure changes that support immediate and cumulative learning effects induced by two types of

* Corresponding author at: Section on Development and Affective Neuroscience, National Institute of Mental Health, 9000 Rockville Pike, Bldg. 15K, Bethesda, MD, 20892, USA.
E-mail address: rany.abend@nih.gov (R. Abend).
[1] This work reflects equal contribution of the first two authors.

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attention training protocols in adults. These comprised an active ABM training regimen designed to train attention away from threat and an attention control training (ACT) regimen designed to induce no such changes. Brain microstructure was measured by fractional anisotropy (FA), a diffusion tensor imaging (DTI) based index (Assaf & Pasternak, 2008; Assaf, 2018). Analyses focused on identifying training-induced changes in FA informing on microstructural changes in local connectivity; follow-up analyses explored changes in whole-brain global connectivity associated with clusters exhibiting significant changes in FA. To identify changes in microstructure that support immediate and accumulating learning (Abend et al., 2013; Abend, Naim et al., 2019), brain structure was assessed at three time points: immediately before and after the first training session (immediate effects), and following a five-session training series (cumulative effects). In addition, behavioral measures of learning were analyzed for the five training sessions. Given that ABM training in adults induces both immediate and cumulative learning effects that are stronger than those produced by ACT (Abend et al., 2013; Abend, Naim et al., 2019), we hypothesized these differential behavioral effects to also manifest as differences in structural connectivity in relevant brain regions (Hofstetter, Tavor, Tzur Moryosef, & Assaf, 2013; Sagi et al., 2012; Tavor, Hofstetter, & Assaf, 2013). Since ABM potentially targets attention allocation mechanisms, we expected that such structural changes might involve components in the ventral and dorsal attention networks (Britton, Bar-Haim et al., 2013; Clarke, Browning, Hammond, Notebaert, & MacLeod, 2014; De Witte & Mueller, 2017; Sylvester et al., 2012; Viviani, 2013; Vossel, Weidner, Driver, Friston, & Fink, 2012; White et al., 2016; Zhang et al., 2015). In addition, we expected structural changes in prefrontal regions involved in the processing of threat-related visual cues (e.g., Britton, Grillon et al., 2013; Calder, Ewbank, & Passamonti, 2011; Taylor et al., 2014). However, given the novelty of the current investigation, we did not limit analyses to specific regions, and instead applied a whole-brain-corrected analytic approach.

2. Methods and materials

2.1. Participants

Thirty-two participants entered the study (18 females; mean age = 24.2 years, SD = 2.9, range = 19–29) and performed each six lab visits, including five training sessions and three MRI scans (a total of 96 MRI sessions). Recruitment was conducted through local advertising and social media. All participants were with normal or corrected-to-normal vision, did not report any mental illness, signed informed consent prior to participation, and were paid $50 for their effort. Participants were randomly assigned to either ABM or ACT training condition (described below). The groups did not differ in age, gender, and education (all *ps* > .11). Two participants (one from each training condition) were excluded from imaging analyses due to technical failure, but included in behavioral analyses; one additional participant from the ACT group was excluded from all analyses due to a new-onset medical problem. The study was performed at Tel Aviv University (Israel) in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), and approved by the Tel Aviv University and Sheba Medical Center institutional review boards.

2.2. Psychological measures

To ascertain that the two training groups did not differ in trait anxiety or depression, which may influence learning (Abend, Pine, Fox et al., 2014), we administered the State-Trait Anxiety Inventory and Patient Health Questionnaire-9, respectively, prior to the first training session. See Table S1 for mean scores in the sample.

2.2.1. State-Trait Anxiety Inventory (STAI)

The STAI (Spielberger, Gorsuch, & Lushene, 1970) consists of 20 items relating to general anxious moods answered on a 4-point scale (1 = Almost never to 4 = Almost always). Item scores are summed to a total score (range: 20–80). The STAI possesses strong psychometric properties (Elwood, Wolitzky-Taylor, & Olatunji, 2012). Cronbach's alpha for this sample was 0.87.

2.2.2. Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is the depression module from the full PHQ instrument (Spitzer, Kroenke, & Williams, 1999). It consists of 9 items representing depressive symptom criteria occurring in the last two weeks, which are answered on a 4-point scale (0 = Not at all to 3 = Nearly every day). Item scores are summed to a total score (range: 0–27). It was found to be a reliable and valid measure of depression severity (Kendel et al., 2010; Kroenke, Spitzer, & Williams, 2001). Cronbach's alpha for this sample was 0.90.

2.3. The dot probe task

2.3.1. Stimuli

For comparability, we used the same stimuli as those used in our previous studies on ABM learning effects (Abend, Pine, Fox et al., 2014; Abend, Naim et al., 2019; Abend et al., 2013) and efficacy (e.g., Naim, Kiviti, Bar-Haim, & Huppert, 2018; Pergamin-Hight, Pine, Fox, & Bar-Haim, 2016) and in studies taking part in the TAU-NIMH international collaborative effort (Abend, Pine, & Bar-Haim, 2014). Faces of 10 actors (5 male) taken from the NimStim stimulus set (Tottenham et al., 2009) were used. On each trial, two photographs (50 x 37.5 mm each) of the same actor were presented one above the other in pairs, 15 mm apart, on a green background. The distance between the edge of the top photograph and the top edge of the screen was 30 mm, and both photographs were centered horizontally. Each trial contained either two neutral expressions (neutral-neutral: NN) or one neutral and one angry expression (neutral-angry: NA). Angry faces were used to convey threat in line with their well-established effect on attention hypothesized to reflect selective processing of environmental threat (Vuilleumier, 2002, 2005) and with our previous research (see above).

2.3.2. Task description

The task was comprised of 400 trials presented in eight blocks, each of which had 50 trials. Each trial (Fig. 1A) began with a fixation cross presented for 500 ms, at which participants were asked to focus their gaze. Following the fixation cross, a face pair was presented for 500 ms, followed by a target probe (*E* or *F*,[2] font *Arial,* size 14, bold) (Abend, Pine, Fox et al., 2014, 2013) presented until response. Participants were asked to respond as quickly as possible without compromising accuracy via mouse-button press. Between blocks, a 60-seconds break was given during which the average reaction time (RT) during the preceding block was presented. In all blocks, 80% of trials presented NA face pairs, and 20% of trials presented NN face pairs. NN trials were counterbalanced with regard to actor identity, with probe location and type equally divided throughout trials. NA trials were fully counterbalanced with regard to probe type, angry-face location, and actor identity but differed on distribution of target locations based on training condition. Two training conditions were used. In the ABM condition, the probe appeared at the location of the neutral face in all NT trials, thereby creating a contingency between neutral-face location and probe location. In the ACT condition, the probe appeared at the location of the neutral and angry faces with equal probability.

[2] Future studies should consider using more intuitive discrimination probes and response keys pairings (e.g., left/right arrowheads and left/right mouse buttons) to minimize working memory demands of maintaining arbitrary associations during the task. Moreover, avoiding alphabet-based probes might diminish language-related effects in non-English countries.

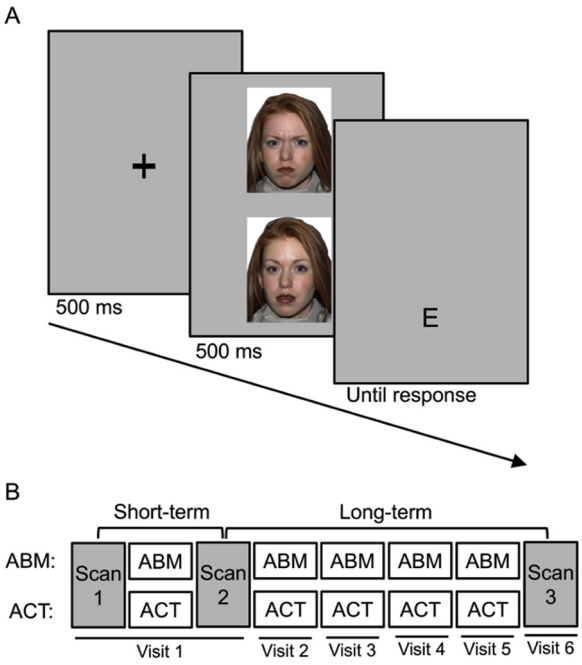

Fig. 1. Trial sequence and experimental design. (A) A single trial of the dot-probe task: fixation cross (500 ms), faces pair (500 ms), probe (until response). (B) Study design for the ABM and ACT groups: Participants in the ABM and ACT conditions underwent DTI scans immediately before and after the first training session (visit 1); over the following two weeks, four additional training sessions were held on different days (visits 2–5), followed by a final DTI scan (visit 6). *Note*: ABM = attention bias modification, ACT = attention control training, DTI = diffusion tensor imaging.

2.3.3. Performance gains

Training-related effects were indexed by RT performance gains. Gains were calculated by normalizing the mean RT in each training session relative to the mean RT in session 1, yielding relative gains normalized to individual performance levels (Abend, Pine, Fox et al., 2014, 2013; Korman et al., 2007; Lazarov et al., 2017). An increasing gains curve would therefore indicate performance improvement.

2.4. DTI acquisition and pre-processing

MRI data were acquired on a Siemens Magnetom Prisma 3 T MRI scanner (Siemens, Erlangen, Germany) using a standard 64-channel RF head coil. DTI scanning was done using a single-shot diffusion weighted spin-echo echo-planar imaging (ss-DWEPI) sequence with the following parameters: TR/TE = 6900/53 ms; FOV 208 mm; acquisition matrix 122 × 122; slice thickness 1.7 mm without gap; isotropic voxel size 1.7 mm^3; B 1000s/mm^2 (Δ/δ = 23.1/11.4 ms) and 3 images of b0. DTI was applied on 64 non-collinear directions. Total scanning time was 8:05 min. Anatomical imaging was obtained using a three-dimensional T1-weighted, Axial-oriented magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence of the whole brain (TR/TE/TI 1750/2.59/900 ms, matrix 224 × 224, FOV 224 × 224 mm, flip angle 8°, slab 208 mm) with 1 mm^3-isovoxel resolution.

The outcome measure derived from the DTI scan was fractional anisotropy (FA). FA is a DTI index of anisotropic diffusion processes in brain tissue ranging from 0 to 1. Higher FA values indicate macroscopic anisotropic diffusivity along neural fibers (axons, neurites) while lower FA values indicate similar diffusivity in all directions and characterize non-ordered regions such as gray matter and white matter where multiple fibers crosses (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). Changes in FA following training reflect related changes in brain microstructure. Although FA is usually associated with white matter integrity studies, recent studies indicate that it is also meaningful in characterizing changes in gray matter (Assaf, 2018). Increasing FA values would indicate microstructural increases in local connectivity (Assaf, 2018). Specifically, changes in FA values between the first and second scans and between the second and third scans would indicate short-term and longer-term brain microstructural changes due to training, respectively. DTI has been shown to be sensitive to both short- and long-term changes in structure (Dong, Li, & Potenza, 2017; Hofstetter et al., 2013; Sagi et al., 2012).

DTI data were preprocessed and analyzed using SPM8 software and the ExploreDTI toolbox (Wellcome Department of Imaging Neuroscience, University College London, London, UK; Leemans, Jeurissen, Sijbers, & Jones, 2009) and following procedures reported previously (Hofstetter et al., 2013; Sagi et al., 2012; Tavor et al., 2013). Correction of head motion image artifacts, registration, and normalization were performed using SPM. FA maps were created using ExploreDTI which corrects for susceptibility-induced distortions, eddy currents, and motion. Single-subject b0 images were normalized to MNI space and then to the Automated Anatomic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) using a 12-parameter affine transformation followed by non-linear transformations; these transformations were then applied to the participant's FA maps. The AAL atlas was used since we examined changes in white as well as gray matter. An averaged FA map based on the 3 study scans was then created for each participant. Then, each scan's FA map was normalized to the participant's averaged FA map (using a 12-parameter affine and non-linear transformation), as well as to the AAL template. This ensured that all images are aligned to the same atlas space and that distortions were corrected. Normalization procedures included smoothing of 2-mm Gaussian kernels of the source image as well as 8-mm spatial smoothing of the preprocessed images to improve inter-subject comparability, in line with prior work (Hofstetter et al., 2013; Sagi et al., 2012; Tavor et al., 2013). Following that procedure, voxel-based whole-brain analysis was performed to reveal changes in FA (see Data Analysis section), using in-house MATLAB code. Significant voxels were considered when reaching $p < 0.05$ following FDR whole-brain correction for multiple comparisons.

To complement analyses on local microstructural changes due to training, follow-up analyses attempted to identify training-induced changes in fiber tracts indicative of changes in global structural connectivity (e.g., Fling et al., 2011; Reijmer et al., 2016; Ruddy, Leemans, Woolley, Wenderoth, & Carson, 2017). This was implemented using a deterministic streamline fiber approach whereby fibers are reconstructed following the path of anatomically defined fiber bundles (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000). In this analysis, whole-brain tractography was conducted, and the magnitude of connectivity (i.e., number of tracts) and average FA between each cluster emerging in the previous analysis and each region in the AAL atlas were assessed. These measures in a deterministic tractography procedure index the strength of their structural connections (Fling et al., 2011; Reijmer et al., 2016; Ruddy et al., 2017). This was performed via the ExploreDTI toolbox (Leemans et al., 2009), following the procedure described by Reijmer et al. (2016).

2.5. Procedure

Participants were randomly assigned to either the ABM or ACT condition; allocation was maintained throughout the study, and participants and experimenters were blind to it. Participants completed a total of six lab visits each (Fig. 1B). In visit 1, participants first underwent a DTI scan to provide a baseline for brain structure measures. Next, they performed the first computerized training outside the scanner, followed by another DTI scan to identify short-term training effects on brain structure. Over the following two weeks, four additional training sessions were provided (in different visits; visits 2–5), with a minimum of one day between sessions. Finally, participants arrived for the 6th visit in which they were scanned again to identify

cumulative, longer-term effects of training. The training protocol was given over an average of 14.37 days (SD = 4.59), with no difference between the groups, $p = 0.85$. Of note, in line with previous studies on learning in ABM, attention bias to threat was not assessed in this study, so as to avoid learning interference effects due to confounding similarities between bias assessment and ABM training tasks (Abend, Pine, Fox et al., 2014, 2013; Lazarov et al., 2017; Robertson, Pascual-Leone, & Miall, 2004). Instead, the outcome measures were behavioral and neural indices of learning. Each task session was approximately 15 min long; each scan session was approximately 30 min long.

2.6. Data analysis

Prior to analysis, we excluded trials with RT < 150 ms or > 2000 ms, or incorrect response. Then, for each participant, we calculated mean RT per session, and excluded trials with RTs deviating by more than 2.5 SDs from the mean (Abend, Pine, Fox et al., 2014, 2013; White et al., 2017). Performance gains between training conditions were compared via repeated-measures ANOVA on normalized RT gains, with Session (Sessions 1–5) as a within-subject factor and Group (ABM, ACT) as a between-subjects factor.

FA values between training conditions were compared via whole-brain voxel-wise repeated-measures ANOVA, with Time (Scan 1, Scan 2, Scan 3) as a within-subject factor and Group (ABM, ACT) as a between-subjects factor, applying FDR voxel-wise correction to control for multiple comparisons. Specific dependent-samples *t*-test contrasts decomposed higher-order interactions including those involving Time, related to either immediate or longer-term changes in FA. All tests were two-sided, and a significance level of $\alpha = 0.05$ was used to detect significant effects.

3. Results

3.1. Psychological measures

Mean STAI and PHQ-9 scores are presented in Table S1. The training groups did not differ in mean STAI scores, $t(28) = 1.53$, $p = 0.14$, or PHQ-9 scores, $t(28) = 1.46$, $p = 0.16$. Importantly, anxiety levels in this sample were consistent with its non-selected status, based on prior research (Abend, Dan, Maoz, Raz, & Bar-Haim, 2014, Abend, Pine, Fox et al., 2014; Bieling, Antony, & Swinson, 1998).

3.2. Training-related behavioral performance gains

Mean raw and normalized RTs per training session and group are presented in Table S2. A repeated-measures ANOVA on the normalized gains revealed a significant main effect of Time, $F(3,84) = 6.68$, $p < .001$, indicating improvement in task performance over time. No other significant effects were observed. Mean performance accuracy across sessions (see Table S2) was 92.7%. A repeated-measures ANOVA on mean session accuracy did not reveal any significant effects, $ps > .27$, suggesting that improvement in RT did not come at the expense of accuracy, in line with previous findings (Abend, Pine, Fox et al., 2014, 2013).

3.3. Training-related structural changes

Whole-brain repeated-measures ANOVA on FA values yielded three significant clusters surviving the pre-defined threshold. Peak coordinates for these clusters are presented in Table 1; raw FA values are presented in Table 2.

A Group × Time interaction manifested in the inferior temporal cortex (ITC), $F(2,54) = 12.76$, $p = .00001$, indicating differential effects of training (Fig. 2A). Further testing indicated a significant effect of Time in the ABM condition, $F(2,28) = 12.76$, $p = .0001$, with follow-up contrasts revealing no significant change in FA values from Scan 1 to Scan 2, $p = .745$, and a significant decrease in FA from Scan 2 to Scan 3, $p = .001$. No effect of Time was observed in the ACT condition, $F(2,28) = 2.16$, $p = .134$. This demonstrates ABM-specific changes in connectivity associated with cumulative training.

A significant main effect of Time emerged in the ventromedial prefrontal cortex (vmPFC; Fig. 2, top). Follow-up contrasts revealed a significant decrease between Scan 1 and Scan 2, $p = .003$, and a significant increase in FA from Scan 2 to Scan 3, $p = .001$, indicating an immediate decrease followed by a longer-term increase in structural connectivity, respectively, across conditions. Finally, a cluster in the middle occipital gyrus (MOG; Fig. 2, bottom) exhibited a significant main effect of Time, $F(2,54) = 15.72$, $p < .00001$. A significant increase in FA between Scan 1 and Scan 2, $p = .02$ was followed by a significant decrease in FA from Scan 2 to Scan 3, $p < .0001$. Correlational analyses indicated that, across the sample, change in FA from Scan 1 to Scan 2 in the vmPFC cluster was not associated with change in FA in the MOG cluster, $r(29) = -0.15$, $p = 0.43$. In contrast, a significant negative correlation emerged between longer-term changes in FA (Scan 2 to Scan 3) in the vmPFC and MOG clusters, $r(29) = -0.53$, $p = 0.003$ (see Fig. S1).

Follow-up whole-brain tractography analyses explored changes in structural connectivity as a function of training. No significant changes in the number of tracts or mean FA along any of the tracts were found.

Table 1
Clusters in which significant effects ($p < 0.05$, FDR-corrected) emerged when testing the Group × Time effect on fractional anisotropy in a whole-brain analysis. Peak coordinates are in Automated Anatomical Labeling coordinates.

Effect	Peak coordinates			Cluster	*p*-value	Cluster size (voxels)
	x	y	z			
Group × Time	56	−31	−29	Inferior temporal cortex	.00001	262
Time	4	75	−28	Ventromedial prefrontal cortex	.0000001	298
	32	−72	−30	Middle occipital gyrus	.000004	214

Table 2
Mean (and SD) fractional anisotropy values for significant clusters that emerged in the whole-brain (FDR-corrected) analysis, by Scan (1–3) and Group (ACT, ABM).

Scan	Group	Fractional Anisotropy Values		
		ITC	vmPFC	MOG
1	ACT	0.125 (0.017)	0.112 (0.013)	0.035 (0.016)
	ABM	0.136 (0.018)	0.108 (0.013)	0.034 (0.017)
	Total	0.13 (0.018)	0.11 (0.013)	0.035 (0.016)
2	ACT	0.126 (0.017)	0.11 (0.011)	0.036 (0.016)
	ABM	0.136 (0.017)	0.104 (0.012)	0.035 (0.018)
	Total	0.131 (0.017)	0.107 (0.012)	0.036 (0.017)
3	ACT	0.127 (0.017)	0.115 (0.011)	0.034 (0.013)
	ABM	0.128 (0.016)	0.111 (0.012)	0.029 (0.016)
	Total	0.127 (0.016)	0.113 (0.012)	0.031 (0.015)

Note: ACT = attention control training, ABM = attention bias modification, ITC = inferior temporal cortex, vmPFC = ventromedial prefrontal cortex, MOG = middle occipital gyrus.

4. Discussion

This study compared changes in brain microstructure between two forms of attention training. A cluster in the ITC showed decreases in FA that occurred only with cumulative ABM training. Across both training groups, clusters in the vmPFC and MOG showed opposite patterns of time-related changes in FA. These results indicate specific ABM-induced changes alongside non-specific training-related changes in local gray

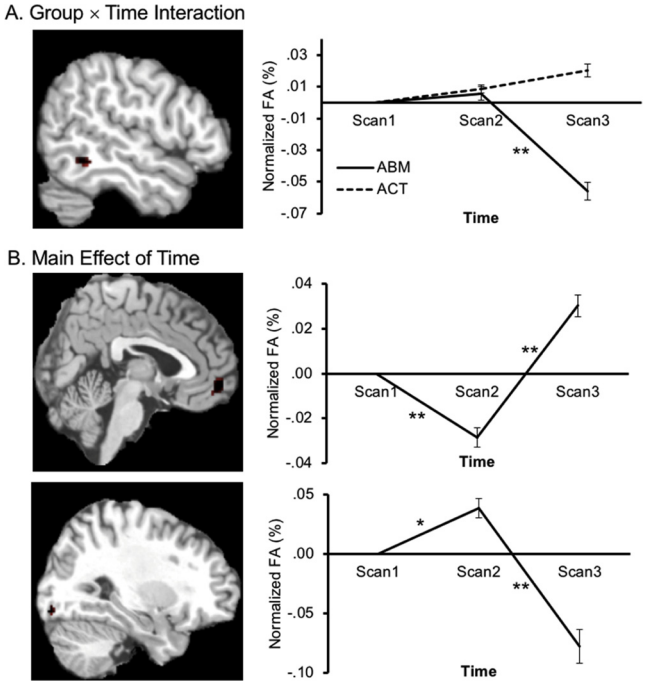

Fig. 2. Structural changes induced by training. Left panels show locations of significant clusters (FDR-corrected, whole-brain); right panels delineate effects in terms of mean FA values normalized to Scan 1 values. (A) Significant Group × Time interaction in the inferior temporal cortex. (B) Significant main effect of Time in the ventromedial prefrontal cortex (top) and the middle occipital gyrus (bottom).

Note: FA = fractional anisotropy, ABM = attention bias modification, ACT = attention control training. *, $p < .05$, **, $p < .01$, *t*-tests for dependent-samples for mean changes between scans. Error bars signify standard error of the mean.

matter organization and connectivity, complementing previous functional imaging research on ABM tasks.

ABM-related findings for the ITC extend previous studies linking activity in this region to face-emotion processing. Part of the ventral visual and attentional processing stream, the ITC is involved in processes relating to emotional cues as well as face recognition (Haxby, Hoffman, & Gobbini, 2000, 2001; Ungerleider & Haxby, 1994; Viviani, 2013). Many studies find correlated patters of activation in the ITC and amygdala, a key structure mediating the processing of threats (LeDoux, 2000; Phelps, 2004), including threat-related facial expressions (Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005; Sabatinelli, Lang, Keil, & Bradley, 2007; Sabatinelli, Keil, Frank, & Lang, 2013). Since ABM trains individuals to shift their attention away from threat faces, the current findings of training-related decreases in ITC structural connectivity and density could reflect effects of training on circuitry connecting this region to the amygdala, in the service of threat-related face processing. The emergence of this effect only after repeated practice sessions suggests that it may be the result of cumulative learning effects of ABM (Abend et al., 2013; Abend, Pine, Fox et al., 2014). This finding could also explain why multiple ABM training sessions may be required to induce robust clinical effects (Hakamata et al., 2010; Hertel & Mathews, 2011). Interestingly, the effects of ABM were observed in terms of localized ITC connectivity, and not global ITC-related connectivity, suggesting that induced effects on this circuitry manifest as ITC-specific structural changes.

Other work links ABM to ITC function. Two prior ABM training studies relate ABM to temporal cortex function. White et al. (2017) found that pre-treatment functional connectivity between the amygdala and temporal cortex predicted clinical response to ABM-augmented cognitive-behavioral therapy. Similarly, Browning, Holmes, and Harmer (2010)) reported changes in functional connectivity between temporal visual association cortex and PFC following ABM. Given evidence of relations between functional and structural connectivity (Greicius, Supekar, Menon, & Dougherty, 2009; Honey et al., 2009), these previous findings are relevant to the current study observations on ABM-related changes in ITC structure.

In addition to the ABM-specific ITC finding, changes in structure over time were observed across groups in the MOG and vmPFC, indicative of their involvement in the task. The effect observed in the MOG may reflect structural alterations related to visual spatial processing. Imaging studies suggest that the MOG plays a key role in such processes, including the allocation of attention (Bentley, Husain, & Dolan, 2004; Renier et al., 2010; Tootell et al., 1998). Practice on the dot-probe task essentially involves continuous training of a spatial attention allocation skill; the current results suggest that such practice may be associated with specific changes in structure in the MOG. Since we could not identify changes in global connectivity relating to this region, additional studies are needed to further explore how local changes in MOG structure impact visual processing streams in the context of ABM.

The changes in vmPFC microstructure across the study protocol may reflect changes in processing related to the emotional content of task stimuli. The vmPFC is attributed a key role in the processing of emotion and emotion regulation (Etkin, Egner, & Kalisch, 2011; Phillips, Ladouceur, & Drevets, 2008). Structural changes in vmPFC following practice in the task may reflect its greater involvement in regulation of limbic activity over repeated exposure to the emotional faces in the task. This is in line with previous findings of increased vmPFC activation during safety learning (Britton, Lissek, Grillon, Norcross, & Pine, 2011; Etkin et al., 2011; Milad et al., 2005), whereas reduced vmPFC structural integrity relates to anxiety and stress-related symptoms (Kim & Whalen, 2009; Koch et al., 2017).

The MOG and vmPFC showed opposite patterns of change over time. That is, while FA in the MOG has increased in the short-term and then decreased in the longer-term, in the vmPFC the opposite pattern was noted. Moreover, follow-up analyses indicated that longer-term structural changes in these clusters were negatively correlated. These findings may suggest complementary effects, particularly over repeated practice, in which weakening of local structural connectivity in one region is related to strengthening in another. Though found in different brain regions, a complementary pattern has been shown before in both structural (Doyon & Benali, 2005) and functional studies (Grossberg, 2000). At the same time, we could not detect changes in global connectivity between these vmPFC and MOG clusters. Additional research is needed to elucidate the nature of association between structural changes in these regions. These patterns of temporal changes in structure also suggest that repeated practice on the dot-probe task, regardless of training condition, may not necessarily lead to uniform structural changes in brain structures relevant to performance. Instead, divergent patterns of structural change with practice in these regions may reflect differential optimization of specialized processing, which may support the distinct neural processes underlying short- vs. long-term learning and memory consolidation effects (Debas et al., 2010; Robertson et al., 2004; Walker, Brakefield, Hobson, & Stickgold, 2003).

The current findings add to a limited, but growing, literature on the plasticity effects associated with ABM and related cognitive training, and their neural correlates. Aside from contributing to our understanding of the dynamic processes taking place during training, insights from such work may inform ABM protocol development. For example, characterizing the behavioral learning effects within and between ABM training sessions can aid in designing ABM protocols in terms of duration of a session and how many sessions are required to maximize learning (Abend, Pine, Fox et al., 2014, 2013). Learning effects can further inform protocol design by identifying learning deficits in target populations (Abend, Pine, Fox et al., 2014) and testing the effects of other protocol administration parameters, such as whether participants

should be explicitly made aware of the attentional contingency embedded in the task (Lazarov et al., 2017). Imaging studies may aid in elucidating the brain networks mediating the effects of ABM (Britton, Bar-Haim et al., 2013; Browning, Holmes, Murphy et al., 2010). Consequently, ABM may be applied, within a neuroscience-based framework, in conjunction with treatment that is complementary in mechanism (LeDoux & Pine, 2016; Shechner & Bar-Haim, 2016). Moreover, such imaging findings may identify targets for non-invasive brain stimulation applied to enhance the effects of ABM clinical outcomes (Clarke et al., 2014; Heeren et al., 2017). The current findings complement and extend these efforts by identifying training-related effects on brain microstructure.

Of note, group differences were observed in terms of microstructural changes but did not manifest behaviorally. ABM has been shown to decrease anxiety symptoms without specific effects on task behavior (attention bias; e.g., Pergamin-Hight et al., 2016; White et al., 2017). Moreover, neural measures have been shown to produce more reliable task effects and stronger group effects with the dot-probe task than behavioral measures (Abend, Swetlitz et al., 2019; Britton, Bar-Haim et al., 2013; Kircanski et al., 2018; White et al., 2016). Thus, behavioral measures may not constitute a sufficiently reliable indicator of attention modification processes taking place ABM training, whereas neural measures may be more sensitive to such processes since their measurement does not rely on additional "noisy" down-stream processes (e.g., response selection, preparation, and execution). Nevertheless, a combination of neural and behavioral findings would have allowed us to more directly associate the neural effects of training with their behavioral manifestation. As such, we urge future studies on ABM-related learning processes to follow prior recommendations for improving behavioral outcomes in the ABM tasks (Price et al., 2015).

This study should be viewed in the light of some limitations. First, the sample size used was small; a larger sample would have increased the robustness of observed effects, and may have unveiled additional effects. Longitudinal imaging studies may incur considerable costs (e.g., 96 scans were performed in the current study), and thus cross-site collaborations are encouraged in this context. Second, participants were not selected for high levels of anxiety, whereas ABM is ultimately intended to be administered to anxious patients. The aim of this study was to examine whether repeated training on an ABM task is reflected in structural changes, and as such a normative population was designated. The current results indicate that such changes are indeed evident, and thus encourage extension of the findings by examining ABM-induced structural changes in an anxious population, ideally within a full ABM trial. This may also allow to associate ABM-induced changes in symptom severity with neural changes. Finally, this study aimed to uncover structural brain changes underlying ABM training, and was not designed to examine co-occurring functional changes. Based on these findings, future studies may wish to concurrently examine the effects of ABM on brain structure and function, and thus further characterize its effect on brain circuitry.

In conclusion, the current study provides preliminary evidence for specific changes in brain microstructure associated with ABM training, and for microstructural changes common to ABM and control training. These results complement previous research on functional brain activity underlying ABM, and shed light on the neural mechanisms underlying this novel therapeutic approach.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biopsycho.2019.107736.

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