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Christopher G. Beevers, Peter C. Clasen, Philip M. Enock, and David M. Schnyer

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Attention Bias Modification for Major Depressive Disorder: Effects on Attention Bias, Resting State Connectivity, and Symptom Change

Christopher G. Beevers and Peter C. Clasen
University of Texas at Austin

Philip M. Enock
Harvard University

David M. Schnyer
University of Texas at Austin

Cognitive theories of depression posit that selective attention for negative information contributes to the maintenance of depression. The current study experimentally tested this idea by randomly assigning adults with Major Depressive Disorder (MDD) to 4 weeks of computer-based attention bias modification designed to reduce negative attention bias or 4 weeks of placebo attention training. Findings indicate that compared to placebo training, attention bias modification reduced negative attention bias and increased resting-state connectivity within a neural circuit (i.e., middle frontal gyrus and dorsal anterior cingulate cortex) that supports control over emotional information. Further, pre- to post-training change in negative attention bias was significantly correlated with depression symptom change only in the active training condition. Exploratory analyses indicated that pre- to post-training changes in resting state connectivity within a circuit associated with sustained attention to visual information (i.e., precuenus and middle frontal gyrus) contributed to symptom improvement in the placebo condition. Importantly, depression symptoms did not change differentially between the training groups—overall, a 40% decrease in symptoms was observed across attention training conditions. Findings suggest that negative attention bias is associated with the maintenance of depression; however, deficits in general attentional control may also maintain depression symptoms, as evidenced by resting state connectivity and depression symptom improvement in the placebo training condition.

Keywords: depression, attention training, cognitive bias manipulation, resting-state fMRI

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Major depressive disorder (MDD) is a common, recurrent, and impairing condition that predicts future suicide attempts, interpersonal problems, unemployment, substance abuse, and delinquency (Kessler et al., 2012; Wells, Burnam, Rogers, Hays, & Camp, 1992). According to the World Health Organization, 121 million people are currently suffering from MDD and it is one of the leading causes of disability worldwide. The annual economic cost of MDD in the United States alone due to medical expenditures, lost productivity, and other costs is substantial (Greenberg et al., 2003).

Despite its clear societal importance, the psychological mechanisms that maintain an episode of MDD have not been clearly identified. Cognitive theory (Beck, 1967; Beck et al., 1979) asserts that negatively biased attention (among other cognitive biases) has an important role in the maintenance of the disorder. That is, depressed individuals selectively attend to negative information and have difficulty disengaging attention from negative stimuli. These attention biases, in turn, reinforce sad mood and contribute to a persistent depressive episode.

A great deal of research to date supports the idea that depressed individuals' attention is negatively biased (Disner, Beevers, Haigh, & Beck, 2011). A recent meta-analysis found that depressed participants have a stronger attention bias toward negative stimuli than nondepressed participants, particularly when assessed with a dot-probe task ($k = 12$, $n = 937$, $d = 0.52$, $p < .001$). This effect was not moderated by a number of characteristics, such as age, sex, type of stimuli, or date of publication (Peckham, McHugh, & Otto, 2010).

This prior work also indicates that negatively biased attention in depression is rarely observed at stimulus durations of less than 1,000 ms, but is consistently observed at longer (i.e., >1,000 ms) stimuli durations (for a review see De Raedt & Koster, 2010). Indeed, work using eye tracking methodology, which provides a

Christopher G. Beevers and Peter C. Clasen, Department of Psychology and Institute for Mental Health Research, University of Texas at Austin; Philip M. Enock, Department of Psychology, Harvard University; David M. Schnyer, Department of Psychology and Institute for Mental Health Research, University of Texas at Austin.

Peter Clasen is now affiliated with the Department of Psychology at Stanford University.

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Correspondence concerning this article should be addressed to Christopher G. Beevers, Institute for Mental Health Research, University of Texas at Austin, 305 East 23rd Street, Stop E9000, Austin, TX 78712. E-mail: beevers@utexas.edu

relatively continuous assessment of attention bias, shows that adults with MDD have a sustained attention bias for negative stimuli for up to 30 seconds compared to nondepressed adults (Kellough, Beevers, Ellis, & Wells, 2008). Importantly, negatively biased attention predicts future increases in depression symptom severity (Beevers & Carver, 2003; Beevers, Lee, Wells, Ellis, & Telch, 2011), and more prolonged mood persistence among people with MDD (Clasen, Wells, Ellis, & Beevers, 2013; Sanchez, Vazquez, Marker, LeMoult, & Joormann, 2013).

Significant work has examined the neural systems that support attention bias. The lateral prefrontal cortex (PFC), including the right inferior frontal gyrus, appears to have a particularly important role in modulating attention biases for emotional information. In general, this region is implicated in cognitive control, especially when competing responses have to be inhibited or new information is selected (Aron & Poldrack, 2005; Helfinstein et al., 2014; Nee, Wager, & Jonides, 2007). The lateral PFC contributes to action selection and execution using external (e.g., cues in the environment) rather than internal cues as a guide (Matsumoto & Tanaka, 2004). Prior research indicates that the lateral PFC is critically involved during successful cognitive regulation of emotional information (Ochsner & Gross, 2005; Ochsner, Bunge, Gross, & Gabrieli, 2002).

There is evidence that altered lateral PFC function contributes to negatively biased attention observed in depression. Consistent with this possibility, compared to women with few symptoms of depression, women with elevated depression symptoms showed weaker activation in the inferior frontal gyrus, middle frontal gyrus and the supramarginal gyrus, primarily in the right hemisphere, when required to shift attention away from negative stimuli. In contrast, no depression group differences were observed in the lateral prefrontal cortex for shifting attention away from nonemotional cues (Beevers, Clasen, Stice, & Schnyer, 2010).

Further, adolescents at risk for depression by virtue of having a parental history of MDD, who have been shown to have a negative attention bias (Joormann, Talbot, & Gotlib, 2007), showed lower levels of functional connectivity within a circumscribed network of brain regions underlying attentional control, including the right lateral PFC. More specifically, whole-brain omnibus functional connectivity maps indicated lower levels of connectivity between the right inferior frontal gyrus seed and regions of right dorsal lateral prefrontal cortex and left and right mesial prefrontal cortex in the high-risk group relative to the low-risk group. Similarly, using a priori, unbiased ROIs from Beevers et al. (2010), adolescents with a parental history of depression had lower levels of resting-state connectivity between the right middle frontal gyrus and the right inferior gyrus region and right supramarginal gyrus (Clasen, Beevers, Mumford, & Schnyer, 2014), compared to adolescents with no parental history of MDD.

These studies suggest that depressive symptoms are associated with impaired function and connectivity of neural circuitry implicated in the control of attention, such as the ability to shift attention away from irrelevant stimuli. More specifically, reduced right lateral PFC activity and connectivity is associated with inefficient attention control that likely contributes to attention bias for emotional information and may contribute to depression and depression risk. Enhancing neural function within brain regions that support attention control, and in particular within the critical right lateral PFC region, appears to be an important target for attention training. Importantly, utilizing attention bias modification allows for an experimental test of whether improving negative attention bias and the underlying neurobiology that supports it leads to improvements in depression symptoms.

Previous Attention Training Studies With Dysphoric and Clinically Depressed Samples

Recent work has attempted to experimentally alter a negative attention bias with the goal of improving symptomatic function (Mogoaşe, David, & Koster, 2014). Most of this work has been completed with anxious populations; the few studies of attention bias modification in depression have mainly been completed among adults with dysphoria (or residual symptoms of depression) rather than clinical depression.

One study with dysphoric college students found that active attention training (i.e., directing attention away from negative picture stimuli and toward neutral stimuli) led to significantly greater reductions in depression symptoms 1 month after initiating attention bias modification than placebo training. Further, mediation analyses indicated that change in attention bias was responsible for this improvement (T. T. Wells & Beevers, 2010).

Similarly, undergraduate students with mild or greater symptoms of depression (i.e., Beck Depression Inventory-II [BDI-II] >14 but did not meet criteria for MDD) were randomly assigned to active attention training (8 sessions over a 2-week period), placebo attention training, or assessment only. Results indicated significant improvement in depression symptoms in the active training condition that were maintained at 3-month follow-up. However, by the 7-month follow-up, all three conditions no longer differed, primarily because improvements were observed in the placebo training and assessment only conditions (Yang, Ding, Dai, Peng, & Zhang, 2014).

An attention training study that involved dysphoric college students and a separate depressed clinical sample utilized an exogenous cueing task with word stimuli to modify a negative attention bias. Findings from this study indicated that 10 days of attention training reduced depressive symptoms (pre- to posttraining) among individuals with mild symptoms of depression, but not for more severely depressed adults (Baert, De Raedt, Schacht, & Koster, 2010). Similarly, in a study with a community sample of nonsymptomatic adults with recurrent lifetime MDD, active attention bias modification with image stimuli reduced depression risk and lowered cortisol awakening response 1 month posttraining compared to placebo training—notably attention training with word stimuli did not produce similar beneficial effects (Browning, Holmes, Charles, Cowen, & Harmer, 2012).

Other single session attention training studies with dysphoric samples have been completed, but these studies have not found substantial support for the utility of attention bias modification for altering attention bias or mood states in dysphoric subjects (Kruijt, Putman, & Van der Does, 2013; Tsumura, Shimada, Nomura, Sugaya, & Suzuki, 2012). Nevertheless, it is notable that only one prior study has used attention bias modification with a clinically depressed sample (Baert et al., 2010). Such studies are clearly needed to determine whether attention training alters attention bias, the neurobiology that supports the bias, and depression symptom trajectories over time—a critical test of whether negatively biased attention maintains depression.

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Although this prior attention training work is promising, a number of questions about attention training in clinically depressed samples remain unanswered. First, does attention training alter a negative attention bias? This was investigated in the present study by examining whether attention bias modification reduces bias on the same task as they were trained but with different stimuli (near transfer) and with an attention bias task that was substantively different from the one on which they were trained (far transfer). Generalization of training to different tasks is critical for establishing the efficacy of attention bias modification (Hertel & Mathews, 2011)—attention bias modification is unlikely to be therapeutic if it only alters responses on the training task. We hypothesized that active attention training would lead to improvements in attention bias for near and far transfer tasks.

Second, this study examined how attention training alters the neurobiology that supports attention bias. There is some evidence that attention bias modification can alter neural circuits that support attention biases in healthy individuals (Browning, Holmes, Murphy, Goodwin, & Harmer, 2010). The current study examined whether there were significant pre- to posttraining changes in brain connectivity within a previously identified attention control network (Clasen et al., 2014), using resting-state fMRI. Resting-state connectivity allows us to examine intrinsic connectivity within neural circuits without the influence of task-related demands (Buckner, 2012; Turk-Browne, 2013). We hypothesized that brain changes associated with active attention training would be reflected in improved functional connectivity within the attention control network, particularly connectivity involving the right middle frontal gyrus in the lateral PFC.

Third, longitudinal change in depression symptoms during the course of attention training (4 weeks) and 1 month after training was examined. As stated earlier, only one prior attention bias modification study has been completed with a clinically depressed sample. We hypothesized that active attention training would reduce negative bias and therefore lead to greater reductions in depressive symptoms over time than placebo attention training. This represents one of the first experimental tests of whether negative attention bias maintains symptoms of depression in a clinically depressed sample.

Method

Participants

Fifty-two treatment-seeking participants with *DSM–IV* Major Depressive Disorder (MDD) were recruited for this study from advertisements placed online, in newspapers, and on late-night TV. Participants were screened for medical or physical conditions that would preclude participation in an fMRI study (e.g., orthodontic braces). They also completed an abbreviated Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) to determine provisional MDD diagnosis. Diagnoses were subsequently confirmed in-person with a Structured Clinical Interview for the *DSM–IV* Disorders (SCID) administered by a trained research assistant.

Participants qualified for the study if they met diagnostic criteria for MDD and did not meet criteria for past year substance abuse or dependence, current or past psychotic disorder, bipolar disorder, and schizophrenia. Consistent with previous research (Amir et al., 2009), participants receiving pharmacological treatment were allowed into the study if there has been no medication change in the 12 weeks prior to study entry. To minimize brain changes associated with aging, individuals were between the age of 18 and 55. As can be seen in Table 1, participants were well matched across the attention training conditions.

Assessments

Dot-probe. The dot-probe task was used to assess attention bias for negative and positive stimuli before and after attention training. In this task, two images depicting an emotional or neutral facial expression from the KDEF stimuli collection (Calvo & Lundqvist, 2008) are presented concurrently on the left and right half of a 20-in LCD screen. One facial expression was either positive (happy) or negative (sad) and the second was a neutral expression. Each trial consisted of a white fixation cross on a black background for 500 ms followed by the stimulus pair for 1,000 ms. The location of the emotion and neutral stimulus varied randomly. Following the stimuli offset, a probe appeared on screen (either the

Table 1
Participant Demographics Presented as a Function of Attention Training Condition

	Placebo (n = 23)	Active (n = 29)	Test statistic	p-value
Age, mean (*SD*)	28.13 (10.25)	28.65 (9.59)	$t = -0.19$	.85
Gender (M/F)	9/14	13/16	$\chi^2 = 0.17$	.68
Married (Other/No)	5/18	6/23	$\chi^2 = 0.01$	.92
Race (Caucasian/Minority)	7/16	8/21	$\chi^2 = 0.05$	.82
Ethnicity (Hispanic/Non-Hispanic)	3/20	5/24	$\chi^2 = 0.17$	.67
Family income, mean (*SD*)	52,086 (44,969)	35120 (35,384)	$t = 1.47$	.15
Current depression meds (Yes/No)	2/21	6/23	$\chi^2 = 1.41$	.23
Therapy history (Yes/No)	10/13	18/11	$\chi^2 = 1.78$	.18
Home training sessions, mean (*SD*)	9.00 (6.14)	7.27 (4.84)	$t = 1.13$	.26
BDI-II, mean (*SD*)	33.34 (10.32)	30.69 (6.00)	$t = 1.16$	.25
IDAS—Social anxiety, mean (*SD*)	10.52 (4.04)	12.48 (4.94)	$t = 1.53$	.13
IDAS—Panic symptoms, mean (*SD*)	12.61 (4.71)	12.76 (5.53)	$t = 0.10$	.91
IDAS—Traumatic intrusions, mean (*SD*)	6.82 (3.07)	8.21 (3.44)	$t = 1.50$	.14

Note. BDI-II - Beck Depression Inventory-II; IDAS = Inventory of Depression and Anxiety Symptoms (Watson et al., 2008).

letter *O* or *Q*) in the same location as one of the images, randomized to appear behind the emotional and neutral image with equal frequency. Participants responded by identifying the probe using a button box. The task consisted of 192 trials (96 trials per block) with 12 pairs of sad and neutral images and 12 pairs of happy and neutral images randomly presented four times each within each block of trials. Stimuli were matched for actor so that the only difference between stimuli pairs was emotion expression. Emotional faces that were different from the training stimuli were utilized to examine generalizability of training across stimuli types.

Attention bias measured with the dot-probe was operationalized according to standard conventions (Mogg, Holmes, Garner, & Bradley, 2008). Response latencies only from correct responses were analyzed. Eliminating incorrect responses resulted in a loss of 1.6% of data. In addition, to minimize the influence of outliers, response latencies for each participant that were two standard deviations faster or slower than the mean response latency for that participant were also eliminated. This resulted in a loss of 4.78% of the data.

In line with prior work (Gotlib, Krasnoperova, Yue, & Joormann, 2004), attention bias scores for positive and negative stimuli were calculated separately for each participant at pre- and post-training assessments in the following manner:

$$\text{Attention bias score} = 1/2[(\text{RpLe-RpRe}) + (\text{LpRe-LpLe})]$$

where R = right position, L = left position, p = probe, and e = emotional (positive/negative) stimulus. Therefore, RpLe indicates the mean response latency when the probe is in the right position and the emotional stimulus is in the left position, and so on. This bias score reflects the degree to which attention is captured by the emotion stimuli, as RTs should slow when the cue captures attention and the probe is located in the opposite side of visual field relative to when the cue and target are located in the same side of visual field. Higher scores indicate a bias toward emotion stimuli, whereas negative scores indicate a shift of attention away from emotion stimuli.

Exogenous cueing. The exogenous cuing task, initially developed by Posner (1980), has since been modified to incorporate emotional cues (Koster, De Raedt, Goeleven, Franck, & Crombez, 2005). Each trial sequence began by presenting a fixation cross in the center of the screen for 500 ms. Then, a word cue that varied in emotional content (sad, positive, neutral) was presented on either the left or the right side of visual field for either 500 ms or 1,500 ms. Two stimulus durations were used to assess attention disengagement from stimuli presented briefly and for more prolonged durations. Biases for the latter are typically associated with depression (Koster et al., 2005).

After cue offset, a probe (either * or **) appeared immediately on the left or right side of visual field and remained on the screen until the participant responded. The participant's task was to identify the probe type as quickly and accurately as possible. Participants pressed a corresponding button on a response box to indicate the type of probe that appeared. After the participant responded, the screen was black for 500 ms before the next trial began. Fifty percent of probes appeared on the same side of visual field as the visual cue (a valid trial) and 50% of the probes appeared on the opposite side of visual field as the cue (an invalid trial). Both valid and invalid trials had a 50% chance of having either the single- or double-asterisk probe.

Participants completed 10 practice trials using neutral words as cues. Anyone failing to respond accurately to at least eight of the 10 trials repeated the practice trials until they had achieved 80% accuracy. Participants then completed 20 trials per condition across all conditions—cue valence (neutral, sad, positive), cue validity (valid, invalid), and cue duration (500 ms, 1,500 ms)—for a total of 240 trials. The task consisted of 20 negative words, 20 positive words, and 40 neutral words presented four times each. Positive and negative word lists were matched for valence strength (M. M. Bradley & Lang, 1999; Doost, Moradi, Taghavi, Yule, & Dalgleish, 1999). Emotion words were paired with a randomly selected neutral word of the same length. Order of stimulus presentation was randomized for each participant, with the stipulation that each of the 80 stimuli were viewed once before stimuli were repeated.

Throughout each trial, participants' gaze location and duration were assessed using a remote optics eye tracking system model R6 from Applied Science Laboratories (Bedford, MA). Gaze coordinates were sampled at 60 Hz (every 16.7 ms). Fixations were defined as any period of 100 ms or longer where eye movements were stable within 1° of visual angle.

The primary outcome for the exogenous cueing task was time to first fixation on the target following cue offset. To determine first fixation on target, we identified an area of interest around the target with a boundary of 1° of visual angle to account for error. All trials where no pupil was detected and/or there was no fixation on cue were dropped (3.4% of trials), as were trials where participants did not fixate on the target stimulus (9.8% of trials).

Using time to first fixation on the target, attention bias scores were computed as suggested by Mogg et al. (2008) using the following formula:

(2) Attention bias score (ABS) = (mean first fixation invalid emotion cue—mean first fixation valid emotion cue)–(mean first fixation invalid neutral cue—mean first fixation valid neutral cue).

Positive values reflect the degree to which fixations on targets are slowed by invalid emotion cues relative to invalid neutral cues. Thus, positive scores indicate greater difficulty disengaging attention from emotional cues relative to neutral cues, whereas negative values reflect greater difficulty disengaging attention for neutral cues relative to emotional cues. Bias scores were calculated for each emotional valence: sad and happy.

For secondary analyses, an ABS score was computed in the same fashion using behavioral reaction time (RT). Given that RT is used to infer attention, and eye tracking is a more direct assessment of visual attention, we anticipated that the fixation data would be a more sensitive outcome than RT.

MRI Scanning Acquisition

Resting-state fMRI scans were acquired on a whole body 3T GE MRI with an 8-channel phase array head coil. The scanning protocol involved collection of a localizer followed by a high-resolution T1 structural scan, two resting-state scans of 6 minutes each, and then a series of three functional scans while participants engaged in an exogenous attention cueing task. Following the cueing task, a second high-resolution structural scan and a diffu-

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sion tensor (DTI) scan were collected. The resting-state scans always occurred before the performance of any task-based scanning and the current examination involves only analysis of the pre- and posttraining resting-state scans. Future reports will examine other neurobiological assessments collected as part of this study.

The T1 structural scans were 3D SPGR volume acquisitions with 1.4 mm thick sagittal slices for a total of 134 slices (Flip = 10 degrees, repetition time (TR) = 9.7 ms, echo time (TE) = 4 ms, inversion time (TI) = 20 ms, dwell time (TD) = 0 ms, field of view (FOV) = 25 cm, Matrix = 256 × 256, number of repetitions (NEX) = 1). Functional images were acquired using a GRAPPA parallel imaging EPI sequence that reduces typical EPI distortions and susceptibility artifacts. Images were collected utilizing whole head coverage with slice orientation to reduce artifact (approximately 20 degrees off the AC-PC plane and oriented for best whole head coverage, TR = 2,000 ms, GRAPPA acceleration factor of two, TE = 30 ms, 31 axial slices, voxel size = 3.125 × 3.125 × 3 mm^3 with a .6 mm interslice gap). The first four EPI volumes were discarded to allow scans to reach equilibrium. Resting-state scan instructions were presented utilizing a back projection screen located in the MR bore and viewed through a mirror mounted on the top of the head coil. Prior to the acquisition of resting-state scans participants were instructed to remain awake and alert and keep their gaze on a fixation cross (+) presented approximately at the center of their field of view for the 6-min duration of the scan. Participant head motion was minimized by instruction and the use of foam inserts.

Analysis of resting-state data. Data were processed using a combination of FSL's FMRI Expert Analysis Tool (FEAT; Smith et al., 2011) and in-house scripts for unix and R (R Core Team, 2013). Analysis followed a 3-step process: a) Functional images were preprocessed to remove nuisance variables such as motion and global pulsatility; b) the resulting time series were assessed for excessive motion and then "motion scrubbed" to remove time points with excessive motion above a predefined threshold (see Power, Barnes, Snyder, Schlaggar, & Petersen, 2012); and c) motion scrubbed time series were extracted from seven nodes of a predefined attention control network and correlations/partial correlations between nodes were calculated and then Fisher *Z* normalized.

Step 1. Blood oxygen level dependent (BOLD) volumetric time series were corrected for motion, spatially smoothed using a 6 mm Gaussian filter, and high pass filtered (100 secs). Residual 4D volumes were then calculated after motion parameters and the global mean calculated from all brain voxels and all time-points within the subject were modeled as nuisance variables. The residual 4D volumes were also aligned to standard space through a 2-step process: aligning the participant's EPI scan to their own T1 structural image using a 7 DOF transformation and then aligning that T1 image to the standard average T1 MNI152 image with a 12 DOF transformation. The resulting transformation matrix is used to transform the attention network nodes to subject specific native space in order to extract the motion scrubbed time series for analysis in step 3.

Step 2. The residual 4D image resulting from Step 1 is then "motion scrubbed" using a procedure recommended by Power et al. (2012). First the FSL tool fsl_motion_outliers is applied to the original "raw" time series data and performs motion correction, calculating key metric values for each time point. Time points whose mean frame displacement exceeds 0.2 mm were marked for removal. No upper limit was applied. The identified motion outliers were added to a confound matrix for removal and interpolation. Then, using the residual 4D file, time points 1TR before frames identified with too much motion and 2TRs after are then eliminated from the time series. The scrubbed time series is then normalized to a mean intensity value of 100 for the next stage of analysis. Resting state images for which there were not a minimum of 100 time points remaining after scrubbing were excluded from analysis. In cases where neither of the 2 resting state fMRI scans met threshold during either the pretreatment or posttreatment session, those participants were dropped from the analysis.

Step 3. The attention control network (ACN) was identified in the same manner as our previous work (Beevers et al., 2010) where attention control was operationalized as the network engaged when presenting an invalidly cued target relative to a validly cued one. Rather than use the previous data, an omnibus ACN map was generated from 32 depressed participants in the current study along with 23 matched normal controls for a total *N* of 55 individuals (see Figure 1, projected background red [dark gray]).

Seven critical nodes from this network were identified and ROI masks generated by creating an 8 mm sphere around the voxel with the maximal *Z* value in the region. The seven nodes and their corresponding MNI coordinates were: right inferior frontal gyrus (50, 22, 14), right middle frontal gyrus (44, 10, 34), dorsal anterior cingulate gyrus (6, 24, 36), left middle frontal gyrus (−38, 0, 46), right supramarginal gyrus (28, −50, 46), left supramarginal gyrus (−26, −58, 46), and, finally, a node located in the precuneus region of the occipital lobe (0, −74, 16) was used as representative of the occipital/temporal activation associated with visual object processing. The time series within each node was extracted for each person by translating the nodes from MNI standard space to individual native space. The native space time-series from each

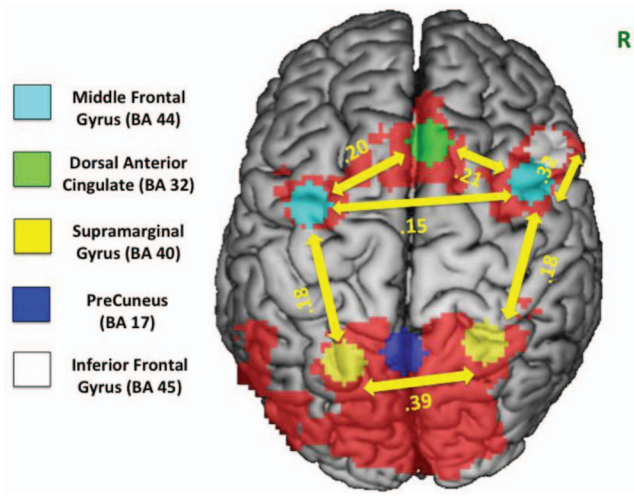

Figure 1. Baseline resting-state connectivity within the attention control network (ACN). The underlying red color reflects the activation in 55 depressed and control participants when required to shift attention away from cue stimuli (invalid > valid cue condition). Seven critical nodes were identified from the statistical Z-max of each region within this network. Significant node-to-node pathways ($p < .01$) are indicated in yellow with their associated partial correlations.

node were then a zero-lag cross-correlation was performed between each node to generate node-to-node Pearson correlation coefficients.

The Pearson correlation coefficients were then subjected to a partial correlation transformation in order to eliminate spurious indirect connections (Smith et al., 2011). These coefficients then normalized using Fisher's *r*-to-*z* transform ($z = 0.5 \text{ Ln } [(1 + r)/(1 - r)]$) to correct for non-normality in the distribution of *r*-values. Positive node-to-node pathways whose mean value across all subjects was significantly greater than zero ($p < .01$) established the baseline attention network connectivity prior to attention training (see Figure 1). These node-to-node correlations represent the intrinsic connectivity between these brain regions and were then used to examine associations with negative attention bias and the effects of attention training on network connectivity.

Depression Symptoms

The BDI-II (Beck, Steer, & Brown, 1996) is a widely used self-report questionnaire that assesses depression severity. The BDI-II consists of 21 items and measures the presence and severity of cognitive, motivational, affective, and somatic symptoms of depression. Past reports have indicated test–retest reliability and validity is adequate among psychiatric outpatient samples (Beck, Steer, & Carbin, 1988).

Attention Training

Attention training procedures were identical to those used in prior work (T. T. Wells & Beevers, 2010). Stimuli included 12 pairs of faces, each from a different actor and each expressing sad and neutral emotions, from the Pictures of Facial Affect (POFA) collection (Ekman & Friesen, 1976). Twenty images from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2008) were used, 10 displaying a neutral scene or image and 10 displaying a dysphoric scene or image. The following neutral IAPS images: 2102, 2393, 2745, 2850, 5390, 5731, 7009, 7041, 7053, and 7493 and the following dysphoric images: 2141, 2205, 2276, 2455, 2700, 2703, 2799, 2900, 9421, and 9530 were used in this study. Faces and images were utilized in order to increase the variety of content participants viewed during the training sessions.

The set of 22 image pairs (12 POFA face pairs and 10 IAPS image pairs) was presented in nine blocks in each session for a total of 196 trials per session. Each POFA pair consisted of one sad face and one neutral face of the same actor. One IAPS neutral image was always paired with one IAPS dysphoric image in the IAPS pairs; however, the pairings were randomly chosen during each new block. After completing the first three blocks, participants were given a 2-min break where they remained at the computer but did not perform a task. They received another 2-min break after the completing Blocks 4 though 6. Breaks were provided in order to reduce participant fatigue. Total time to complete each training session was approximately 25 minutes.

Each trial consisted of a white fixation cross on a black background in the middle of the screen for 1,500 ms, followed by an image pair. POFA pairs were presented for 3,000 ms and IAPS pairs were presented for 4,500 ms. It has been hypothesized that longer stimulus duration times may allow for more elaborated processing and greater activation of relevant cognition (Mogg & Bradley, 2005). IAPS images were presented for a longer duration because they are typically more complex than the POFA faces. Following the offset of the images, a small single or double white asterisk probe on a black background appeared in the location of one of the images and remained on the screen until the participant pushed a corresponding response box button to indicate whether they saw one or two asterisks. Latency and accuracy of each response was recorded. Each type of emotional stimulus (sad or neutral) appeared on each side of the screen with equal probability. Each type of probe stimulus (single or double asterisk) also appeared with equal probability.

E-Prime software controlled stimulus duration and was used to record response latency and accuracy. The size of each POFA image was approximately 12.7 × 19 cm when presented on the screen. Each IAPS image was approximately 17.1 × 12.7 cm. The pictures in each pair were approximately 21-cm apart when measured from each center and were presented in the left and right halves of the screen. Participants' eyes were approximately 58 cm from the screen. Participants were instructed to determine number of asterisks by pressing a corresponding button on a response box.

To train attention, the probability that the target would appear in the location of the neutral stimulus was manipulated. In the placebo condition, the target appeared in the location of the neutral stimulus and the dysphoric stimulus with equal probability (50%). In the active training condition, the probe appeared in the location of the neutral stimulus 80% of the time. Including the trials where the probe appeared in the location of the dysphoric stimulus was also designed to keep the intent of the study from being transparent given the longer stimulus duration times. The distribution of targets served as the critical manipulation whereby participants in the active training condition were putatively trained to allocate their attention preferentially to the neutral stimuli and away from the dysphoric stimuli. A complete sequence of attention training consisted of eight training sessions (i.e., twice a week) during a 1-month period.

Homework attention training. We were concerned that eight sessions may not be an adequate dosage of training, so participants were encouraged to complete "homework" sessions of attention training during the same 4-week training period. Although everyone was encouraged to complete the home training sessions at least once per week, we decided to allow participants to utilize home training at their discretion. This was done to emulate real-world treatment conditions where homework is encouraged during treatment but often completed at the discretion of the participant.

The at-home training task was implemented on a website using JavaScript and HTML programming, with a MySQL database, so that participants could train on their home computers. We attempted to match parameters, where possible, to the laboratory training task, hence the stimuli and presentation timing were the same. On-screen instructions suggested that participants train in a quiet environment where distractions were less likely. The sessions were briefer, however, with only 56 trials, aiming for 5 minutes of training and omitting breaks. Stimulus size varied based on participants' monitors and active training participants' sessions involved the probe in the neutral stimulus's location 80% of the time. Participants completed, on average, 7.27 ($SD = 4.83$; range 0–16)

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and 9.00 ($SD = 6.14$; range 0–21) at-home training sessions in the active and placebo conditions, $t(52) = 1.13$, $p = .26$, respectively.

Procedure

Upon meeting the inclusion criteria, participants completed a pretraining appointment where they completed questionnaires, dot-probe task, and the exogenous cueing task. They were then scheduled for the pretraining imaging assessment within 1 week. Following the pretraining assessments, participants were randomly assigned to attention training condition (active or placebo) by a computerized algorithm, thus keeping the experimenter and participant unaware of which condition each participant was assigned. Participants were then scheduled to complete eight sessions of in-laboratory attention training in the following month combined with optional at-home attention training homework sessions. Following the eighth in-laboratory attention training session, the behavioral posttraining assessment was completed. Participants were then scheduled to complete a posttraining imaging session within 1 week of the posttraining behavioral assessment. Participants were contacted 1 month following the behavioral posttraining assessment and reported their current depressive symptoms. Participants received a total of $50 compensation for completing pre- and posttraining sessions. They did not receive compensation for completing the attention training sessions.

Results

Attrition

Of the 52 participants who were randomized to an attention training condition (intent-to-treat), 45 competed all eight training sessions, one completed seven training sessions, one completed five training sessions, and five completed five training sessions or less. Study participants completed an average of 7.36 in-laboratory attention training sessions. There were no differences between active and placebo conditions for number of sessions completed, $t(50) = 0.11$, $p = .90$. Forty-four participants completed the posttraining assessments, 20 in the placebo condition and 24 in the active training condition.

Change in Attention Bias Measured With Dot-Probe Task

Random intercept mixed effects regression examined the effects of time (pre, post), attention training condition (active, placebo), and their interaction on bias for sad stimuli measured with RT. Results indicated a significant interaction between training condition and time, b = −31.58, $SE = 12.27$, z = −2.57, $p = .01$. There were no significant differences between training conditions in sad bias at the pretraining assessment (see Table 2). However, significant differences emerged at posttraining. The active training condition had a significantly smaller attention bias for sad stimuli than the placebo training condition. Further, there was a significant reduction of sad bias from pre- to posttraining within the active training condition ($z = -3.62$, $p < .001$, effect size $r = .45$), but not the control condition ($z = 0.20$, $p = .84$, effect size $r = .01$). One participant had a very large standardized residual ($sr = 6.7$). With this participant removed, the interaction remained significant, b = −35.01, $SE = 11.96$, $z = -2.93$, $p = .003$.

The same analyses were completed for positive stimuli. Results indicated a nonsignificant interaction between training condition and time, b = −4.54, $SE = 16.01$, $z = -0.28$, $p = .78$. There was a significant main effect for time, b = 30.25, $SE = 7.97$, $z = 3.80$, $p < .001$, but not for condition, b = 3.07, $SE = 7.98$, $z = 0.39$, $p = .70$. As can be seen in Table 2, the main effect for time indicates that attention bias for positive stimuli increased from pre- to posttraining similarly across training conditions. Finally, one participant had a very large standardized residual ($sr = 6.8$), but with this participant removed the findings were unchanged.

Change in Attention Bias Measured With Exogenous Cueing Task

Time to first fixation on target. Bias for time to first fixation on target following presentation of a sad cue was examined using a mixed effects regression model with main effects and interactions for attention training condition (active, placebo), time (pre, post), and cue duration (500 ms, 1,500 ms). The three-way interaction was significant, b = −0.18, $SE = .07$, z = −2.57, $p = .01$ (see Table 3). Pairwise comparisons indicate that the slopes (change in bias from pre to post) were significantly different between the active and placebo training groups at 1,500 ms, ($z = -3.70$, $p < .001$, effect size $r = .46$) but not at 500 ms ($z = -0.07$, $p = .94$, effect size $r = .01$). In the 1,500 ms condition, placebo and active training groups were significantly different at posttraining (z = −4.71, $p < .001$, effect size $r = .55$) but not at pretraining (z = 0.23, $p = .81$, effect size $r = .03$). No attention training group differences were observed within the 500 ms condition ($ps > .5$). There was one individual in the active condition at post training with a very large improvement in attention bias (standardized residual = 8.6). With this case removed, the training condition × assessment × cue duration remained significant, b = −0.12, $SE = .05$, $z = -2.25$, $p = .02$.

The same statistical model was utilized for time to first fixation on target following presentation of a happy cue. In contrast to sad cues, the three-way interaction was not significant, b = −0.06, $SE = .04$, $z = -1.35$, $p = .17$. However, there was one case with a very strong reduction in positive bias whose standardized residual appeared to be an outlier (standardized residual = −5.9). When removing this individual, a significant interaction emerged, b = −0.09, $SE = .04$, $z = -2.27$, $p = .02$. Pairwise comparisons indicate that active training produced greater improvement in positive bias from pre to post compared to placebo at 1,500 ms,

Table 2
Dot-Probe Reaction Time (Standard Error) Bias to Sad and Positive Stimuli Presented as a Function of Time and Training Condition

	Placebo ($n = 23$)	Active ($n = 29$)	Test Statistic	p-value	Effect size r
Sad Stimuli					
Pre	−1.39 (6.21)	8.01 (5.53)	$z = 1.13$	.25	.15
Post	0.39 (6.66)	−21.77 (6.08)	$z = 2.46$	.01	.32
Positive Stimuli					
Pre	−7.80 (8.10)	−2.64 (7.21)	$z = 0.48$	.63	.06
Post	24.95 (8.69)	25.57 (7.93)	$z = 0.05$	.95	.01

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Table 3
Exogenous Cueing Descriptive Statistics for (A) Time to First Fixation on Target Bias (Standard Error), and (B) Reaction Time Bias (Standard Error) for Sad and Positive Stimuli Presented as a Function of Time, Training Condition, and Stimulus Duration

	500 ms		1,500 ms	
	Placebo (n = 23)	Active (n = 29)	Placebo (n = 23)	Active (n = 29)
A. First fixation (ms)				
Sad-Neutral				
Pre	−5 (18)	−19 (16)	19 (18)	31 (16)
Post	10 (21)	−9 (18)	87 (22)	−28 (18)
Positive-Neutral				
Pre	−2 (16)	−4 (14)	−2 (16)	6 (14)
Post	−20 (18)	10 (15)	24 (18)	−32 (15)
B. Reaction time (ms)				
Sad-Neutral				
Pre	−2 (20)	1 (18)	12 (20)	3 (17)
Post	17 (23)	4 (20)	48 (22)	24 (19)
Positive-Neutral				
Pre	−9 (26)	−33 (23)	9 (26)	−42 (23)
Post	−36 (28)	9 (28)	−9 (28)	−7 (24)

($z = -2.10$, $p < .03$, effect size $r = .28$) but not at 500 ms (z = 1.07, $p = .29$, effect size $r = .15$).

Compared to placebo training, active attention training helped individuals to more quickly disengage from sad stimuli presented for longer (but not shorter) durations. A similar pattern was observed for positive stimuli, although this was only observed when an outlier was removed from the sample.

Behavioral RT. The same analyses were completed for attention bias for sad stimuli using behavioral RT. In contrast to time to first fixation on the target, the three-way interaction between attention training condition (active, placebo), time (pre, post), and cue duration (500 ms, 15,00 ms) was not significant, b = −85.34, $SE = 129.21$, $z = 0.66$, $p = .51$. A similar patter was observed for positive stimuli, as the same three-way interaction was nonsignificant, b = −15.63, $SE = 57.88$, z = −0.27, $p = .78$. This interaction remained nonsignificant with the removal of outliers. The lower order interactions and main effects were also nonsignificant (ps > .11), with the exception that training condition had a main effect on RT bias for positive stimuli, such that RT bias was faster for the active training condition (b = −51.38, $SE = 26.23$, z = −1.96, $p = .05$).

Given the lack of convergence across eye tracking and RT results, associations between RT bias and eye tracking bias were also examined. For cues presented at 1500ms, regression analyses using eye tracking negative bias as the outcome and RT negative bias, time (pre, post), training condition (active, placebo), and their interactions as predictor variables indicated a significant interaction between negative bias and time, b = 0.01, $SE = 0.00$, z = 2.37, $p = .02$. At pretraining, there was a relatively weak association between eye tracking and RT measures of negative bias for 1500ms cue durations within both the training, $r = -.14$, $p = .45$ and placebo, $r = -.06$, $p = .78$ conditions. However, at posttraining, the same correlations were significant within both the training, $r = .39$, $p = .06$ and placebo, $r = .66$, $p = .003$ conditions. This indicates that the association between RT and eye tracking increased from pre- to posttraining. However, the increased association did not differ across training conditions, as the three-way interaction between negative bias, time, and training condition was nonsignificant, b = −0.02, $SE = 0.00$, z = −1.49, $p = .14$. Taken together, this suggests that the eye tracking and RT results for the exogenous cueing task differed due to a lack of a strong correspondence between the assessments of bias, particularly at the pretraining assessment.

Resting-State Brain Connectivity Within the Attention Control Network (ACN)

Baseline connectivity within the ACN. We first established baseline functional connectivity (prior to any training) within the seven identified nodes of the ACN using the entire sample with usable imaging data (see above for criteria). This included a total of 38 participants, 17 placebo and 21 active training. Mean partial correlations across the entire sample that were greater than $p < .01$ are shown in Figure 1. Of note, there was strong connectivity between the right middle frontal gyrus (rMFG), right inferior frontal gyrus (rIFG), and the dorsal anterior cingulate (dACC), critical regions of the previously defined ACN.

Correlations between baseline ACN resting state and attention bias. To identify which resting state node-to-node associations support attention bias (and therefore would be good targets to examine the effects of training), correlations were examined between pretraining resting state ACN connectivity and pretraining negative attention bias measured with the dot-probe. One significant resting state node-to-node correlation with negative attention bias was observed: dACC–rMFG, $r = -.37$, $p = .02$ (see Figure 2). Weaker connectivity between these two regions at pretraining

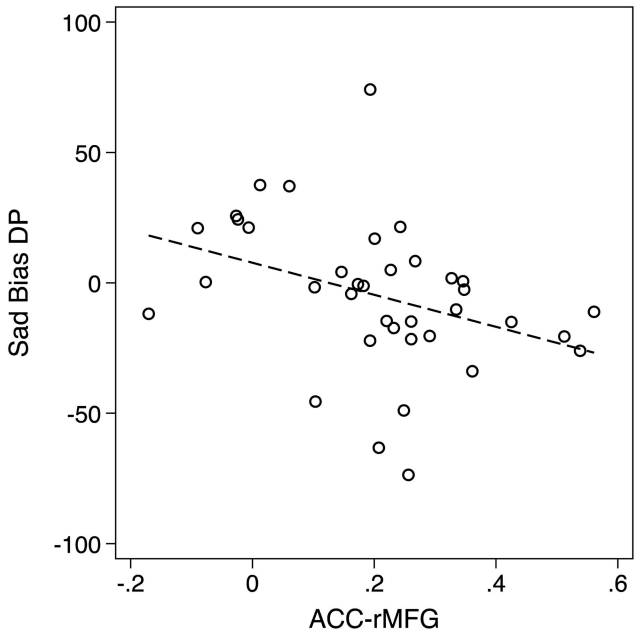

Figure 2. Correlation between pretraining negative attention bias and pretraining resting state connectivity between the dACC and rMFG nodes ($r = -.37$, $n = 37$). dACC = dorsal anterior cingulate; rMFG = right middle frontal gyrus.

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was associated with stronger negative attention bias. No other correlations were significant (*p*s = .08–.80). Thus, the primary node-to-node connection to examine connectivity change was the dACC–rMFG.

Change in ACN resting state from pre- to posttraining. To examine change in resting-state connectivity, resting state change scores (post–pre) were computed. Change in connectivity between the dACC–rMFG was significantly different across training conditions, $t(35) = -2.08$, $p = .04$, effect size $r = .33$. Resting state connectivity between these two nodes increased for the training group ($M = .04$, $SE = .04$) compared to the placebo group ($M = -.07$, $SE = .04$). Further, change in dACC–rMFG connectivity was moderately associated with change in negative attention bias, measured with the dot-probe task, in the active training condition, $r = .40$, $p = .06$ and only weakly associated with change in negative attention bias in the control condition, $r = .10$, $p = .70$.

Change in resting-state connectivity did not significantly differ across training groups in any of the remaining nodes (*p*s > .05), although the effect of training on change in connectivity between lMFG and lSMG approached significance, $t(35) = 1.69$, $p = .09$, effect size $r = .27$. Change in resting state connectivity within this node was smaller for the training group ($M = -.02$, $SE = .04$) than the placebo group ($M = .07$, $SE = .04$). No other nodes exhibited significant differential change in connectivity as a function of attention training condition (*p*s > .29). In sum, active attention training increased connectivity between the dACC–rMFG, a resting-state connectivity node that was correlated with negative attention bias prior to attention training.

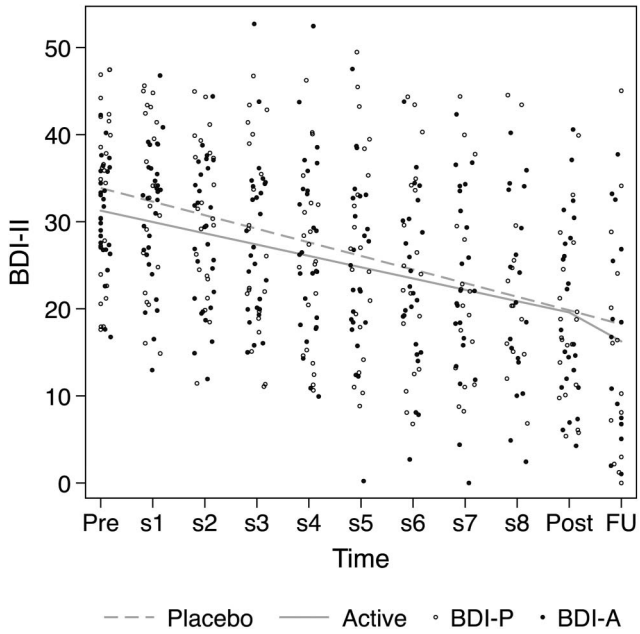

Figure 3. Scatterplot of self-reported depression symptoms, Beck Depression Inventory-II (BDI-II), at pretraining (Pre), training Sessions 1–8 (s1–s8), posttraining (Post), and 1-month follow-up (FU). Lines indicate mean change in depression symptoms for each training group. BDI-P indicates data points for the placebo condition. BDI-A indicates data points for the active training condition.

Change in Depression Symptoms

Model selection. Mixed effects regression was used to examine change in depression symptoms over the course of attention training. To determine the best fitting model, time was operationalized as (a) assessment number (i.e., pre, Session 1–8, post) and (b) number of days from baseline assessment. Linear, quadratic, and piecewise models of symptom change were examined that included training condition and its interaction with time in each of the models. The best fitting model, based on the Akaike information criterion (AIC), was a piecewise model that utilized assessment number as a continuous variable and included linear change in symptoms from baseline to post (10 assessments) and linear change in symptoms from post to 1-month follow-up. The piecewise model was therefore retained for all subsequent analyses.

Training effect. The piecewise model included: (a) main effects for each time component (time piece 1, time piece 2), which tested for change over each time piece; (b) a main effect for training condition (active, placebo), which tested for initial group differences; (c) interactions between training condition and each time piece, which tested for whether change over time was different for each training condition.

There was no main effect for training condition, b = −2.69, $SE = 2.31$, $z = -1.17$, $p = .24$. There was a significant main effect for change over time during the first time piece (baseline to post), b = −1.54, $SE = .25$, $z = -6.21$, $p < .001$; symptoms significantly decreased (1.54 points on the BDI per assessment) over the course of training. There was no main effect for change over time during the second time piece (post to 1-month follow-up), b = −1.89, $SE = 3.00$, z = −0.63, $p = .53$, suggesting symptoms were relatively stable from posttraining to 1-month follow-up. Further, there were no significant interactions between training condition and the first time piece, b = .31, $SE = .33$, $z = 0.93$, $p = .35$, or between training condition and the second time piece, b = −1.50, $SE = 4.16$, z = −0.36, $p = .72$. No outliers were identified. Depression symptoms decreased over time but symptom change did not differ between attention training conditions (see Figure 3). Overall, BDI-II decreased by 12.80 points from pre- to posttraining, a decrease of approximately 40% in depression symptoms (i.e., $(19.068_{post}–31.865_{pre})/31.865_{pre}*100$).

Correlation between change in bias and improvement in pre- to posttraining depression symptoms. To examine whether change in attention bias was associated with symptom change, intercepts and slopes for BDI-II change from pre- to posttraining for each participant were estimated. Change in attention bias was then correlated with change in depression symptoms, controlling for the intercept (i.e., initial BDI severity). The partial correlation indicated that greater change in negative attention bias was strongly associated with reductions in symptoms for the active training condition ($r_p = -.42$, $p = .04$) but not in the control training condition ($r_p = -.05$, $p = .83$), although the difference between these correlations was not significant ($z = -1.34$, $p = .18$).

Exploratory analyses were conducted to examine predictors of symptom change in the placebo condition. Analyses indicated that increases in pre- to post-training resting state connectivity between two different nodes predicted symptomatic improvement in the placebo condition: (a) the precuneus and the right middle frontal

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gyrus ($r_p = -.56$, $p = .02$) and (b) the left and right orbital frontal cortex ($r_p = -.62$, $p = .01$). When simultaneously entered into a regression analysis with initial depression as a covariate, change in connectivity was associated with symptom change for both nodes (precuneus-rMFG: b = −1.78, $t = -1.93$, $p = .07$, effect size $r = .31$; lOFC-rOFC: b = −3.81, $t = -2.39$, $p = .03$, effect size $r = .37$), suggesting change in both nodes contributed to symptomatic change. No other improvements in resting-state connectivity were correlated with symptom change in the placebo condition. However, these exploratory analyses were post hoc and should be considered very tentative.

Discussion

This study examined whether training attention away from negative stimuli with a dot-probe task and affective images (both emotion faces and dysphoric images) compared to placebo training changed attention bias, altered the underlying neurobiology that supports attention bias, and impacted depression symptom trajectories over time among individuals with MDD. Few studies to date have experimentally tested whether negative attention bias maintains depression symptoms among adults diagnosed with MDD.

Findings from the current study suggest that attention bias modification can improve attention bias for negative stimuli measured across a number of different modalities. Active attention training resulted in moderate bias improvement for negative stimuli when measured with a behavioral dot-probe task using stimuli content that differed from the training stimuli (different sets of emotional images). Minimal training group differences were observed for attention bias for positive stimuli with the dot-probe.

Further, and perhaps more convincingly, active attention training facilitated disengagement of attention from negative stimuli compared to placebo training when direct line of gaze was measured with eye tracking during an exogenous cueing task. Again, these effects were moderate and were observed despite using assessment stimuli that differed from training stimuli (words vs. images). Notably, attention training effects were observed for stimuli presented for longer durations (1,500 ms) but not short durations (500 ms). The preponderance of evidence suggests that attention biases in depression are most pronounced at longer stimulus durations (Gotlib & Joormann, 2010). Indeed, the attention training approach utilized in the current study targeted these longer stimulus duration biases by presenting training stimuli for relatively long durations.

Thus, these results suggest that this training task effectively influenced the type of attention biases that are most commonly associated with MDD. Further, improvements in attention bias were specific to negative stimuli, as robust training effects were not observed for disengagement from positive stimuli. It should also be noted that the current study used relatively long stimulus durations during training (3,000–4,500 ms). Future work should also examine whether stimulus duration influences the effectiveness of attention training, as relatively few direct tests of stimulus duration have been completed.

These data indicate that attention bias modification altered attention bias. This finding may not be surprising; however, it is notable that a number of attention training studies that have failed to alter attention bias (Kruijt et al., 2013; McNally, Enock, Tsai, & Tousian, 2013). Why might attention training successfully alter negative bias in the current study? One possibility is that participants had repeated sessions of attention training distributed over a relatively long period of time. There is evidence to suggest that distributed practice over a long time period is more effective for long-term retention of learning than an equivalent amount of learning over a short time period (Cepeda, Pashler, Vul, Wixted, & Rohrer, 2006). Of course, mass practice over a long period of time may produce the strongest alterations in attention bias. Future attention training trials should consider increasing the training dosage. Indeed, conducting dose-response attention training studies would be particularly helpful to determine optimal training dosages for producing sustained change in attention bias.

This study is among the first to demonstrate that attention training can alter functional brain connectivity within neural networks that support attention bias in depression, particularly between the anterior cingulate cortex and the middle frontal gyrus, a region of ventral lateral PFC. Consistent with these findings, our prior research indicates that when required to shift attention away from sad stimuli, depressed individuals show altered activation in the lateral PFC, including the middle frontal gyrus, and parietal regions compared to the nondepressed group (Beevers et al., 2010). This finding is consistent with prior work documenting that MDD is associated with an attenuated neural response in the ventral lateral PFC when responding to targets that were preceded by sad distracters compared to healthy controls (Dichter, Felder, & Smoski, 2009; Wang et al., 2008) and with research examining control over emotion in healthy individuals (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008).

What is novel about the current study is the demonstration that attention bias modification can improve brain connectivity within a critical part of the attention control network—specifically, attention training enhanced connectivity between the middle frontal gyrus and the dorsal anterior cingulate cortex (ACC). The dorsal ACC has been implicated in conflict monitoring (MacDonald, Cohen, Stenger, & Carter, 2000) and attentional control via its connectivity with other frontal regions (De Raedt & Koster, 2010) and appears important for in the modulation of emotion (Pessoa, 2009). Indeed, alterations within ACC activity have been observed in depressed samples, particularly during tasks that require cognitive control (Banich et al., 2009; A. J. Holmes & Pizzagalli, 2008). Thus, it is notable that change in node-to-node connectivity between the middle frontal gyrus and the dorsal ACC was associated with change in attention bias in the active training condition but not the placebo training condition. Consistent with the Research Domain Criteria project (Insel et al., 2010), attention training modified a basic dimension of functioning (i.e., attention bias) across multiple units of analysis. Altering a basic domain of functioning is arguably an important outcome in its own right.

Given that attention bias modification successfully altered negative attention bias and the neurobiology that supports it, one perplexing issue is why did depression symptom change not significantly differ between the training groups? It should be noted that there was significant depression symptom change during training. On average, symptoms decreased by approximately 40%. However, symptom change did not differ between groups.

One possibility is that negative attention bias, as measured in the current study, does not maintain negative mood symptoms and, therefore, altering attention bias has no impact on mood change. Although very few studies have addressed this topic, there is some

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laboratory evidence to suggest that negative attention bias does contribute to the maintenance of sad mood. Two recent studies documented that negative attention bias predicted slower mood recovery following laboratory manipulations that induce negative mood (Clasen et al., 2013; Sanchez et al., 2013). Further, other attention training research suggests that modifying negative attention bias is associated with reductions in symptoms (Browning et al., 2012; T. T. Wells & Beevers, 2010), although there are exceptions (Mogoaşe et al., 2014).

Importantly, pre- to posttraining change in negative attention bias was strongly correlated with improvements in depression, but only in the active training condition. This finding suggests that the attention training groups experienced symptom change via different mechanisms. In the active training condition, symptom change may have been due in part to improvement in negative attention bias. The placebo training group, which experienced relatively little change in negative attention bias, may have benefitted from regularly engaging with a task that required focused and sustained attention.

Consistent with this possibility, exploratory analyses indicated changes in resting-state brain regions in the attention control network, more specifically, increasing connectivity between the precuneus and right middle frontal gyrus node and the right and left orbital frontal cortex node, predicted symptom improvement in the placebo condition. The precuneus, located in the posteromedial portion of the parietal lobe, is involved in directing visual attention, particularly when shifting attention to different spatial locations (Cavanna & Trimble, 2006; Wenderoth, Debaere, Sunaert, & Swinnen, 2005). Thus, improved control over spatial attention, irrespective of the emotional content of the stimuli, may have conferred some mood benefits. Similarly, changes in connectivity between bilateral regions of orbital frontal cortex were recently shown to be the strongest predictor of decreases in sustained attention associated with mental fatigue (Sun et al., 2014). Taken together, these results indicated that engaging in a cognitive training, irrespective of the focus on attention bias, may confer some benefits in terms of one's ability to sustain attention and symptom reduction.

Interestingly, a recent study utilizing a smart phone to deliver attention training found similar effects on anxiety symptoms for the active and placebo training conditions (Enock, Hofmann, & McNally, 2014). Thus, the so-called "placebo" training condition may in fact be more active than first thought. Additional work examining the impact of placebo training is needed, as these findings should be considered very preliminary because they were derived from exploratory analyses. Nevertheless, these results suggest that decrements in sustained attentional in general may also contribute to the maintenance of depression.

There are a number of study limitations that need to be addressed by future research. First, this study is somewhat small for a clinical trial, although arguably sample size was reasonable for a study with an fMRI component (larger *N* is almost always better, of course). The relatively small sample size minimizes the likelihood of finding small to medium effects, such as internode connectivity. Future work should strive for larger sample sizes to enhance confidence regarding effect size estimates. Second, future larger studies should also consider additional training conditions. At a minimum, a no-training control group should be included for attention training studies that also involve placebo training. Third, although in-person diagnostic interviews were completed to determine study eligibility, only self-reported symptom change was utilized to measure response to treatment. Future work should also incorporate interviewer assessments of symptom change. Fourth, the symptom change follow-up period was short-term (i.e., 1 month following posttraining). It would be ideal to examine symptom change over much longer periods of time in order to determine whether changes observed in the current study are durable and/or predict the return of symptoms.

Despite these limitations, this study makes a number of important contributions to this area of research. First, attention bias modification can significantly improve negative attention bias in an MDD sample. Second, this is the first study to demonstrate that attention training alters neural circuitry that supports negative attention bias in a clinical population. This evidence further suggests that attention bias modification is producing important changes in how depressed individuals attend to negative information and the neural systems that support attention control. Third, attention training (and placebo training) was associated with significant changes in depression. There is a dearth of attention training research with clinically depressed samples, so this is an important contribution in its own right.

Findings from this study suggest that multiple attentional mechanisms may support the maintenance of depression. Consistent with cognitive theories (Beck et al., 1979), negatively biased attention contributes to the maintenance of depression, as modifying this bias was associated with improvements in depression. However, findings indicate that improved connectivity in the neural circuitry that supports control over spatial attention also predicts symptomatic improvement. If replicated by future work, this suggests that enhancing attention control in general (i.e., irrespective of affective content of stimuli) may also be an effective intervention for depression. Additional experimental psychopathology work is necessary to test these possibilities, which hold the promise of simultaneously isolating the attentional mechanisms that contribute to the maintenance of depression and determining whether these novel attention training approaches will become a useful treatment option for clinically depressed individuals.

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