

Running title: ABM and Spontaneous Brain Activity Changes

Attentional Bias Modification (ABM) Training Induces Spontaneous Brain Activity Changes in Young Women with Subthreshold Depression: A Randomized Controlled Trial

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Abstract

Background: Attention bias modification (ABM) training has been suggested to effectively reduce depressive symptoms, and may be useful in the prevention of the illness in individuals with subthreshold symptoms, yet little is known about the spontaneous brain activity changes associated with ABM training.

Methods: Resting-state functional MRI was used to explore the effects of ABM training on subthreshold depression (SubD) and corresponding spontaneous brain activity changes. Participants were 41 young women with SubD and 26 matched non-depressed controls. Participants with SubD were randomized to receive either ABM or placebo training during 28 sessions across 4 weeks. Non-depressed controls were assessed before training only. Attentional bias, depressive severity, and spontaneous brain activity before and after training were assessed in both training groups.

Results: Findings revealed that compared to active control training, ABM training significantly decreased depression symptoms, and increased attention for positive stimuli. Resting-state data found that ABM training significantly reduced amplitude of low-frequency fluctuations (ALFF) of the right anterior insula (AI) and right middle frontal gyrus which showed greater ALFF than non-depressed controls before training; Functional connectivity strength between right AI and the right frontoinsula and right supramarginal gyrus were significant decreased after training within ABM group; Moreover, the improvement of depression symptom following ABM significantly correlated with the connectivity strength reductions between right AI and right frontoinsula and right supramarginal gyrus.

Conclusion: These results suggest that ABM has the potential to reshape the abnormal patterns of spontaneous brain activity in relevant neural circuits associated with depression.

Keywords: subthreshold depression; attentional bias modification; resting-state fMRI; brain plasticity

Introduction

Cognitive theories of depression have proposed that biased attention for negative information plays a pivotal and causal role in the development and maintenance of the illness (Beck, 1976, 2008). Considerable empirical research has demonstrated that not only depressed patients but also individuals at risk for depression selectively attend to negative information (De Raedt & Koster, 2010; Gotlib et al. 2014). This suggests that negative attentional bias may act as a risk factor for depression and that it may thus be regarded as a target for preventative interventions (Browning et al. 2012; Yang et al. 2014). Attentional bias modification (ABM), which is a computerized procedure that targets negative bias in attention (MacLeod et al. 2002), is a promising intervention for a variety of psychiatric disorders including depression (e.g. Hakamata et al. 2010; Hallion & Ruscio, 2011; MacLeod & Mathews, 2012; Mogoşe et al. 2014). Although inconsistent findings concerning the effects of ABM intervention on depression have been reported (e.g. Hallion & Ruscio, 2011; Mogoşe et al. 2014; Pennant et al. 2015), a number of studies have found that ABM is an effective tool in reducing depressive symptoms (Baert et al. 2010; Browning, Holmes & Harmer et al. 2010; Wells & Beevers, 2010; Browning et al. 2012).

Previous neuroimaging studies have been conducted on patients with depression, before and after psychological interventions. Taken together, these studies suggest a normalization of abnormal brain activity after treatment in the amygdala, insula, dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), and the posterior

cingulate/precuneus (Brody et al. 2001; Goldapple et al. 2004; Frewen et al. 2008; Disner et al. 2011; Hamilton et al. 2012; Ma, 2015). Brody et al. (2001) examined metabolic changes from before to after interpersonal psychotherapy in patients with major depression disorders (MDD) using resting-state positron emission tomography (PET). Results found that interpersonal psychotherapy normalized activity in ACC, DLPFC, VLPFC, insula and temporal lobe (Brody et al. 2001). Another study investigated neural changes underlying response to cognitive behavior therapy in patients with MDD using resting-state PET (Goldapple et al. 2004). The results showed pre- to post-treatment decreases in metabolic activity in DLPFC, VLPFC, orbital frontal regions, the posterior cingulate, and the inferior parietal regions. Increases were found in hippocampus gyrus and dorsal ACC. More recently, a resting-state PET study on patients with MDD also found that activity of anterior insula and amygdala can be used to predict differential response to medication or psychotherapy (McGrath et al. 2013).

Task-related functional magnetic resonance imaging (fMRI) has also been used to explore neural changes attributable to ABM in anxious or healthy participants with altered function of the amygdala, insula and lateral PFC being reported (Browning, Holmes & Murphy et al. 2010; Månsson et al. 2013; Taylor et al. 2014; Britton et al. 2015). For instance, Browning et al (2010) used selective attention tasks to assess the neural changes associated with ABM and found greater activation in the lateral PFC (DLPFC and VLPFC) and rostral ACC under the conditions in which the direction of participants' attention conflicted with their training (Browning, Holmes & Murphy et

al. 2010). The lateral PFC (DLPFC and VLPFC) is thought to play a role in modulating attention bias towards emotional cues. When shifting attention away from negative stimuli, high depressive individuals showed smaller activation in lateral PFC (DLPFC and VLPFC) than low depressive individuals (Beevers et al. 2010).

An outstanding question regarding the effects of ABM is how it influences neural function specifically in participants at risk for depression. While there is initial evidence that ABM may be useful in reducing the risk of depression in high-risk individuals (Browning et al. 2012), the neural effects of the procedure in such participants is unclear. In the present study, we explored this question among young women with subthreshold depression (SubD), which is known to be a risk factor for developing the illness, using ABM and resting-state fMRI. Resting-state fMRI provides not only regional amplitude of low-frequency fluctuations (ALFF) but also data about functional connectivity. Where ALFF analysis measures the intensity of regional spontaneous brain activity (Zang et al. 2007), functional connectivity detects the synchronization of spatially remote regions within a network and thus provides a complementary measure of network function (Biswal et al. 1995). Subthreshold depression is regarded as the prodromal phase of MDD and can predict the occurrence of depressive disorders two years later (Cuijpers et al. 2007; Karsten et al. 2011). Subthreshold depression, therefore, provides an ideal model for assessing the neural effects of ABM relevant to the prevention of depression.

Thus, the aim of the present study was to explore the effects of ABM on SubD and corresponding spontaneous brain activity (both regional activity and functional

connectivity patterns) changes among young women with SubD using resting-state fMRI. Based on previous studies found that depressive disorders are associated with impaired function and connectivity of neural circuitry considered to be important for several domains of mental functioning such as attentional control (e.g., VLPFC and inferior parietal cortex), emotional regulation (DLPFC, VLPFC and MPFC), and salience detection (amygdala and insula), and therapies (e.g. cognitive behavior therapy and interpersonal therapy) outcomes were primarily associated with normalized functioning in the cortical and subcortical regions cited above. We further hypothesized that ABM training would reduce individuals' depressive symptoms over time to a greater extent than participants in placebo training group and neural changes associated with ABM training would be observed in regions considered to be important for attentional control, emotional regulation and salience detection.

Materials and Methods

Participants

The participants were 41 female undergraduate aged 18 to 24 years and screened with SubD and 26 matched non-depressed controls female participants (Table S1 in Supplement material). Participants with SubD had a BDI score of ≥ 14 and non-depressed controls had a BDI score ≤ 6 at the two-stage assessment. All participants were interviewed using the Structured Clinical Interview for the DSM-IV (First et al. 2001) to exclude potential affective disorders and other current Axis I Disorders. Participants with SubD were randomly assigned to receive either ABM or active

control (AC) placebo training (n=24 in the ABM group and n=17 in the AC group), the ABM and AC groups did not differ in general intelligence, depression, state and trait anxiety (Table S1 and Figure S2 in Supplement material). The study was approved by the Southwest University Brain Imaging Center Institutional Review Board, and informed consent was obtained from all participants. More details are provided in Supplementary material.

Procedure

Participants with SubD underwent a battery of neuropsychological assessments (Beck depression inventory-II, (Beck et al. 1996); Spielberger state-trait anxiety inventory, (Spielberger et al. 1983) and Combined raven's test, (Sun et al. 1994)), dot-probe task and resting-state fMRI scans before and after training on day 1 and day 30. Non-depressed controls only completed the neuropsychological assessments and underwent resting-state fMRI scans on day 1. Between day 1 and day 30, each participant in the ABM and AC group completed the training or control training task every day for 4 weeks (day2-29) at the laboratory. All participants in the ABM and AC group were unaware of the study's real purposes and were not informed of their experimental condition until they were debriefed at the end of the experiment.

Training task

The ABM task was developed to train participants' attention toward relatively positive information using a computerized, modified dot-probe procedure (MacLeod et al. 2002). In this task, positive, neutral and negative faces (positive: happy faces; neutral: neutral faces; negative: sad and angry faces) were selected from the NimStim Face

Stimulus Set (Tottenham et al. 2009) to create positive-neutral and negative-neutral pairs. Participants were instructed to press one of two buttons to indicate the type of dot probe (i.e. horizontal or vertical) as quickly and as accurately as possible. In the ABM group, the probe appeared in the location of the relatively positive face on 87.5 % of the trials. In the AC group, the probe appeared in the location of the positive and negative face with equal probability (50%). In both groups, the positive and negative faces appeared randomly and equally on either the upper or lower location of the screen. More details are provided in Supplementary material.

Dot probe task

A standard dot-probe task was used to measure attentional bias (MacLeod et al. 2002) both before and after training. The task was similar to the AC training task with the exception that novel facial stimuli were presented. A measure of attentional bias toward emotional stimuli was calculated separately for positive and negative stimuli by subtracting the mean reaction time on congruent (e.g., negative congruent) trials from incongruent (e.g., negative incongruent) trials. Positive scores reflect a biased attention towards emotional stimuli and negative scores reflect a biased attention away from emotional stimuli.

Regional analysis: ALFF calculation

Following previous calculation procedures (Zang et al. 2007), the preprocessed time series was transformed into the frequency domain in order to estimate the power spectrum for each voxel. The averaged square root of the power spectrum calculated within 0.01- 0.08 Hz at each voxel was taken as ALFF. For standardization purposes,

the ALFF of each voxel was divided by the global mean ALFF values within the gray matter mask.

Network analysis: functional connectivity analysis

We investigated the connectivity between the regions (right IFG, right AI, right MFG, left IFG, left precentral cortex and postcentral cortex, see Results section) in which ABM influenced ALFF and a broader network of regions throughout the brain, following ABM training. The rationale was to first use the observed region(s) in which ALFF was modified by ABM as seed(s) to perform functional connectivity analyses and thus to map out the regions which were functionally connected with the seeds as a network. Next, we examined whether the connectivity within this network changed following ABM treatment and whether these changes were able to predict symptoms improvement.

Statistical analysis

An initial group analysis was performed on ALFF maps before training to determine whether participants with SubD (combined ABM and AC group) differed from non-depressed controls when under resting state. In order to obtain a relative full-scale results which can comprehensively reflect the differences between SubDs and non-depressed controls, two samples t-test were conducted in SPM8 with a liberal threshold (voxel level $p < 0.005$, uncorrected and a cluster size $> 540 \text{ mm}^3$).

The ALFF maps and functional connectivity z-maps of participants in the ABM and AC group before and after training were compared using a two-sample t-test in SPM8. To investigate regions that showed ALFF and connectivity strength changes

following training, paired-t tests were used on ALFF maps and functional connectivity z-maps of pre-training and post-training in the ABM and AC group. To explore whether spontaneous brain activity changes was associated with depressive symptom reductions after training, mean ALFF and functional connectivity strength changes (post-training minus pre-training) from each subject were extracted from clusters identified as significant in the analysis to determine whether these results correlated with the improvement of depressive symptoms.

All analyses were corrected for multiple comparisons using topological false discovery rate (FDR) correction (Chumbley et al. 2010) except where noted above. Overall significance was achieved when FDR-corrected threshold of $p < 0.05$ with an underlying voxel level threshold of $p < 0.001$, uncorrected.

Results

Behavioral data

Group Characteristics and Baseline Measures

Characteristics of participants in the subthreshold depression (SubD) and non-depressed controls are presented in Table 1. Participants with subthreshold depression and non-depressed controls did not differ in age ($p = 0.78$) and scores in Combined raven's test ($p = 0.31$), but they differed in severity of depression ($p < 0.001$) and trait anxiety ($p < 0.001$).

Insert Table 1 here

The effect of ABM on Symptom Changes

Results from a Time (pre-training, post-training) \times Group (ABM, AC) repeated measures ANOVA on BDI score revealed a significant main effect of Time [$F(1, 39) = 33.67; p < 0.001$], depressive symptoms significantly reduced from pre- to post-training. Importantly, we found a significant Time by Group interaction [$F(1, 39) = 20.91; p < 0.001$, Fig. 1A]. Post hoc comparisons revealed that there was significant reduction of depression in the ABM group ($p < 0.001$) but no significant improvement was observed in the active control (AC) group ($p = 0.45$). The depression of participants in the ABM was significantly smaller than participants in the AC group at post-training ($p < 0.01$).

Results from state anxious symptoms demonstrated the same training effects as that observed for BDI [$F(1, 39) = 4.18; p < 0.05$, Fig. 1B]. There were significant reductions of anxious symptoms in the ABM group ($p < 0.05$) but no significant improvement was observed in the AC group ($p > 0.1$).

Insert Figure 1 here

The effect of ABM on attentional bias

A repeated measures ANOVA on Time (pre-training, post-training) \times Group (ABM, AC) \times Bias score (negative, positive) revealed that the three way interaction was not significant. However, a significant interaction of Time \times Bias interaction [$F(1, 39) = 6.26; p < 0.05$] was found. Participants show a tendency of decreased attention away from positive stimuli and increased attention away from negative stimuli ($p = 0.05$) after training. When conducting repeated measures ANOVA on Time \times Bias score for ABM and AC group separately. Significant Time by Bias

interaction was found for individuals in the ABM group [$F(1, 23) = 5.54; p < 0.05$] but not those in AC group [$F(1, 16) = 1.69; p > 0.1$]. Participants in ABM group displayed an increased attention toward positive stimuli ($p < 0.05$) and a tendency to shift attention away from negative stimuli over time (Supplementary Table S2).

Insert Table 2 here

Resting state fMRI data

The effect of SubD on ALFF

Before training, an initial group analysis was conducted on ALFF maps to explore the differences in regional activity between SubD and the non-depressed control group. The results indicate that subjects with SubD showed greater ALFF in the right anterior insular (AI), right middle frontal gyrus (MFG), right superior temporal gyrus, and right fusiform gyrus and less ALFF in the lingual gyrus than non-depressed controls (Fig. 1C; Supplementary Table S3).

The effect of ABM on regional ALFF

Analyses of ALFF maps before and after training revealed significantly decreased ALFF in the right AI, right MFG, and bilateral inferior frontal gyrus (IFG) and increased ALFF in the left precentral and postcentral cortex within the ABM group ($p_{\text{corrected}} < 0.05$; Fig. 1D; Table 2), but no significant change was observed in the active control training group except significantly increased ALFF in the right occipital lobe ($p_{\text{corrected}} < 0.05$). No other significant results were observed.

Insert Table 3 here

The effect of ABM on Functional Connectivity

The ABM group showed a significantly greater connectivity strength reduction from pre- to post-training between the seed of right AI and the right frontoinsula (FI), right supramarginal gyrus (SMG), left AI, bilateral dorsal anterior cingulate cortex and right inferior temporal gyrus ($p_{\text{corrected}} < 0.05$; Fig. 2; Table2), but no significant connectivity strength change was found in the AC group. The ABM group also showed a significantly larger reduction of connectivity strength after training between the seed of left IFG and the bilateral posterior insula and putamen ($p_{\text{corrected}} < 0.05$; Table 2; Supplementary Fig. S1), but no significant connectivity strength change was observed in the AC group. No any other significant results were found from pre- to post-training in functional connectivity when seeded at other regions (right IFG, right MFG, left precentral or left postcentral cortex) among both the ABM and AC group.

Insert Figure 2 here

Brain-Behavior Correlation Analyses

We then investigated whether changes in ALFF and connectivity strengths contribute to depressive symptoms reduction. Despite significant decreases in ALFF being found in several regions within the ABM group, changes in ALFF were not associated with symptoms improvements in depression and anxiety.

Rather, the reduction of symptoms in the ABM group were significantly related to the connectivity strength changes identified in the above connectivity analysis. The improvement of depressive symptoms following training in the ABM group were significantly correlated with the reduction of right AI connectivity with right frontoinsular ($r = 0.51$, $p_{\text{(bonferroni corrected)}} = 0.05$; Fig. 2) and right SMG ($r = 0.56$, p

(bonferroni corrected) < 0.05 ; Fig. 2). No other significant associations were found between symptoms reduction and functional connectivity changes when seeded at other regions.

Discussion

To the best of our knowledge, this is the first study to investigate the effect of attentional bias modification (ABM) on improving depressive symptoms and corresponding spontaneous brain activity changes (both regional activity and functional connectivity patterns) among young women with subthreshold depression (SubD) using resting-state fMRI. Attentional bias modification changed the measure of attentional bias in the expected direction--increased attention toward positive stimuli and decreased attention toward negative stimuli--although the difference between the ABM and active control training groups was not significant. More importantly, ABM, relative to the active control group, significantly reduced symptoms of depression and anxiety.

Analysis of the resting-state data revealed that ABM training normalized increased ALFF in the regions of right anterior insula (AI), right middle frontal gyrus (MFG) and bilateral inferior frontal gyrus (IFG) within the ABM group. Moreover, functional connectivity strength between (1) right AI and the right frontoinsula, right supramarginal gyrus (SMG), left AI and bilateral dorsal anterior cingulate cortex (dACC); (2) left IFG and bilateral posterior insula and putamen significantly decreased after training within ABM group. Finally, the improvements of depressive

symptoms within the ABM group significantly and positively correlated with the strength reduction of right AI connectivity with right frontoinsula and right SMG. These results suggest that ABM might have the potential to reshape the abnormal patterns of spontaneous brain activity in relevant neural circuits which are thought to be associated with a predisposition for depression.

Cognitive theories of depression argue that negative attentional bias are causally associated with the development and maintenance of the illness (Beck, 2008; Disner et al. 2011). Consistent with this, previous studies have found that modifying biased attention through ABM tasks can reduce the severity of depressive symptoms among healthy individuals with elevated depression (Wells & Beevers, 2010; Yang et al. 2014) and patients with recurrent depression (Browning et al. 2012). Our finding that ABM also reduces symptoms in a sub-syndromal population is consistent with these results and suggests that ABM may be an efficacious tool for the treatment and prevention of depression. In other words, the present study provides initial empirical evidence that ABM training may represent an alternative method for preventing the progress of the illness. Application of ABM may help protect against the development of subsequent psychopathology in at risk subjects (Browning et al. 2012; Cuijpers et al. 2007).

Individuals with SubD displayed greater ALFF in the right AI and right MFG at pre-training that seemed to change in the direction of normalization with ABM training. These findings are consistent with previous studies which have observed that depressed individuals displayed increased ALFF in several regions (Liu et al. 2012;

Liu et al. 2013) and psychological or pharmacological therapy could change these abnormal brain activity in the direction of normalization (Brody et al. 2001; Goldapple et al. 2004; Kennedy et al. 2007). For example, resting-state studies found that patients with major depression disorders (MDD) displayed increased ALFF (Liu et al., 2013; Chen et al 2015) and regional homogeneity (an index that measures the synchronization of spontaneous BOLD signal oscillations within spatially neighboring voxels; Zang et al. 2004; Wu et al. 2011) in the anterior insula. Moreover, resting state PET studies of MDD treatment found that the increased insula metabolism can be significantly reduced after pharmacological therapy (Goldapple et al. 2004) and psychological therapy (Kennedy et al. 2007). Anterior insula activity changes have also been reported in various treatments for MDD, including antidepressant medication (McGrath et al. 2013), mindfulness training (Farb et al. 2012), and deep brain stimulation (Mayberg et al. 2005), suggesting its important role in mediating response to antidepressants and remission in the treatment of depression (Fu et al. 2013; McGrath et al. 2013). Additional analyses on baseline predictors of response in the current data also found that pre-training functional connectivity between right AI and left insular and inferior parietal lobule significantly correlated with depressive symptoms improvement, and these findings will be published in a separate manuscript devoted wholly to the baseline predictors. A recent meta-analysis reported that negative stimuli evoked greater insula activation among depressed patients (Hamilton et al. 2012), and this is regarded as reflecting more marked negative cognitive biases (Herwig et al. 2007). The current study observed that ABM reduced activity in the AI

suggesting that it may act to normalize the function of the salience detection and attentional control systems in participants with SubD. This is consistent with prior task-evoked fMRI studies (Browning, Holmes & Murry et al. 2010; Taylor et al., 2014) suggesting that ABM training modulated the activity in the top-down emotion control brain regions (AI and lateral PFC).

Functional connectivity strength between right anterior insula (AI) and right frontoinsula, right supramarginal gyrus (SMG), left AI and bilateral dorsal anterior cingulate cortex (dACC) decreased significantly after training within ABM group. These regions were regarded as mainly constituting key nodes of two brain network, the ventral attention network (i.e. SMG; Corbetta & Shulman, 2002; Vossel et al. 2014) and the salience network (i.e. dACC, AI; Menon & Uddin, 2010; Seeley et al. 2007), which have a pivotal role in attentional control, and salience monitoring and detection, and the dysregulation of these networks in MDD may explain the negative bias and abnormal cognitive control common in MDD (Disner et al. 2011; Roiser et al. 2011; Hamilton et al. 2012; Foland-Ross et al. 2013). Previous studies on depression have proposed that depression is a disorder of functional brain network (Sheline et al. 2010; Menon 2011) such as aberrant spontaneous brain activity in salience network (Zhou et al. 2010; Avery et al. 2014; Pannekoek et al. 2014) and ventral attentional network (Sylvester et al. 2013) among depressed individuals. A previous review proposed that psychotherapy treatments for depression may modulate networks that are dysfunctional in depression (Weingarten & Strauman, 2015) with a recent study reporting that patients with nonrefractory MDD showed distributed

decrease in connectivity than patients with refractory MDD in the bilateral insula, anterior cingulate cortex and other limbic regions (Lui et al. 2011). This suggests that effective treatment of depressive individuals may showed decreased connectivity in insula and ACC. In the current study, decreased functional connectivity strength between right AI and right frontoinsula, right SMG, left AI and bilateral dorsal anterior cingulate cortex following ABM and its association with depressive symptoms reductions may conceivable reflect a more efficient functioning of these regions. That is, improvement in the attribution of salience to stimuli that are related to negative attention and affective bias in depression (Disner et al. 2011), and improvement of attentional control resulting in the allocation of more attentional resources to positive emotional stimuli (Roiser et al. 2011).

Notwithstanding its potential implications, the limitations of this study should be acknowledged. Although we found differences in ALFF across training when the groups were analyzed separately, a significant time by group interaction was not found. This reduces our ability determine whether the changes in spontaneous brain activity were specifically induced by ABM. While brain-behavior correlation analysis found a significant change in spontaneous brain activity associated with improvement in depressive symptoms, which supports the contention that the ABM procedure did induce changes in spontaneous brain activity (Thomas & Baker, 2013), it would have been reassuring to demonstrate this relationship in the overall analysis of ALFF data. The significant effect of ABM on depressive symptoms, and the relationship between the ALFF measure and change in these symptoms, suggests that it would be possible

to detect this relationship in a larger sample of individuals. Second, only young women were recruited in the present study, which may limit the generalizability of the findings to men. However, previous studies have reported that both depression and anxiety disorders are more prevalent among women than among men (Kessler, 1994). In addition, little is known about possible gender differences in spontaneous brain activity in depression, thus, we decided to recruit only female participants to reduce the heterogeneity of our sample. Future work needs to explore the gender differences in spontaneous brain activity among depression. Third, we have framed the effect of ABM in terms of its intended impact on negative bias in attention (MacLeod et al. 2002) and on activity in the lateral prefrontal attention control system (Browning, Holmes & Murry et al. 2010). However, we cannot exclude the possibility that ABM training may influence other cognitive or emotional processes related to affective states among individuals with SubD. Future studies should explore whether ABM training may target other processes related to affective state, such as rumination which was found associated with introspective focus on negative thoughts and feelings and attentional deployment (Johnson, 2009; Arditte & Joormann, 2014). Fourth, the current study did not explore aberrant connectivity within the default mode network and between the default and other network node linked to depressive symptoms which were reported in previous studies (Sheline et al. 2009; Kaiser et al. 2014). However, the current study took a different approach to analysis of the data. Specifically we explored ABM training effects on regional spontaneous neural activity (i.e., ALFF) among individuals with SubD using a whole-brain survey analysis. Then, based on the

results of this ALFF analysis, functional connectivity changes were explored.

Examining the connectivity changes within the default mode network among individuals with SubD is extremely interesting, we therefore propose to explore the changes within canonical functional networks, including the default mode network, the executive control network, and the salience network induced by ABM training in a separate paper.

In conclusion, the current study is the first to find that individuals with subthreshold depression displayed reduced symptoms after ABM training corresponding to a significant reduction in pre-training hyperactivity within neural regions implicated in salience detection and attentional control using resting-state fMRI. The results highlight the promise of ABM as an effective intervention to improve depression through reshaping abnormal patterns of spontaneous brain activity. Finally, the findings may provide potential neural biomarkers for future neurostimulation studies on depression.

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Conflict of interest

None.

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Figure Legends

Figure 1. The effects of attentional bias modification training on depressive (A) and anxious (B) symptoms changes. Group comparison between individuals with subthreshold depression and non-depressed controls on ALFF (C); ALFF activity changes after 4 weeks of attentional bias modification training (displayed at $p_{\text{corrected}} < 0.05$) (D).

Figure 2. The effects of attentional bias modification training on functional connectivity strength changes seeded in the right anterior insula (AI, displayed at $p_{\text{corrected}} < 0.05$). Scatter plots above showed that connectivity strength reductions between right AI and frontoinsular and right supramarginal gyrus significantly correlated with depressive symptoms reduction. For display purposes, the change values of depression and connectivity strength multiplied -1 such that higher scores indicate more depression and connectivity strength changes. AI, anterior insula; FI, frontoinsular; SMG, supramarginal gyrus.

Table 1 Characteristics for individuals with subthreshold depression and non-depressed controls

	Subthreshold depression (41)		Non-depressed controls (26)		<i>t score</i>	<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>		
Age	20.27	0.89	20.35	1.32	0.29	0.78
CRT	63.44	6.26	64.88	4.52	1.02	0.31
STAT-T	52.00	8.75	36.85	6.95	7.46	0.001
BDI	22.76	5.88	3.87	2.11	16.80	0.001

Note: CRT: Combined Raven's Test; STAT-T, Spielberger State-Trait Anxiety Inventory-Trait; BDI, Beck Depression Inventory-II.

Table 2 Dot Probe performance (reaction time: ms) from pre-training to post-training among participants in the ABM and AC group.

	ABM group (24)		AC group (17)	
	<i>Pre-Training</i>	<i>Post-Training</i>	<i>Pre-Training</i>	<i>Post-Training</i>
Accuracy (%)	94.66±2.23	93.36±3.93	95.40±2.11	94.38±2.60
Negative bias	5.70±28.85	-2.86±16.99	7.23±23.39	-4.00±15.12
Negative Con	539.11±66.28	459.14±55.98	538.75±58.17	443.29±43.63
Negative InCon	544.81±69.70	456.28±56.19	545.98±69.42	439.28±42.82
Positive bias	-10.00±2.42	2.98±15.21	-3.44±17.82	-3.45±17.26
Positive Con	548.50±71.46	461.32±57.64	535.71±66.95	442.91±41.33
Positive InCon	538.50±63.59	464.30±53.33	532.27±69.64	439.45±45.43

Note: Con, congruent; InCon, incongruent; ABM, attentional bias modification; AC, active control.

Table 3. ALFF and functional connectivity strength changes among individuals with subthreshold depression in the ABM and AC group at pre-training and post-training.

Brain regions			MNI coordination			Cluster	Peak
			x	y	z	size (mm ³)	T-Value
ABM post > pre							
IFG	R	48	42	-6	945	-6.17	
AI	R	42	9	0	1323	-5.84	
MFG	R	33	51	27	1080	-4.76	
IFG	L	-54	36	0	783	-4.70	
PreC/PostC gyrus	L	-30	-21	63	1809	5.93	
PreC/PostC gyrus	L	-54	-15	36	864	4.61	
AC post > pre							
Cuneus	R	12	-96	21	1458	5.63	
Rai seeded FC							
ABM post > pre							
IFG/AI	R	42	15	0	3132	-6.15	
SMG	R	51	-36	36	4617	-5.75	
AI	L	-39	6	3	1296	-5.14	
dACC	L/R	12	9	48	2322	-4.86	
ITG	R	45	-57	-9	1323	-4.37	
AC post > pre							
Nonsignificant							
LiFG seeded FC							
ABM post > pre							
Posterior insula/Putamen	L	-33	-21	3	1458	-5.28	
Posterior insula/Putamen	R	30	-24	9	1836	-5.32	
AC post > pre							
Nonsignificant							

Note: ABM, attentional bias modification; AC, active control; MNI, montreal neurological institute; IFG, inferior frontal gyrus; AI, anterior insula; MFG, middle frontal gyrus; SMG, supramarginal gyrus; dACC, dorsal anterior cingulate cortex; ITG, inferior temporal gyrus; FC, Functional Connectivity; L, left; R, right.

* A positive T value indicates increased activity. A negative T value indicates decreased activity.

Figure 1

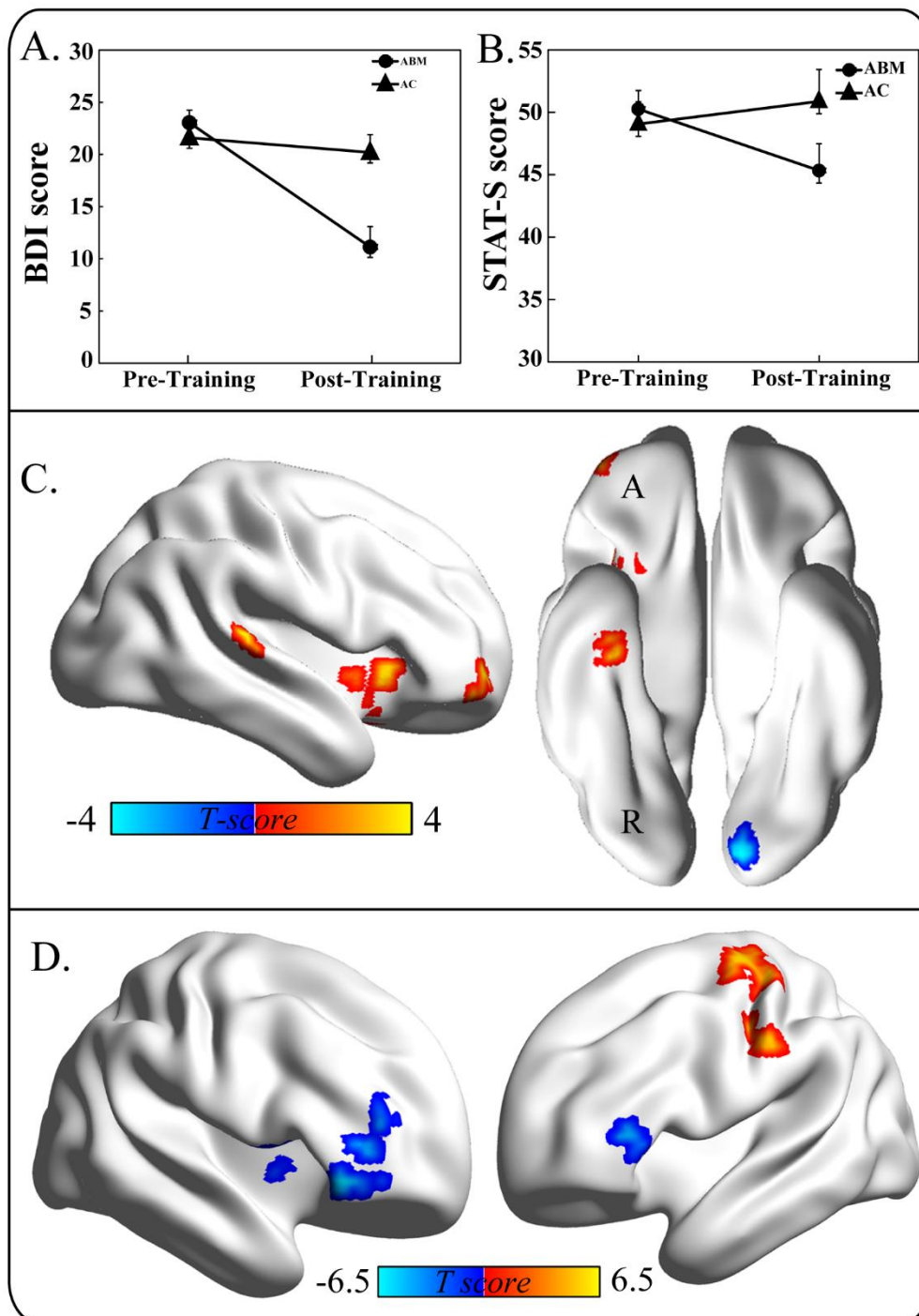


Figure 2

