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Biobehavioral Markers of Attention Bias Modification in Temperamental Risk for Anxiety: A Randomized Control Trial

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Objective: Children with behavioral inhibition, a temperament characterized by biologically based hypervigilance to novelty and social withdrawal, are at high risk for developing anxiety. This study examined the effect of a novel attention training protocol, attention bias modification (ABM), on symptomatic, behavioral, and neural risk markers in children with behavioral inhibition.

Method: Nine- to 12-year-old typically developing children identified as having behavioral inhibition (N = 84) were assigned to a 4-session active ABM training (n = 43) or placebo protocol (n = 41) using a double-blinded, randomized, controlled trial approach. Anxiety symptoms (Diagnostic Interview Schedule for Children–Fourth Edition), attention bias (AB; measured by a dot-probe task; AB = incongruent reaction time − congruent reaction time), and AB-related neural activation (measured by functional magnetic resonance imaging activation for the incongruent > congruent contrast in the dot-probe task) were assessed before and after the training sessions.

Results: Results showed that active ABM (n = 40) significantly alleviated participants' symptoms of separation anxiety, but not social anxiety, compared with the placebo task (n = 40); ABM did not modify behavioral AB scores in the dot-probe task; and at the neural level, active ABM (n = 15) significantly decreased amygdala and insula activation and increased activation in the ventrolateral prefrontal cortex compared with placebo (n = 19).

Conclusion: These findings provide important evidence for ABM as a potentially effective protective tool for temperamentally at-risk children in a developmental window before the emergence of clinical disorder and open to prevention and intervention.

Clinical trial registration information—Attention and Social Behavior in Children (BRAINS); *http://clinicaltrials.gov/*; NCT02401282.

Key words: behavioral Inhibition, dot probe, anxiety, attention bias modification, fronto-limbic activation

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Behavioral inhibition (BI) is a biologically based, early-appearing, and relatively stable temperament trait. BI is characterized by hypervigilance to novelty in infancy[1] and social withdrawal in childhood.[2,3] BI is a risk factor for subsequent anxiety, with an up to 7-fold increase in risk for social anxiety.[4-6] The parallels between BI and social anxiety are observed in behavioral,[4-6] psychophysiologic,[2,7,8] and neuroimaging[9] measures. One factor shown to strengthen BI–anxiety links is attention bias (AB) to threat.[10,11] Individuals with a history of BI and heightened AB, manifested in behavior[12-15] or reflected in neuroimaging measures[16,17] and psychophysiology,[18] are at greater risk for anxiety or internalizing problems compared with children with equal BI but no AB.

The larger clinical literature has suggested that AB could play a causal role in developing anxiety.[19,20] Building on the presumption of causality, many studies have examined AB modification (ABM) as a potential intervention. AB has been typically assessed by the dot-probe paradigm, which presents salient cues and examines the response to subsequent targets based on their relative spatial position to the cues (incongruent versus congruent). ABM is a modified dot-probe task designed to shift attention away from threat and, as a result, alleviate anxiety symptoms by always presenting the target in the spatial location opposite the salient cue.[21,22] The comparison placebo task counterbalances the cue and target locations. The positive effect of ABM has been reported in clinically and subclinically anxious adults[21-25] and youth.[26-30] However, there has been limited work on the neural mechanisms underlying the observed ABM effects.[31-33] Further, recent work has called into question the premise and effectiveness of ABM as an intervention.[34,35] Emerging data suggest that neural measures might show greater sensitivity and stability in capturing patterns of AB and ABM response than scores based on reaction time (RT).[36]

A recent BI study found that 9- to 12-year-old children show significant activation in fronto-limbic regions, including the amygdala, ventrolateral prefrontal cortex (vlPFC), dorsolateral PFC, and medial PFC, when they orient attention away from threat (incongruent > congruent contrast).[16] Importantly, hyperactivation in the right dorsolateral PFC was observed in children with higher BI, which in turn predicted anxiety levels. These findings suggest that children with BI might have to engage more effortful control resources to shift attention away from threat. However, currently there are no published data regarding the impact of ABM in the context of childhood BI. This study represents the first attempt to examine the degree to which ABM affects neural, behavioral, and symptom markers of risk in school-age children with BI.

Recent neuroimaging studies have documented changes in AB-related neural correlates after ABM in anxious and sub-anxious[31,33,37] and healthy[32] adults. Although results have been mixed

due to methodologic variations, ABM appears to influence the fronto-limbic network incorporating the vlPFC[33] and amygdala,[31,33] reflecting top-down control processes[38] and bottom-up reactive processes,[39,40] respectively, during threat-related processing. In addition, baseline activation within the same fronto-limbic network predicted the magnitude of ABM-induced symptom decrease. A recent study on youth with anxiety found that combining cognitive-behavioral therapy (CBT) and active ABM led to greater anxiety decrease than CBT combined with placebo ABM.[30] Further, in the CBT plus placebo group, youth with weaker amygdala–insula connectivity at baseline showed less response to treatment.[30] Other data suggested that adults with anxiety with higher baseline amygdala activation benefit more from active ABM.[31]

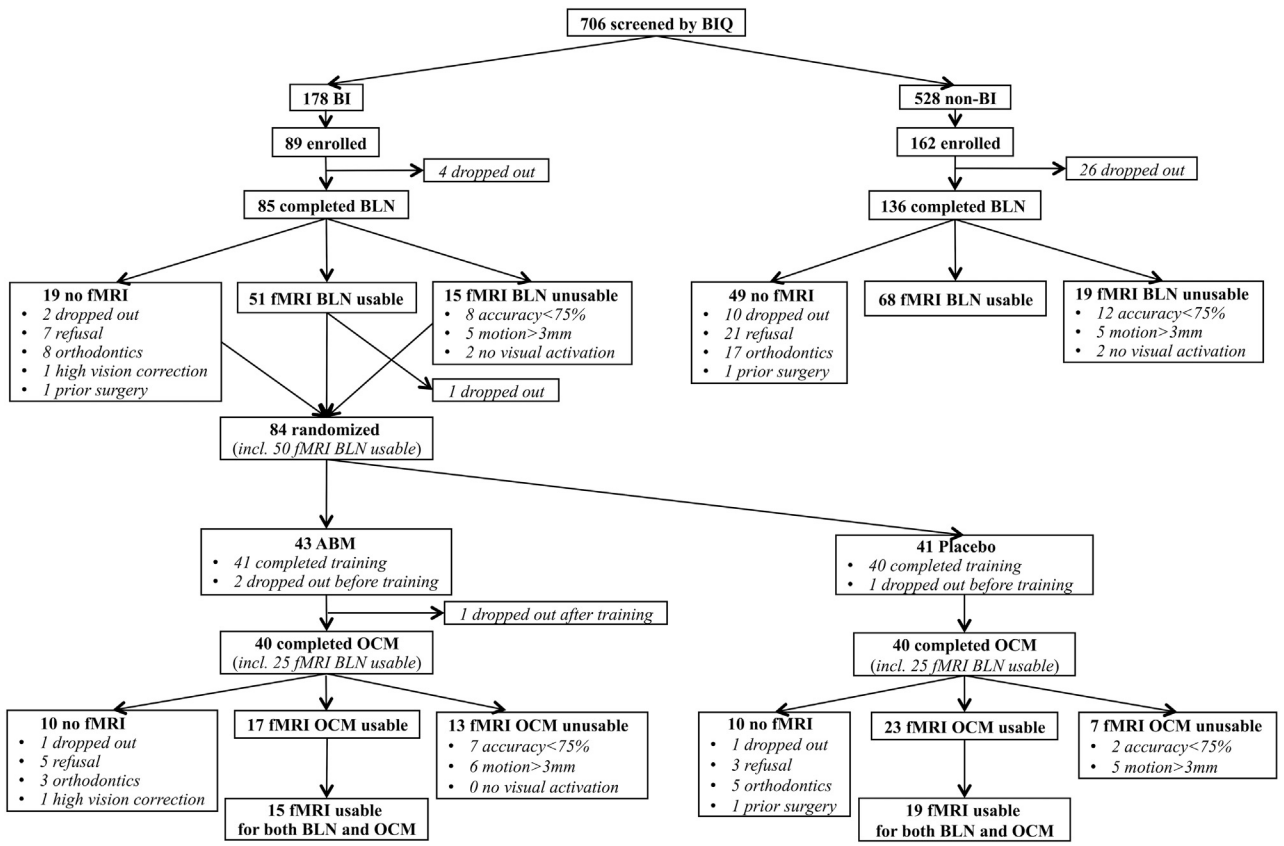
Building on this work, the present study randomly assigned children with BI to an active ABM condition, in which they were consistently directed toward nonthreat and neutral stimuli and away from threat, or a placebo task, in which they were directed to neutral and threat stimuli with equal probability. We assessed anxiety symptoms, behavioral AB (by dot-probe task), and AB-related neural underpinnings (by functional magnetic resonance imaging [fMRI]) before and after manipulation. Based on the existing literature, we hypothesized that ABM would effectively lessen anxiety symptoms in children with BI and potentially modulate AB-related fronto-limbic neural functions. In particular, we expected that the demand of shifting attention away from threat in the incongruent (versus congruent) condition would potentiate the salience of the incongruent trials. Previous work has associated attention shifting with hyperactivation in the limbic areas (amygdala, insula), especially for anxious and/or anxiety-prone individuals.[31,33,38,39] Accordingly, we hypothesized that active ABM would decrease limbic activation and/or increase frontal (vlPFC) activation in children with BI. We also expected that the magnitude of any ABM-induced anxiety decrease would be associated with individual differences in fronto-limbic activity. Although findings of an ABM effect on behavioral AB have been mixed,[12,13] the present results speak to the suggestion that neural measures are more sensitive to ABM effects than RT measures. Secondary analyses were conducted to test the robustness of the primary findings, including intent-to-treat imputation and sensitivity analysis (reported in Supplement 1, available online). By studying the neurocognitive mechanisms of ABM-induced effects in children with BI, we aimed to provide an important avenue for the understanding of anxiety pathways ahead of the developmental window within which clinical anxiety typically emerges.

METHOD

Participants and Procedure

Participants were 9- to 12-year-old children recruited in central Pennsylvania for a larger study of the relation among BI, attention, and anxiety. Seven hundred six children were screened by parent report using

FIGURE 1 Study flow.



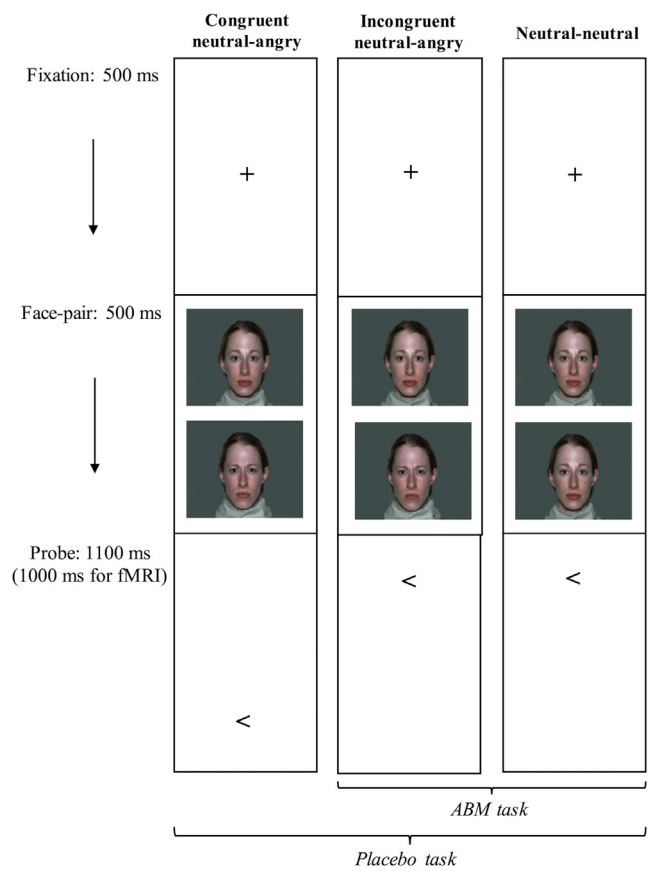
Note: ABM = attention bias modification; BI = behavioral inhibition; BIQ = Behavioral Inhibition Questionnaire; BLN = baseline; fMRI = functional magnetic resonance imaging; OCM = outcome.

the Behavioral Inhibition Questionnaire (BIQ)[41]; 178 children met criteria for BI. Of these, 89 children were enrolled. An additional 162 children without BI were enrolled for the baseline (BLN) assessments only (Supplement 1, available online). The study was approved by the institutional review board at The Pennsylvania State University (State College, PA). Parents and children provided written consent and assent, respectively, at the first visit.

Figure 1 illustrates a detailed study flow. Potential participants were invited to the laboratory for a BLN (pre-training) behavioral visit. Eighty-nine families agreed to enroll in the larger study. The children's anxiety symptoms (social and separation anxiety) were assessed using the Diagnostic Interview Schedule for Children—Fourth Edition (C-DISC-IV)[42] administered to parents and children, and their AB to threat was measured by a behavioral version of the dot-probe task.

The dot-probe task toolkit, including the ABM training protocol, is part of the Tel Aviv University and National Institute of Mental Health Attention Bias Measurement Toolbox Initiative.[43] As shown in Figure 2, a pair of faces (500 ms) is replaced in each trial by an arrow probe (1,100 ms) in either face's position. Participants indicated whether the probe pointed to the left or right by pressing 1 of 2 buttons as accurately and quickly as possible. Four trial types were presented: congruent angry-neutral trials in which the probe replaces the angry face; incongruent angry-neutral faces in which the probe replaces the neutral face; neutral-neutral trials in which the probe appears at either location; and blank trials as fillers. There were 80 trials per type, 320 trials in total, divided into 2 blocks with 160 each (500-ms intertrial interval). The stimuli consisted of 20 NimStim faces from 10 adults (half male, 1 angry and 1 neutral per actor).[44] Angry face location, probe location, probe direction, and face identity were counterbalanced across participants. AB toward threat was quantified as a difference score between incongruent and congruent conditions, which captures the individuals' relative speed in disengaging from threat in incongruent trials and/or orienting toward threat in congruent trials. As such, we inferred the participants' preferential attention allocation to threat over nonthreat stimuli through the RT difference score.

FIGURE 2 The dot-probe paradigm.



Note: The active attention bias modification (ABM) task includes only the incongruent angry-neutral condition (and the neutral-neutral condition); the placebo task includes incongruent and congruent conditions in an equal number of trials (and the neutral-neutral condition). fMRI = functional magnetic resonance imaging.

Next, eligible participants were invited to a second BLN visit for fMRI assessment. Reasons for exclusion included orthodontics, high vision correction, and prior surgery; reasons for not participating included child refusal and dropout (Figure 1 presents details). The fMRI participants completed an fMRI dot-probe task identical to the behavioral version except that the probe was displayed for 1,000 ms and the intertrial interval was jittered between 250 and 750 ms (average 500 ms).

A scanner upgrade occurred during data collection, such that data were collected on a 3-T Siemens Trio (before upgrade) and a 3-T Siemens Prisma^{fit} (after upgrade; Siemens Medical Solutions, Erlangen, Germany) using the identical scanning protocol (T2-weighted echo planar imaging, 3- × 3- × 3-mm voxel, repetition time 2,500 ms; T1-weighted magnetization prepared rapid acquisition gradient recalled echo, 1- × 1- × 1-mm voxel, repetition time 1,700 ms). Scanner upgrade (old versus new) was included as a covariate in analyses. Characteristics of the fMRI and no-fMRI subgroups and the old and new scanner subsets are presented in Table S1 (available online). The visit order information is reported in Supplement 1, available online.

Children with BI continued on to the ABM training and subsequent outcome assessments. At completion of BLN visits, they were randomly assigned to an active ABM or a placebo task (50% in each). Training started the week after BLN and continued for 4 consecutive weeks, during which a research assistant administered the assigned task in the child's home once a week in a double-blinded manner (Table S2, available online). In the ABM task, the probe always replaced the neutral face of the angry-neutral face pair. In the placebo task, the probe replaced angry and neutral faces with equal probability. Two sets of faces were used to lessen stimuli-induced repetition effects and demonstrate generalization of the task. Each participant was randomly assigned to set A or B for BLN and outcome (OCM) assessments, and the other set (B or A) was used for training.

OCM (post-training) assessments were administered within 2 weeks of the last training session using identical procedures as at BLN.

Data Analyses

Raw data from the C-DISC-IV, behavioral dot-probe task, and fMRI dot-probe task were processed to measure participants' symptoms, behavioral AB, and neural AB profiles at 2 time points, BLN and OCM. For each measure, only participants who contributed usable data for the 2 time points were included in the pre-post analysis examining the ABM effect. Accordingly, data processing resulted in different numbers of available data points (range 34–80), creating overlapping subgroups of participants for each measure.

Anxiety and Behavioral AB Score. Composite anxiety scores were calculated by standardizing and averaging the raw scores across parents

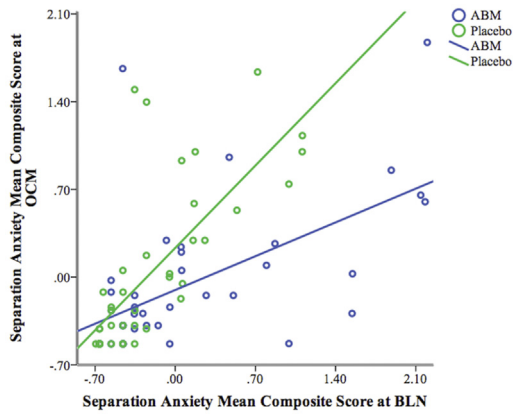
and children (within the BI group) for the social and separation anxiety submodules of the C-DISC-IV. Behavioral AB scores (AB = mean RT to probes of incongruent trials – mean RT to probes of congruent trials) were calculated for participants with an accuracy of at least 75%.

For anxiety and behavioral AB measures, 1-way analyses of covariance (ANCOVAs) examined the OCM score with training (ABM versus placebo) as the independent variable and the BLN score and age as the covariates (all statistics were 2-tailed). For randomized control designs, this approach is more powerful than the full factorial time × training analysis of variance models when examining group difference in change from BLN to OCM, because it controls for potential between-group differences at BLN, which can occur in randomized control designs despite randomization, and estimates the population regression slope predicting the OCM from the BLN.[45]

fMRI Data Processing. Preprocessing for fMRI (SPM8, Wellcome Trust Center for Neuroimaging, London, UK; MATLAB 7.14.0, Mathworks, Inc., Natick, MA) included motion correction, co-registration, normalization, and 6-mm spatial smoothing. A first-level fixed-effects analysis was run on each participant with 3 condition-related regressors (congruent angry-neutral, incongruent angry-neutral, and neutral-neutral), 1 invalid trial regressor (responses that were missing, incorrect, and/or with outlier RTs), 1 BLN regressor (including filler trials), and 24 motion regressors. Regressors were convolved by the canonical hemodynamic response function locked in time to the onset of the face pair. After first-level analysis, participants meeting all 3 criteria (accuracy ≥75%, motion <3 mm, detected visual activation to faces) were retained for second-level analysis. Consistent with the behavioral quantification of AB, neural activity underlying AB was quantified by the incongruent > congruent contrast from angry-neutral trials, which was the focus of second-level analysis.

In second-level modeling, a 2-way ANCOVA with time (BLN versus OCM) and training (ABM versus placebo) as independent variables and scanner (old versus new) and sibling pair (with versus without a sibling included, n = 3) as covariates was conducted to explore ABM-induced changes, with a focus on the time × training interaction. We conducted small volume correction within a priori anatomic regions of interest of the limbic-vlPFC circuitry, including the left and right amygdala, insula, and vlPFC (Automated Anatomical Labeling[46]). Results were set at a threshold at the whole-brain voxel level at an uncorrected p value less than .005. Then, small volume correction was used within each of the a priori regions of interest, and clusters with a p value less than .05 corrected by familywise error were identified as significant activation. The literature has identified the amygdala and vlPFC as responsive to threatening stimuli during the dot-probe task in youth with anxiety, with symptom severity correlated negatively with vlPFC activation and positively with amygdala activation.[38,39] Adults with anxiety show increased vlPFC[33] and decreased amygdala–insula activation[31] after ABM, accompanied by attenuated anxiety reactivity to laboratory stressors.[33]

FIGURE 3 Separation anxiety scores for the attention bias modification (ABM; n = 40) and placebo (n = 40) groups at baseline (BLN) and outcome (OCM).



Note: *The full-color figure is available online.*

Next, to probe the specific patterns of the time × training interaction and control for potential between-group differences at BLN, percentage of signal change (%SC) values were extracted from clusters showing a significant time × training interaction for each participant and subjected to secondary ANCOVA analyses (with training as an independent variable, BLN %SC and age as covariates, and OCM %SC as a dependent variable) in SPSS 24.0.0.1 (IBM Corp, Armonk, NY).

Correlation Analysis. Bivariate Pearson correlations were conducted on the BLN measures between core variables to examine their interrelations. Difference scores were calculated for each variable (Δ = OCM − BLN) as direct indicators of ABM-induced change. Correlations between difference scores were tested to see whether ABM-induced changes were related to each other across anxiety, behavioral, and neural measures.

Secondary Analyses. A group of secondary analyses are reported in Supplement 1 (available online), including behavioral AB results of the

TABLE 1 Results of the Significant Clusters Yielded by Time × Training Second-Level Modeling in SPM and the Mean Percentage of Signal Change (Standard Deviation) Extracted From Each Cluster

	Small Volume Correction					Mean Percentage of Signal Change		
A Priori ROIs	**Peak MNI Coordinates**	**Voxels, n**	***F***	***Z***	p_{FWE}	**Time**	**ABM**	**Placebo**
Right amygdala (87 voxels)	18, −1, −17	8	11.56	2.91	.05*	BLN	0.71 (1.11)	−0.49 (1.37)
						OCM	0.00 (0.89)	0.64 (1.44)
Right insula (597 voxels)	36, 11, −14	14	17.84	3.56	.04*	BLN	1.27 (1.95)	−0.68 (1.88)
						OCM	0.40 (1.24)	1.06 (1.22)
Left vlPFC (809 voxels)	−39, 56, −8	13	22.25	3.92	.02*	BLN	−0.28 (0.60)	0.02 (0.40)
						OCM	0.43 (0.48)	−0.18 (0.42)

Note: *ABM = attention bias modification; BLN = baseline; FWE = familywise error; MNI = Montreal Neurological Institute; OCM = outcome; ROIs = regions of interest; vlPFC = ventrolateral prefrontal cortex.*

*$p<.05$.

fMRI dot-probe task (Table S3, available online), neural activation in incongruent and congruent conditions, respectively (Figure S1, available online), fMRI results without siblings (Table S4, Figure S2, available online), regression models examining whether BLN fMRI moderates Δanxiety (Table S5, Figure S3, available online) and whether ΔfMRI mediates ABM effect on Δanxiety (Table S6, Figure S4, available online), whole-brain fMRI analyses (Table S7, available online) and exploratory comparisons between children with and without BI at BLN (Table S8, Figure S5, available online), and examination of the potential influence of visit order on the results (Table S9, available online); and intent-to-treat imputation of missing data and sensitivity analysis on the imputed datasets (Tables S10-S15, Figures S6-S7, available online).

RESULTS

ABM-Related Effects on Behavioral, Anxiety, and Neural Measures

One-way ANCOVAs examining the training effect on OCM score (controlling for BLN) yielded no training effect for behavioral AB (ABM = 33, placebo = 32; $p = .21$). ANCOVAs on anxiety scores (ABM = 40, placebo = 40) showed a significant training effect on OCM separation anxiety ($F_{1,76} = 5.67$, $p = .02$, eta squared [η^2] = 0.07; Figure 3), with less anxiety in the ABM group (mean −0.05, standard deviation [SD] 0.58) than in the placebo group (mean 0.04, SD 0.65). No training effect was found for social anxiety ($F_{1,76} = 0.15$, $p = .70$, $\eta^2 = 0.00$). No age effects were observed ($p \geq .40$ for all comparisons). See descriptions presented in Table S3, available online.

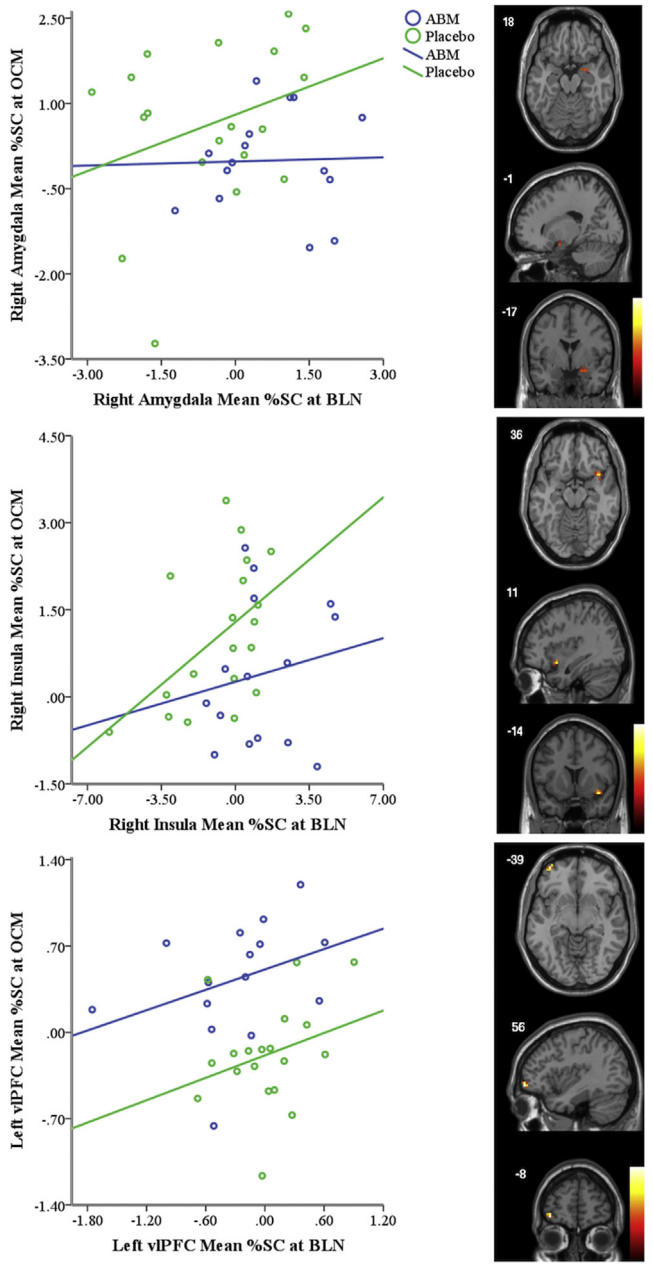
Second-level analysis of fMRI data (ABM = 15, placebo = 19) within a priori regions of interest for the incongruent > congruent contrast identified 3 clusters showing a significant time × training interaction in the right amygdala, right anterior insula, and left vlPFC, respectively. Table 1 and Figure 4 present results of second-level modeling and secondary ANCOVAs on the extracted %SC values from each cluster. ANCOVAs showed that with BLN %SC controlled, the training effect was significant on OCM %SC for clusters within the right insula ($F_{1,30} = 5.83$, $p = .02$, $\eta^2 = 0.16$) and left vlPFC ($F_{1,30} = 19.52$, $p = .00$, $\eta^2 = 0.40$) and approaching significance in the right amygdala ($F_{1,30} = 3.94$, $p = .06$, $\eta^2 = 0.12$). The ABM group showed lower %SC values at OCM than the placebo group in the right amygdala and right insula and higher OCM %SC values in the left vlPFC. These results suggest that after controlling for group differences at BLN, active ABM and placebo led to distinct patterns of neural change over time within the fronto-limbic system. No age effects were observed ($p \geq .16$ for all comparisons).

Relations Among Behavioral, Anxiety, and Neural Measures

Table 2 presents correlation coefficients between variables across the 2 training groups, with bootstrapped 95% CIs reported. For behavioral AB, neither BLN nor Δ scores were correlated with any other variable ($p \geq .12$ for all comparisons). As expected, BIQ scores were positively correlated with BLN anxiety. Separation and social anxiety were correlated with each other for BLN and Δ. BLN separation anxiety was positively correlated with BLN activation in the insula, but with the CI containing 0. Importantly, among the Δ scores, positive correlations were observed between Δseparation anxiety and Δamygdala/Δinsula, with all CIs higher than 0. The amygdala and insula were strongly correlated with each other for BLN and Δ. ΔvlPFC was negatively correlated with Δinsula (greater vlPFC increases were accompanied by greater insula decreases), but with the CI containing 0.

Correlation analyses conducted within each training group did not yield any significant results, potentially because of the modest sample size of each group. However, we did observe a trend for a positive Δseparation anxiety-Δamygdala correlation in the ABM group ($r_{13} = 0.51$, $p = .05$, CI −0.11 to 0.81).

FIGURE 4 Three brain clusters showing a significant time × training interaction and the extracted percentage of signal change (%SC) values for attention bias modification (ABM; n = 15) and placebo (n = 19) at baseline (BLN) and outcome (OCM).



Note: The full-color figure is available online. vlPFC = ventrolateral prefrontal cortex.

TABLE 2 Pearson Bivariate Correlations Across the 2 Training Groups

		BLN					Δ				
BLN	**BIQ (BLN)**	**1**	**2**	**3**	**4**	**Δ**	**BIQ (BLN)**	**1**	**2**	**3**	**4**
1. Separation anxiety	0.33‡ (81)					1	−0.27* (78)				
	[0.12–0.55]						[−0.44 to −0.09]				
2. Social anxiety	0.33‡ (81)	0.27* (81)				2	−0.17 (78)	0.27* (78)			
	[0.09–0.53]	[0.06–0.47]					[−0.40 to 0.08]	[0.02–0.49]			
3. Right amygdala	0.18 (32)	0.28 (32)	−0.17 (32)			3	−0.18 (32)	0.56‡ (32)	−0.03 (32)		
	[−0.15 to 0.44]	[−0.17 to 0.63]	[−0.53 to 0.25]				[−0.51 to 0.15]	[0.11–0.66]	[−0.29 to 0.29]		
4. Right insula	−0.01 (32)	0.38* (32)	−0.22 (32)	0.75‡ (32)		4	0.03 (32)	0.51‡ (32)	−0.15 (32)	0.65‡ (32)	
	[−0.31 to 0.27]	[−0.08 to 0.69]	[−0.51 to 0.07]	[0.58–0.88]			[−0.36 to 0.37]	[0.05–0.67]	[−0.43 to 0.20]	[0.26–0.89]	
5. Left vlPFC	−0.03 (32)	−0.13 (32)	−0.20 (32)	0.17 (32)	−0.13 (32)	5	0.09 (32)	−0.08 (32)	0.08 (32)	−0.17 (32)	−0.40* (32)
	[−0.30 to 0.23]	[−0.49 to 0.13]	[−0.45 to 0.09]	[−0.11 to 0.44]	[−0.43 to 0.26]		[−0.17 to 0.36]	[−0.45 to 0.19]	[−0.24 to 0.40]	[−0.48 to 0.17]	[−0.64 to 0.01]

Note: Degrees of freedom are presented within parentheses, 95% bias-corrected accelerated confidence intervals (generated by 1,000 bootstrapping in SPSS) are presented within brackets, and significant correlations are displayed in boldface type. BIQ = Behavioral Inhibition Questionnaire; BLN = baseline; Δ = difference; vlPFC = ventrolateral prefrontal cortex.

*$p < .05$, ‡$p < .005$.

DISCUSSION

This study investigated potential ABM-induced decreases in anxiety in 9- to 12-year-old children with BI, a temperamental risk factor for anxiety. Adopting a double-blinded randomized control trial approach, children with BI were assessed before and after ABM (or placebo) training for symptom levels and biobehavioral markers of risk. Our data indicate that active ABM attenuated separation anxiety, but not social anxiety, compared with placebo. The ABM group showed decreased activation in the right amygdala and insula but increased activation in the vlPFC after training.

ABM-related decreases in clinical and subclinical anxiety symptoms have been reported in adults[21,22] and children.[26,30] Our study is the first to show a similar effect in children at risk for anxiety. Interestingly, in our data, this effect was evident for separation anxiety, but not for social anxiety, which is often the focus of the literature. Different factors could have contributed to this finding.

First, anxiety was assessed by parental and child report using the C-DISC-IV. The manifestation of anxiety symptoms might be driven by the daily "task demands" facing children. For 9- to 12-year-old children, most of their social encounters occur at school, and parents rarely witness children's feelings and behaviors in this context directly. Rather, a child's (social) anxiety might manifest as distressed feelings and behaviors that parents perceive (and children experience) when they have to part with caregivers and face social encounters by themselves.[47] As such, anxiety was reported by parents (and by children themselves) specifically as separation anxiety. Further, the literature suggests that children tend to report fewer symptoms compared with parents in structured clinical interviews.[48] This could be due to children's inability to identify or articulate pathologic experiences or their unwillingness to disclose themselves to an adult stranger.[48] As a result, children's social anxiety symptoms, of which parents might have less knowledge, were not captured by child- and parent-report assessments.

Second, from a developmental perspective, the typical onset of separation anxiety is earlier than that of social anxiety. For example, 75% of children with separation anxiety develop the syndrome by 10 years and 90% do so by 13 years,[49] with its prevalence decreasing with age throughout adolescence. In contrast, the onset of social anxiety typically occurs during adolescence (range 12–16 years).[49] Separation anxiety also predicts the later emergence of,[50] and is often comorbid with,[49] social anxiety. Moreover, stranger anxiety during infancy, as an indicator of BI, predicts separation anxiety at a mean age of 8.8 years.[51] Future studies using a multimethod approach to assess anxiety (e.g., evaluation from clinician, teachers, or peers, observation from laboratory or classroom) would help discriminate subcategories of anxiety, better identify target symptoms for ABM, and examine the proposed trajectory of BI to separation anxiety to social anxiety.

We found no ABM-related effect for behavioral AB or correlations between AB and other variables. This is not surprising. In the literature, Eldar *et al.*[52] found that an ABM task training children to attend to threat successfully increased their AB, but a second task training them to attend away from threat did not change their AB. Roy *et al.*[53] reported heightened AB in youth with clinical anxiety, whereas other studies failed to find similar patterns in children with anxiety.[54,55] Similarly, although Pérez-Edgar *et al.*[12] found heightened AB in adolescents with childhood BI, other studies did not observe a direct BI-to-AB relation in younger children.[13,55]

Quantifying behavioral AB as a difference score has been criticized for poor reliability in capturing individual differences during the dot-probe task, which could be a dynamic process differentially expressed from trial to trial over time.[56] Novel computational procedures have been

proposed to account for dynamic features throughout the task, such as the trial-level bias score.[57] However, the validity of the new approach has been questioned.[58] Indeed, computing trial-level bias scores in a dot-probe dataset aggregated across 6 studies encompassing 364 participants 5 to 22 years old did not find significant behavioral AB or significant relations between AB and BI.[59] Behavioral dot-probe measures might not reliably capture individual differences in behavioral AB. Therefore, examining more sensitive bio-neural measures, such as fMRI, is important for AB-related research.

Although an ABM-related effect was not found in behavioral AB, the fMRI measurements were modulated by ABM. From BLN to OCM, the 2 groups showed differentiated patterns of neural changes for the incongruent > congruent contrast. It is likely that it was the active ABM task, rather than the placebo, that induced decreased activation in the right amygdala and insula and increased activation in the left vlPFC. However, the present results cannot rule out the possibility that the placebo task might have affected the participants' neural activities, contributing to the observed effect. Future studies with larger samples and/or additional control groups without any task could be helpful in further disentangling the effects of active ABM versus placebo. Nevertheless, our findings converge with the adult literature reporting ABM-related modulation of fronto-limbic functions, including the amygdala and insula[31,33] and/or ventral PFC.[32,33]

The limbic system, including the amygdala and anterior insula, is critical to immediate threat processing. Limbic hyperactivity is directly linked with, and potentially underlies, increased anxiety symptoms.[38,39] This pattern aligns with our observation that insula activation was positively correlated with separation anxiety at BLN. The magnitude of ABM-induced decrease in separation anxiety also was positively correlated with decreases in amygdala and insula activation, consistent with ABM data from adults with anxiety.[33] In the clinical literature, attenuation of limbic activation also has been reported in other anxiolytic treatments, including psychotherapy[60] and medication.[61]

We also found an ABM-induced enhancement in the vlPFC. In addition, our exploratory mediation analysis (Supplement 1, available online) found that increases in vlPFC activation accounted for the relation between ABM and decreases in anxiety symptoms. The ventral area of the PFC, among other prefrontal subregions, might be closely related to limbic reactivity, playing a down-regulatory role in threat-evoked limbic hyperactivity.[10,13] Specifically, vlPFC resources might be recruited during longer exposure to threats, following and inhibiting the initial limbic reactivity to maintain goal-directed behaviors.[38,39] Indeed, when comparing children with and without BI, the BI group showed relatively lower baseline vlPFC activity than the non-BI group (Supplement 1, available online), suggesting a link between hypofunction of the ventral PFC and fearful temperament.

In sum, our study demonstrated for the first time the effectiveness of ABM in attenuating anxiety symptoms and its potential neural correlates in children with BI, a population at temperamental risk for anxiety. However, given the current limitations, further exploration is warranted. Although we found that ABM altered symptomatic and fronto-limbic profiles, the underlying mechanism linking the 2 is unclear. To better understand the exact mechanism, future studies need to recruit larger samples sufficiently powered to enable connectivity and mediation analyses, which would help demonstrate the directionality and related causal mechanism underlying ABM; use multimethod assessments of BI anxiety to identify the risk and symptom targets for ABM; and conduct longitudinal research with multiple post-training follow-ups across different tasks, examining the generalizability and long-term effect of ABM. Overall, our findings suggest the potential of ABM to be used as an effective prevention tool for temperamentally vulnerable children, before the developmental window within which clinical anxiety typically emerges.

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