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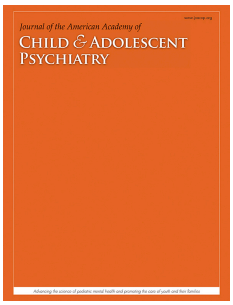

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ABSTRACT

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

Method: Nine- to twelve-year-old typically-developing children identified as BI (n=84) were assigned to a four-session active ABM training (n=43) or placebo protocol (n=41) using a double-blind, randomized control trial approach. Anxiety symptoms (Diagnostic Interview Schedule for Children–Fourth Edition), attention bias (measured by a dot-probe task, attention bias [AB]=incongruent reaction time [RT]-congruent RT) and AB-related neural activation (measured by functional magnetic resonance imaging activation for the incongruent>congruent contrast in the dot-probe task) were assessed both before and after the training sessions.

Results: Our results showed that (1) active ABM (n=40) significantly alleviated participants' symptoms of separation anxiety, but not social anxiety, compared with the placebo task (n=40); (2) ABM did not modify behavioral AB scores in the dot-probe task; and (3) at the neural level, active ABM (n=15) significantly reduced amygdala and insula activation and enhanced activation in ventrolateral prefrontal cortex relative to placebo (n=19).

Conclusion: Our findings provide important evidence for ABM as a potentially effective protective tool for temperamentally at-risk children, in a developmental window prior to 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

INTRODUCTION

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 seven-fold increase in risk for social anxiety.[4-6] The parallels between BI and social anxiety are observed in behavioral,[4-6] psychophysiological,[2,7,8] and neuroimaging measures.[9] One factor shown to strengthen BI-anxiety links is attention bias to threat (AB).[10,11] Individuals with a history of BI and heightened AB, either manifested in behavior[12-15] or reflected in neuroimaging measures[16,17] and psychophysiology,[18] are at greater risk for anxiety or internalizing problems relative to children with equal BI but no AB.

The larger clinical literature has suggested that AB may play a causal role in developing anxiety.[19,20] Building on the presumption of causality, a number of studies have examined attention bias 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 vs. 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 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 may show greater sensitivity and stability in capturing patterns of AB and ABM response than reaction time (RT)-based scores.[36]

A recent BI study found that 9-12-year-old children show significant activation in fronto-limbic regions, including amygdala, ventrolateral prefrontal cortex (vlPFC), dorsolateral PFC, and medial PFC, when they orient attention away from threat (incongruent>congruent contrast).[16] Importantly, hyperactivation in right dorsolateral PFC (dlPFC) was observed in children with higher BI, which in turn predicted anxiety levels. These findings suggest that children with BI may have to

engage more effortful control resources to shift attention away from threat. However, we currently have 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 impacts neural, behavioral, and symptom markers of risk among behaviorally inhibited school-age children.

Recent neuroimaging studies have documented changes in AB-related neural correlates following ABM in anxious/subanxious[31,33,37] and healthy[32] adults. Although results have been mixed due to methodological variations, ABM appears to influence the fronto-limbic network incorporating vlPFC[33] and amygdala,[31,33] reflecting top-down, control processes[38] and bottom-up, reactive processes,[39,40] respectively, during threat-related processing. Additionally, baseline activation within the same fronto-limbic network predicted the magnitude of ABM-induced symptom reduction. A recent study[30] on youth with anxiety found that combining cognitive-behavioral therapy (CBT) and active ABM leads to greater anxiety reduction than CBT combined with placebo ABM. Further, in the CBT+placebo group, youth with weaker amygdala-insula connectivity at baseline showed less response to treatment.[30] Other data has 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, where they were consistently directed towards non-threat/neutral stimuli and away from threat, or a placebo task, where 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]) both pre- and post-manipulation. Based on the existing literature, we hypothesized that ABM would effectively reduce 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 may 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 will decrease BI children's limbic activation and/or increase their

frontal (vlPFC) activation. We also expected that the magnitude of any ABM-induced anxiety reduction would be associated with individual differences in fronto-limbic activity. While findings of an ABM effect on behavioral AB have been mixed,[12,13] our results speak to the suggestion that neural measures are more sensitive to ABM effects than RT measures. Finally, secondary analyses were conducted to test the robustness of our 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 9-12-year-old children recruited in Central Pennsylvania for a larger study of the relation between BI, attention, and anxiety. Seven-hundred-and-six children were screened by parent report using 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 assessments only (see Supplement 1, available online). The study was approved by the institutional review board at The Pennsylvania State University. Parents and children provided written consent/assent at the first visit.

Insert Figure 1

Figure 1 illustrates a detailed study flow. First, potential participants were invited to the laboratory for a baseline (BLN/pretraining) 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/National Institute of Mental Health (NIMH) Attention Bias Measurement Toolbox

Initiative.[43] As shown in Figure 2, a pair of faces (500ms) is replaced in each trial by an arrow probe (1100ms) in either face's position. Participants indicated whether the probe pointed to left or right by pressing one of two buttons as accurately and quickly as possible. Four trial types were presented: (1) congruent angry–neutral trials where the probe replaces the angry face; (2) incongruent angry–neutral faces where the probe replaces the neutral face; (3) neutral–neutral trials where the probe appears at either location; (4) blank trials as fillers. There were 80 trials per type, 320 trials in total, divided into 2 blocks with 160 each (500ms ITI). 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 counter-balanced across participants. AB towards threat was quantified as a difference score between incongruent and congruent conditions, which captures the individuals' relative speed in 1) disengaging from threat in incongruent trials and/or 2) orienting towards threat in congruent trials. As such, we inferred the participants' preferential attention allocation to threat over non-threat stimuli through the RT difference score.

Insert Figure 2

Next, eligible participants were invited to a second baseline visit for the fMRI assessment. Reasons for exclusion included orthodontics, high vision correction, and prior surgery; reasons for not participating included child refusal and dropout (see details in Figure 1). The fMRI participants completed an fMRI dot-probe task identical to the behavioral version except that (1) the probe was displayed for 1000ms, and (2) the inter-trial interval was jittered between 250-750ms (average=500ms).

A scanner upgrade occurred during data collection, such that data were collected on a 3T Siemens Trio (pre-upgrade) and 3T Siemens Prisma^{fit} (post-upgrade; Siemens Medical Solutions, Erlangen, Germany) using the identical scanning protocol (T2-weighted EPI, 3×3×3mm voxel, TR=2500ms; T1-weighted MP-RAGE, 1×1×1mm voxel, TR=1700ms). Scanner upgrade (old vs 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 the online supplement.

Children with BI continued on to the ABM training and subsequent outcome assessments. Upon completion of baseline visits, they were randomly assigned to an active ABM or a placebo task (50% in each). Training started the week after baseline and continued for four consecutive weeks, during which a research assistant administered the assigned task in the child's home once a week in a double-blind 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 baseline and outcome assessments, while the other set (B or A) was used for training.

Outcome (OCM/posttraining) assessments were administered within two weeks of the last training session using identical procedures as baseline.

Data Analyses

Raw data from the C-DISC-IV, behavioral dot-probe, and fMRI dot-probe task were processed to measure participants' symptoms, behavioral AB, and neural AB profiles at two time points, BLN and OCM. For each measure, only participants that contributed usable data for both time points were included in the pre-post analysis examining the ABM effect. Accordingly, data processing resulted in varying numbers of available data points (ranging 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 C-DISC-IV. Behavioral AB scores (AB=M_{RT} to probes of incongruent trials-M_{RT} to probes of congruent trials) were calculated for participants with accuracy≥75%.

For both anxiety and behavioral AB measures, one-way analyses of covariance (ANCOVAs) examined the OCM score with training (ABM vs. placebo) as the independent variable (IV) and BLN score and age as the covariates (all statistics were two-tailed). For randomized control designs, this approach is more powerful than the full factorial Time×Training analysis of variance (ANOVA)

models when examining group difference in change from BLN to OCM, as it (1) controls for potential between-group differences at baseline, which can occur in randomized control designs despite randomization, and (2) estimates the population regression slope predicting the outcome from the baseline.[45]

fMRI Data Processing. fMRI preprocessing (SPM8, Wellcome Trust Center for Neuroimaging, London, UK; MATLAB 7.14.0, Mathworks, Inc., Natick, MA) included motion correction, coregistration, normalization, and 6mm spatial smoothing. A first-level-fixed-effects analysis was run on each participant with three condition-related regressors (congruent angry–neutral, incongruent angry–neutral, neutral–neutral), one invalid-trial regressor (responses that were missing, incorrect, and/or with outlier RTs), one baseline regressor (including filler trials), and 24 motion regressors. Regressors were convolved by the canonical hemodynamic response function, time-locked to the onset of face-pair. Following first-level analysis, participants meeting all three criteria (accuracy≥75%, motion<3mm, 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 two-way ANCOVA with time (BLN vs. OCM) and training (ABM vs. placebo) as IVs and scanner (old vs. new) and sibling pair (with vs. 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 anatomical regions of interest (ROIs) of the limbic-vlPFC circuitry, including left and right amygdala, insula, and vlPFC (Automated Anatomical Labeling[46]). Results were first thresholded at whole-brain voxel-level at $p<.005$ uncorrected. Small volume correction was then used within each of the a priori ROIs, and clusters with $p<.05$ family-wise-error corrected were identified as significant activation. The literature has identified the amygdala and vlPFC as responsive to threatening stimuli during 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] following ABM, accompanied by attenuated anxiety reactivity to laboratory stressors[33].

Next, to probe the specific patterns of the Time×Training interaction and control for potential between-group differences at BLN, percent-signal-change values (%SC) were extracted from clusters revealing significant Time×Training interaction for each participant and submitted to secondary ANCOVA analyses (Training as IV, BLN %SC and age as covariates, and OCM %SC as dependent variable) in SPSS (24.0.0.1, IBM, Armonk, NY).

Correlation Analysis. Bivariate Pearson's 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 if 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 (1) behavioral AB results of the 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 if BLN fMRI moderates Δanxiety (Table S5, Figure S3, available online), and if 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 baseline (Table S8, Figure S5, available online), and examination of the potential influence of visit order on the results (Table S9, available online); and (2) 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) revealed a significant training effect on OCM separation anxiety

(Figure 3), $F(1,76)=5.67$, $p=.02$, $\eta^2=.07$, with less anxiety in the ABM group, M(SD)= -0.05(0.58), than the placebo, M(SD)=0.04(0.65). No training effect was found for social anxiety, $F(1,76)=.15$, $p=.70$, $\eta^2=.00$. No age effects were observed (*p's*≥.40). See descriptions in Table S3, available online.

Insert Figure3

Second-level analysis of fMRI data (ABM=15, placebo=19) within a priori ROIs for the incongruent>congruent contrast identified three clusters showing a significant Time×Training interaction in 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 from each cluster. ANCOVAs revealed that with BLN %SC controlled, the training effect was significant on OCM %SC for clusters within right insula, $F(1,30)=5.83$, $p=.02$, $\eta^2=.16$, and left vlPFC, $F(1,30)=19.52$, $p=.00$, $\eta^2=.40$, and approaching significance in right amygdala, $F(1,30)=3.94$, $p=.06$, $\eta^2=.12$. The ABM group showed lower %SC at OCM than the placebo in right amygdala and right insula, and higher OCM %SC in left vlPFC. These results suggest that after controlling for group differences at baseline, active ABM and placebo lead to distinct patterns of neural change over time within the fronto-limbic system. No age effects were observed (*p's* ≥.16).

Insert Table1 and Figure4

Relations Between Behavioral, Anxiety, and Neural Measures

Table 2 presents correlation coefficients between variables across the two training groups, with bootstrapped 95% CIs reported. For behavioral AB, neither baseline nor Δ scores were correlated with any other variable (*p*'s≥.12). As expected, BIQ scores were positively correlated with baseline anxiety. Separation and social anxiety were correlated with each other, for both BLN and Δ. Baseline separation anxiety was positively correlated with baseline activation in insula, but with the CI containing zero. Importantly, among the difference scores, positive correlations were observed between Δseparation anxiety and Δamygdala/Δinsula, with all CIs above zero. Amygdala and insula were strongly correlated with one another for both BLN and Δ. ΔvlPFC was negatively correlated with Δinsula (greater vlPFC increases were accompanied by greater insula decreases), but again with the CI containing zero.

Insert Table2

Correlation analyses conducted within each training group did not yield any significant results, potentially due to the modest sample size of each group. However, we did observe a trend for a positive Δseparation anxiety–Δamygdala correlation in the ABM group, $r(13)=.51$, $p=.05$, $CI=-.11$-.81.

DISCUSSION

This study investigated potential ABM-induced reductions in anxiety in 9-12-year-old children with BI, a temperamental risk factor for anxiety. Adopting a double-blind 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 right amygdala and insula, but enhanced activation in vlPFC, following training.

ABM-related reductions in anxiety symptoms, both clinical and subclinical, 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 social anxiety, which is often the focus of the literature. A number of factors may have contributed to this finding.

First, anxiety was assessed by parental and child report using C-DISC-IV. The manifestation of anxiety symptoms may be driven by the daily "task demands" facing children. For 9-12-year-old children, a majority 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 to parents in structured clinical interviews.[48] This may be due to children's inability to identify or articulate pathological experiences, or their unwillingness to disclose themselves to an adult stranger.[48] As a result,

children's social anxiety symptoms, of which parents may 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 age 10 and 90% do so by age 13,[49] with its prevalence declining with age throughout adolescence. In contrast, the onset of social anxiety typically occurs during adolescence, within the 12-16 years range.[49] Separation anxiety also predicts the later emergence of,[50] and is often comorbid with,[49] social anxiety. Finally, 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 multi-method 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 BI-to-separation anxiety-to-social anxiety trajectory.

We found no ABM-related effect for behavioral AB nor 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 elevated their AB, but a second task training them to attend away from threat did not change AB. Roy et al.[53] reported heightened AB in clinically-anxious youth, whereas other studies failed to find similar patterns in anxious children.[54,55] Similarly, while Pérez-Edgar et al. found heightened AB in adolescents with childhood BI,[12] 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 may be a dynamic process differentially expressed 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 also been questioned.[58] Indeed, computing trial-level bias scores in a dot-probe dataset aggregated across six studies encompassing 364 participants ages 5 to 22 years did not find significant behavioral AB nor significant relations between AB and BI.[59] Behavioral dot-probe measures may not reliably capture individual differences in behavioral AB.

Therefore, examining more sensitive bio-neural measures, such as fMRI, is important for AB-related research.

While an ABM-related effect was not found in behavioral AB, the fMRI measurements were modulated by ABM. From BLN to OCM, the two 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 right amygdala and insula, and increased activation in left vlPFC. However, our current results cannot not rule out the possibility that the placebo task might have also affected the participants' neural activities, contributing to the observed effect. Future studies with larger sample sizes and/or additional control groups without any task may be helpful in further disentangling the effects of active ABM versus placebo. Regardless, our findings converge with the adult literature reporting ABM-related modulation of fronto-limbic functions, including amygdala and insula,[31,33] and/or ventral PFC.[32,33]

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

We also found an ABM-induced enhancement in vlPFC. In addition, our exploratory mediation analysis (see 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 PFC, among other prefontal subregions, may be closely related with limbic reactivity, playing a down-regulatory role in threat-evoked limbic hyperactivity.[10,13] Specifically, vlPFC resources may 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 (see Supplement 1, available online), suggesting a link between hypofunction of 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. While we found that ABM altered both symptomatic and fronto-limbic profiles, the underlying mechanism linking the two is unclear. To better understand the exact mechanism, future studies need to (1) recruit larger samples sufficiently powered to enable connectivity and mediation analyses, which would help demonstrate the directionality and related causal mechanism underlying ABM; (2) use multi-method assessments of BI anxiety to identify the risk and symptom targets for ABM; and (3) conduct longitudinal research with multiple posttraining 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.

Lay Summary

Children with behavioral inhibition (i.e., temperamental shyness) are at greater risk for developing anxiety disorders. This study introduces a computerized attention modification task, which trains children to shift attention away from threatening information, as an effective tool to mitigate shy children's anxiety symptoms and eventually prevent them from developing subsequent anxiety disorders.

Clinical Guidance

- Developing targeted, effective, and economical tools to prevent at-risk children from developing clinically significant disorders is of great significance.
- This study provides important empirical evidence on using attention modification as a potential prevention tool for children at risk for anxiety disorders.
- Further empirical research examining the long-term effect of attention modification in preventing anxiety disorders is warranted to better inform clinical decisions and practices.

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

A priori ROIs	**Small volume correction**					**Mean % signal change**		
	Peak MNI coordinates	# of voxels	*F*	*Z*	p_{FWE}	*Time*	ABM	Placebo
Right amygdala (87 voxels)	18, -1, -17	8	11.56	2.91	.05*	*BLN*	.71(1.11)	-.49(1.37)
						OCM	.00(.89)	.64(1.44)
Right insula (597 voxels)	36, 11, -14	14	17.84	3.56	.04*	*BLN*	1.27(1.95)	-.68(1.88)
						OCM	.40(1.24)	1.06(1.22)
Left vlPFC (809 voxels)	-39, 56, -8	13	22.25	3.92	.02*	*BLN*	-.28(.60)	.02(.40)
						OCM	.43(.48)	-.18(.42)

Note: ABM = attention bias modification; BLN = baseline; MNI = Montreal Neurological Institute; OCM = outcome; ROI = region of interest; vlPFC = ventrolateral prefrontal cortex.

Table 2. Pearson's Bivariate Correlation Across the Two Training Groups

		BIQ (*BLN*)	***BLN***			
			1.	2.	3.	4.
BLN	1.Separation Anxiety	**.33**(81) [.12, .55]**				
	2.Social Anxiety	**.33**(81) [.09, .53]**	**.27*(81) [.06, .47]**			
	3.Right Amygdala	.18(32) [-.15, .44]	.28(32) [-.17, .63]	-.17(32) [-.53, .25]		
	4.Right Insula	-.01(32) [-.31, .27]	**.38*(32) [-.08, .69]**	-.22(32) [-.51, .07]	**.75**(32) [.58, .88]**	
	5.Left vlPFC	-.03(32) [-.30, .23]	-.13(32) [-.49, .13]	-.20(32) [-.45, .09]	.17(32) [-.11, .44]	-.13(32) [-.43, .26]

		BIQ (*BLN*)	**Δ**			
			1.	2.	3.	4.
Δ	1.	**-.27*(78) [-.44, -.09]**				
	2.	-.17(78) [-.40, .08]	**.27*(78) [.02, .49]**			
	3.	-.18(32) [-.51, .15]	**.56**(32) [.11, .66]**	-.03(32) [-.29, .29]		
	4.	.03(32) [-.36, .37]	**.51**(32) [.05, .67]**	-.15(32) [-.43, .20]	**.65**(32) [.26, .89]**	
	5.	.09(32) [-.17, .36]	-.08(32) [-.45, .19]	.08(32) [-.24, .40]	-.17(32) [-.48, .17]	**-.40*(32) [-.64, .01]**

Note: *df* is shown in parentheses, 95% bias-corrected-accelerated confidence interval (generated by 1000 bootstrapping in SPSS) in brackets, and significant correlations in bold. BIQ = Behavioral Inhibition Questionnaire; BLN = baseline; vlPFC = ventrolateral prefrontal cortex.
$^{**}p<.005$, $^{*}p<.05$

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.

Figure 2. The dot-probe paradigm. Note: The active attention bias modification (ABM) task includes incongruent angry-neutral condition only (and neutral-neutral condition); the placebo task includes incongruent and congruent conditions of equal number of trials (and neutral-neutral condition). fMRI = functional magnetic resonance imaging.

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

Figure 4. Three brain clusters showing significant time×training interaction, and the extracted percent signal change (%SC) values for attention bias modification (ABM; n=15) and placebo (n=19) at baseline (BLN) and outcome (OCM). Note: vlPFC = ventrolateral prefrontal cortex.