Patterns of Neural Connectivity During an Attention Bias Task Moderate Associations Between Early Childhood Temperament and Internalizing Symptoms in Young Adulthood

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Background: Biased attention to threat is found in both individuals with anxiety symptoms and children with the childhood temperament of behavioral inhibition (BI). Although perturbed fronto-amygdala function is implicated in biased attention among anxious individuals, no work has examined the neural correlates of attention biases in BI. Work in this area might clarify underlying mechanisms for anxiety in a sample at risk for internalizing disorders. We examined the relations among early childhood BI, fronto-amygdala connectivity during an attention bias task in young adulthood, and internalizing symptoms, assessed in young adulthood.

Methods: Children were assessed for BI at multiple age points from infancy through age seven. On the basis of a composite of observational and maternal report data, we selected 21 young adults classified as having a history of BI and 23 classified as non-BI for this study ($n = 44$). Participants completed an event-related functional magnetic resonance imaging attention-bias task involving threat (angry faces) and neutral trials. Internalizing symptoms were assessed by self-report and diagnostic interviews.

Results: The young adults characterized in childhood with BI exhibited greater strength in threat-related connectivity than non-behaviorally inhibited young adults. Between-group differences manifested in connections between the amygdala and two frontal regions: dorsolateral prefrontal cortex and anterior insula. Amygdala-insula connectivity also interacted with childhood BI to predict young adult internalizing symptoms.

Conclusions: Behavioral inhibition during early childhood predicts differences as young adults in threat and attention-related fronto-amygdala connectivity. Connectivity strength, in turn, moderated the relations between early BI and later psychopathology.

Key Words: Attention bias, functional connectivity, Granger causality, imaging, internalizing problems, temperament

Behavioral inhibition (BI) is a temperament characterized by fear of novelty in infancy (1,2), social reticence in childhood (3,4), and internalizing difficulties in later life (5–8). However, only a subset of behaviorally inhibited children manifest psychopathology as adults (9). Unique patterns of neural connectivity might impact the relations between early childhood BI and later-emerging socio-emotional maladjustment. This study examined the neural correlates of attention bias to threat in young adults with a childhood history of BI. The study then considered the degree to which these correlates moderate the relations between childhood BI and adult internalizing symptoms.

Anxiety and depression are associated with biased orienting toward threat (10–13), which might play a causal role in the emergence of socio-emotional difficulties (14,15). Threat bias might moderate the long-term outcomes of BI, strengthening the link between early BI and later social withdrawal (16,17). Imaging studies have delineated the neural circuitry supporting biased orienting to threats in anxious individuals (18–20), but no imaging studies have examined attention biases in BI. Such work might help explain the interrelations among childhood BI, adult maladjustment, and the neural correlates of attention bias.

Attention orienting engages brain circuitry encompassing the amygdala and three areas of the prefrontal cortex (PFC): ventrolateral PFC; insula; and dorsolateral prefrontal cortex (dlPFC) (21,22). Individual differences in this circuitry are evident during a standard attention bias task—the dot-probe task (11). To date, four dot-probe functional magnetic resonance imaging (fMRI) studies (18,19,23,24) and a fifth magneto-encephalography study (20) have examined threat bias in adolescent anxiety disorders. One additional study examined these mechanisms in adults with post-traumatic stress disorder (25). Together, these studies show that anxiety is associated with perturbed activation patterns in the amygdala and PFC, although their precise nature varies with participant-related and study-design features (21,26,27).

Most dot-probe studies compare individual activation levels in response to the presentation of angry faces, noting perturbations in the amygdala and PFC among anxious versus healthy participants. However, recent dot-probe imaging studies examined fronto-amygdala connectivity, better reflecting the networks supporting observed behavior (19). The current study extends

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this work by comparing the strength and directionality of connectivity in young adults initially assessed for BI as children. Specifically, we tested the hypothesis that fronto-amygdala connectivity differs in young adults with a history of early-childhood BI, relative to participants with no such history. Given prior findings (16,17), a second analysis considered the degree to which connectivity impacts the relations between early-childhood BI and young-adult internalizing problems (28). Prior work (29–31) suggests that BI is linked to unique neural responses to both aversive and appetitive stimuli. Thus our analyses considered relations both with threats (12) and with positive stimuli, to evaluate specificity of the findings for threat and extend prior work on reward responding (32).

Methods and Materials

Participants

Fifty-six young adults participated, drawn from 153 individuals initially selected at 4 months (33,34) and behaviorally assessed for BI at ages 14 months, 24 months (33,35), 4 years, and 7 years (33,36). Maternal ratings were collected at each time point (37,38). A composite score was used to index stable BI, on the basis of observations and maternal-report data from each time point (Supplement 1) (16). Higher scores reflect higher levels of BI (Full cohort sample: mean = .019, SD = .60; Cronbach's $\alpha = .83$).

Potential participants were selected from the larger cohort on the basis of childhood BI to reflect the span of scores and were invited to participate in the fMRI study. Individuals taking psychotropic medications or presenting with acute psychopathology in need of urgent treatment were excluded, although other psychopathology was permissible (see following). Fifty-six participants were included in the final sample. Of these, 12 did not provide usable data, due to excessive movement, technical difficulties, or low task accuracy (<80% correct). Of the remaining 44 participants, 21 were behaviorally inhibited, and 23 were non-BI as children.

There were no significant differences in BI scores, gender, or IQ between the included and excluded participants (p values > .14). Included BI and non-BI participants did not differ in gender or IQ (p values > .15) (Table 1). Participants were screened with the Structured Clinical Interview for DSM Disorders (39), revealing current psychiatric diagnoses in five participants: major depressive disorder (two BI; one non-BI); and anxiety (one BI and one non-BI). Removing these five individuals from the data analyses did not affect the findings; thus, they were included in the analyses.

Current internalizing symptoms were rated by participants with Achenbach's Adult Self Report (40). We focused on the broad-band internalizing scale, because of the low incidence of ongoing diagnoses and previous links between BI and internalizing difficulties (41). The use of the broad-band scale also minimized Type I errors that would accrue from individual tests for the many measures of anxiety and depression that can be obtained.

The study was approved by the institutional review boards at the National Institute of Mental Health, Bethesda, Maryland, the University of Maryland, College Park, and George Mason University, Fairfax, Virginia. All participants provided informed consent before the study.

Dot-Probe Task

We used the same procedures as Monk *et al.* (18). Each trial began with a 500-msec fixation point (Figure 1) followed by a face pair of the same individual (42) displaying an angry/neutral, happy/neutral, or neutral/neutral expression (500 msec). A pair of dots then appeared in one hemi-field (1100 msec), and participants indicated by button-press whether the dots were vertical or horizontal. All participants completed 24 practice trials outside of the scanner before the experiment.

The scanner task involved 192 trials (intertrial interval average 400 msec; 200–600 msec min/max) divided across two runs, each with five trial types: 1) angry/neural face pair followed by a dot pair in the same position as the angry face (congruent); 2) angry/neutral face with a dot pair in the position of the neutral face (incongruent); 3) happy/neutral face pair with congruent dot presentation; 4) happy/neutral face pair with incongruent dot presentation; 5) neutral/neutral face pair with dot presentation. There were 24 trials for each condition across both runs, except for neutral/neutral trials, which were shown 48 times, providing comparisons for emotion conditions. Forty-eight blank trials of the same duration as the other five trial types were included to introduce random jitter and provide an additional baseline. For each participant, trial order was randomly determined. Emotional faces and dots were displayed an equal number of times to each hemi-field. Twelve separate actors were used, and each appeared in all five conditions.

Task stimuli were viewed with mirrors on the head coil. Foam padding constrained head movement. A custom built two-button box recorded behavioral data.

Behavioral analyses and results appear in Supplement 1.

Table 1. Demographic Characteristics and Behavioral Results

	Included Participants		Excluded Participants	
	BI ($n = 21$)	Non-BI ($n = 23$)	BI ($n = 5$)	Non-BI ($n = 7$)
Gender	12 M/9 F	8 M/15 F	3 M/2 F	3 M/4 F
Age	19.91 (.86)	20.03 (.70)	20.1 (.87)	20.1 (.81)
IQ	114.71 (8.81)	116.10 (10.42)	113.0 (11.69)	109.0 (9.22)
BI Score	.61 (.72)	−.43 (.24)	.38 (.46)	−.60 (.45)
Internalizing Score	8.52 (7.51)	8.35 (5.48)	5.80 (5.70)	13.67 (11.59)
Accuracy Rate	89.29% (7.17)	88.80% (10.22)	78.39% (12.93)	81.02% (12.74)
Reaction Time (msec)	766.56 (64.76)	776.77 (84.23)	824.10 (84.99)	802.57 (84.19)
Threat Bias Scores	13.45 (32.43)	6.29 (30.69)	−6.23 (28.77)	8.50 (36.64)
Happy Bias Scores	2.23 (31.17)	−6.49 (39.89)	18.21 (34.06)	−3.00 (36.23)

Demographic characteristics and behavioral results for included and excluded participants for both the behavioral inhibition (BI) and non-BI groups. All calculations are reported as the mean unless otherwise noted. The SDs (±) are presented in parentheses.

F, female; M, male.