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.

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): ventro-lateral 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

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 α = .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.
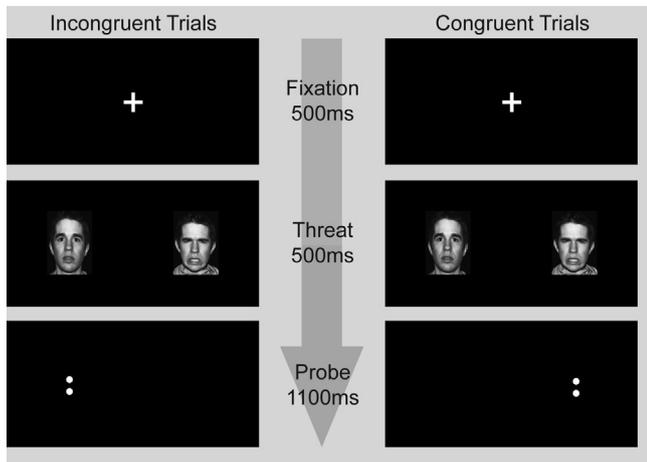
Figure 1. Example of visual task illustrating congruent and incongruent threat trials. The only difference between trial types is the location of the probe (dots) relative to the angry face. In congruent trials the probe appeared on the same side as the angry face (threat), for incongruent trials the probe appeared on the same side as the neutral face. Trials with happy/neutral and neutral/neutral face pairs were also shown. The same actor always appeared for the two expressions within a single trial. Here the dots are vertical; however, in half of the trials the dots were horizontal.

fMRI Analysis

Data Acquisition. The first 27 participants were scanned with a Signa VH/i 3 Tesla scanner (General Electric, Waukesha, Wisconsin). The final 17 participants underwent scanning on a GE Signa HDx 3 Tesla scanner, due to scanner decommissioning. Both scanners used the same GE head coil. Analyses found no significant differences in blood oxygen level-dependent activity across scanners in the regions of interest (ROIs) for this study (.60 < *p* values < .95). Each brain volume consisted of 36 interleaved slices 2.6-mm thick, acquired in the axial plane with a T2*-weighted echo-planar sequence with a repetition time (TR) of 2300 msec, echo time of 25 msec, and flip angle of 90. Voxel dimension was 2.5 × 2.5 × 2.6 mm. Matrix size was 96 × 96, and field of view was 24 cm. To allow for signal stabilization, four acquisitions were obtained before task onset. A high-resolution structural image was also acquired for each participant with a T1-weighted standardized magnetization prepared spoiled gradient recalled echo sequence: 124 1.2-mm slices; 8100-msec TR; 32-msec echo time; 15° flip angle; 256 × 256 matrix; 24-cm field of view.

Preprocessing. Functional imaging data were analyzed with Analysis of Functional and Neural Images (AFNI) software (43), including slice-time correction, motion correction, and 6-mm full-width half-maximum smoothing kernel. For motion correction, we censored TRs with motion in excess of the Euclidean norm of .8 mm. The echo planar imaging time series of each participant was manually placed in Talairach space and normalized by the voxel-wise temporal mean so that the effect estimates could be interpreted as percentage signal change. Only correct and within-range (150 msec < reaction times < 1100 msec) trials were included in the analyses.

Regression. Preprocessed time series data were analyzed by multiple regression in a model including six regressors of interest; six regressors for residual motion in x, y, and z planes and in the yaw, pitch, and roll dimensions; and two regressors for baseline and linear trends for each of the runs.

Regressors of interest comprised emotion type and dot pair location, modeling angry-congruent, angry-incongruent, happy-congruent, happy-incongruent, and neutral trials separately. They were created through convolving the stimulus timing with a γ variate function that modeled a prototypical hemodynamic response (44). Idealized signal time courses were estimated on the basis of even onset times, with blank trials providing implicit baseline. An additional regressor modeled excluded nuisance (incorrect, out-of-range, and null response) trials.

Analysis. Details of our initial activation analysis for angry, happy, and neutral faces are presented in Supplement 1. Briefly, bilateral amygdala activation occurred for the angry and neutral trials across the entire sample (BI and non-BI together). These results support our use of anatomically delineated amygdala seeds in the psychophysiological interaction (PPI) analysis.

PPI Analysis. This analysis delineated between-group differences in amygdala-PFC connectivity in the context of angry-versus-neutral trials with established procedures (45,46). At the individual level, the first eigenvariate time series incorporated the anatomically defined amygdala, as defined by the Talairach atlas, as the "seed" in two separate analyses for the right amygdala and left amygdala on the basis of the initial fMRI group analysis. These time series were deconvolved with a presumed hemodynamic response function before a PPI term was created between the angry/neutral pair versus neutral/neutral pair conditions. This maps differences in amygdala-PFC connectivity across the angry, relative to neutral, dot-probe trials. Group differences were analyzed.

Post hoc analyses extracted mean connectivity between the amygdala and voxels identified in the insula and the dlPFC. These data were then used to both decompose significant results and examine associations with concurrent internalizing symptoms. The interrelations between the variables of interest were examined in a moderated mediation model (28) (Supplement 1).

Granger Causality. Regions that differed between groups in the PPI analysis were submitted to a secondary Granger causality analysis designed to model the strength and direction of connectivity among the amygdala, dlPFC, and insula—PPI maps only magnitude differences in connectivity among nodes. This analysis began by selecting as nodes the anatomically delimited whole amygdala and the two PFC regions functionally defined from the PPI analysis. Directionality was assessed in Granger causality models, with vector autoregressive modeling that estimated lag effects by capturing the temporal and cross-regional interactions in the designated network (47). Lag effects for each condition formed the basis for inferring causality between experimental manipulation and regional activation.

Statistics were determined with a two-step process at the individual and group levels. At the individual level, the average time series for each participant in each condition was extracted, yielding two average time series for each ROI; these were submitted to the AFNI program 1dGC, which estimated the 1-TR lag path coefficients for each condition and ROI separately. At the group level, the path coefficients among the regions in the network were compared between the BI and non-BI groups. The 1dGC program tested group differences in the direction of the path coefficients between nodes in each condition separately, plus any possible differences between the conditions. In this analysis, data from 12 participants (4 BI; 8 non-BI) were omitted, due to excessive time-period censoring.

Statistical Thresholds. For all analyses, the statistical threshold was set at the cluster-level *p* = .05, family-wise-error–corrected for multiple comparisons. This statistical threshold

was accomplished with a voxel-wise $p < .005$ threshold, followed by cluster thresholds set through Monte Carlo simulations with 3dClustSim in AFNI.

Results

fMRI Results

Findings from the initial activation and behavioral analyses are noted in Supplement 1.

PPI. Analyses of between-group differences in fronto-amygdala connectivity identified two right-hemisphere clusters surpassing statistical thresholds, one in the dlPFC (x, y, z = 49, 4, 21; 14 voxels) and the other in the anterior insula (x, y, z = 36, 14, 6; 14 voxels) (Figure 2). Both findings reflected significantly greater negative right fronto-amygdala connectivity in response to angry-versus-neutral contrast in BI relative to non-BI particpants, with large effects (dlPFC: $t_{42} = -3.81$, $d = -1.15$; insula: $t_{42} = -4.03$, $d = -1.23$). Weights for the angry-versus-neutral PPI contrast values were extracted for right amygdala-insula and right amygdala-dlPFC connectivity to decompose these effects and to correlate with behavioral measures.

Specifically, BI participants exhibited greater differences in connectivity, whereas the non-BI group did not show significant connectivity. For the BI group, this pattern resulted from positive connectivity to neutral faces (dlPFC: mean = 5.38 ± 7.81; insula: mean = 5.71 ± 13.25) and negative connectivity to angry faces (dlPFC: mean = −1.13 ± 6.01; insula: mean = −1.94 ± 8.37). Among non-BI adolescents connectivity to angry (dlPFC: mean = .83 ± 7.28; insula: mean = 3.34 ± 12.89) and neutral (dlPFC: mean = −1.51 ± 7.81; insula: mean = −1.47 ± 10.18) faces were nonsignificant in both ROIs. This pattern generated the

Figure 2. Psychophysiological interaction activation in the behavioral inhibition group (vs. non-behavioral noninhibition) for angry relative to neutral faces. Fronto-amygdala connectivity revealed between-group differences in the right (R) dorsolateral prefrontal cortex (dlPFC) (top panel; x, y, z = 49, 4, 21; 14 voxels) and the right insula (bottom panel; x, y, z = 36, 14, 6; 14 voxels). Activation is shown at $p = .005$.

significantly greater negative contrast weight in the angry-versus-neutral condition for the BI (dlPFC: mean = −3.81 ± 4.88; insula: mean = −4.45 ± 5.08) relative to non-BI group (dlPFC: mean = 1.54 ± 4.41; insula: mean = 3.25 ± 7.27), explaining the opposite connectivity signs seen between the two groups.

Reinforcing the categorical group analysis, fully continuous individual BI scores across the full sample were correlated with the extracted coefficients for both amygdala-dlPFC ($r = −.43$, $p = .003$) and amygdala-insula ($r = −.49$, $p = .001$) connectivity in the angry-versus-neutral contrast (Figure S1 in Supplement 1). Self-reported internalizing in adulthood also correlated with amygdala-dlPFC ($r = −.32$, $p = .04$) but not amygdala-insula ($r = −.25$, $p = .12$) connectivity. The correlation between BI and self-reported internalizing problems was not significant ($r = .11$, $p = .49$).

For the happy-neutral analyses, no between-group difference in connectivity was found above our statistical thresholds in the main ROIs. However, an area of the posterior frontal cortex (x, y, z = 29, −26, 46, $t = 5.53$) survived a whole-brain-corrected threshold. In contrast to findings for threat trials, this difference reflected greater connectivity in the non-BI versus BI group.

Granger Causality. Granger causality analyses extended results from PPI by modeling the strength and direction of connectivity among amygdala, dlPFC, and insula nodes. Significant group differences were found for the strength of the connection for the dlPFC-insula path coefficients, for both the angry (+.24; $p < .05$) and neutral (+.20; $p < .05$) trials. These differences reflected a significant, positively weighted dlPFC-insula path in the BI group, both for angry (+.33, $p < .001$) and neutral (+.30; $p < .001$) trials, with no significant path coefficients in the non-BI group.

Moderated Mediation Model. Finally, exploratory moderated-mediation models examined the relations among early temperament, connectivity, and adult self-reported internalizing problems (Table 2; Figures S2 and S3 in Supplement 1).

For amygdala-insula connectivity, the direct path between early BI and connectivity was significant ($t = −3.88$, $p < .001$), whereas the connectivity-internalizing ($t = −1.67$, $p = .10$) and the BI-internalizing ($t = −1.05$, $p = .30$) paths were nonsignificant. However, the interaction between BI and insula connectivity significantly predicted internalizing symptoms ($t = −2.03$, $p = .05$), reflecting stronger relation in the BI than the non-BI group.

For amygdala-dlPFC connectivity, the direct path between BI and connectivity was significant ($t = −2.84$, $p = .007$), as was the connectivity-internalizing path ($t = −2.01$, $p = .05$) but not the BI-internalizing path ($t = −1.25$, $p = .22$). Thus, a mediation relation was not supported. Although resembling the pattern with BI and insula connectivity, the BI-dlPFC connectivity interaction was not significant ($t = −1.73$, $p = .09$).

Discussion

Behaviorally inhibited children are at risk for internalizing difficulties in adolescence and young adulthood. The current study suggests for the first time that dynamic neural patterns in threat processing might support these documented developmental relations. For two frontal regions (dlPFC and anterior insula), childhood BI was associated with negative fronto-amygdala connectivity, evident across trials containing threat faces compared with neutral faces. In addition, connectivity patterns moderated the relations between childhood BI and

adult internalizing symptoms. These relations suggest that negative fronto-amygdala functional connectivity places individuals with a history of BI uniquely at risk. Our analyses with happy faces suggest that this pattern is specific to threat processing. As such, previously observed perturbations in reward processing might not extend to attention biases (29).

Most research on the neural correlates of anxiety has quantified individual differences in risk on the basis of measures of behavior acquired contemporaneously with measures of brain function (21,23). The current study, however, examines young adults classified on the basis of the degree to which they manifested the temperament of BI as young children. Brain function was examined more than 10 years after the last assessment of temperament. Our findings suggest that early-life temperament exhibits a unique relation with brain function that endures into adulthood, even after the initial behavioral or phenotypic markers are no longer evident (48). Moreover, these long-term associations shed light on factors that shape adaptive functioning in adulthood. The current study builds on accruing evidence of the long-term imprint of childhood temperament on amygdala (49) and striatal (29) circuitry as well as on the central role of attention in socioemotional development (50). Our findings in this relatively healthy sample echo prior research with clinically anxious participants noting prefrontal dysfunction, including the insula and dlPFC (18,19,23–25). Therefore, these data suggest underlying mechanisms of risk that might inform our understanding of the neural underpinnings of anxiety.

Prior fMRI studies using the dot-probe task differ in important respects from the current study. Those studies compared frontal function in groups differing on concurrent levels of anxiety, to the extent where overt psychopathology was manifest, and found differences in mean levels of activation during threat trials. The current study found differences in fronto-amygdala connectivity as a function of early BI rather than direct-group differences in activation across standard condition-based contrasts. In particular, we found greater negative connectivity for both the amygdala-dlPFC and amygdala-insula circuits among young adults with a history of BI, in line with one previous study of adolescent generalized anxiety disorder (19). This pattern suggests that there might be an altered inhibitory response among individuals with a history of BI in brain regions supporting the regulation of negative affect.

Of note, the current study also examined the direction of functional connections that manifest during the dot-probe task. We found a stronger input from the dlPFC to the insula in BI relative to non-BI participants. The insula possesses rich anatomical connections with both the amygdala and the dlPFC; the latter

two are less strongly connected. Thus, these findings suggest that frontal regions might uniquely modulate between-group differences in amygdala function through connections from the dlPFC to the insula. The Granger causality method thus captured individual differences in the delayed effects of activation as the PFC works to modulate initial reactivity.

The available longitudinal data allow the current study to delineate relations among early-childhood temperament, brain function, and internalizing symptoms in young adulthood. Prior work in this and other samples found associations between early-childhood BI, internalizing difficulties, and adolescent anxiety (9,51). Supporting these relations, behavioral attention biases during the dot-probe task to threat linked early BI to subsequent social withdrawal (16,17). Here, our exploratory analysis examined whether the neural correlates of the task display a similar relation. A mediation model was only partially supported. Although amygdala-dlPFC connectivity was significantly associated with both BI and internalizing symptoms, BI and symptom levels did not correlate in this relatively small sample. Rather, the data suggested that amygdala-insula connectivity moderates the link between early BI and later socioemotional difficulties, consistent with prior research noting moderation across various measures of information processing (52–54). Although statistical significance was only evident for amygdala-insula connectivity, the direction of effects was the same for amygdala-dlPFC connectivity.

No evidence emerged for temperament-related differences in amygdala function (Supplement 1); this was not unexpected. Individual differences in amygdala function are sensitive to relatively subtle variations in task parameters. Prior studies finding enhanced amygdala activation in youth characterized in childhood with BI (49) used tasks on which anxiety disorder patients also exhibit amygdala hyper-activation (46). In the current dot-probe paradigm, we employed 500-msec threat-cue exposures. Monk *et al.* (18) found no differences in amygdala activation between clinically anxious and healthy adolescents with the same protocol.

The current study has some limitations. The use of two scanners was an unavoidable limitation, although analyses revealed no evidence that this influenced findings. Moreover, by introducing variability, this limitation is more likely to produce Type II than Type I errors. Most importantly, the current study was based on a small sample, with low rates of ongoing psychopathology. Thus, we were not able to compare participants with and without psychopathology who also were with or without a history of BI to examine the degree to which fronto-amygdala connectivity might moderate risk among individuals characterized in childhood with BI.

Table 2. Predicting Internalizing Symptoms in Young Adulthood

	BI-PPI (a)		PPI-INT (b)		BI-INT (c')		BI × PPI-INT (ab)	
	β (SE)	t	β (SE)	t	β (SE)	t	β (SE)	t
Amygdala-dlPFC	−2.99 (1.05)	−2.84[a]	−.40 (.20)	−2.01[b]	−2.38 (1.91)	−1.25	−.46 (.27)	−1.73[c]
Amygdala-Insula	−5.11 (1.32)	−3.88[a]	−.27 (.16)	−1.67[c]	−1.84 (1.74)	−1.05	−.40 (.20)	−2.03[b]

Predicting internalizing symptoms in young adulthood with measures of early temperament (behavioral inhibition [BI] composite) and neural connectivity (amygdala-dorsolateral prefrontal cortex [dlPFC] and amygdala-insula) in young adulthood. The table presents the path coefficients (standard errors) and *t* values for the separate moderated mediation models. a, b, c', and ab represent the paths depicted in Figures S2 and S3 in Supplement 1.

INT, internalizing raw score from Adult Self Report; BI × PPI, interaction between BI and PPI; PPI, connectivity measure.

[a]$p < .01$.
[b]$p < .05$.
[c]$p < .10$.

The current findings set the stage for future work in which longitudinal brain imaging studies might assess at-risk individuals. Given the pattern of findings in the current study, this approach might powerfully predict outcome among behaviorally inhibited individuals. Recent work (19,55) suggests that our noted pattern of activation and connectivity might vary with the length of exposure to threat (e.g., increased amygdala response to masked faces). We do not know whether this shift in neural functioning to rapid presentation is similarly associated with variations in observed patterns of socioemotional functioning. An examination in progress will help elucidate these questions.

Finally, recent work suggests that attention biases to threat might play a causal role in the emergence of internalizing difficulties (56). Indeed, attention-retraining techniques might alter long-term risk for anxiety, potentially through effects on the PFC (15,18,24,57,58). A number of open questions remain, because it is not clear whether effects are reliant on specific training paradigms, are transferrable across contexts, or will impact risk for disorder, as opposed to current symptomatology. Importantly, the neural mechanisms underlying attention-training are, at the moment, unclear (12). The current data suggest that assessments should focus on shifts in fronto-amygdala connectivity. Current work taking advantage of this unique sample might address these open translational questions.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2013.01.036.

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