Developmental Change in Amygdala Reactivity during Adolescence: Effects of Family History for Depression and Stressful Life Events

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Abstract

Objective—Though heightened amygdala reactivity is observed in patients with major depression, two critical gaps in our knowledge remain. First, it is unclear whether heightened amygdala reactivity is a premorbid vulnerability or consequence of the disorder. Second, it is unknown how and when this neural phenotype develops. The objective of this study was to address these gaps by evaluating developmental change in threat-related amygdala reactivity in adolescents at high or low risk for depression based on family history, before the onset of disorder.

Method—Adolescents (initially aged 11–15 years) completed an fMRI paradigm that elicited threat-related amygdala reactivity at baseline and again 2 years later. After quality control, data from 232 adolescents at Wave 1 and 197 adolescents at Wave 2 were available. Longitudinal data (meeting quality control at both waves) were available for 157 of these participants. Change in amygdala reactivity was assessed as a function of family history of depression and stressful life event severity.

Results—Threat-related amygdala reactivity increased with age in those with a positive family history regardless of the severity of life stress reported, and in adolescents with a negative family history when they reported relatively severe life stress. Critically, these changes in amygdala reactivity with age occurred in the absence of clinical disorder or increases in depressive symptoms.

Conclusions—These results suggest that heightened amygdala reactivity emerges during adolescence prior to the development of depression as a function of familial risk or, in the absence of familial risk, stressful life events.

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Introduction

Heightened amygdala reactivity to negative emotional stimuli is commonly observed in patients with major depressive disorder (1, 2). However, the extent to which such amygdala reactivity is a premorbid risk factor for the emergence of disorder remains unclear. Cross-sectional studies reporting increased amygdala reactivity in patients compared with controls cannot determine if this reflects a premorbid risk factor or pathophysiologic consequence of disorder. Prospective evaluation of amygdala reactivity in individuals prior to disorder is thus necessary to determine if this neural phenotype represents a premorbid risk factor.

Positive family history of psychopathology represents a robust and replicated individual risk factor for depression (3–5). Thus, a prospective neuroimaging study of individuals at differential familial risk for major depressive disorder represents a viable strategy for evaluating amygdala reactivity as a premorbid risk factor. Positioning such a prospective study during the transitional developmental window of adolescence, which marks the beginning of a period of heightened risk for the development of mood disorders (6–7), allows for assessment of neural markers prior to the emergence of disorder but within a relatively short temporal frame that allows for mapping of these markers onto subsequent psychopathology.

To date, only a handful of studies have examined differences in neural function associated with familial risk (8–13), with several reporting heightened amygdala reactivity in those at increased risk for depression. For instance, adolescents at familial risk for depression evidence increased amygdala reactivity during sad mood induction (8) and viewing of fearful facial expressions (9). However, sample sizes have been small, age ranges have been wide, there has not been explicit consideration of current depressive symptoms, and due to the cross-sectional nature of these studies, it is still unknown how this potential neural risk marker emerges.

Identifying the developmental emergence of neural phenotypes associated with risk can inform efforts for early risk detection and intervention. Research on structural brain development suggests that developmental trajectories may be more predictive of outcomes than a single measurement at one time point (14). Moreover, Casey and colleagues (15) proposed that developmental trajectories can serve as endophenotypes when examining the influence of genetic risk on psychopathology. Identifying the timing and nature of atypical development of amygdala reactivity will also be critical in advancing our ability to predict, and ultimately prevent, the emergence of clinical disorder. Nevertheless, the longitudinal development of amygdala reactivity has not been characterized in a high-risk cohort.

One hypothesis suggests that the heightened amygdala reactivity associated with depression and other internalizing disorders may emerge due to altered trajectories of neural development during adolescence (16). Specifically, cross-sectional studies indicate that typical development in adolescence entails a decrease in amygdala reactivity to emotional facial expressions with age (17, 18). This therefore led us to predict that adolescents at familial risk for depression would fail to evidence this typical decline in reactivity.

Although family history of depression is a robust predictor of risk for disorder, many individuals will develop depression without having a family history. For these individuals, environmental stressors such as childhood maltreatment and stressful life events appear to play a critical role in increasing vulnerability for the disorder (19–21). Childhood maltreatment and adolescent life events are associated with heightened amygdala reactivity to negative stimuli (22, 23), suggesting that these may impact amygdala development. Therefore, we also examined the effect of these risk factors on the development of amygdala function.

While there is evidence for main effects of family history and life stress, no work yet has examined the interaction of these risk factors on amygdala reactivity. On the one hand, some evidence indicates that life stress may further compound vulnerability in individuals with a family history for disorder (24). On the other hand, high amounts of life stress may not be necessary for individuals with a positive family history to develop depression. Indeed, individuals who develop depression but have a negative family history for disorder are more likely to report experiencing a life event prior to the onset of disorder compared to individuals with a positive family history (25). Likewise, unaffected adult relatives with a positive family history of depression report higher depressive symptoms than individuals with a negative family history, but this association is not moderated by early life stress (26). Thus, individuals with a family history for disorder may evidence altered amygdala development even when experiencing relatively low levels of life stress.

In the present paper, we examine the development of amygdala reactivity in adolescents at high or low risk for disorder as a function of family history of depression, and the moderating effects of stress. Individuals were on average 13 and 15 years old at the first and second waves, respectively. Given that the peak period of onset for major depression in individuals with a positive family history is 15 to 20 years old (4, 5), we expected to observe differences in amygdala reactivity before the emergence of categorical disorder, in line with our hypothesis that increased amygdala reactivity is a premorbid neural biomarker of risk. Based on the developmental model proposed above, the following hypotheses were examined. First, threat-related amygdala reactivity will vary as a function of familial risk, with low-risk adolescents from families with no history of depression exhibiting decreases in reactivity with age, whereas high-risk adolescents with a positive family history will exhibit no change or an increase in reactivity with age. Second, individuals with higher levels of childhood and adolescent life stress will also fail to show declines in amygdala reactivity with age, and these effects may differ based on presence or absence of a family history for disorder. Importantly, to confirm that differences in amygdala reactivity are premorbid, we examined these hypotheses in our full sample and in a subsample which excluded participants diagnosed with an internalizing disorder subsequent to their enrollment in our study.

Methods

Participants

Participants were recruited as part of the Teen Alcohol Outcomes Study (TAOS), the aim of which is to examine the association between the development of depression and alcohol use

disorders in adolescence. Sampling and recruitment procedures for the TAOS have been described in detail previously (27, 28). After complete description of the study to the participants, parents provided written informed consent and participants provided assent following procedures approved by the Institutional Review Board at the University of Texas Health Sciences Center San Antonio. Adolescents were 11–15 years old during the first wave of data collection. Inclusion criteria for the high risk group were the presence of a first- and second-degree relative with a history of major depressive disorder. Inclusion in the low risk group required that participants have no first- and second-degree relatives with a history of depression, consistent with our prior research (4). Additional inclusion criteria required that participants were free of psychiatric diagnoses at the baseline assessment; the one exception was that an anxiety diagnosis was permitted in the high risk group. Diagnoses were assessed through structured clinical interviews with the adolescent and parent separately using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (29). Participants were also excluded if they met criteria for a substance use disorder or reported any binge drinking at baseline following National Institute on Alcohol Abuse and Alcoholism guidelines.

Participants were re-contacted annually to complete diagnostic interviews and questionnaire measures, and underwent a follow-up fMRI during the third wave of data collection, although a small portion (14%) completed the second fMRI at the fourth wave. Mean time between first and second scan was 2.07 years (SD=.40). Attrition and exclusion of participants for quality control are reported in the supplement. The final sample consisted of 232 participants (120 high risk and 112 low risk) during the baseline scan and 197 participants (101 high risk and 96 low risk) at the second scan (Table 1; Figure 1). Of these participants, 157 (85 high risk and 72 low risk) provided usable fMRI data at both the first and second scans.

Within the final sample, approximately 57% of participants were White/Caucasian, 39% were Hispanic, 3% were African American, and 1% were Asian or American Indian. There was no difference in the distribution of race/ethnicity across the high risk and low risk groups, $\chi^2(3)$=2.49, p=.48. Fifty-one percent of the high risk and 49% of the low risk group was female; there was no difference between groups in gender ratio, $\chi^2(1)$=.24, p=.63. Nine percent of participants in the high risk group and 10% of the low risk group were left-handed; there was no difference between groups in handedness, $\chi^2(1)$=.044, p=.83. A portion of the participants were siblings (11 high risk pairs, 13 low risk pairs). Thirty-two participants in the high risk group had an anxiety diagnosis at baseline (see Supplement). Sixteen participants (15 in the high risk group) developed major depressive disorder and 3 participants (2 in the high risk group) developed an anxiety disorder before the second scan.

Procedure

fMRI Paradigm—Participants performed an emotional face matching task that has been shown to reliably elicit amygdala reactivity in numerous studies of adults and, more importantly, in the baseline scan of the current sample (27, 28). Task blocks consisted of matching angry and fearful facial expressions while control blocks consisted of matching geometric shapes. Further task details are reported in the supplement.

Depressive symptoms—Depressive symptoms were assessed with the child-report version of the Mood and Feelings Questionnaire (30).

Childhood maltreatment—Childhood maltreatment was assessed using the Childhood Trauma Questionnaire (31). In line with prior research in this sample (27, 28), the emotional neglect subscale was selected due to its greater variability.

Stressful life events—Stressful life events occurring the year prior to each scan were assessed using the Stressful Life Events Schedule (32). The schedule was designed specifically to assess stressful life events in children and adolescents and probes for life events that are relevant to this age group. Each event is given a subjective rating of threat by the participant, as well as an objective rating by independent raters. Objective severity ratings for all events occurring within 12 months of scanning were then squared and summed, and this summed value divided by the number of events reported, thereby yielding a measure of life event severity more heavily weighted by severe events (see Supplement for additional details). In order to reduce the number of comparisons performed, objectively rated life stress was used (correlations with subjective life stress at each wave were ~.5), based on stronger evidence for effects of stressful life events on depression when objective measures are used (33).

Analysis of fMRI data—BOLD fMRI data were analyzed using SPM8. Images from the first and second scans were then entered into second-level models and a conjunction analysis was performed to extract BOLD parameter estimates from functional clusters activated across both scanning sessions within the left or right amygdala at $p<.05$ family-wise error corrected. Further details on quality control procedures and extraction of amygdala reactivity values are provided in the supplement.

Hypothesis 1: Developmental change in amygdala reactivity as a function of family history for major depression—After extracting mean parameter estimates of amygdala reactivity in SPM8, all subsequent analyses were performed in SPSSv21. To examine whether the association between amygdala reactivity and age differed between the groups, linear mixed models were applied following the procedures of prior longitudinal neuroimaging research (34–35). Using the methods specified by (36), a three-level linear mixed model was constructed in SPSS with wave (level 1) nested within participant (level 2) nested within family (level 3). A risk group × age interaction was evaluated to test whether change in amygdala reactivity with age was moderated by risk group. We also re-ran analyses excluding any participants with an internalizing disorder and controlling for depressive symptoms at each wave. Further details about the modeling procedure are provided in the supplement.

Hypothesis 2: Developmental change in amygdala reactivity as a function of life stress—Linear mixed models were conducted to examine the effect of childhood and adolescent stress on change in amygdala reactivity with age. Centered scores on the emotional neglect subscale of the Childhood Trauma Questionnaire, the Stressful Life Events Schedule for Wave 1, and the Stressful Life Events Schedule for Wave 2 were simultaneously entered as covariates in a linear mixed model with amygdala reactivity as the

dependent measure. Main effects and interactions with age and risk group were also entered, and gender was included as a covariate.

Results

Hypothesis 1: Developmental change in amygdala reactivity as a function of family history for major depression

First, the main effect of task was examined in SPM8 to ensure that amygdala reactivity was elicited. Mean whole-brain activation maps for the main effects of task contrast (i.e., all faces>shapes) were visually inspected. As seen in the overlap between the two activation maps (Figure 2), the task reliably elicited reactivity in expected corticolimbic regions to a similar spatial extent at both waves. More specifically, the task produced robust bilateral amygdala reactivity at both waves; Wave 1: left amygdala, $t(231)=15.75$, $p<.001$, peak coordinates: $(-22, -2, -18)$; right amygdala, $t(231)=19.03$, $p<.001$, $(22, -4, -18)$; Wave 2: left amygdala, $t(196)=17.83$, $p<.001$, $(-20, -4, -16)$; right amygdala, $t(196)=18.38$, $p<.001$, $(20, -4, -16)$.

Next, we examined the risk group×age interaction using linear mixed models in SPSS to test whether the groups differed in changes in amygdala reactivity with age. This model provided a significantly better fit to the data relative to the null model, $\chi^2(5, N=427)=21.13$, $p<.001$. There was a risk group×age interaction for left amygdala reactivity to fearful faces, which survived Bonferroni correction for multiple comparisons, $F(1,220)=6.67$, $p=.010$ (Figure 3). This was driven by a significant increase in amygdala reactivity in the high risk group ($p<.001$), whereas the low risk group remained stable with age. The effects of age, risk group, and their interaction explained an additional 9% of variance (7% for main effects and 2% for their interaction). This interaction remained significant controlling for mean head displacement, mean accuracy, and mean reaction time on the task, $F(1,217)=6.37$, $p=.012$. This effect also remained significant when excluding participants with an internalizing diagnosis and controlling for depressive symptoms, $F(1,131)=5.29$, $p=.023$. Effects of gender or a quadratic effect of age were not significant and did not improve model fit. There was a similar pattern for right amygdala reactivity to fearful faces, although the interaction was not significant (Supplementary Figure 1). Results were specific to fearful faces, as the interactions for angry faces were not significant ($p's>.20$). Thus, only left amygdala reactivity to fearful facial expressions was used in subsequent analyses to reduce the number of comparisons performed.

Hypothesis 2: Developmental change in amygdala reactivity as a function of life stress

The overall test of model fit including childhood trauma and life stress at both waves was significant, with the interaction between risk group and stressful life event severity assessed at Wave 1 having an effect on amygdala reactivity ($F(1,180)=8.25$, $p=.005$). Given that the test of model fit penalizes for including parameters that do not predict the dependent variable, we removed the effects of childhood trauma and stressful life events at Wave 2 from the model. The simplified version of the model was a significantly better fit relative to the null model, $\chi^2(12, N=415)=35.18$, $p<.001$. Within this model, three interaction terms were significant predictors of the change in left amygdala reactivity to fearful faces: the risk

group×age interaction, $F(1,185)=6.41$, $p=.012$, the interaction between risk group and stressful life event severity assessed at Wave 1, $F(1,42)=6.87$, $p=.012$, and the interaction of age×stressful life event severity, $F(1,151)=4.27$, $p=.04$. Adding the effects of life stress accounted for an additional 2% of variance, for a total of 11% variance explained. These effects remained significant controlling for accuracy, reaction time, and head displacement. These interactions were also significant excluding participants with an internalizing disorder and controlling for depressive symptoms: risk group×age, $F(1,104)=5.54$, $p=.021$; risk group×stress, $F(1, 51)=8.05$, $p=.007$; age×stress, $F(1, 86)=9.29$, $p=.003$. To interpret these effects, predicted outcomes for amygdala reactivity were estimated as a function of the parameters in the model, as recommended by (37). As illustrated in Figure 4, participants in the high-risk group evidenced increases in amygdala reactivity with age, regardless of the amount of life stress experienced in early adolescence. In contrast, low risk adolescents evidenced the expected pattern of decreasing amygdala reactivity with age under conditions of low stress; however, under higher levels of stress, low risk adolescents evidenced increases in reactivity with age.

Discussion

Our aim was to address two gaps in our knowledge involving if and how variability in threat-related amygdala reactivity contributes to the development of major depression. The first was whether heightened amygdala reactivity is a premorbid neural risk marker for depression, observable in at-risk individuals before the onset of clinical symptoms or disorder. The second was identifying how and when this neural phenotype emerged. Our results work to fill these gaps by demonstrating that heightened amygdala reactivity is observed prior to the emergence of clinical symptoms or disorder and represents a divergence of developmental trajectories over adolescence.

Our results reveal that positive family history of depression and stressful life event severity alter the development of amygdala reactivity during adolescence. Adolescents with a positive family history for disorder consistently evidenced a pattern of increasing amygdala reactivity with age, even if they experienced relatively mild life stress in early adolescence. Adolescents with a negative family history of depression evidenced decreases in amygdala reactivity with age under low stress, in line with our predictions based on cross-sectional work. However, adolescents in the low risk group experiencing relatively high levels of life stress in early adolescence evidenced increases in amygdala reactivity with age, similar to the high risk group. This interaction suggests that two distinct risk factors (family history for depression and life stress) may influence risk for disorder via a common developmental pathway of altered development of amygdala reactivity during adolescence. These findings also fit within the framework of allostatic load, which posits that chronic dysregulation of the stress response will induce structural and functional changes in the brain, including the amygdala (38). Dysregulation of the stress response (either through a combination of genetic and environmental risk factors in the high risk group, or through severe life stress in the low risk group) could therefore over time lead to long-term changes in amygdala reactivity, as demonstrated here. Our results also suggest that group differences in amygdala reactivity are minimal in early adolescence and grow stronger with age (Figures 3 and 4). This could partially reflect the fact that we excluded participants with psychiatric disorders at baseline;

however, future research is needed to investigate whether stress-related changes in amygdala reactivity are accelerated by developmental factors in adolescence (e.g., pubertal developmental, the transition to high school).

In line with our conceptualization of increased amygdala reactivity as a premorbid biomarker of risk, differences in reactivity were evident in participants who had not yet developed internalizing disorders and when controlling for depressive symptoms. Individuals at familial risk for depression are most likely to develop the disorder in late adolescence and young adulthood, with a peak period of onset between 15 and 20 years (4, 5). Therefore, the changes in amygdala reactivity observed in early-to-mid adolescence may increase vulnerability for disorder later in development. The TAOS is an ongoing longitudinal study and data continue to be collected. We plan to further evaluate the predictive utility of our observed differences in the developmental trajectories of amygdala reactivity on the emergence of clinical disorder as the cohort is followed into late adolescence and early adulthood. Indeed, if it is possible to detect heightened risk for disorder through neuroimaging measures before dysfunction becomes apparent through self-report of symptoms, this could be of clinical utility in the early detection of risk.

There are several limitations to note. First, the current paradigm only included fearful and angry facial expressions; thus, it is unclear whether similar results would be observed for other negative or positive emotional stimuli (e.g., sad or happy facial expressions) previously implicated in risk for depression (8, 9, 12). Additionally, most participants reported experiencing relatively mild levels of stress as assessed by the Childhood Trauma Questionnaire and the Stressful Life Events Schedule. Indeed, the low levels of emotional neglect reported on the Childhood Trauma Questionnaire may explain the lack of a significant effect on amygdala development. Finally, while our effects explained 11% of the total variance in amygdala reactivity, identifying additional genetic, epigenetic, and environmental moderators of these effects (27, 28, 39, 40), may further help account for individual differences in amygdala reactivity over development.

These limitations notwithstanding, our prospective design, stratification based on familial risk, repeated neuroimaging with a reliable probe of amygdala reactivity, and large sample size all represent major strengths. Future research with the current sample will be necessary to determine whether the altered pattern of amygdala development observed predicts the onset of clinical disorder during later adolescence and young adulthood. If so, this pattern of development could inform efforts for the early detection of risk for the development of depression and, possibly, other psychopathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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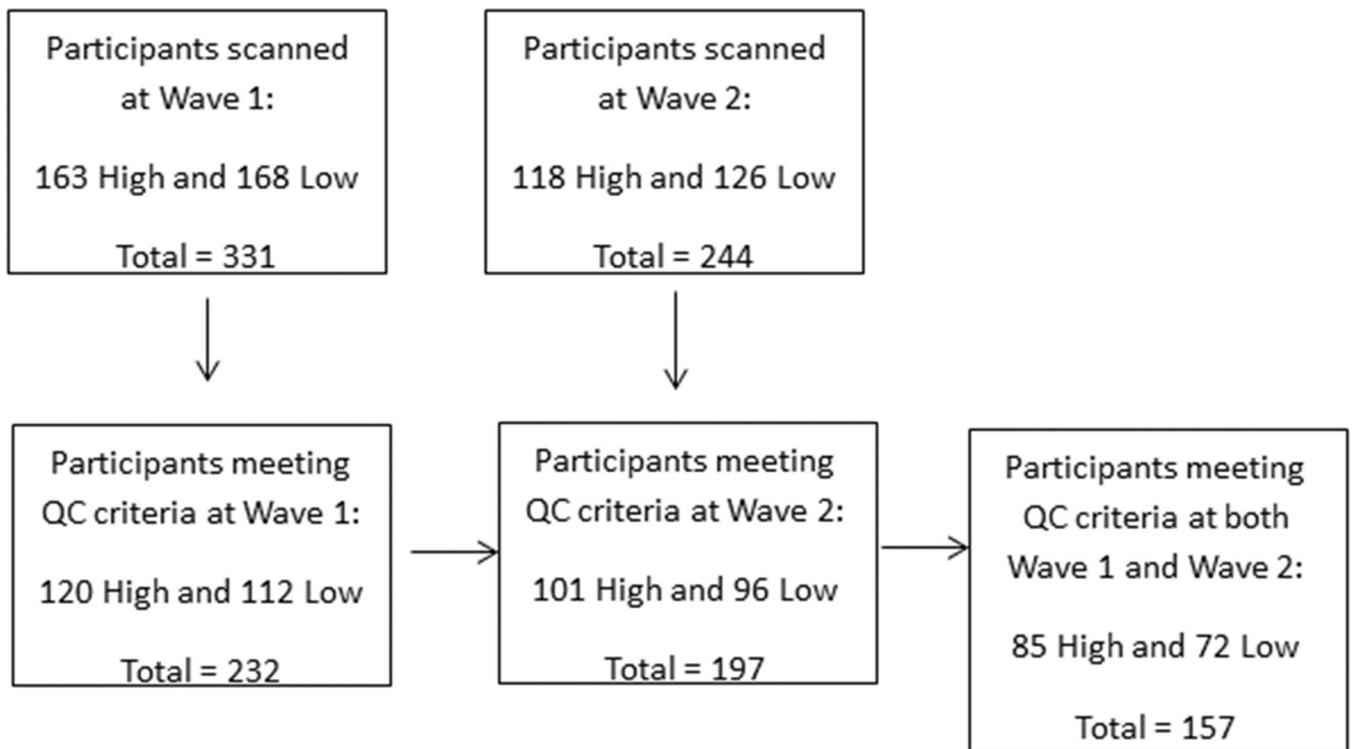
Figure 1. Participant inclusion/exclusion procedure
Participants undergoing fMRI were excluded based on quality control (QC) criteria including problems with raw data, excessive motion or artifact, amygdala coverage <90%, and task accuracy <70%. For analyses using questionnaire measures, participants were excluded if they completed the questionnaires >1 month before scanning. High = High Risk; Low = Low Risk.
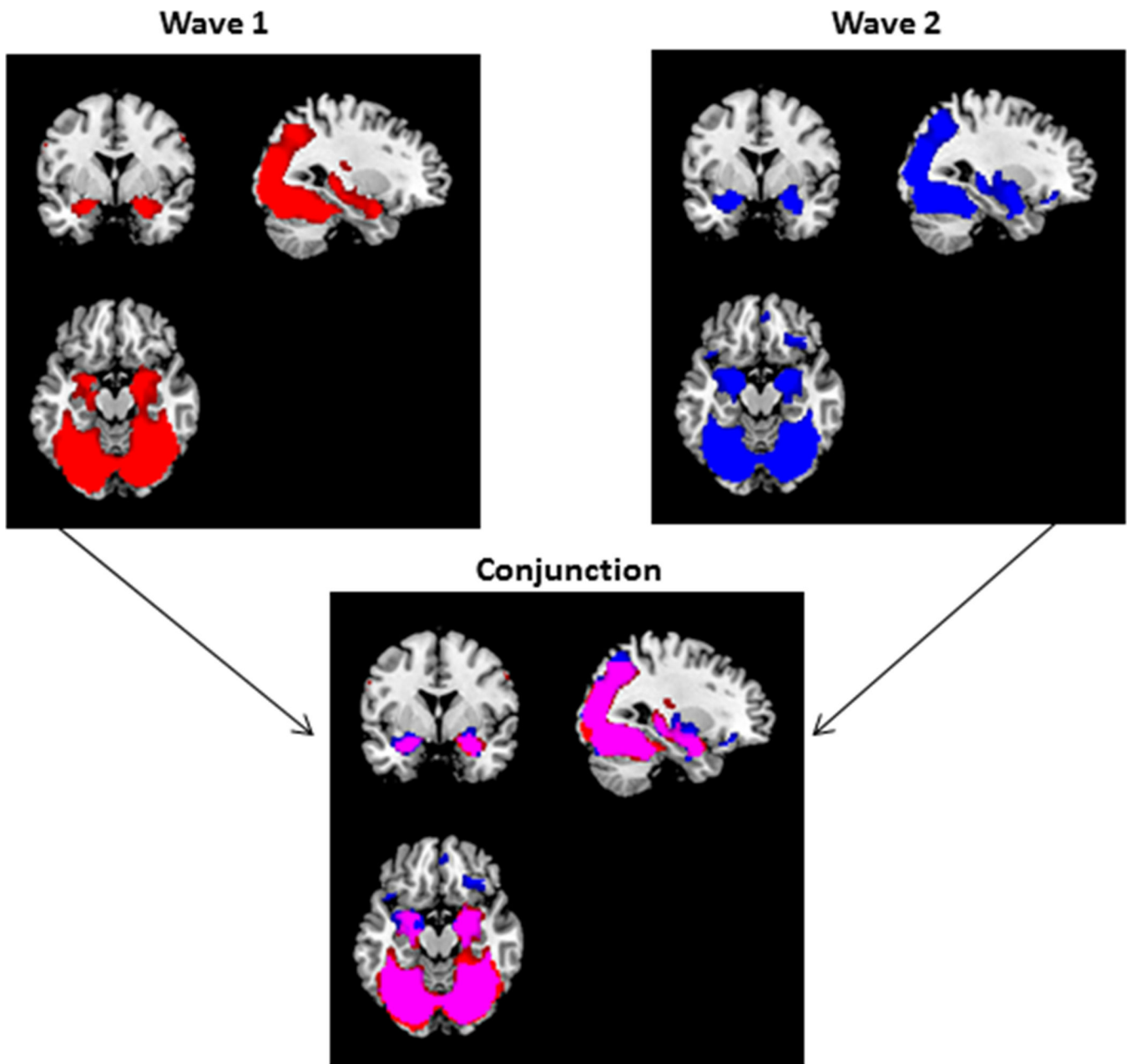
**Figure 2. Overlap in task-related activation at Wave 1 and Wave 2**
Main effects of task (i.e., faces > shapes) at $p<.05$ family-wise error whole-brain corrected.
Red regions demonstrate activation at wave 1, blue regions wave 2, and purple regions are
activated at both waves. Contrast values were extracted from voxels exhibiting activation at
both waves of scanning within the amygdala region of interest (purple voxels).
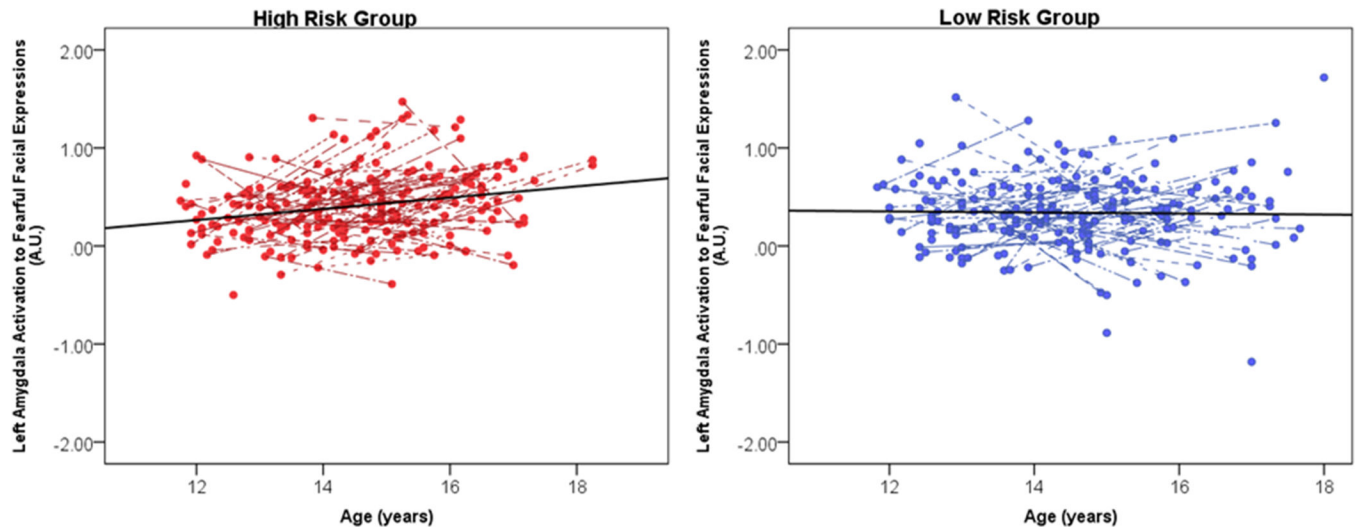
Figure 3. Differential developmental change in amygdala reactivity
The y-axis contains mean BOLD parameter estimates extracted from amygdala clusters exhibiting significant reactivity to fearful facial expressions. Points connected by lines represent within-person change.
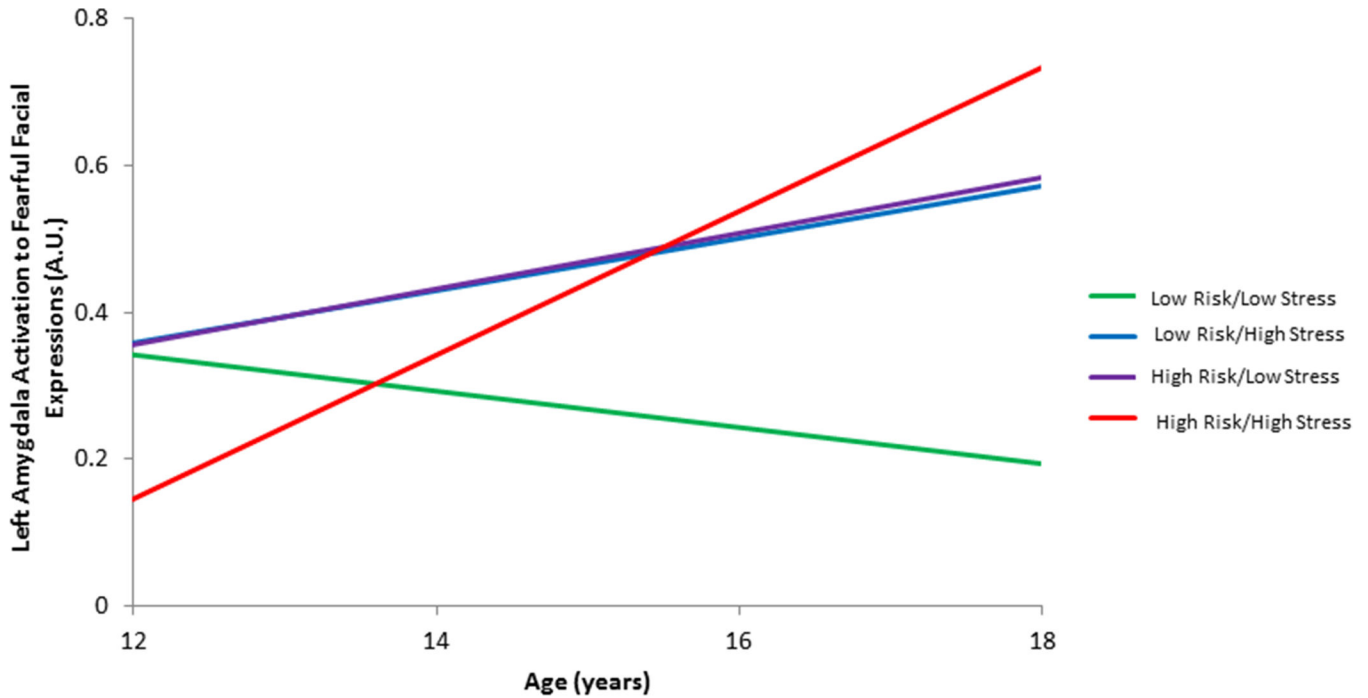
Figure 4. Change in amygdala reactivity as a function of risk group and stressful life event severity

Left amygdala reactivity to fearful faces was estimated using the model that included the interactions of age, risk group, and stressful life event severity assessed at Wave 1 with the Stressful Life Events Schedule (SLES). Values were estimated at 1 standard deviation below the mean SLES score (Low Stress) and 1 standard deviation above the mean (High Stress). Figure is based on the model using all participants, but results looked similar excluding participants with an internalizing disorder and controlling for depressive symptoms.

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Table 1

Participant characteristics

	High-Risk Group		Low-Risk Group			
	Mean	SD	Mean	SD		
Age Wave 1 (n=232)	13.61	1.0	13.55	.94	t(230)= .43	p=.67
Age Wave 2 (n=197)	15.69	1.0	15.63	1.1	t(195)= .39	p=.70
Emotional Neglect	8.42	3.4	7.49	2.6	**t(221)= 2.29**	**p=.02**
Depressive Symptoms 1	10.24	8.9	8.16	6.4	**t(230)= 2.04**	**p=.04**
Depressive Symptoms 2	7.27	9.0	5.79	7.6	t(194)= 1.24	p=.22
Stressful Life Event Severity 1	2.44	1.4	2.47	1.5	t(221)= −.15	p=.88
Stressful Life Event Severity 2	2.49	1.3	2.21	1.3	t(187)= 1.49	p=.14
Mean Accuracy 1	98.5%	3.0	98.6%	3.1	t(222)= −.21	p=.83
Mean Accuracy 2	98.4%	3.6	97.8%	4.4	t(193)= .98	p=.33
Mean RT 1	1290.3	239	1306.6	244	t(222)= −.50	p=.62
Mean RT 2	1236.3	292	1243.0	266	t(193)= −.17	p=.87
Mean Head Displacement 1	.044	.01	.046	.01	t(230)= −1.24	p=.22
Mean Head Displacement 2	.045	.01	.044	.01	t(195)= .84	p=.40

Note: Emotional Neglect was assessed with the Childhood Trauma Questionnaire Emotional Neglect subscale; Depressive symptoms were measured with the Mood and Feelings Questionnaire; Stressful Life Event Severity is assessed with objective ratings of the Stressful Life Events Schedule; Mean Accuracy=Accuracy for face and shape matching conditions on fMRI task; Mean RT=Reaction time for face and shape matching conditions in milliseconds. See supplementary methods for the formula used to calculate mean head displacement. Significant differences are bolded.