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Cumulative stress in childhood is associated with blunted reward-related brain activity in adulthood

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Abstract

Early life stress (ELS) is strongly associated with negative outcomes in adulthood, including reduced motivation and increased negative mood. The mechanisms mediating these relations, however, are poorly understood. We examined the relation between exposure to ELS and reward-related brain activity, which is known to predict motivation and mood, at age 26, in a sample followed since kindergarten with annual assessments. Using functional neuroimaging, we assayed individual differences in the activity of the ventral striatum (VS) during the processing of monetary rewards associated with a simple card-guessing task, in a sample of 72 male participants. We examined associations between a cumulative measure of ELS exposure and VS activity in adulthood. We found that greater levels of cumulative stress during childhood and adolescence predicted lower reward-related VS activity in adulthood. Extending this general developmental pattern, we found that exposure to stress early in development (between kindergarten and grade 3) was significantly associated with variability in adult VS activity. Our results provide an important demonstration that cumulative life stress, especially during this childhood period, is associated with blunted reward-related VS activity in adulthood. These differences suggest neurobiological pathways through which a history of ELS may contribute to reduced motivation and increased negative mood.

Key words: early life stress; fMRI; ventral striatum; reward; neurodevelopment

Introduction

Early life stress (ELS) is associated with compromised physical and mental development as well as long-term physical and mental difficulties (Shonkoff *et al.*, 2012). Meta-analyses suggest ELS, such as abuse or neglect, is associated with a 68% increase in anxiety and depression (Norman *et al.*, 2012). Although these linkages have been well studied in psychology, epidemiology and other related disciplines, the biological mechanisms mediating such relations are poorly understood. Identifying such mechanisms is important for better conceptualizing, treating

and, ultimately, preventing the negative mental health consequences of ELS.

Initial investigations aimed at understanding the neurodevelopmental linkage between ELS and mental health issues have focused on changes in corticolimbic circuitry, specifically the amygdala, which supports recognition and reaction to threat-related stimuli. However, emerging research suggests ELS may also affect functioning of another affective processing network, the corticostriatal circuit (Southwick *et al.*, 2005). Central in this neural circuitry is the ventral striatum (VS), a

subcortical structure supporting motivation and action including reward responsiveness and learning (Berridge and Robinson, 2003). VS dysfunction has been theorized to underlie aspects of affective dysfunction including anhedonia and apathy. Neuroimaging studies have reported decreased reward-related VS activity in depressed individuals (Forbes and Dahl, 2012; Pizzagalli, 2014) and a large body of preclinical data has linked ELS to alterations in reward-related neural circuitry, particularly dopaminergic modulation of VS activity (Pani *et al.*, 2000; Matthews and Robbins, 2003).

Despite these suggestive links, only a small number of descriptive studies have noted differences in corticostriatal circuitry associated with ELS, with lower activity found in samples of children and adolescents exposed to early social deprivation (Mehta *et al.*, 2010; Goff *et al.*, 2013) and in adults who had suffered maltreatment (Dillon *et al.*, 2009). More recently, our research group found that emotional neglect, one form of ELS, is related to a significant blunting of reward-related VS activity from ages 13 to 15, and this developmental blunting predicts affective dysregulation in adolescence (Hanson *et al.*, 2015). These neural differences may result from alterations in the hypothalamic–pituitary–adrenal axis or immune system, which commonly occur after ELS (for review, see Nusslock and Miller, 2015). Associated changes in circulating concentrations of cortisol or pro-inflammatory cytokines may subsequently influence signaling pathways, including dopamine, which directly modulate VS function (Kaufman and Charney, 2001; Brenhouse *et al.*, 2013). Resulting alterations in VS function may have profound behavioral consequences, as lower neural activity in the VS is associated with abnormal responsiveness to rewarding stimuli, decreased motivation, and negative mood.

In service of elucidating mechanisms of risk and resilience, past studies have typically focused on a single risk factor (e.g. physical abuse), tying a specific environmental experience to circumscribed neurobiological and psychological alterations. However, multiple forms of ELS might operate similarly, to lead to altered brain development and later behavioral dysfunction. Thus, models of cumulative risk have been advanced to capture broadly the impact of ELS on later negative outcomes (Evans and Kim, 2010, 2012; Evans *et al.*, 2013). Such models have several advantages over single-risk factor approaches and may more quickly advance efforts to identify particularly vulnerable individuals. First, a number of reports in developmental science have found that cumulative indices of ELS exposure are more effective in predicting negative developmental outcomes than single risk factors in isolation (Greenberg *et al.*, 1999; Evans, 2003; Appleyard *et al.*, 2005). Second, single risk factor approaches may overestimate effect magnitude if the factor being examined is correlated with other risk factors (Evans *et al.*, 2013). Third, cumulative risk approaches parallel neurobiological models such as allostatic load and the aggregated dysregulation across neurobiological and psychological domains (Danese and McEwen, 2012).

Past neuroscience research on ELS is limited in the developmental characterizations of observed effects. Cross-sectional research focused on pediatric populations is unable to forecast whether neurobiological alterations are long-lasting, as brain circuitry may reorganize during adolescence and other developmental periods of change (Kolb and Elliott, 1987; Kolb and Gibb, 1991; Mychasiuk *et al.*, 2014). These studies neglect the possibility that the impact of exposure to stress may vary as a function of the age of this experience. Furthermore, most studies in adults have typically used retrospective reports of early adversity collected at the time of neuroimaging. Thus, the measure of ELS might be biased by the effect of current status on recall such that individuals experiencing heightened psychological distress at the time of measurement are both more likely to recall early adversity and to manifest altered neural function. In addition, the lack of timing specificity of most retrospective ELS measures limits our ability to draw conclusions regarding the effects of stress during specific developmental epochs. The timing of stress exposure may be a critical moderator of the effect of ELS on behavioral development (Manly *et al.*, 2001; Conti *et al.*, 2012; Campbell *et al.*, 2014). Neurobiological alterations may also differ depending on the timing of exposure. Research tracking basic neurobiological development and stress exposure suggests important maturational changes pre- and post-puberty. For example, the amygdala reaches peak gray matter volume between 9 and 11 years (Payne *et al.*, 2009; Uematsu *et al.*, 2012), and amygdala gray matter volume is associated with stress occurring at 10–11 years of age, with adversity during this period contributing to larger amygdala volumes in adulthood (Pechtel *et al.*, 2014).

Despite the growing evidence summarized above suggesting the impact of stress on reward-related brain function, research is lacking on the effects of developmental timing on corticostriatal circuitry. This fact is further surprising given a number of studies suggesting that development of the VS may peak at similar times to the amygdala (Ostby *et al.*, 2009; Mills *et al.*, 2014; cf. Raznahan *et al.*, 2014). Understanding the influence of stress during different developmental epochs may inform the search for strategies to offset the negative sequelae of stress and improve resiliency and wellbeing. Utilizing cohorts followed from early childhood may be particularly powerful to fill in these gaps, as stress exposure at specific developmental epochs could be connected to resultant neurobiology in adulthood (Gilliam *et al.*, 2014; Caldwell *et al.*, 2015).

Here, we report on the relation between cumulative stress exposure during distinct periods in childhood and adolescence on reward-related VS activity in young adulthood assayed in a prospective longitudinal study. We hypothesized relatively blunted VS activity as a function of greater amounts of early cumulative stress. Based on past work tracking potential sensitive periods (Pechtel *et al.*, 2014), we also hypothesized that stress early in development (before the age of 9) would have the greatest impact.

To understand potential relations between cumulative stress and reward-related VS activity more fully, we also conducted two exploratory analyses. First, we examined associations between early stress exposure and neural responses to specific valences of feedback (i.e. positive or negative). Based on past theoretical and empirical reports linking lower VS activity to anhedonic features of depression, we predicted lower VS activity to positive feedback in individuals exposed to higher levels of stress. Second, we explored whether different types of cumulative stress would be related to differences in VS activity, focusing on the effects of interpersonal stressors *vs* physical/non-social adversities. Based on past work focused on the classes of events that precede affective psychopathology (for review, see Hammen, 2005), we hypothesized that cumulative interpersonal stress would have greater influence on reward-related VS activity than would material stress.

Methods

Participants

Our sample was comprised of a subgroup of participants from the Fast Track Program, a prevention trial implemented in the

early 1990s to test whether the outcomes of young children at high risk for long-term antisocial behavior could be improved through a multicomponent behavioral intervention. Participants completed annual assessments starting in kindergarten and lasting through Grade 12. The Fast Track Program has been detailed extensively (e.g. Greenberg *et al.*, 1999; The Conduct Problems Prevention Research Group, 1999, 2002) and comprehensive documentation about the study is available at http://www.fasttrackproject.org and in our Supplementary Materials.

Of the 207 male participants enrolled in the Fast Track study from the Durham site, we successfully contacted 148 and invited them to participate in the study. Ten participants declined. MRI screening procedures disqualified an additional 40 participants; exclusion criteria included current drug or alcohol abuse and standard MRI safety exclusions (e.g. metal implants, history of gunshot). Ninety-eight participants met inclusion criteria and provided informed consent to study procedures, in accordance with the Declaration of Helsinki and university research review committee approval and oversight.

These participants completed a neuroimaging protocol assessing brain structure and function. Of these 98 participants, 26 were excluded from fMRI analyses because of (1) excessive motion during the MRI session ($n = 1$), (2) inadequate behavioral responding during the reward task ($n = 12$, for additional details, see Supplementary Materials), (3) missing behavioral data ($n = 6$) and (4) missing data about stress exposure ($n = 7$). Quality-control cutoffs and additional information about exclusion are detailed in our discussion of each of these measures later in this section. Resulting data from 72 participants were available for current analyses. Of note, the same cohort used in this study has been used to examine the effects of early physical abuse on corticolimbic circuit function (Albert *et al.*, in prep).

The mean age of participants was 26.3 years (s.d. = 1.1). The majority of participants were African American (91.8%). The subsample of men studied here includes participants from the intervention condition ($n = 28$) of the Fast Track randomized control trial, in addition to participants from the control ($n = 29$) and normative ($n = 15$) groups. Intervention and control participants were those individuals who were screened as high-risk for long-term serious violence at the beginning of the project and then assigned randomly to intervention or control conditions, whereas normative participants were selected to represent the entire population (for additional information, see Supplementary Materials). Of important note, although random assignment to intervention had a long-term effect on internalizing and externalizing outcomes in the full sample of 891 participants, there were no effects of the Fast Track intervention on internalizing or externalizing symptomatology in our neuroimaging subsample (internalizing $F(2,69) = 0.07$, $P = 0.9$; externalizing $F(2,69) = 0.79$, $P = 0.45$; boxplots shown in Supplementary Materials). This was likely due to MRI screening procedures and exclusion criteria. No differences in total cumulative stress exposure or stress exposure in specific developmental epochs were found among the three groups (Total Cumulative Stress $F(2,69) = 0.3$, $P = 0.7$; Cumulative Stress During Early Developmental Epoch $F(2,69) = 0.7$, $P = 0.4$; Cumulative Stress During Middle Developmental Epoch $F(2,69) = 0.08$, $P = 0.9$; Cumulative Stress During Late Developmental Epoch $F(2,69) = 1.3$, $P = 0.27$).

Measures

Beginning in kindergarten and lasting through Grade 12, stressful life events were assessed annually via a 16-item parent report instrument, the Life Changes measure (Dodge *et al.*, 1990; Greenberg *et al.*, 1999). This questionnaire assessed major life stressors experienced by the child during the previous year (e.g. move, medical problems, divorce or separation of parents, death of an important person). Each item was weighted 2 for major events and 1 for minor events, based on parental report of the severity of the event for the family. A sum of the items experienced was computed reflecting life events for each year. Z-scores were then computed and normalized for each year for our sample. We also created a composite stress score, averaging these z-scores from Kindergarten to grade 12. We next created developmental epoch specific z-scores for early (Kindergarten-Grade 3), middle (Grade 4–7) and late (Grade 8–12) eras of childhood. This division was motivated by past research on potential sensitive periods on affective brain circuits and to ensure reliable estimation of stress exposure during development (i.e. similar number of scores included in each epoch). For these analyses, participant data were excluded (full list-wise deletion) if stress data were missing from >50% of any developmental time period ($n = 7$).

As an exploratory analysis, we also divided our measure of cumulative life stress into meaningful clusters of events, across all of development and also during specific developmental epochs. Motivated by the work of Evans *et al.* (2013), we grouped the questions on the Life Changes measure into interpersonal *vs* physical/non-social stressors. Interpersonal stressors included events such as the death of an important person or parental divorce, while events such as moving or major home remodeling were grouped as physical/non-social adversities. We computed z-scores for each of these types of events and normalized for each year in our sample. We then averaged these z-scores from Kindergarten to grade 12 and also created developmental-specific epoch z-scores (for early, middle and late developmental epochs).

To rule out potential confounds, the following covariates were included in all analyses: ethnicity (binary-coded of white/not white), and Fast Track treatment group. Further, to probe the specificity of our effect, we also investigated relations between familial socioeconomic status (SES) in grade 1 (based on Hollingshead, 1975, unpublished data) and current SES (based on a factor-score constructed from level of education and full-time employment, see Supplementary Materials). These analyses examined cumulative stress exposure in a continuous fashion, but additional analyses detailed in the Supplementary Materials also focused on potential 'threshold' effects, looking at individuals exposed to extremely high levels of stress.

Measures of internalizing and externalizing symptoms were collected at age 26 using the Adult Self-Report (Achenbach and Rescorla, 2003; additional information in the Supplementary Materials). Additional analyses examining stress exposure and reward-related VS activity, while controlling for psychopathology, are also reported in the Supplementary Materials.

VS activity paradigm

To probe reward-related VS activity, participants completed a commonly used, blocked-design fMRI card guessing game involving positive and negative (i.e. win and loss) feedback. During each task trial, participants guessed whether the value of a visually presented card would be higher or lower than 5. After a choice was made, the numerical value of the card was presented and followed by feedback (green upward-facing arrow for positive feedback; red downward-facing arrow for negative feedback). Each of nine randomly-ordered task blocks

comprised five trials. Three blocks consisted of predominantly positive feedback (80% correct) and three of predominantly negative feedback (20% correct) interleaved with three control blocks during which participants made alternating button presses at the presentation of an 'x' which was followed by an asterisk and a yellow circle. This blocked-design fMRI task has consistently elicited reward-related VS activity in prior studies (Hariri *et al.*, 2006; Gianaros *et al.*, 2011; Nikolova *et al.*, 2013); however, of note, the task's blocked design does not allow for the parsing of different components of reward processing (i.e. reward anticipation and outcome). Additional information about this task is available in Supplementary Materials.

MRI acquisition, processing and statistical analyses

Structural and functional MRI data were acquired for each participant using a research-dedicated GE MR750 3T scanner (General Electric Healthcare; Waukesha, WI, USA). Specific information about acquisition parameters are detailed in the Supplementary Materials. Pre-processing and analysis of imaging data were conducted using Analysis of Functional Neuroimages (AFNI; http://afni.nimh.nih.gov; Cox, 1996). Individual subject data were realigned to the first volume in the time series, high-pass filtered, percent signal change normalized, aligned to individual subject high-resolution structural images, spatially smoothed using a Gaussian filter set at 6-mm full-width at half-maximum and then analyzed using a general linear model (GLM). Our GLM included separate regressors for each feedback type (positive, negative, control) convolving a stimulus boxcar function with a canonical hemodynamic response function. These first-level GLMs included nuisance covariates of the second-order polynomial used to model the baseline and slow signal drift, six motion estimate covariates and binary flags corresponding to neuroimaging frames with excessive motion (>2 mm). Participants with $>10\%$ of total frames censored due to motion were excluded from all analyses ($n = 1$). Structural images were then normalized to a standard stereotactic space (Montreal Neurological Institute template) using a non-linear diffeomorphic registration algorithm. The resulting warps were applied to all functional data (re-sampled to 2 mm³). Second-level (main-effect) neuroimaging GLMs were then constructed using mixed effects analysis, with subjects as a random factor. An initial (uncorrected) statistical threshold of $P < 0.005$ was used and false discovery rate correction based on the extent of suprathreshold voxels (i.e. cluster size) was then applied to control for voxel-wise multiple comparisons, yielding a corrected $P = 0.05$ (similar to past reports, e.g. Bjork *et al.*, 2007; Wager *et al.*, 2008; Gianaros *et al.*, 2013). These results are detailed in Supplementary Table S1.

We focused on our canonical contrast previously used to assess reward-related VS activity, specifically positive > negative feedback for each participant (Hariri *et al.*, 2006; Gianaros *et al.*, 2011; Nikolova *et al.*, 2013). Mean BOLD values from VS clusters exhibiting a main effect of task were then extracted using AFNI. By extracting VS BOLD parameter estimates from the functional clusters activated by our paradigm rather than clusters specifically correlated with our independent variables of interest (i.e. cumulative stress exposure), we limit potential correlation coefficient inflation. This is similar to past reports from our research group (Hyde *et al.*, 2011; Carre *et al.*, 2012;). Supplemental region of interest derivation using the NeuroSynth platform (www.neurosynth.org; Yarkoni *et al.*, 2011) are also described in the Supplementary Materials.

Regression models were then constructed to examine how stress exposure at different time periods related to VS activity. We entered race (binary coded as white or non-white), treatment group (Fast Track intervention or not) and stress exposure (either our measure of cumulative adversity or at specific developmental epochs) as independent variables. Similar exploratory analyses were conducted using interpersonal and physical/nonsocial stress variables. Relationships between stress exposure and brain activity across the whole brain are detailed in Supplementary Materials.

To understand the effects of stress exposure on reward-related brain function more fully, we also investigated the effects of feedback valence (positive or negative). For these analyses, we extracted the contrasts of positive feedback > control blocks and negative feedback > control blocks for our VS ROI. Due to the brief nature of our task and limited past research studies focused on such effects, these analyses were considered exploratory.

Results

Descriptive statistics for stress exposure

The means for all stress exposure scores were 0 (s.d. = 1), due to z-transformations. For cumulative stress across childhood and adolescence, the range was -1.74 to 3.425. For each developmental epoch, the ranges were as follows: early developmental epoch -1.713 to 3.19, middle developmental epoch -1.753 to 2.55 and late developmental epoch -1.617 to 3.9.

Stress exposure and reward processing

Consistent with prior work, our contrast produced significant reward-related VS activity (see Supplementary Materials for details). There was no effect of the Fast Track intervention on neural responses to reward (Right VS Positive > Negative Feedback $\beta = -0.08$, $P = 0.54$), but we retained intervention group as a covariate in analyses.

As hypothesized, higher cumulative life stress during childhood and adolescence was associated with blunted VS response to reward (right VS $\beta = -0.26$, $P = 0.04$). Subsequent analyses revealed a specific association between cumulative stress during early childhood and blunted right VS response to reward ($\beta = -0.327$, $P = 0.009$; Figure 1). This association remained significant when controlling for stress exposure later in development ($\beta = -0.32$, $P = 0.036$), which was not significantly associated with VS activity (Middle Developmental Epoch $\beta = 0.015$, $P = 0.9$; Later Developmental Epoch $\beta = 0.08$, $P = 0.57$). A formal test of the difference between correlations indicated the association between VS activity and early stress exposure was different from that between VS activity and stress exposure at other developmental periods (Differences between VS-early stress and VS-middle stress $t = -2.81$, $P = 0.01$; differences between VS-early stress and VS-late stress $= -3.87$, $P < 0.001$).

Stress exposure and feedback valence

We next examined whether cumulative stress had effects on the processing of positive or negative feedback. Cumulative stress exposure across childhood and adolescence was related to lower right VS signal for positive feedback > control blocks ($\beta = -0.22$, $P = 0.049$). This relation was not seen for right VS signal for negative feedback > control blocks ($\beta = -0.1$, $P = 0.353$). These two correlations were significantly different from one another ($t = -3.5$, $P < 0.001$). Similarly, exposure to stress early in
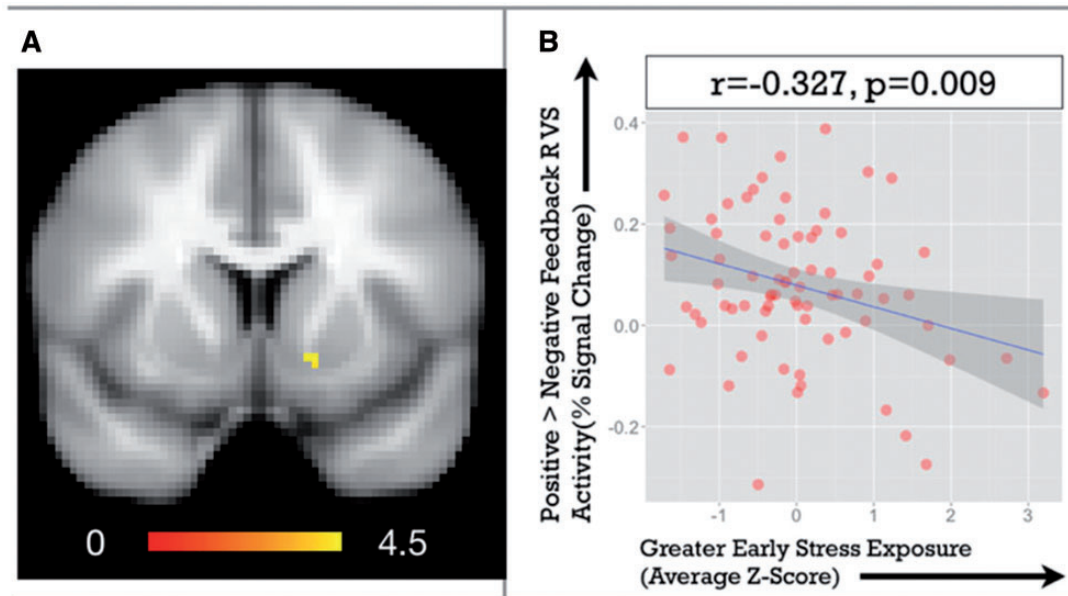
Fig. 1. The left side (A) depicts our right VS region of interest, while the scatterplot for early stress exposure and VS activity is shown on the right side (B). In this scatterplot, right VS activity to positive > negative feedback (as indexed by percent signal change) is shown on the vertical axis and early stress exposure (an average of stress exposure Z-scores) is depicted on the horizontal axis.

development was related to lower right VS signal for positive feedback > control blocks ($\beta = -0.22$, $P = 0.045$). This relation was not seen for right VS signal for negative feedback > control blocks ($\beta = 0.01$, $P = 0.87$) and these two correlations were again significantly different from one another ($t = -2.5$, $P = 0.01$).

Analyses focused on specific types of stress

Examining interpersonal *vs* physical/non-social adversities, we found lower right VS activity in participants exposed to higher interpersonal cumulative life stress across all of childhood and adolescence ($\beta = -0.282$, $P = 0.02$). This relation was not seen for physical/non-social adversities ($\beta = -0.14$, $P = 0.256$), and these two correlations were significantly different from one another ($t = -4.46$, $P < 0.001$). Looking at specific developmental epochs, early interpersonal stress was related to lower right VS activity ($\beta = -0.29$, $P = 0.01$), while early physical/non-social adversity was related to lower right VS activity at a trend level ($\beta = -0.248$, $P = 0.047$). These correlations were, however, not statistically different from one another ($t = -0.45$, $P = 0.66$). No other significant relations were found for exposure to interpersonal or physical/non-social stress during other developmental epochs (all P's > 0.18).

Brain–behavior relations

Exploratory analyses focused on brain–behavior relationships did not find any associations between VS activity and adult internalizing or externalizing symptoms (all P's > 0.25). Additional analyses using ensemble classification techniques and also controlling for current levels of psychopathology are discussed in Supplementary Materials.

Discussion

We found that greater cumulative exposure to stress during childhood was related to lower VS activity during reward processing. Particularly novel, we then found that stress early in development (between kindergarten and grade 3) but not later in development (grades 4 through 7; grades 8 through 12) was specifically associated with this blunted activity. These neural differences may reflect changes in the responding to and processing of important environmental information, specifically reduced engagement with positive stimuli relative to engagement with negative stimuli.

Our results fit well with previous studies charting the impact of ELS on reward-related neural circuitry, specifically the VS. One report in adults found lower VS activity to reward-predicting cues (Dillon *et al.*, 2009), while two reports in pediatric samples have noted similar VS hypoactivity to reward (Mehta *et al.*, 2010; Goff *et al.*, 2013). Our findings also extend prior work (Hanson *et al.*, 2015) by demonstrating a unique effect of early cumulative stress (before the age of 10) on VS activity.

Of note, we found VS activity to positive feedback lower in those exposed to greater levels of stress during childhood and adolescence. This result is consistent with work showing that lower reward-related VS activity explains reductions in positive affect after stressful life events in young adults (Nikolova *et al.*, 2012), as well as theoretical models that posit VS activity may be critically related to psychological aspects of resilience such as optimism (Charney, 2004; Southwick *et al.*, 2005). An inability to maintain positive affect may be one pathway through which ELS conveys risk for affective psychopathology such as depression. Breaking stress exposure into different classes of events, we found strong relationships between interpersonal adversity and decreased VS activity. Again, thinking about affective psychopathology, this finding relates to a large body of research findings that suggest events with greater interpersonal significance often precipitate the onset of depression (Hammen, 2005).

Alterations in dopamine signaling may contribute to the decreased VS activity observed as a function of ELS, which has been linked with alterations in HPA axis and immune system function (for review, see Nusslock and Miller, 2015). Changes in the HPA axis have previously been linked to decreased density in mesolimbic dopamine receptors in the nucleus accumbens, a

key subregion of the VS (for review, see Goff and Tottenham, 2014). Similarly, pro-inflammatory cytokine levels can influence dopamine signaling through changes in metabolism and precursor availability in brain (Dunn, 2006).

Our study is not without limitations. First, the work was conducted in an all-male sample, with a portion of the participants undergoing an intervention early in life. While we did not see any associations between this treatment and VS activity, future work should aim to leverage similar longitudinal designs in more heterogeneous samples. That said, our design can be considered advantageous as significant associations were found even after potential clinical mediation. Second, though we found associations between ELS and brain function, we did not find evidence connecting these differences to emergent behavior. This is, however, similar to much of the past neurobiological research on ELS. For example, while a number of studies have reported associations between ELS and functional alterations in the amygdala, few have connected them to negative outcomes, such as self-report measures of negative effect. Such observations may reflect the relative sensitivity of fMRI to subtle alterations in physiology that are not readily detected by distal measures of behavior. It is also possible that latent differences in brain function may manifest as dysfunctional behavior later in time or in other behavioral domains. Third, the experimental paradigm employed here assays only one facet of reward processing. Recent work has noted that such processing is a complex, non-unitary phenomenon (Berridge and Robinson, 2003; Richards et al., 2013). Future work focused on reward anticipation, modulation and other components of reward processing may aid in explaining the effects of ELS and/or connections with different forms of psychopathology. Finally, the effects of ELS may be conveyed through indirect pathways and our neuroimaging measures were cross-sectional in nature. Future prospective examinations with multiple measures of brain functioning could move past such shortcomings, by more rigorously examining developmental trajectories of VS activity and subsequent effects on behavior. In fact, emerging work suggests that trajectories of neurobiological development rather than a snapshot are more closely related to behavior (Shaw et al., 2006).

These limitations notwithstanding, our study suggests that cumulative stress exposure in childhood impacts reward-related brain function. It is possible that blunted VS activity associated with higher cumulative stress in early life represents a potential neural marker of lower positive psychosocial characteristics necessary for resilience to stress (such as hopefulness). Future research is needed to explicate these relations more fully. More generally, this study underscores that a constellation of stressors in children's lives may affect neurobiological markers of risk and resilience, which may subsequently inform the development of novel targets for intervention and prevention.

Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest. None declared.

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Supplemental Materials

Additional Information about the Fast Track Project

Participants were drawn from the Fast Track Program, a prevention trial implemented in

the early 1990s to test whether the developmental outcomes of young children at high

risk for long-term antisocial behavior could be improved through a multicomponent

behavioral intervention. As children, participants for the larger project were originally

selected from three kindergarten cohorts at four geographic sites using rigorous

multiple-gating, multi-informant screening procedures to screen for aggressive,

disruptive behavior and to match based on numerous demographic characteristics

(Conduct Problems Prevention Research Group, 1999). Participants were randomly

assigned to a control condition or an intervention protocol that included a teacher-led

classroom curriculum focused on development of emotional concepts, social

understanding, and self-control; parent training groups complementing the classroom

curriculum; home visits to further foster parents' problem-solving skills, self-efficacy, and

life management; and child skill training (in both academic and social skills). In addition

to the control and intervention groups, a normative sample of children was selected

from the comparison schools at the beginning of the project. These children were from

each decile of the distribution of scores on a teacher-report screen for behavior

problems, which consisted of items from the Teacher Observation of Child Adaptation-

Revised study (Werthamer-Larsson, Kellam, & Wheeler, 1991).

Supplemental Information about Behavioral Measures

Current SES was assessed through a composite factor derived through principal component analyses. In brief, binary coded responses of completion of high school and whether an individual was employed full-time were transformed using the FactoMineR package in the R statistical environment. The first eigenvector of this data transformation explained 64.83% of the variance in responses and was used as a measure of an individual's current SES.

Psychiatric symptomatology was assessed using the Adult Self-Report (ASR; Achenbach & Rescorla, 2003). This self-report questionnaire is an adult adaptation of the Youth Self Report and the Child Behavior Checklist, two self-report measures commonly used to assess psychiatric symptoms in children and adolescents. The ASR includes 132 items regarding behavioral, emotional, and social problems, is widely used, has strong psychometric properties, and assesses adaptive functioning in adults aged 18–59 years of age (Achenbach & Rescorla, 2003). Scoring of this screening tool results in a Total Problem Score, which is then subdivided into Internalizing (e.g. depressive or anxious behavior) and Externalizing (e.g. aggressive, disruptive behavior) Problem Behavior Scores, with higher scores indicating greater distress. Internalizing and externalizing symptoms are shown in Figure S1 in relation to our treatment groups, a nuisance variable in all statistical models.

Scores from the ASR were used to generate binary Diagnostic and Statistical Manual of Mental Disorders-IV criteria indicators (0=no, 1=yes) for antisocial personality, attention deficit hyperactivity disorder, avoidant personality, somatic problems, anxiety, and

depression disorders. This is similar to past research with the FastTrack cohort (e.g., Dodge et al., 2015). In addition, the Tobacco, Alcohol, and Drugs survey was employed to assess frequency and problem level for tobacco, alcohol, and illegal drug use (based on measures from the Bureau of Labor Statistics, US Department of Labor, 2002; see Dodge et al., 2015 for information). A binary indicator was constructed if a participant presented with any externalizing, internalizing, or significant substance use (scored 1 if criteria for any of the following problems were present, or 0 otherwise).

Looking at the relationship between stress exposure and psychopathology, cumulative stress during childhood and adolescence was not related to internalizing or externalizing symptomatology (all p's>.2). Similarly, cumulative stress during the different developmental epochs did not relate to internalizing or externalizing symptomatology (all p's>.2).

When we examined different classes of stress (interpersonal versus physical/non-social), we found that interpersonal stress across childhood and adolescence was related to externalizing symptomatology in adulthood (p=.04). A trend-level association also emerged cumulative interpersonal stress was related to internalizing symptomatology in adulthood (p=.09). Physical/non-social cumulative stress across childhood and adolescence was not related to internalizing or externalizing symptomatology (all p's >.7). Focusing on different types of stress during different developmental epochs, only interpersonal stress early in development was related to psychopathology (internalizing β=0.245, p=0.028; externalizing β=0.263, p= 0.023). All

other classes of stress during the other developmental epochs were not related to

psychopathology (all p's>.3).

Reward Reactivity Paradigm

Participants completed a commonly used, block-design fMRI card guessing game

where they received positive or negative (i.e., win or loss) feedback for each trial.

During each trial, participants had 3 seconds to guess, via button press, whether the

value of a visually presented card was higher or lower than 5 (index and middle finger,

respectively). After a choice was made, the numerical value of the card was presented

for 500 milliseconds and followed by feedback (green upward-facing arrow for positive

feedback; red downward-facing arrow for negative feedback) for an additional 500

milliseconds. A crosshair was then presented for 3 seconds, for a total trial length of 7

seconds. Each block comprised five trials, with three blocks each of predominantly

positive feedback (80% correct) and three of predominantly negative feedback (20%

correct) interleaved with three control blocks. During control blocks, participants were

instructed to simply make alternating button presses during the presentation of an 'x' (3

seconds) which was followed by an asterisk (500 milliseconds) and a yellow circle (500

milliseconds). Participants were unaware of the fixed outcome probabilities associated

with each block and were led to believe that their performance would determine a net

monetary gain at the end of the scanning session. Instead, all participants received $10.

We included one incongruent trial within each task block (e.g., one of five trials during

positive feedback blocks was incorrect resulting in negative feedback) to prevent

participants from anticipating the feedback for each trial and to maintain participants'

engagement and motivation to perform well. The total task length was 342 seconds and was selected with the aim of robustly engaging the VS. Participants were excluded if the average percentage of winning or losing per block was <60% (due to missed behavioral responses).

MRI Acquisition

Each participant was scanned using a research-dedicated GE MR750 3T scanner (General Electric Healthcare; Waukesha, WI) equipped with high-power high-duty-cycle 50-mT/m gradients at 200 T/m/s slew rate and an eight-channel head coil for parallel imaging at high bandwidth up to 1MHz at the Duke-UNC Brain Imaging and Analysis Center. A semi-automated high-order shimming program was used to ensure global field homogeneity. A series of 34 interleaved axial functional slices aligned with the anterior commissure–posterior commissure plane were acquired for full-brain coverage using an inverse-spiral pulse sequence to reduce susceptibility artifact (TR/TE/flip angle=2000 ms/30 ms/60; FOV=240 mm; 3.75 x 3.75 x 4 mm voxels; interslice skip=0). Four initial RF excitations were performed (and discarded) to achieve steady-state equilibrium. To allow for spatial registration of each participant's data to a standard coordinate system, structural images were acquired in 162 axial slices (voxel size=0.938 x 0.938 x 1mm, interslice skip=0, TR/TE/flip angle=8.148s/3.22 ms/12, FOV=240 mm).

MRI Data Quality Control and Task Validation

Due to the common signal loss and noise typically observed in the VS, single-subject

BOLD fMRI data were included in subsequent analyses only if there was a minimum of

90% signal coverage in our regions of interest. No participants were excluded for this

data quality control measure. Similar to past reports (Nikolova & Hariri, 2012; Nikolova,

Bogdan, Brigidi, & Hariri, 2012), our fMRI paradigm elicited robust reward-related (i.e.,

positive>negative feedback) VS activity.

Supplemental Analyses Controlling for Psychopathology

Additional analyses were conducted to rule out the potential influence of current

psychopathology. Controlling for the presence of any psychopathology (by use of a

binary coded variable noting any internalizing or externalizing diagnoses), we found that

all relationships between stress exposure and right VS activity for positive > negative

feedback remained significant (Cumulative stress exposure across childhood and

adolescence, $\beta=-0.269$, $p= 0.023$; early stress exposure $\beta=-0.41$, $p=0.003$). Use of

continuous measures of psychiatric symptomatology yielded similar results. All

relationships between stress exposure and right VS activity remained significant when

controlling for internalizing and externalizing symptoms from the ASR (Cumulative

stress exposure across childhood and adolescence, $\beta=-0.265$, $p= 0.02$; early stress

exposure $\beta=-0.391$, $p=0.006$).

Analyses Focused on Non-Linear Stress Effects

Though we found linear effects of stress in the main manuscript, we also conducted

exploratory analyses focused on potential non-linear effect of exposure to stress. We

completed additional analyses by dividing our participants into two groups: high stress exposure (those with $\geq$ 1 standard deviation of stress exposure) and lower stress exposure (those with < 1 standard deviation of stress exposure). We then constructed regression models with race (binary coded as white or non-white), treatment group (Fast Track intervention or not), and stress exposure (now as a binary variable) as independent variables. Right VS activity was entered as a dependent variable.

Similar effects were found to those reported in the main manuscript. Lower right VS activity for positive > negative feedback was found for participants with high stress exposure. This was found when looking at cumulative stress exposure across childhood and adolescence (β=-0.297, p=0.01) and also at stress exposure in early development (β=-0.476, p<.005). Bar graphs depicting these relationships are shown in supplemental Figure S2. No such relationships were found for the middle (β=-0.053, p=.64) and later (β=-0.055, p=.65) developmental epochs.

Exploratory Whole-Brain Analyses

To examine the relationship between stress exposure and reward processing across the whole brain, whole brain regressions were completed in AFNI's 3dRegAna. Each individual's level of stress was regressed against the BOLD response for positive > negative feedback. This was done separately for the different stress exposure variables, yielding 4 whole-brain regressions:

1) Cumulative stress across all of childhood and adolescence

2) Cumulative stress in the early developmental epoch

3) Cumulative stress in the middle developmental epoch

4) Cumulative stress in the later developmental epoch

These separate whole-brain stress correlations were thresholded at p < .005 (uncorrected) and combined with the main effect of positive>negative feedback (initial statistical threshold of p<.005, uncorrected) using a logical AND conjunction. This analytic approach was employed to identify the brain regions that were related to stress exposure and also consistently activated during reward processing. Such an approach has been used previously in similar reports (Hanson et al., 2013; 2012). Assuming independence of these tests, these results are significant at 0.000025 (0.005 x 0.005), uncorrected.

For the conjunction of (stress exposure early in development and positive>negative feedback) AND the (main effect of positive>negative feedback; t-test versus 0), clusters emerged in the frontal pole, the angular gyrus, the paracingulate gyrus, and the middle frontal gyrus. The results are noted in supplemental table S2 and supplemental figure S3. Activity in these regions was negatively related to stress exposure and positively activated during the processing of positive>negative feedback. No other clusters emerged when combining the other stress exposure regressions and the task main effects.

Alternative Region of Interest Derivation via NeuroSynth

Motivated by ongoing debate in the neuroimaging community (for discussion of this

issue, see Kriegeskorte et al., 2010), we also derived VS values through use of the NeuroSynth platform and database (neurosynth.org). NeuroSynth is an automated brain-mapping application that uses text-mining, meta-analysis, and machine-learning techniques to generate a large database of mappings between neural and cognitive states (Yarkoni, Poldrack, Nichols, Essen, & Wager, 2011). A key benefit of this approach is the ability to distinguish forward inference quantitatively (given a known psychological manipulation, one can quantify the corresponding changes in brain activity) from reverse inference (given an observed pattern of activity, one can determine the associated cognitive states). Reverse inference maps of the terms "reward" were thresholded at 95% of their robust range to identify regions commonly activated during reward neuroimaging studies, yielding two brain regions of interest (left VS; right VS).

Using VS values from our NeuroSynth ROIs, we found comparable results to those detailed in the main manuscript. Higher cumulative life stress during childhood and adolescence was associated with blunted VS response to reward. This was seen for the right (β=-0.248, p=0.03) but not left (β=-0.07, p=0.5) VS. Subsequent analyses revealed a specific association between cumulative stress during early childhood and blunted right VS response to reward (β=-0.38, p=0.001). This association remained significant when controlling for stress exposure later in development (β =-0.46, p=0.001), which was not significantly associated with VS activity (Middle Developmental Epoch β=0.2, p=0.1; Later Developmental Epoch β=0.097, p=0.49). Similarly, cumulative stress exposure across childhood and adolescence was related to lower right VS signal for

positive feedback > control blocks (β=-0.29, p=0.01). This relationship was not seen for right VS signal for negative feedback > control blocks (β=-0.05, p=0.6; test of difference between correlations, t=2.1, p=0.03). Exposure to stress early in development was related to lower right VS signal for positive feedback > control blocks (β=-0.28, p=0.01). This relationship was not seen in the right VS signal for negative feedback > control blocks (β=0.05, p=0.62, test of difference between correlations, t=3.4,p=0.001).

Finally, examining interpersonal versus physical/non-social adversities, we found lower right VS activity in participants exposed to higher interpersonal cumulative life stress across all of childhood and adolescence (β=-0.34, p=0.003). This relationship was not seen for physical/non-social adversities during childhood and adolescence (β=-0.13, p=0.23; test of difference between correlations, t=2.05, p=0.04). Looking at specific developmental epochs, early interpersonal stress was related to lower right VS activity (β=-0.349, p=0.006), while early physical/non-social adversity was related to lower right VS activity at a trend level (β=-0.24, p=0.07). These correlations were however not statistically different from one another (t=0.99, p=0.32). No other significant relationships were found for exposure to interpersonal or physical/non-social stress during other developmental epochs (all p's>.18).

Supplemental Analyses using Ensemble Classifiers

In addition to the ordinary least-squares (OLS) regression models detailed in the main manuscript, we also conducted a Random Forest analysis (Breiman 2001) as implemented in the randomForest package (Liaw and Wiener 2002) in the R statistical

environment, using similar independent and dependent variable specification to the main manuscript (independent variable: stress exposure at early, mid, and late developmental epochs; dependent variable: one ROI [left VS; right VS from NeuroSynth]). This approach is an ensemble tree-based method that extends standard classification and regression tree (CART) methods by creating a collection of classification trees (the forest). The classification uncertainty of each tree is assessed using randomly selected cases, which are withheld during its construction (the out-of-bag or OOB cases). The importance of each independent variable is determined by evaluating the decrease in prediction accuracy when those variables are permuted and this decrease is averaged over all trees to produce a final measure of importance. The significance of the importance measures were assessed with 1,000 permutations of the dependent variable (Left or Right VS signal) using the rfPermute package for R.

Using this ensemble classification technique, we found that cumulative stress exposure accounted for 22.93% of the variance in VS signaling. This effect appeared to be driven by cumulative stress exposure early in development as eliminating this variable from our analyses (by permutation) produced a 12.15 (1.00 SD) mean decrease in accuracy (as indexed by an increase in MSE, p=.045; Supplemental S4). Stress exposure during the other two developmental periods was not significant when removed from classification analyses by permutation (Mid Developmental Epoch p=.4; Late Developmental Epoch p=.8).

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Supplemental Table S1.

Activation For Positive Feedback > Negative Feedback, p<.05, corrected

| Brain Region	Peak Voxel (t)	Cluster Size (k)	Peak Voxel (x,y,z)
Right Lateral Occipital Cortex, superior division	5.76	624	+33,-63,+42
Left Supramarginal Gyrus, posterior division	4.36	79	-37,-47,+36
Left Frontal Pole	4.42	48	-39,+53,+10
Left Precentral Gyrus	4.17	37	-37,+3,+36
Right Middle Frontal Gyrus	4.11	21	+33,+7,+56
Right Precentral Gyrus	4.07	13	+41,+3,+38
Right Ventral Striatum	4.52	12	+13,+7,-4
Right Frontal Pole	4.07	10	+27,+57,+12

Activation For Negative Feedback > Positive Feedback, p<.05, corrected

| Brain Region	Peak Voxel (t)	Cluster Size (k)	Peak Voxel (x,y,z)
none			

Supplemental Table S2.

Results from logical AND conjunction (Negative correlation with cumulative life stress

during early development epoch AND positive activation For Positive Feedback >

*Negative Feedback, both initial threshold p<.005, uncorrected)*

| Brain Region	Cluster Size (k)	Peak Voxel (x,y,z)
Frontal Pole	43	-32, 56, 12
Angular Gyrus	34	+46, -50, +48
Middle Frontal Gyrus	12	+42, +16, +44
Paracingulate Gyrus	12	+2, +16, +50

Supplemental Figure S1.
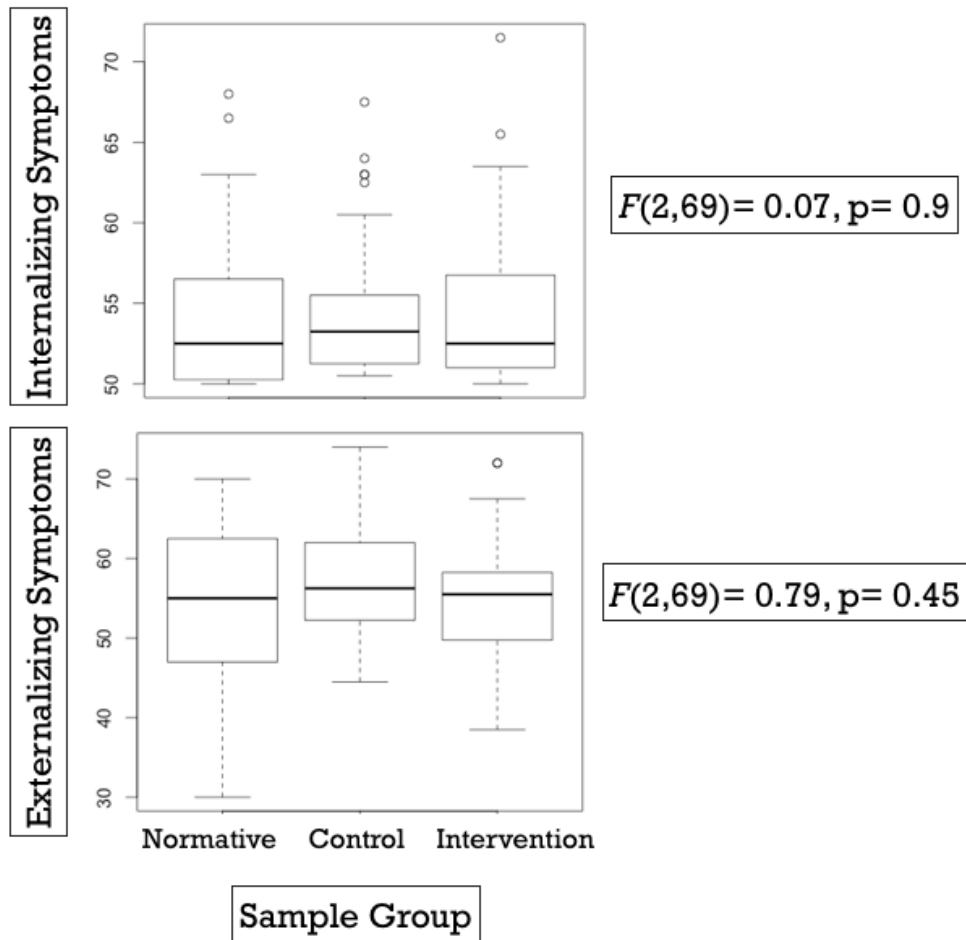
Caption: This figure depicts self-reported internalizing (top) and externalizing (bottom) symptomatology in the three Fast Track groups in our neuroimaging subsample. No differences in either type of symptomatology were found across groups (as noted in the main manuscript).

Supplemental Figure S2.
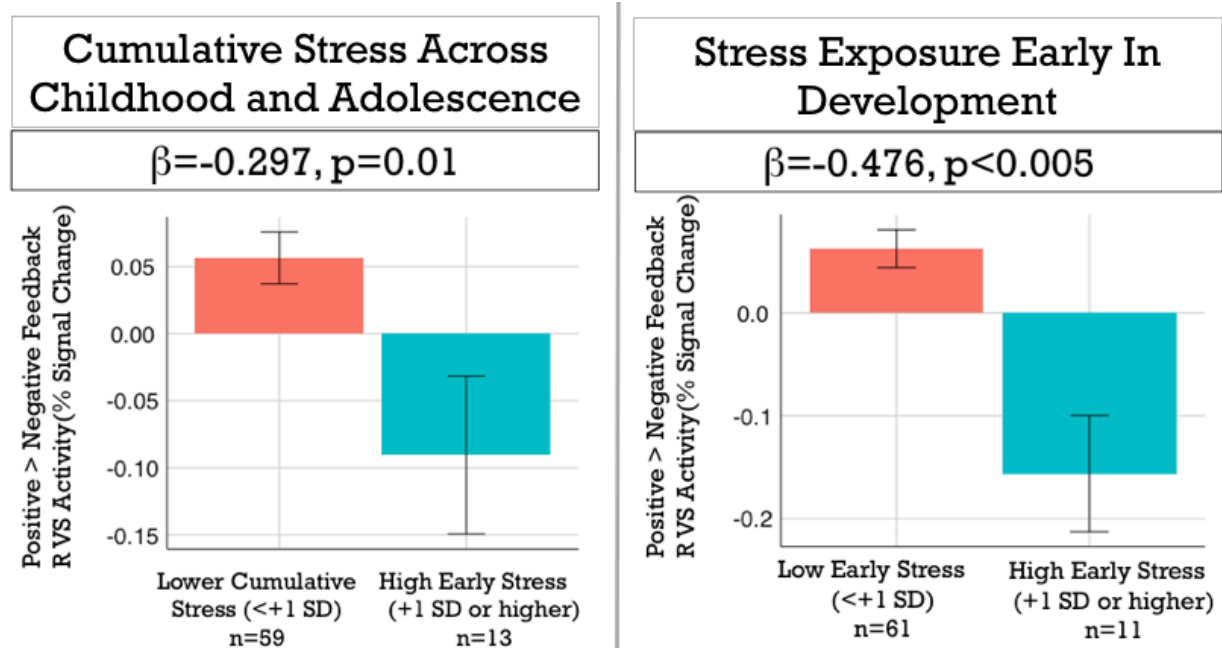
Caption: This figure depicts mean activity for positive > negative feedback in our right

VS ROI in relation to stress "threshold" effects. The left panel focuses on cumulative

stress across childhood and adolescence, finding lower right VS activity for participants

exposed to high levels of stress (+1 SD or higher). The right panel focuses on

cumulative stress early in development, again finding lower right VS activity for

participants exposed to high levels of stress (again, +1 SD or higher).

Supplemental Figure S3.
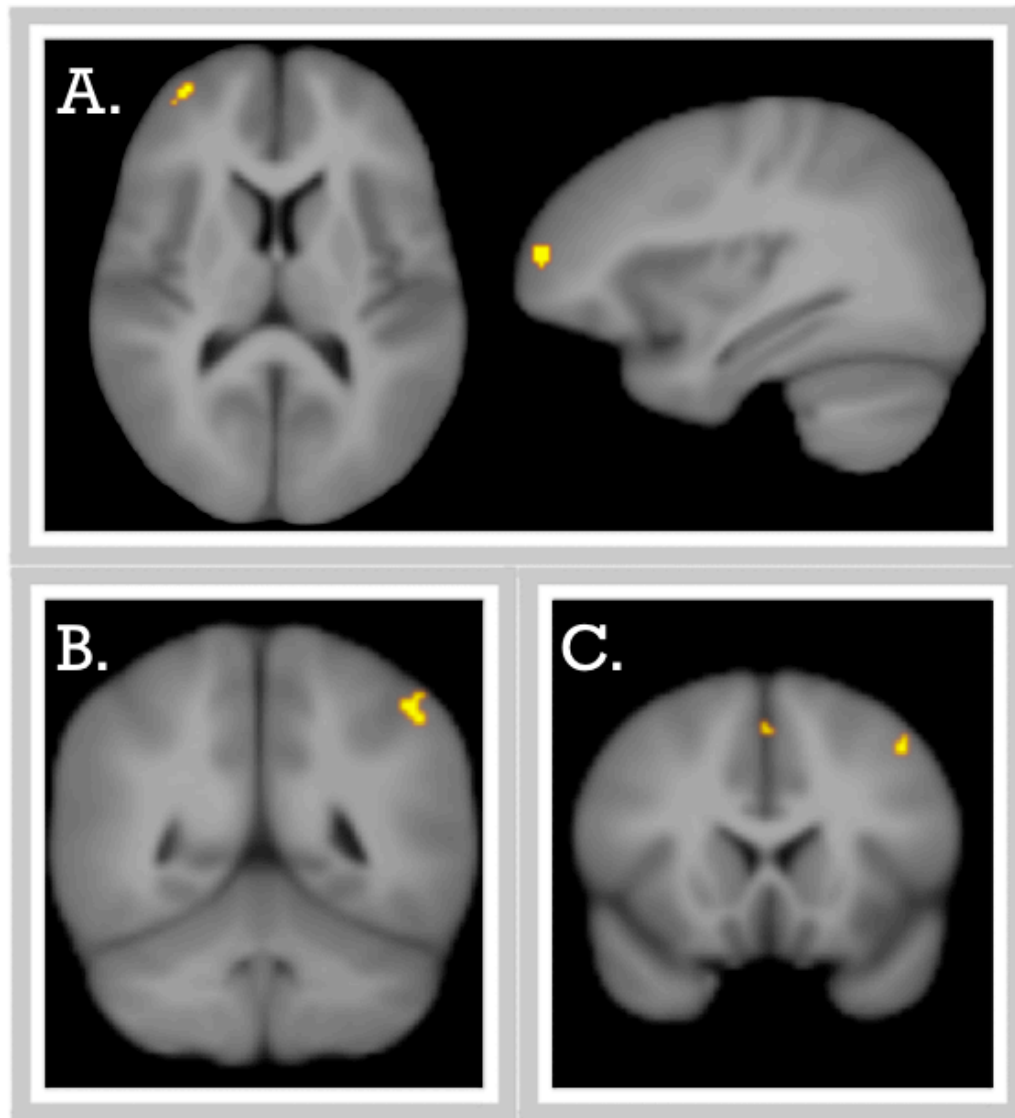
Caption: This figure shows brain regions that emerged from the logical AND conjunction analyses for stress exposure early in development and the main effect of positive > negative feedback. Panel A shows axial and sagittal views of a cluster in the frontal pole that emerged from our logical AND conjunction. Panels B and C show sagittal views of additional clusters that emerged for these analyses (Panel B: Angular Gyrus; Panel C: Paracingulate Gyrus and Middle Frontal Gyrus)

Supplemental Figure S4.

Permutation Testing	
Epoch	Significance
Early	p=.045
Mid	p=.4
Late	p=.8
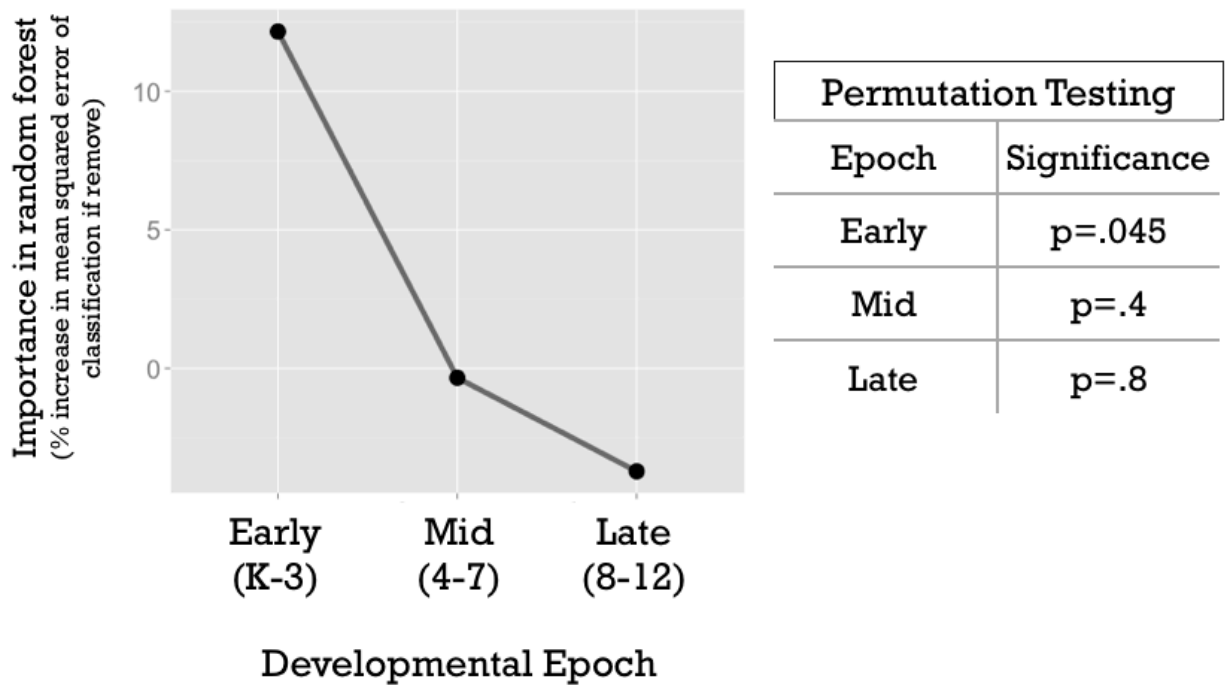
Caption: The left side of this figure shows the relative importance (as indexed by increase in mean squared error of classification, if removed from the model) of each developmental epoch in our random forest classification models. P-values of these importance values are noted on the right side of this figure.