Exposure to violence as an environmental pathway linking low socioeconomic status with altered neural processing of threat and adolescent psychopathology

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Abstract

Background: Low childhood socioeconomic status (SES) is associated with increased risk for psychopathology, due in part to heightened exposure to environmental adversity. Adverse experiences can be characterized along dimensions, including threat and deprivation, that contribute to psychopathology via distinct mechanisms. The current study investigated a neural mechanism through which threat and deprivation may contribute to socioeconomic disparities in psychopathology.

Methods: Participants were 177 youths (83 female) aged 10-13 years recruited from a cohort followed since age 3. SES was assessed using the income-to-needs ratio at age 3. At age 10-13, restrospective and current exposure to adverse experiences and symptoms of psychopathology were assessed. At this same timepoint, participants also completed a face processing task (passive viewing of fearful and neutral faces) during a functional magnetic resonance imaging scan.

Results: Lower childhood SES was associated with greater exposure to threat and deprivation experiences. Both threat and deprivation were associated with higher depression symptoms, whereas threat experiences were uniquely linked to PTSD symptoms. Greater exposure to threat, but not deprivation, was associated with higher activation in dorsomedial prefrontal cortex (dmPFC) and precuneus to fearful compared to neutral faces. Precuneus activation in this contrast mediated the association between SES and PTSD symptoms.

Conclusion: Precuneus and dmPFC are hubs of the default mode network thought to be involved in internally directed attention and cognition. Greater engagement of these regions in response to threat cues may contribute to PTSD symptomatology. Threat and contributes to socioeconomic disparities in adolescent psychopathology through distinct neural mechanisms from deprivation.

Introduction

About 1 in 7 children in the United States are estimated to live in poverty as of 2019 (US Census Bureau, 2019). The resulting strain that this lack of financial resources places on families and the communities in which they live increases the likelihood that children raised in families with low socioeconomic status (SES) will experience environmental adversities, including exposure to violence, family conflict, parental separation, low cognitive stimulation, and a less predictable environment (Evans, 2004; Rosen et al., 2020). These adverse childhood experiences have potent and enduring influences on children's development, contributing to SES-related disparities in mental health (Green et al., 2010; Kessler et al., 1997; McLaughlin, Green, et al., 2012). However, the associations between adversity and psychopathology involve a complex and varied set of mechanisms that may differ depending upon the nature of the adverse experience. Understanding the neural mechanisms linking SES and co-occurring experiences of environmental adversity with psychopathology may help generate novel targets for interventions aimed at reducing socioeconomic disparities in mental health. Here we focus on neural responses to threat-related stimuli as a potential mechanism underlying socioeconomic disparities in psychopathology specifically among children who have been exposed to violence.

Children raised in families with low SES are more likely to develop psychopathology in childhood and adolescence than those from higher SES backgrounds (Peverill et al., 2021), including mood, anxiety, behavior, and substance use disorders (McLaughlin, Costello, et al., 2012). Low SES is associated with increased likelihood of experiencing many forms of environmental adversity (Evans, 2004; Evans & Cassells, 2014; McLaughlin et al., 2011; Rosen et al., 2020), and adverse experiences are strongly related to the emergence of psychopathology across the lifespan (Green et al., 2010; Kessler et al., 1997; McLaughlin, Green, et al., 2012).

Therefore, exposure to adversity is an environmental pathway through which low childhood SES is likely to contribute to risk for psychopathology in children and adolescents. Indeed, cumulative exposure to adversity mediates the association between childhood poverty and psychopathology in early adulthood (Evans & Cassells, 2014). Existing work on this topic has relied on aggregate measures of adversity—often termed cumulative risk or an adverse childhood experiences score. This approach involves creating a count of the different types of adverse experiences to which a child has been exposed (Evans et al., 2013; Felitti et al., 1998). Cumulative risk scores reflect the fact that negative developmental and mental health outcomes are more likely among children who have experienced multiple co-occurring adversities that impact developmental outcomes through their impact on physiological stress response systems (Evans et al., 2013). However, such an approach precludes the ability to examine the potential for different types of adverse experiences influencing developmental outcomes through unique neurobiological mechanisms, which appears increasingly likely (see McLaughlin et al., 2021 for a review).

The dimensional model of adversity (McLaughlin, Sheridan, & Lambert, 2014; McLaughlin & Sheridan, 2016) proposes that complex environmental experiences can be distilled into core underlying dimensions that cut across many forms of adversity, and these dimensions have differential influences on cognitive, emotional, and neural development. Two initial dimensions proposed by the theory are threat and deprivation. Threat is characterized by experiences involving harm or threat of harm to the physical integrity of the child, such as exposure to abuse or violence. The dimensional model argues that experiences characterized by threat are associated with heightened behavioral and neural sensitivity to potential danger cues, including heightened neural response in the amygdala and broader salience network

(McLaughlin, Sheridan, & Lambert, 2014; McLaughlin & Sheridan, 2016; Sheridan & McLaughlin, 2014). Deprivation, in contrast, is characterized by the absence of social and cognitive inputs that the brain has evolved to expect during development, including cognitive stimulation and the presence of a responsive caregiver (McLaughlin, Sheridan, & Lambert, 2014; McLaughlin & Sheridan, 2016). The dimensional model posits that environments characterized by deprivation constrain children's learning opportunities leading to pronounced changes in higher-order cognitive functioning, including difficulties with language and executive function. Moreover, the model posits that children raised in deprived environments demonstrate altered structure and function of brain circuits underlying higher-order cognition, including the fronto-parietal network (Sheridan & McLaughlin, 2016). Here, we focus on neural mechanisms proposed in the dimensional model to be specifically related to experiences of threat.

Existing evidence on exposure to violence and developmental outcomes is largely consistent with the predictions of the dimensional model of adversity. Youth exposed to threat, but not deprivation, can detect anger with less perceptual information (Pollak et al., 2009; Pollak & Sinha, 2002), are more likely to perceive neutral or ambiguous expressions as angry (Pollak et al., 2000), and exhibit heightened attention to threat-related cues (Pollak et al., 2005; Pollak & Tolley-Schell, 2003) than youth never exposed to threat. In a recent systematic review, we found that threat exposure is consistently associated with elevated activation in amygdala and anterior insula to negative emotional cues in children and adolescents; in contrast, neither deprivation nor cumulative measures of adversity are consistently associated with neural responses to negative emotional cues (McLaughlin et al., 2019). Increased salience network reactivity to threat-related cues is associated with depression, anxiety, and post-traumatic stress disorder (PTSD)

(McLaughlin, Busso, et al., 2014; Pagliaccio et al., 2014; Swartz et al., 2015), and may therefore be an important mechanism linking threat-related adversity with psychopathology.

Although prior studies provide preliminary support for the dimensional model, most studies examining childhood adversity and neural functioning recruit children with a particular type of adversity, such as physical abuse or neglect, without careful measurement and control of co-occurring adversity. These exposures are typically measured dichotomously as the presence or absence of adversity—rather than as dimensions and typically in small samples (McLaughlin et al., 2019, 2021). One prior study has simultaneously examined the associations of threat and deprivation with neural responses to emotional faces (Hein et al., 2020). No significant differences were observed in this study between threat-related adversity and neural responses to fearful or angry faces (relative to implicit baseline). However, contrasting the face stimuli with implicit baseline makes it difficult to determine whether the associations with adversity are specific to those emotions, to the emotional valence, or to faces in general. In the present study, we contrasted fearful faces with neutral faces to evaluate if stimuli that specifically reflect the presence of environmental threat, elicit differential neural responses in youth exposed to violence. We examined continuous indicators of threat and deprivation, thereby quantifying a fuller range of variability across these dimensions than dichotomous indicators of exposure to a particular category of adversity. Moreover, we included measures of threat and deprivation in the same analysis, to evaluate whether associations with neural response to fearful vs. neutral faces are specific to threat-related adversity. Finally, we determined whether these neural responses were related to symptoms of internalizing psychopathology. We focused on internalizing problems because associations between neural responses to threat-related cues and externalizing problems are more complex and heterogenous depending on the presence or absence of callous-

unemotional traits (Blair et al., 2016; Dotterer et al., 2017; Viding et al., 2012), which were not measured in this study.

In the current study, we examined the distinct role of environmental experiences of threat and deprivation in explaining socioeconomic disparities in mental health and a potential neural mechanism that may contribute to these disparities. We expected that low SES would be associated with higher exposure to both threat and deprivation, and that experiences of threat and deprivation would mediate the associations between early childhood SES and symptoms of depression and anxiety. In addition, we anticipated that only threat would be associated with PTSD symptoms as well as elevated neural response in the amygdala and salience network (e.g., anterior insula) to fearful relative to neutral faces. Finally, we predicted that heightened neural responses to threat cues would be associated with greater symptoms of depression, anxiety, and PTSD and would mediate the prospective association between low SES and symptoms of psychopathology, suggesting a neural mechanism through which threat uniquely contributes to internalizing psychopathology.

Method

Participants

Participants were drawn from a longitudinal study of youth followed since age 36 months in the Seattle, Washington area (Lengua et al., 2015). Children were recruited from a university-hospital birth registry, daycares, preschools, health clinics, and charitable agencies to have a uniform distribution across SES based on family income. The current report focuses on a sub-sample who participated in a follow-up neuroimaging session performed when children were aged 10-13 years (M=11.0, SD=0.59). A total of 177 youth (83 female) completed the face processing fMRI task with useable data (see fMRI Pre-processing for details). Comprehensive

assessments of adversity experiences and symptoms of psychopathology were also completed at this timepoint. The racial/ethnic composition of the sample approximates the broader Seattle area: White (n=116, 66%), Black (n=21, 12%), Latinx (n=18, 10%), Asian (n=15, 8%), and other (n=7, 4%).

Measures

Socioeconomic Status

When participants were 3 years old, mothers reported on family income and the number of people in the household. Income-to-needs ratio was calculated by dividing the parent-reported family income by the poverty threshold for a family of that size for the year of data collection, as indicated by the U. S. Census Bureau (U.S. Census Bureau, 2019). Consistent with prior work on childhood SES and neurodevelopment (Noble et al., 2015; Rosen et al., 2018) the natural log of income-to-needs ratio was used as a measure of family income in all analyses to reflect that associations of income with neural outcomes are stronger at the lower end of the SES distribution.

Threat Experiences

To quantify threat experiences, we used a composite reflecting the number of distinct types of violence the child had experienced, the frequency of violence exposure, and the severity of violence exposure, all reported when participants were age 10-13.

First, we used a count of exposure to 5 types of interpersonal violence—physical abuse, sexual abuse, domestic violence, witnessing a violent crime or being a victim of a violent crime. Each exposure was counted if it was endorsed by the parent or child on the UCLA PTSD Reactions Index (The University of California at Los Angeles Post-Traumatic Stress Disorder Reaction Index, 2004); physical abuse, sexual abuse, and domestic violence were coded as

present if they were endorsed by the child on the Childhood Experiences of Care and Abuse (CECA) Interview (Bifulco et al., 1994). The PTSD-RI includes a trauma screen that assesses exposure to numerous traumatic events, including physical abuse, sexual abuse, and domestic violence and additionally assesses PTSD symptoms. The PTSD-RI has good internal consistency and convergent validity (Steinberg et al., 2013). The CECA assesses caregiving experiences, including physical, sexual, and emotional abuse. We modified the interview to ask parallel questions about witnessing domestic violence (e.g. "'When you were a child or teenager, did you ever see or hear your parents or caregivers hit each other repeatedly with something like a belt or stick or hit, punch, kick, or burn each other?"). Inter-rater reliability for maltreatment reports on the CECA is excellent, and validation studies suggest high agreement between siblings (Bifulco et al., 1997).

Second, to assess the frequency of violence exposure, we used the summed frequency ratings of witnessed and experienced violence on the Violence Exposure Scale for Children-Revised (VEX-R) (Raviv et al., 1999, 2001). The VEX-R assesses the frequency of exposure to different forms of violence. Children are presented with a cartoon and caption depicting a child of the same sex witnessing a type of violence (e.g., "Chris sees a person slap another person really hard") and experiencing that same type of violence (e.g., "A person slaps Chris really hard"). Children are then asked to report how frequently they have witnessed or experienced that type of violence (e.g., "How many times have you seen a person slap another person really hard?"; "How many times has a person slapped you really hard?") on a Likert scale ranging from 0 (Never) to 3 (Lots of times). The VEX-R demonstrates good reliability and has been validated with children as young as second grade (Raviv et al., 1999, 2001).

Third, to assess the severity of violence exposure, we used the physical and sexual abuse subscales from the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1997). The CTQ is a 28-item scale that assesses the severity of maltreatment during childhood, including physical and sexual abuse (e.g. "People in my family hit me so hard that it left me with bruises or marks."). The CTQ has excellent psychometric properties including internal consistency, test-retest reliability, and convergent and discriminant validity with interviews and clinician reports of maltreatment (Bernstein et al., 1994, 1997).

To create a threat composite, we first standardized each of these three sub-scales of 1) number of violence exposure types, 2) frequency of violence exposure, and 3) severity of physical or sexual abuse exposure, and averaged them together. The construction of this composite has been pre-registered (osf.io/6yf4p/).

Deprivation Experiences

To quantify deprivation, we used a composite comprised of cognitive, emotional, and physical forms of deprivation, all reported when participants were age 10-13.

Cognitive deprivation was assessed using the Home Observation Measurement of the Environment – Short Form (HOME-SF) (Mott, 2004). This measure assesses numerous forms of cognitive stimulation, including the presence of learning materials in the home, the child's engagement with activities outside the home, the degree of caregiver involvement in learning, and the complexity of the linguistic environment. To assess cognitive stimulation, HOME items are scored dichotomously such that the presence of a stimulating activity or experience is coded as 1 and the absence is coded as 0. Because we were interested in quantifying cognitive deprivation, we reversed-scored the measure. To create a cognitive deprivation measure, we created a binary score of the 19 cognitive stimulation items (e.g. "Did you and/or your partner

teach your child colors at home?") such that the presence of each item reflecting cognitive stimulation was scored as a 0 and the absence was scored as a 1. We then standardized this summed variable to create a continuous measure of cognitive deprivation.

Emotional deprivation was assessed with several scales measuring emotional neglect of the child by caregivers. These included the emotional neglect subscale of the Multidimensional Neglectful Behavior Scale (MNBS) (Kantor et al., 2004) and the emotional neglect items from the CECA Interview. The MNBS includes subscales for emotional needs (e.g., "helped you when you had problems"), physical needs, cognitive needs, and supervision needs. It has good internal consistency and convergent validity with related measures of exposure to neglect and other adversity and mental health (Kantor et al., 2004). The CECA neglect scale includes items that assess both emotional and physical neglect by the child's primary male and female parental figures. We included only the 8 items assessing emotional neglect (e.g. "she was concerned about my worries"). For participants who reported on both a female and male parental figure, the higher of the two scores was used. We created a total sum score for each of these scales, standardized each scale, and averaged these z-scores together to create the final composite score of emotional deprivation.

Physical deprivation was quantified using the physical needs subscale of the MNBS (e.g. "Make sure you bathed regularly"), the 4-item Household Food Insecurity Scale as completed by a caregiver (e.g. "How often in the past 12 months did you not have enough money to buy food?"), and the Physical Neglect subscale of the CTQ (e.g. "I had to wear dirty clothes"). Because these measures utilize the same scoring scale and had a nearly identical range in our dataset, we took the mean of these three scales and standardized it to create a composite score of physical deprivation.

To create a composite reflecting all three types of deprivation, we took the mean of the cognitive, emotional, and physical deprivation standardized scores. The construction of this deprivation composite has been pre-registered (osf.io/6yf4p/).

Symptoms of Psychopathology

Depression symptoms were assessed by self-report with the Children's Depression Inventory-2 (CDI), a recently revised version of the widely used self-report measure of depressive symptoms in children and adolescents (Kovacs, 1992, 2011). The CDI has demonstrated good reliability and validity in children and adolescents (Craighead et al., 1998). The CDI demonstrated good internal consistency in our sample (α=.87).

Anxiety symptoms were assessed by self-report with the Screen for Child Anxiety Related Emotional Disorders (SCARED), which measures anxiety disorder symptoms across five domains: panic/somatic, generalized anxiety, separation anxiety, social phobia, and school phobia (Birmaher et al., 1997). The SCARED has sound psychometric properties (Birmaher et al., 1997, 1999) and good internal consistency in our sample (α=.90).

Symptoms of PTSD were assessed using child- and parent-report versions of the UCLA PTSD Reaction Index (PTSD-RI) (The University of California at Los Angeles Post-Traumatic Stress Disorder Reaction Index, 2004). The PTSD-RI assesses PTSD re-experiencing, avoidance/numbing, and hyper-arousal symptoms according to DSM-IV criteria. A total symptom severity score is generated by summing all items. The higher of the parent- and child-reported symptom severity was used. The PTSD-RI has sound psychometric properties (Steinberg et al., 2013), and had excellent internal consistency in our sample (α=.89).

Emotional Faces Task

The face processing task consisted of 2 runs of a face-viewing task in which participants passively viewed emotional face stimuli. Faces were drawn from the NimStim stimulus set (Tottenham et al., 2002). The "calm" faces from this dataset were used as neutral expressions, as these expressions are potentially less emotionally evocative than neutral faces, which can be perceived as negatively valenced (Tottenham et al., 2009). Each run consisted of 3 blocks of calm, fearful, and scrambled faces and 3 fixation blocks displayed in a pseudo-random order that ensured that no block type was displayed twice in a row. During each 18 second block, 36 faces of different actors expressing the same emotion were displayed for 300 ms each, with 200 ms between each face, based on prior face processing tasks (Somerville et al., 2004). At one point during each block participants were prompted to indicate by an index or middle finger button press whether the last face they saw was male or female (or whether a dot appeared on the left or right side of the screen for scrambled face blocks) to ensure they were paying attention to the stimuli. Three participants performed below chance on this attention check and were excluded from analyses.

fMRI Data Acquisition

Before undergoing scanning, youth were trained to minimize head movements in a mock scanner. They watched a movie with a head-mounted motion tracker that stopped playing if a movement of over 2 mm occurred. This method has been shown to significantly reduce head motion once children are in the scanner (Raschle et al., 2012). In the scanner an inflatable head-stabilizing pillow was used to restrict movement.

Scanning was performed on a 3T Phillips Achieva scanner at the University of Washington Integrated Brain Imaging Center using a 32-channel head coil. T1-weighted MPRAGE volumes were acquired (repetition time=2530 ms, TE=3.5ms, flip angle=7°,

FOV=256×256, 176 slices, in-plane voxel size=1mm^3) for co-registration with fMRI data. Blood oxygenation level dependent (BOLD) signal during functional runs was acquired using a gradient-echo T2*-weighted echo planar imaging (EPI) sequence. Thirty-seven 3-mm thick slices were acquired sequentially and parallel to the AC-PC line (TR=2s, TE=25ms, flip angle=79°, Inter-slice gap=.6mm, FOV=224×224×132.6, matrix size=76x74). Prior to each scan, four images were acquired and discarded to allow longitudinal magnetization to reach equilibrium.

fMRI Preprocessing

Preprocessing and statistical analysis of fMRI data was performed in a pipeline using Gnu Make, a software development tool designed for building executables from source files that can be used to create neuroimaging workflows that rely on multiple software packages. The following preprocessing steps were applied: 1) motion correction followed by slice-time correction in FSL; 2) skull-stripping using FSL's bet tool; 3) despiking using AFNI's 3dDespike tool; and 4) smoothing with a 6mm full-width half-max kernel using SUSAN in FSL. Outlier volumes in which framewise displacement exceeded 1mm, the derivative of variance in BOLD signal across the brain (DVARS) exceeded the upper fence (above 75th percentile + 1.5 × inter-quartile range), or signal intensity was more than 3 SD from the mean were regressed out of person-level models. Six rigid-body motion regressors and the time-series extracted from white matter and ventricles were included in person-level models to reduce noise associated with motion and physiological fluctuations. Person- and group-level models were estimated in FSL. Following estimation of person-level models, the resulting contrast images were normalized into standard space, and anatomical co-registration of the functional data with each participant's T1-weighted image was performed using Advanced Normalization Tools (ANTs) software.

Data were visually inspected for the presence of major artifacts or abnormalities in the structural and functional images by two trained researchers. Following person-level analyses, four participants were excluded from group-level analyses because of substantial signal dropout in the ventromedial prefrontal cortex, indicating distortion of data in relevant brain regions for this analysis. One was excluded because of an incidental finding indicating a major structural abnormality, and one participant's data were unusable due to a data storage error. One run of data was excluded for four additional participants: 2 because of excessive motion, one because of a data acquisition error, and one because the scan was interrupted after the first run.

fMRI Analysis

FMRI data processing was performed using FSL FEAT version 6.0.0. Regressors were created by convolving a boxcar function of phase duration with the standard double-gamma hemodynamic response function for each phase of the task (fearful, neutral, and scrambled faces). A general linear model was constructed for each participant. Higher level analysis was carried out using FLAME1.

To investigate study hypotheses, we first conducted a single whole-brain multiple regression analysis using FSL FEAT, with threat and deprivation composites as the continuous independent variables, and neural activation to fearful vs. neutral faces as the outcome variable. Whole-brain analyses were conducted within a gray matter mask created by segmenting the MNI 152 2mm voxel template image using FSL FAST. Cluster thresholding was determined using AFNI's *3dClustSim* (Cox et al., 2017b), which generates Monte Carlo simulations to determine appropriate cluster sizes, and AFNI's *3dFWHMx*, which accounts for the number of voxels and the intrinsic spatial autocorrelation in the data residuals, addressing prior work indicating that failure to account for this autocorrelation in cluster correction can inflate type 1 error (Cox et al.,

2017a; Eklund et al., 2016). Based on output from these programs, a voxel-wise threshold of t=2.58 (p<.01) with a minimum cluster size of 343 voxels was used, to set the corrected family-wise error rate at .05. Sex, age, and income-to-needs ratio were included as covariates.

Because a minimum cluster size limits the ability to detect smaller clusters, particularly in subcortical regions, and given substantial evidence for differences in amygdala response to threat cues in children exposed to violence (McLaughlin, Weissman, & Bitran, 2019), we also conducted a region of interest (ROI) analysis in the amygdala. Bilateral amygdala ROIs were constructed in FSL based on the Harvard Oxford subcortical probabilistic structural atlas, thresholded at 20% probability and warped back into each subjects' native space. The mean of the z-scores of every voxel within the bilateral amygdala ROI were then extracted for the fear vs. neutral contrast for each participant. Differences in amygdala response as a function of threat and deprivation were examined using linear regression, controlling for age, sex, and income-to-needs, using R version 4.0.0.

Mean z-scores were extracted from clusters that were significantly associated with threat or deprivation to examine their associations with psychopathology.

Linear Regression and Mediation analyses

Linear regression was used to investigate the associations of: 1) the income-to-needs ratio in early childhood (referred to hereafter as SES) with experiences of threat and deprivation, controlling for age and sex; 2) SES with symptoms of psychopathology, controlling for age and sex; and 3) the threat and deprivation composites with symptoms of psychopathology, controlling for SES, age, and sex. Indirect effects with bootstrapped confidence intervals (10,000 iterations) were calculated using the "boot" package in R (Canty & support), 2021) to evaluate

whether threat and deprivation experiences mediated associations between early childhood SES and psychopathology symptoms.

Next, we examined the associations of threat and deprivation composites with neural responses during the face processing task for the contrast of fearful > neutral faces. We then examined the association of neural activity within brain regions that were significantly associated with threat or deprivation with symptoms of psychopathology, controlling for the threat and deprivation composites, age, sex, and SES. PTSD symptoms were positively skewed and zero-inflated. Further, because the absence of trauma exposure explains a large portion of the zeroes, many of the zeroes are explainable by a separate process than the positive counts of PTSD symptoms. Therefore, zero-inflated Poisson regression using the "pscl" package (Jackman et al., 2020) was used to evaluate the association between neural response to threat and PTSD symptoms. This approach uses a 2-component mixture model, comprised of a count and zero-inflation model. The count model uses Poisson regression with a log link. The zero-inflation model is binomial with a logit link. The zero-inflation model as implemented in the "pscl" package estimates whether or not the outcome variable is zero. Therefore, a positive coefficient indicates lower incidence of PTSD symptoms, and a negative coefficient indicates greater incidence of PTSD symptoms.

For brain regions that were significantly associated with threat or deprivation, indirect effects with bootstrapped confidence intervals (10,000 iterations) were calculated using the "boot" package in R (Canty & support), 2021) to evaluate whether neural activation in those regions mediated associations between early childhood SES and psychopathology symptoms, controlling for experiences of threat and deprivation. This approach uses brain regions identified through whole brain analyses, but because the independent variables from those analyses are not

variables of interest in the mediation model and are controlled for, it avoids inflated estimates of associations between individual characteristics and brain function (i.e. "double dipping") (Kriegeskorte et al., 2009). Indeed, our analysis approach is especially conservative, likely leading to a deflation rather than an inflation of the associations of between brain regions identified through whole brain analysis and both SES and psychopathology. All regression models were checked for possible multicollinearity problems using the mctest package in R (Muhammad & Muhammad, 2020). The Variance Inflation Factor did not exceed 1.31, and the lowest tolerance was 0.762, indicating no multicollinearity problems (O'brien, 2007).

Results

Descriptive Statistics

Descriptive statistics and zero-order correlations are summarized in Table 1. Reproducible code, data, and complete results of analyses (R markdown) are available online at https://github.com/dgweissman/depthreat.

Early Childhood SES, Adversity Experiences, and Psychopathology Symptoms

Lower early childhood SES was associated with higher symptoms of depression (B=-1.82, SE=0.50, p<.001) and greater incidence (B=.782, SE=.222, p<.001) and severity (B=-.242, SE=.038, p<.001) of PTSD symptoms based on zero-inflated Poisson regression in early adolescence. Early childhood SES was not related to anxiety symptoms.

Lower early childhood SES was associated with greater exposure to threat (B=-.266, SE=.066, p<.001) and deprivation (B=-.352, SE=.062, p<.001) experiences.

Adversity Experiences and Psychopathology

Greater frequency and severity of threat-related experiences (B=1.69, SE=0.54, p=.002) and deprivation experiences (B=2.56, SE=0.58, p<.001) were each associated with higher

depression symptoms. In a mediation analyses, higher levels of both threat (*95% CI*=-.962,-.067) and deprivation (*95% CI*=-1.655,-0.463) each mediated the association between lower childhood SES and depression symptoms (Figure 1A) .

Exposure to threat, but not deprivation, was associated with greater incidence (*B*=-.984, *SE*=.342, *p*=.004) and severity (*B*=.282, *SE*=.033, *p*<.001) of PTSD symptoms based on zero-inflated Poisson regression. Threat mediated the association between lower family SES and both the incidence (*95% CI*=.078,0.581) and severity (*95% CI*=-.159,-.019) of PTSD symptoms (Figure 1B).

Neither threat nor deprivation were significantly associated with anxiety symptoms.

Neural Activation during Emotional Face Viewing

In the entire sample, fearful relative to neutral faces elicited widespread activation, including in the bilateral amygdala, anterior insula, subgenual anterior cingulate cortex, dorsal and ventral regions of both lateral and medial prefrontal cortex, ventral temporal cortex, superior temporal sulcus, and temporal pole (Figure 2, Table 2).

SES, Adversity Experiences and Neural Response to Faces

Whole-brain multiple regression analysis revealed that more frequent and severe experiences of threat-related adversity, controlling for deprivation experiences, were associated with higher activation in the precuneus and the dorsomedial prefrontal cortex (dmPFC; specifically the bilateral superior frontal gyrus), to fearful relative to neutral faces (Table 3, Figure 3). In contrast, deprivation-related adversity experiences were not associated with neural activation to fearful relative to neutral faces, controlling for threat-related experiences. No associations between threat- or deprivation-related adversity and amygdala activation to fearful

relative to neutral faces were observed. Regions that were significantly associated with SES in whole brain analyses are summarized in Table 4

Neural Activation to Faces and Psychopathology Symptoms

Neither activation in the dmPFC nor in the precuneus were significantly associated with depression. Greater activation in the clusters in precuneus and dmPFC that were significantly associated with threat was associated with greater severity of PTSD symptoms in zero-inflated Poisson regression (Table 5, Figure 4). Greater activation in precuneus (*95% CI*=-0.133,-0.005), but not dmPFC (*95% CI*=-0.070,0.007) mediated the association between lower early childhood SES and greater severity of PTSD symptoms, controlling for threat and deprivation experiences.

Discussion

Low childhood SES is associated with increased risk for multiple forms of psychopathology (Peverill et al., 2021). In this study, we provide evidence for both environmental and neural mechanisms that contribute to socioeconomic disparities in mental health. Low family SES in early childhood was associated with higher levels of depression and PTSD symptoms in early adolescence. Children raised in lower SES families experienced higher levels of adversity involving both threat and deprivation, which each mediated the association of SES with depression symptoms. In contrast, only threat-related adversity mediated the association of SES with PTSD symptoms. Exposure to more severe and chronic experiences of threat, but not deprivation, was associated with increased neural activation in the dmPFC and precuneus—two hubs of the default mode network—when viewing fearful compared to neutral faces. Greater activation in dmPFC and precuneus to fearful vs. neutral faces, in turn, was associated with greater severity of PTSD symptoms and mediated the association of low childhood SES with PTSD. Thus, childhood adversity characterized by threat, but not

deprivation may shift neural processing of threat-related cues in the environment, which may contribute to more severe PTSD symptoms. More broadly, these findings support a dimensional approach to characterizing adversity by demonstrating how experiences of threat and deprivation influence socioeconomic disparities in mental health through distinct mechanisms.

Children raised in low SES families are more likely to experience a wide range of adverse experiences than their higher-SES peers (Bradley et al., 2001; Evans, 2004; Evans & Cassells, 2014; McLaughlin et al., 2011; Rosen et al., 2020). Here, we demonstrate that experiences of both threat and deprivation were more common among children from lower SES backgrounds and contributed to socioeconomic disparities in mental health by early adolescence. Greater exposure to both threat and deprivation experiences explained higher levels of depression symptoms among children from low-SES families. This is consistent with prior work, which has demonstrated that threat and deprivation are independently associated with psychopathology (Miller et al., 2018, 2021). In these studies, threat-related adversity had direct associations with psychopathology, whereas deprivation-related adversity to influenced psychopathology indirectly through its impact on language functioning. In contrast, only threat-related adversity mediated the association between low SES and PTSD symptoms. Given that trauma exposure is a prerequisite for a diagnosis of PTSD, it is unsurprising that associations between income and PTSD symptoms would be mediated solely by threat. Conversely, neither SES, threat, nor deprivation were associated with symptoms of anxiety in this sample. Nonetheless, together, these findings highlight an environmental pathway involving elevated exposure to multiple forms of adversity that contributes to socioeconomic disparities in youth mental health.

We additionally document a potential neural mechanism linking low childhood SES with elevations in PTSD symptoms, although they were not the mechanisms we hypothesized. Children who experienced more severe and frequent exposure to violence exhibited greater activation in the dmPFC and the precuneus when viewing fearful relative to neutral faces. The dmPFC and precuneus are among the hubs of the default mode network (Buckner et al., 2008), a set of brain regions involved in mentalizing (i.e. representing the thoughts and emotions of one's self and others), autobiographical memory, and prospection (Spreng et al., 2009). Among youth exposed to higher levels of violence, fearful faces may evoke engagement of mentalizing to a greater degree in order to identify the source of the potential threat. This interpretation is consistent with evidence that children exposed to violence tend to identify threat cues, including fearful faces, faster and with less perceptual information than children who have never experienced violence (Pollak et al., 2009; Pollak & Sinha, 2002). Alternatively, fearful faces may evoke memories of one's own experiences of fear and distress to a greater extent among youth who have more varied, frequent, and severe threatening experiences, consistent with extensive work demonstrating that trauma-relevant cues trigger memory for prior traumatic events, especially among individuals with more severe PTSD symptoms (Amir et al., 2010; Ehring & Ehlers, 2011; Michael et al., 2005). This may explain the association between greater recruitment of these regions to fearful relative to neutral faces and more severe symptoms of PTSD, even after controlling for the degree of exposure to trauma. It is plausible that these patterns of neural activity may, in particular, underlie re-experiencing symptoms of PTSD—the intrusive recollections of traumatic events that are a hallmark of the disorder (Bar-Haim et al., 2021; Brewin, 2015). Adolescents with PTSD have greater resting-state functional connectivity within the default mode network, and greater connectivity within this network is associated with more

severe re-experiencing symptoms (Patriat et al., 2016). Here, precuneus activation to fearful relative to neutral faces mediated the association of early childhood SES with PTSD symptom severity in adolescence, even controlling for trauma exposure. These are speculative interpretations of unexpected findings. However, future work could help validate and disentangle these potential explanations by examining whether greater activation of dmPFC and precuneus to fearful vs. neutral faces in youth exposed to higher levels of threat relates to behavioral measures of acuity and speed at identifying fear or anger in others, or the extent to which fear cues primed recall of autobiographical memories of one's own experiences of fear (Amir et al., 2010; Ehring & Ehlers, 2011; Michael et al., 2005).

In contrast, as expected, experiences of deprivation were not associated with neural responses to fearful relative to neutral faces. This is consistent with the predictions of the dimensional model of adversity, which suggest that while the absence of species typical developmental inputs among children from deprived environments constrains learning opportunities important for cognitive development, neural responses to emotion in the absence of cognitive demands are less likely to be influenced by experiences of deprivation relative to threat (McLaughlin, Sheridan, & Lambert, 2014; McLaughlin et al., 2021). Indeed, a recent systematic review observed no association of deprivation-related adversity with neural responses to threat cues in the amygdala or salience network (McLaughlin, Weissman, & Bitran, 2019). Conversely, reductions in cortical thickness and volume in the frontoparietal control network have consistently been associated with deprivation-related adversity (Edmiston et al., 2011; McLaughlin et al., 2019; McLaughlin, Sheridan, Winter, et al., 2014) in regions that support emotion regulation processes (Eippert et al., 2007; Hartley & Phelps, 2010; Levesque et al., 2004; Niendam et al., 2012). These changes in cortical structure may be a neural pathway

influencing psychopathology among youth who experience high levels of deprivation, a possibility that is important to examine in future research. Overall, these findings add to a growing body of evidence suggesting that threat and deprivation influence the emergence of psychopathology through distinct mechanisms (McLaughlin et al., 2021).

Contrary to our hypothesis, threat-related adversity was not associated with amygdala response to fearful compared to neutral faces, nor was it associated with activation in the insula or other regions of the salience network. Most studies examining measures of threat-related adversity have found elevated activation in amygdala and anterior insula to negative emotional cues in children and adolescents (McCrory et al., 2011, 2013; McLaughlin et al., 2015, 2019; Suzuki et al., 2014). Conversely, and consistent with our findings most studies of deprivation or cumulative measures of adversity have not found increased amygdala reactivity to negative emotional cues (McLaughlin et al., 2019). However, in recent work using this same task in a different sample, we also did not find a significant association between violence exposure and amygdala reactivity to fearful faces (Weissman et al., 2019). It is plausible that the lack of an association between threat-related adversity and amygdala reactivity in the present study is attributable to task design. The task paradigm used in the current study did not constrain attention, a decision made because prior evidence indicates that attentional constraints reduce amygdala reactivity (Costafreda et al., 2008). However, this may have allowed for participants who to divert their attention away from the faces more. Indeed, a prior study found that adults exposed to childhood adversity had greater amygdala reactivity to fearful and angry faces when attention was constrained, but lower amygdala reactivity when it was not (Taylor et al., 2006). In addition, that study included only fearful faces, while many notable studies demonstrating associations between threat-related adversity and amygdala reactivity include angry faces (e.g.

McCrory et al., 2011, 2013). Fearful facial expressions indicate the presence of a potential threat in the environment, as reflected in another person's fear or distress. However, the fearful expression is not threatening in and of itself in the way that an angry expression is. Indeed, the brain regions activated by fearful relative to neutral faces in the current study overall are more consistent with engagement of social information processing in general (Fusar-Poli et al., 2009; Nelson et al., 2005), rather than a salience network response to threat (Menon, 2011).

This study had several strengths, including a well-powered sample recruited to ensure sufficient variability in both threat exposure and deprivation as dimensional measures and integration of multiple measures of threat and deprivation from both youths and parents. However, three primary limitations are important to consider when interpreting these findings. First, because the age range of the participants was constrained to early adolescence, we are unable to definitively characterize the specificity or generalizability of these findings across childhood and adolescence. Future work should examine these questions in a broader age range to determine how deprivation and threat exposure are differentially associated with brain function across development. Second, our measures captured the variety, frequency, and severity of threat and deprivation experiences but may not fully capture other important characteristics such as developmental timing of these exposures or the subjective distress or interpretations of these experiences, which may be important in shaping developmental outcomes (Smith & Pollak, 2020). Finally, the stimuli in the current study included only fearful and neutral faces. Therefore, we are unable to determine whether the greater activation in dmPFC and precuneus among youth exposed to higher threat characterizes a pattern of responding to expressions of fear specifically or negative emotion more generally.

In conclusion, in a prospective design, we identified both environmental pathways and neural mechanisms that contribute to socioeconomic disparities in mental health. Consistent with the dimensional model of adversity, we found that adverse experiences reflecting the dimensions of threat and deprivation made distinct contributions to mental health. Both threat and deprivation played a role in explaining socioeconomic disparities in depression, while only threat experiences were associated with differential neural responses to emotional cues, leading to socioeconomic disparities in PTSD severity.

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Table 1: Descriptive Statistics and Intercorrelations

	N	%	Cohen's d	Correlations						
1. Sex (Female)	83	46.9	-							
	M	SD	1	2	3	4	5	6	7	8
2. Age	11.62	0.51	.184	-						
3. Log income-to-needs	0.89	0.77	-.092	-.032	-					
4. Threat	-0.01	0.70	.172	-.055	-.292*	-				
5. Deprivation	-0.02	0.69	.253	-.022	-.399*	.358*	-			
6. Anxiety Symptoms	17.44	10.47	.094	-.029	-.062	.183*	.168*	-		
7. Depression Symptoms	4.86	5.31	.325*	-.039	-.269*	.373*	.451*	.536*	-	
8. PTSD Severity	4.47	8.64	.156	-.004	-.329*	.478*	.203*	.236*	.444*	-

* p<.05, Cohen's d is provided for all variables in relation to sex. All other bivariate associations are correlations.

Table S1. Mean activation to emotional faces

Voxels	Peak (x, y, z)	Region	Peak voxel z-score
		Fear > Neutral	
17,403	-58, -50, 6	Left Middle Temporal Gyrus	9.11
	-30, 16, 32	Left Superior Temporal Gyrus	5.90
	-4, 50, 28	Left Medial Frontal Gyrus	5.79
4,465	50, 32, -4	Right Middle Temporal Gyrus	8.98
		Neutral > Fear	
378	-30, -62, -6	Left Parahippocampal Gyrus	3.93

Note: Peak (x, y, z)=MNI coordinates for the voxels with the highest coefficients within each cluster, voxel-wise p-threshold = .01, minimum cluster size = 343 voxels.

Table 3: Brain Regions with significant differences in activation to fear vs. neutral faces based on threat

Voxels	Peak (x, y, z)	Region	Peak voxel z-score
		Fear > Neutral	
528	-10, -70, 24	Left Precuneus	3.70
380	-6, 34, 42	Left Dorsomedial Prefrontal Cortex	3.67

Note: Peak (x, y, z)=MNI coordinates for the voxels with the highest coefficients within each cluster

Table 4. Neural activation associated with low age 3 income-to-needs ratio (log transformed)

Voxels	Peak (x, y, z)	Region	Peak voxel z-score
		Fear > Neutral	
460	-28, -68, 48	Left Superior Parietal Lobule	-4.15
344	2, 10,-14	Right Subcallosal Gyrus	-3.64

Note: Peak (x, y, z)=MNI coordinates for the voxels with the highest coefficients within each cluster, voxel-wise p-threshold = .01, minimum cluster size = 343 voxels.

Table 5: Zero-inflated Poisson regressions of the associations between precuneus and dmPFC activation and PTSD symptom severity

Precuneus	Count Model			Zero-inflation model		
	B	*SE*	*p*	*B*	*SE*	*p*
Sex (female)	-.211	.077	.006	.173	.348	.619
Age	.013	.079	.871	-.027	.340	.936
Log income-to-needs	-.203	.042	<.001	.520	.252	.039
Threat	.197	.037	<.001	-.889	.351	.011
Deprivation	-.163	.062	.008	-.138	.280	.623
Precuneus (Fear vs. Neutral)	.201	.040	<.001	-.250	.170	.142

dmPFC	Count Model			Zero-inflation model		
	B	*SE*	*p*	*B*	*SE*	*p*
Sex (female)	-.149	.080	.062	.136	.351	.698
Age	.061	.078	.432	-.060	.335	.859
Income-to-needs	-.174	.042	<.001	.537	.249	.031
Threat	.254	.036	<.001	-.922	.349	.008
Deprivation	-.097	.060	.106	-.162	.279	.562
dmPFC (Fear vs. Neutral)	.073	.034	.035	-.122	.161	.451

Results of 2 component mixture model. The count model uses Poisson regression with a log link. The zero-inflation model is binomial with a logit link; dmPFC=dorsomedial prefrontal cortex.

Figure 1: Deprivation and threat mediate associations between early childhood income and psychopathology

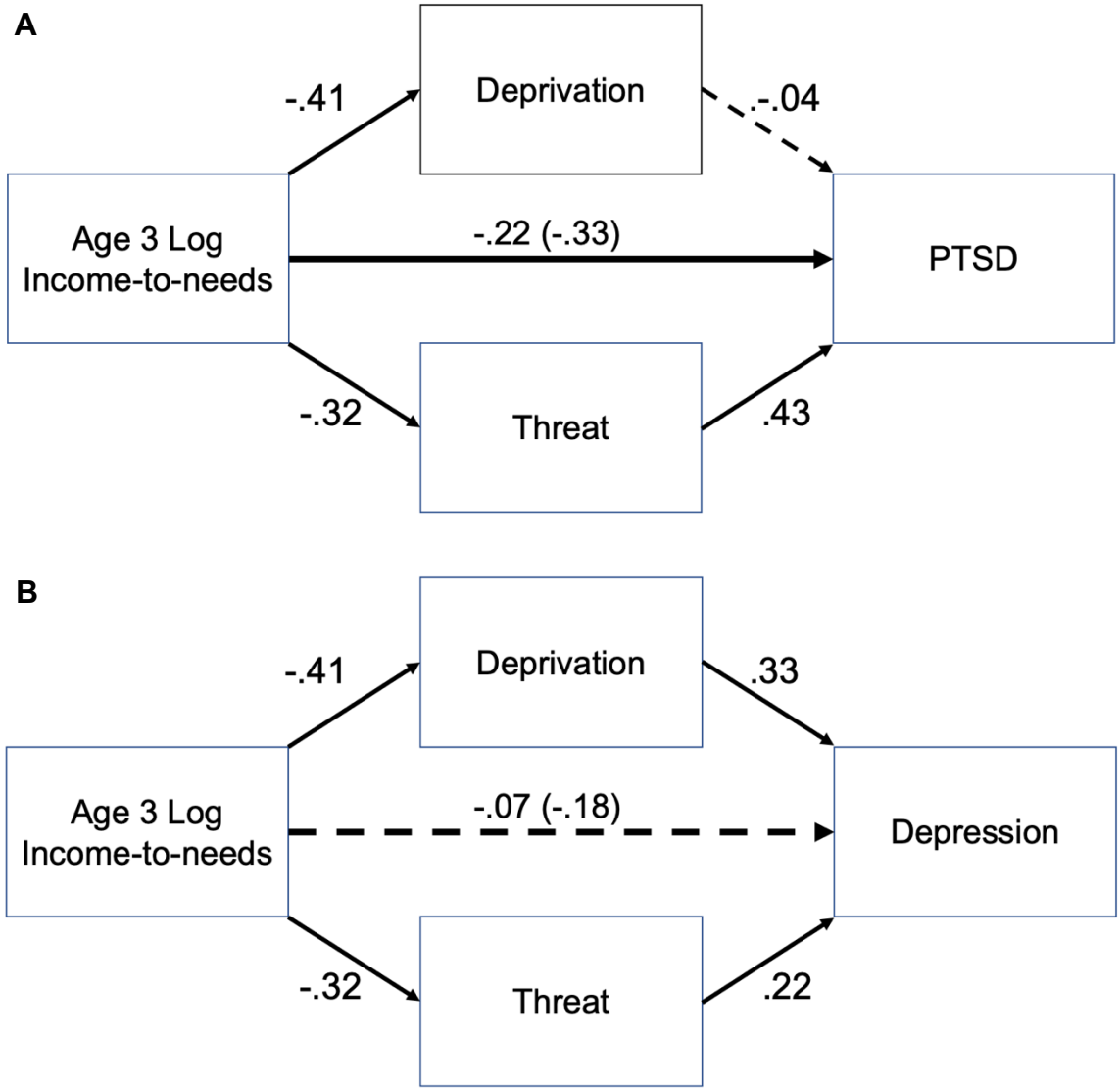

Figure 1: Depiction of mediation models. All paths are standardized coefficients from regression models. Solid lines represent significant regression coefficients. Dotted lines represent nonsignificant coefficients. Coefficients for PTSD are from the count model from zero-inflated poisson regression, which represents the severity of non-zero PTSD symptoms. Values in parentheses represent the standardized coefficient of the c path, the association between Age 3 log income-to-needs and the psychopathology outcome, not controlling for mediators.

Figure 2: Neural activation during emotional face viewing

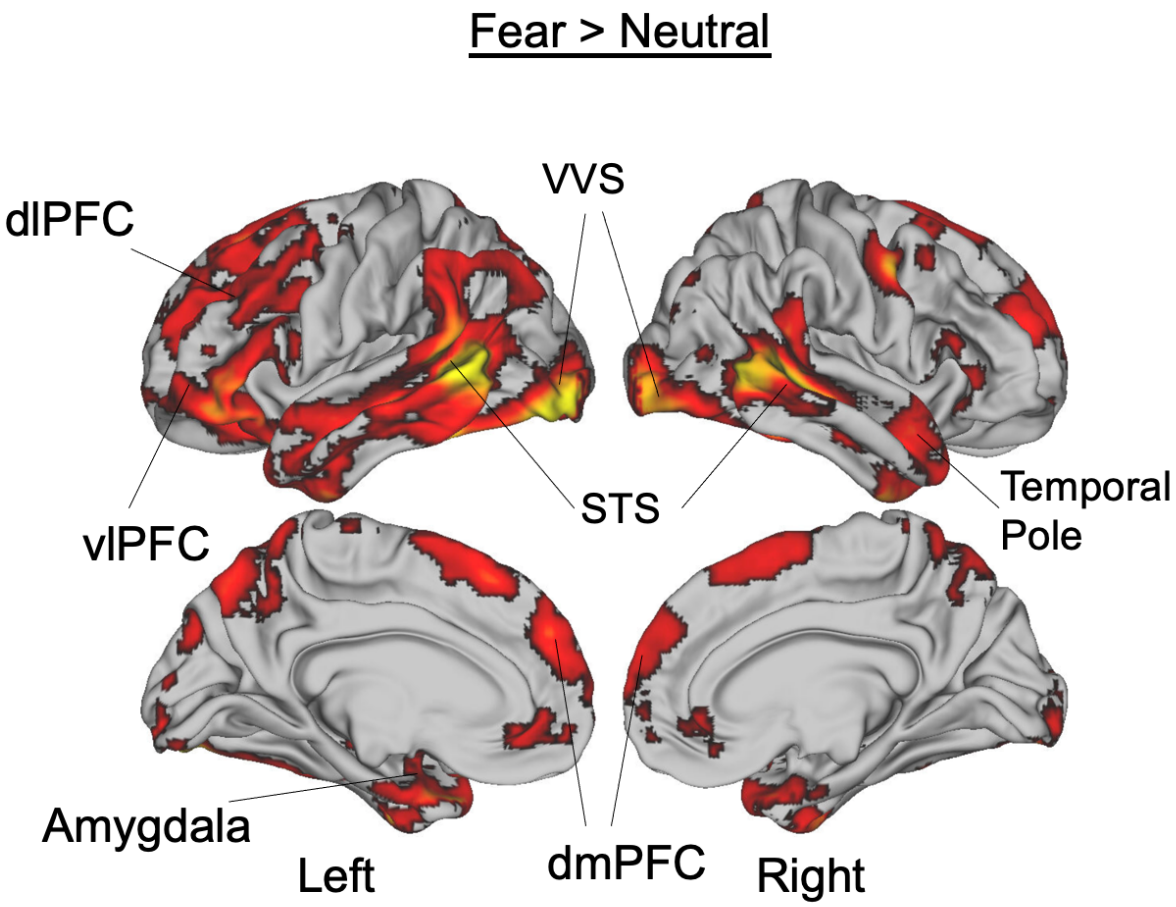

Figure 2: Figure depicts significant activation in the lateral (top) and medial (bottom) surfaces of the brain when participants viewed fearful vs. calm faces. dACC=dorsal anterior cingulate cortex, dlPFC=dorsolateral prefrontal cortex, dmPFC=dorsomedial prefrontal cortex, STS= superior temporal sulcus, vlPFC=ventraolateral prefrontal cortex, VVS=ventral visual stream.

Figure 3: Whole brain analysis: activity to fear vs. neutral faces is associated with threat exposure

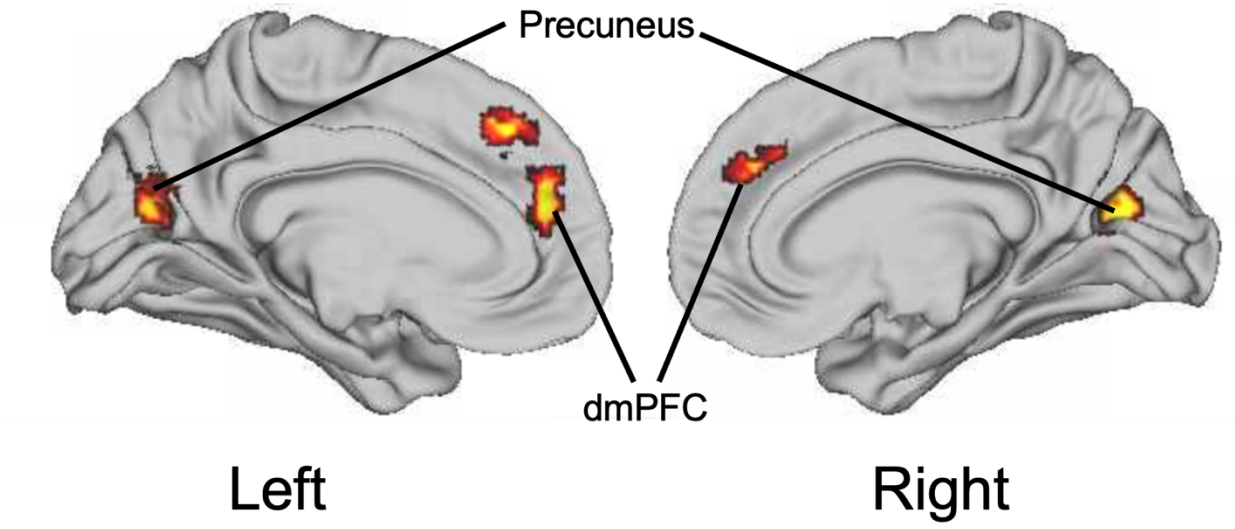

Figure 3: Figure depicts clusters where exposure to threat-related adversity is significantly related to neural activation to fearful vs. calm faces; sagittal slice at MNI x=-1, dmPFC=dorsomedial prefrontal cortex.

Figure 4: Associations between neural activity to fear vs. neutral faces and PTSD Severity

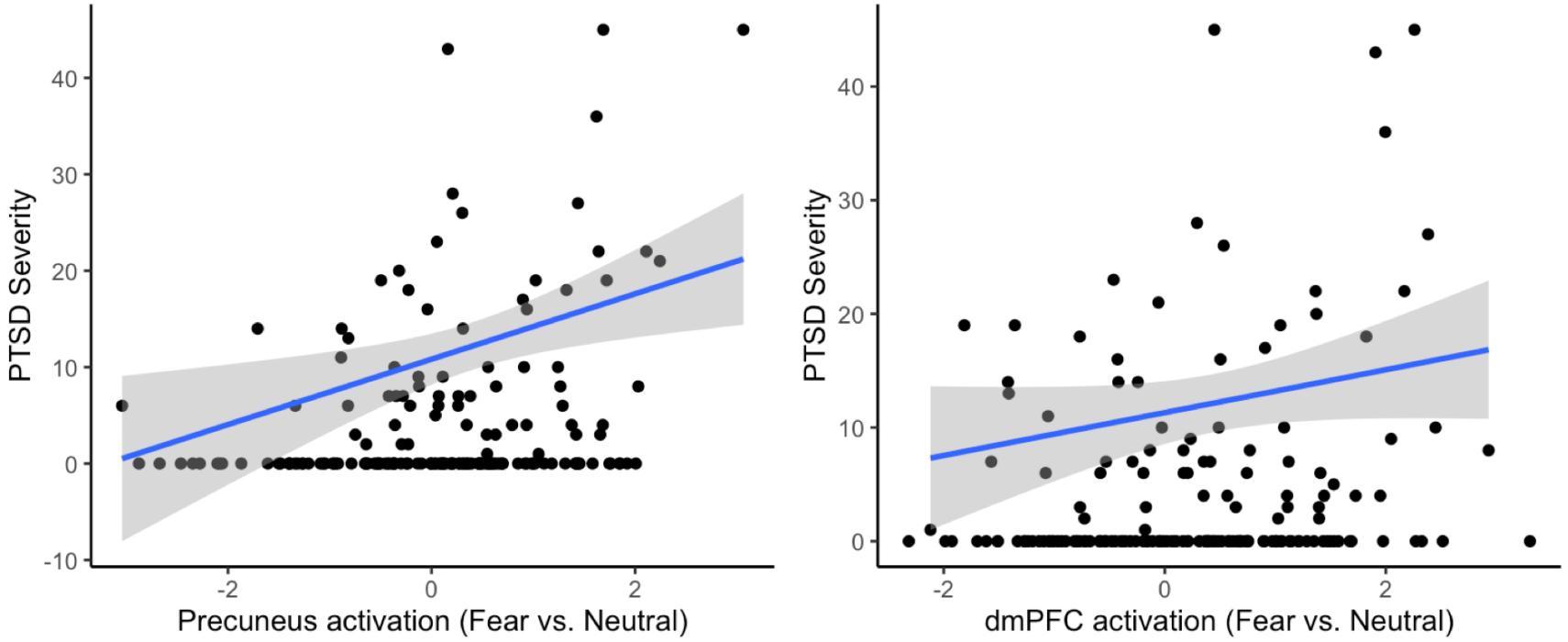

Figure 4: Visualization of the associations between neural activation in precuneus and dorsomedial prefrontal cortex (dmPFC) – regions identified based on their association with threat exposure – on the x-axis and post-traumatic stress disorder (PTSD) symptom severity on the y-axis. Blue lines represent the bivariate association between neural activity and non-zero PTSD severity.