



Socioeconomic disadvantage, brain morphometry, and attentional bias to threat in middle childhood

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Abstract

Socioeconomic disadvantage is associated with higher rates of psychopathology as well as hippocampus, amygdala and prefrontal cortex structure. However, little is known about how variations in brain morphometry are associated with socio-emotional risks for mood disorders in children growing up in families experiencing low income. In the current study, using structural magnetic resonance imaging, we examined the relationship between socioeconomic disadvantage and gray matter volume in the hippocampus, amygdala, and ventrolateral prefrontal cortex in a sample of children ($n = 34$) in middle childhood. Using an affective dot probe paradigm, we examined the association between gray matter volume in these regions and attentional bias to threat, a risk marker for mood disorders including anxiety disorders. We found that lower income-to-needs ratio was associated with lower bilateral hippocampal and right amygdala volume, but not prefrontal cortex volumes. Moreover, lower attentional bias to threat was associated with greater left hippocampal volume. We provide evidence of a relationship between income-related variations in brain structure and attentional bias to threat, a risk for mood disorders. Therefore, these findings support an environment-morphometry-behavior relationship that contributes to the understanding of income-related mental health disparities in childhood.

Keywords Family income · Hippocampus · Amygdala · Attentional bias · Middle childhood · Morphometry

Introduction

Growing up in families experiencing socioeconomic disadvantage (SED) has multiple implications, including behavioral (Hanson et al., 2015; Pachter, Auinger, Palmer, & Weitzman, 2006) and emotional dysregulation in childhood (Evans & Kim, 2013; Raver, Roy, Pressler, Ursache, & Charles McCoy, 2016) and anxiety and mood disorders later in life (Barch et al., 2016; Najman et al., 2010). The link between childhood SED and socioemotional difficulties is well supported (Green & Benzeval, 2013). Children, between the ages of 10 and 15 years, who experience SED are 2.5 times more likely to develop anxiety or depressed mood than their

peers in middle or high socioeconomic positions (Lemstra, 2008). Growing literature suggests that SED is associated with altered brain development, which may further be associated with negative childhood outcomes. However, most studies examining childhood SED and the brain focus on the relationship with cognitive outcomes (Hair, Hanson, Wolfe, & Pollak, 2015; Noble, Wolmetz, Ochs, Farah, & McCandliss, 2006); thus, little is known about potential neurobiological mechanisms for the socioemotional outcomes. SED is associated with greater exposure to adverse psychosocial and physical environment (Brooks-Gunn & Duncan, 1997; Evans, 2004; Raver, Blair, & Garrett-Peters, 2015). The higher levels of exposure to threats may be associated with increased vigilance to negative cues in the environment. Attentional biases to threat refer to tendencies to direct attention towards negative stimuli and are central to mechanistic models of anxiety and mood disorders (Beck, 2008; Dalgleish & Watts, 1990; Hankin, Snyder, & Gulley, 2016; Mathews & MacLeod, 2005). In the current study, we examined whether SED and brain morphometry may be associated with attentional bias to threat in middle childhood.

Previous studies suggest a relationship between family income and brain morphometry in adulthood. While the specific

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mechanisms of this association in humans remains unclear, evidence from nonhuman animal models suggest exposure to chronic stress may lead to alterations in brain morphometry. The hippocampus, amygdala, and prefrontal cortex have emerged as regions that are particularly susceptible to effects of chronic stress (Davidson & McEwen, 2012). Specifically, chronic stress is associated with altered spine density, dendritic length, and dendritic branching in these regions (Bloss, Janssen, McEwen, & Morrison, 2010; McEwen, 2007). These neuronal changes may be due to the association between chronic stress and increased glucocorticoid levels in the brain (Hall, Moda, & Liston, 2015), which play a critical role in the regulation of dendritic development (Liston & Gan, 2011). In the short term, the increased glucocorticoids act to mobilize resources to adapt to the stressor. However, long-term exposure to the increased glucocorticoid levels may have maladaptive effects on brain development and long-term consequences on behavior (McEwen, 1998, 2003; Oitzl, Champagne, van der Veen, & de Kloet, 2010; Welberg & Seckl, 2001).

Neuroimaging studies have identified a relationship between family income and gray matter volume, particularly in the hippocampus and amygdala in childhood (Johnson, Riis, & Noble, 2016). In studies examining childhood, lower family income was consistently associated with reduced gray matter volume in the hippocampus (Hanson, Chandra, Wolfe, & Pollak, 2011; Luby et al., 2013). However, for the amygdala, there have been inconsistent findings regarding the direction of the association. Some studies have found a positive relationship between family income and amygdala gray matter volume (Hanson et al., 2015; Luby et al., 2013), whereas other studies show a negative relationship (Noble, Houston, Kan, & Sowell, 2012a) or no association (Noble et al., 2015). Others have reported a negative association between family income and gray matter volume of other brain regions, including the prefrontal cortex (Hair et al., 2015; Hanson et al., 2013). Studies have begun to examine how SED and brain regions that are associated with it are further related to behavioral outcomes. These studies have primarily focused on cognitive outcomes, such as learning/memory (Hair et al., 2015), language (Noble et al., 2006), and academic achievement (Hair et al., 2015). However, the associations between SED, the brain, and behavioral risks for socioemotional outcomes are unclear.

Middle childhood is a period when children are increasingly vulnerable to the adverse effects of low family income on emotional development (Blair & Raver, 2012; Evans & English, 2002). While clinically significant symptoms may not be present until adolescence, it is possible that children exhibit an early socioemotional and neural risk marker for anxiety disorders in middle childhood (Dia & Bradshaw, 2008; Hankin et al., 2016). Attentional bias to threatening cues are a risk marker for emotion dysregulation and may play a role in the development of anxiety disorders (Bar-Haim, Lamy, Pergamin, Bakermans-

Kranenburg, & Van Ijzendoorn, 2007; Cisler & Koster, 2010) and depression (Mogg, Bradley, & Williams, 1995). Environmental adversity, such as maltreatment, has been associated with greater attentional bias to threatening cues (Pine et al., 2005; Pollak & Tolley-Schell, 2003). Experiencing low family income is associated with increased exposure to adversity, including harsh parenting (Repetti, Taylor, & Seeman, 2002) and exposure to violence (Sampson, Raudenbush, & Earls, 1997). Thus, experiencing low family income may increase threat bias, which in turn is a possible socioemotional risk marker for the development of psychopathology later in life.

Middle childhood also is when the structure of the brain, including the hippocampus, amygdala, and prefrontal cortex, may be vulnerable to adverse environmental influences (Dannowski et al., 2012; Hanson et al., 2010; Hanson et al., 2015). Furthermore, variations in brain development due to exposure to adversity may be linked to the variations in socioemotional processing, such as attentional bias to threat. Based on the connectivity and functional activity of the amygdala, it has been conceptualized to be a hub for cognitive-emotional integration in the brain (Pessoa, 2013). Traditionally thought to be primarily involved in affective processes, such as fear processing, the amygdala has been demonstrated to be involved in several cognitive processes, including attention and associative learning (Holland & Gallagher, 1999), and evidence suggests the amygdala is a center for integrating cognitive appraisal of affective information in the brain (Pessoa, 2008). Variations in amygdala volume are observed in several disorders that are associated with increased attentional bias to threat, specifically among patients with anxiety disorders (Bar-Haim et al., 2007), including pediatric anxiety (Milham et al., 2005).

There is evidence that the hippocampus is involved in attentional bias to threat. Neurobiologically, the role of the hippocampus in threat bias has been hypothesized to be due to its involvement in contextual threat processing and memory (Alvarez, Biggs, Chen, Pine, & Grillon, 2008; Grupe, Wielgosz, Davidson, & Nitschke, 2016; Maren, Phan, & Liberzon, 2013). First, altered hippocampal morphometry was associated with increased attentional bias to threat in carriers of the rs1360780 T allele of FKBP5 (Fani et al., 2013). Furthermore, the hippocampal microstructure was shown to be associated with abnormal threat processing in clinical anxiety and comorbid depression (Grupe et al., 2016). This study suggests that hippocampal microstructure is related to threat processing and may be a common neural pathway for the comorbidity of anxiety and depression (Grupe et al., 2016). Alterations in hippocampal volume have been linked to threat bias in individuals experiencing posttraumatic stress disorder (Grupe et al., 2016). While limbic regions, such as the amygdala and hippocampus, are involved in attentional allocation to emotional stimuli, such as threats, the prefrontal cortex

(specifically the lateral prefrontal cortex) has been demonstrated to be involved in top-down regulation when confronting threats (Bishop, Duncan, Brett, & Lawrence, 2004; MacDonald, Cohen, Stenger, & Carter, 2000). Evidence suggests that the hippocampus, amygdala, and prefrontal cortex are involved in fear acquisition and extinction that may be underlying attentional biases to threat (Hutcherson, Clark, Bolding, White, & Lahti, 2014). However, the associations between SED, morphometry of the hippocampus, amygdala, and prefrontal cortex and threat bias are unclear.

While more studies focused on family income, some examined parental education to observe the role of socioeconomic status (SES) in child brain structure. The two SES indicators, family income and parental education, often are correlated; however, some argue that they may have a unique role in brain development. For example, while family income is more closely linked to access to resources and environmental stressors (Evans & English, 2002), parental education is more closely tied to cognitive stimulation in the home environment (Hoff-Ginsberg & Tardif, 1995). For the hippocampus, two studies found no associations (Hanson et al., 2011; Noble, Houston, et al., 2012b), whereas one study reported that left hippocampal volumes were positively associated with paternal education (Noble et al., 2015). For the amygdala, one study found a negative correlation between maternal education and gray matter volume (Noble et al., 2012), whereas two studies have found no association (Hanson et al., 2011; Luby et al., 2013). Thus, although there are mixed results for parental education, we included testing the association between maternal education and brain structure as a secondary analysis to capture the multidimensional nature of SES.

Thus, in the current study, we examined associations among SED (as defined by INR and maternal education), brain morphometry, and attentional bias to threat in middle childhood. We focused our analysis on the following research questions: (1) Is SED related to gray matter volume in the hippocampus, amygdala, and ventrolateral prefrontal cortex? (2) Are SED and gray matter volumes in the hippocampus, amygdala, and ventrolateral prefrontal cortex related to higher attentional bias to threat? In accordance with previous studies, we hypothesized SED, particularly lower INR, would be associated with lower gray matter volume in the hippocampus and ventrolateral prefrontal cortex. Given the mixed evidence in the literature, we hypothesize that SED will be associated with amygdala volume, but in either a positive or negative direction. Importantly, we hypothesized that SED and gray matter volumes in the hippocampus, amygdala, and ventrolateral prefrontal cortex would be associated with greater attentional bias to threat.

We conducted additional post-hoc analyses to examine the specificity of the results. First, we tested the relative strength of the association of INR versus maternal education with brain morphometry and threat bias. Second, we tested additional

“control” regions to demonstrate that the relationships were specific to the certain brain regions and was not evident in regions that we did not expect to have a relationship with SED, such as the precentral gyrus, basal ganglia, and lateral occipital gyrus. Lastly, we tested if other factors may explain the relationship between SED and the regions of interest. We examined if a child’s IQ (Blair, 2006; Reiss, Abrams, Singer, Ross, & Denckla, 1996), anxiety levels (De Bellis et al., 2000; Pine, 2007), or pubertal status (Blakemore, Burnett, & Dahl, 2010; Peper, Pol, Crone, & Van Honk, 2011) were potential confounds of the relationship between INR and the hypothesized regions.

Materials and methods

Participants

Participants and their biological mothers were recruited from a volunteer database at the University of Denver, as well as via flyers placed in Denver metro area public schools and anti-poverty programs. We obtained a socioeconomically diverse sample by initially screening 149 families and oversampling low-income families (approximately 50% were low-income). Of the 47 families that participated in the home visit, 35 were eligible for and agreed to participate in the magnetic resonance imaging (MRI) scan visit. Of 35 children at age 8–10 years (see Table 1 for demographic information), 1 child was excluded from all analysis due to motion artifacts in the MRI data. Therefore, the total number of children included in the analysis was 34. Only one child per household could participate. Participants were included if they were fluent in English, lived with their biological mother at least 50% of the time, and their family income-to-needs ratio was below 7 (to target low- and middle-income families). Participants were excluded if they had: 1) ferrous metal or other MRI contraindications in their body; 2) received a psychiatric disorder diagnosis and treatment and/or psychotropic medication (to avoid a confounding effect of psychiatric disorder treatment and medication; based on mother-report); 3) a history of a neurological disorder; or 4) an IQ score below 80 as assessed by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

Procedure

After determining eligibility via a phone call, the study was comprised of a home visit and an MRI scan visit. During the home visit, researchers collected demographic information, including a detailed history of family income via extensive interview. Children completed the affective dot probe paradigm during the home visit on a laptop computer. Soon after the home visit, participants were asked to visit the University of Colorado, Boulder Intermountain Neuroimaging

Table 1 Demographic and affective dot probe information for the sample (RT = reaction time; NT = neutral-threat; NH = neutral-happy, WASI = Wechsler Abbreviated Scale of Intelligence, SCARED = Screen for Child Anxiety Related Disorders, PPDS = Petersen Physical Development Scale)

	<i>N</i> (%)	Mean $\pm$ SD	Range
Child age (yr)	18 (52.9)	8.76 $\pm$ 0.65	8-10
Child sex (female)			
Child race/ethnicity			
White/Caucasian	21 (61.8)		
Black/African American	4 (11.8)		
Hispanic	7 (20.6)		
Multi-racial	2 (5.9)		
Income-to-needs ratio		2.1 $\pm$ 1.5	0-6.6
Maternal education (yr)		14.7 $\pm$ 2.9	8-20
Threat bias score (ms)		-3.5 $\pm$ 68.4	-187.6 - 161.5
Happy bias score (ms)		-12.43 $\pm$ 53.0	-113.7 - 113.0
Dot probe accuracy (%)		94.7 $\pm$ 0.04	84-100
Dot probe RT (ms)		808.8 $\pm$ 209.8	511-1263
RT for neutral NT trials (ms)		810.4 $\pm$ 214.3	509-1296
RT for threat NT trials (ms)		814.3 $\pm$ 215.5	521-1230
RT for neutral NH trials (ms)		800.9 $\pm$ 208.8	516-1313
RT for happy NH trials (ms)		813.4 $\pm$ 221.5	492-1292
IQ (WASI)		100.5 $\pm$ 13.1	80-126
Anxiety symptoms (SCARED)		32.6 $\pm$ 16.2	6-70
Pubertal status (PPDS)		4 $\pm$ 1.9	1-8

Consortium (INC) at the Center for Innovation and Creativity. During the MRI scan visit, participants first underwent a “mock” scanning session in which they were trained to stay still in an MRI simulator. After completing the mock session, participants underwent an MRI scan to obtain structural images. Family income information was updated at the MRI visit if the interval between the home visit and MRI visit was more than 3 months. Therefore, the mean interval between the measurement of family income and the MRI visit was 0.97 months ($SD = 2.00$). Written, informed consent was obtained from the mother of each participant, and written, informed and verbal assent was obtained from each child participant. The protocol was approved by the Institutional Review Board of the University of Denver.

Measures

Income-to-needs ratio and maternal education

We used income-to-needs ratio (INR) to assess family income. INR more accurately captures family economic status by

considering how many people are in each family. During the home visit, a standardized interview was conducted to collect parent-reported family income for the last 12 months from the date of the home visit. INR was calculated by computing the ratio of family income to the federal poverty threshold, which is adjusted for the number of family members (Table 1). Consistent with the method the U.S. Census Bureau uses to calculate family income the following were included: earnings, unemployment compensation, workers’ compensation, Social Security, alimony, and child support. However, family income does not include money from welfare programs or financial support from extended family members. Fifty-one percent of the children’s families were considered low income [defined as in poverty ($INR \leq 1$) or near poverty ($INR \leq 2$)]. We assessed maternal education via an interview in which each mother reported the amount of years of education in which they had completed (Table 1).

Affective dot probe paradigm

Children completed one session of the affective dot probe paradigm (Abend, Pine, & Bar-Haim, 2014) to measure attentional biases to threat; the task was compiled and presented using a laptop computer through E-Prime 2.0 software (Schneider & Zuccoloto, 2007). Participants completed the task using the mouse to make responses. In between each trial, a fixation cross was displayed on the screen for 500 ms. For each trial, pairs of neutral, angry, and happy faces appeared on the screen vertically. Face stimuli were selected in pairs from the NimStim, Face Stimulus Set (Tottenham et al., 2009). Face stimuli were presented on the screen for 500 ms. Following the stimulus presentation, the face stimuli disappeared from the screen and a “probe,” in the form of a bracket pointing right or left ($<$ or $>$), appeared on the screen in the previous location of either the neutral, happy, or angry faces until a response was made. After each response was made, there was an intertrial interval of 500 ms. Trials always contained at least one neutral face stimuli and therefore could be NN (both neutral), NT (one neutral, one threat), or NH (one neutral, one happy). Participants completed 120 trials in which 48 were NT, 48 were NH, and 24 were NN. For the task, there were 48 congruent trials (24 in which the probe replaced the location of the angry face and 24 in which the probe replaced the happy face), 48 incongruent trials (the probe replaced the location of the neutral face), and 24 were neutral trials (in which the probe replaced either of the neutral faces in a counterbalanced fashion). The location of the angry face, the probe location, the probe type, and the facial identity were counterbalanced across the task. Participants were instructed to respond as quickly and accurately as possible, using their dominant hand, to the direction of the bracket using the mouse buttons (left mouse button for $<$ and right mouse button for $>$).

Behavioral data analysis was conducted using the TAU/NIMH ABMT Analysis Tool v2.0, which is a standalone tool to analyze dot probe paradigm data files and provide both quality control and quantification of the attentional bias to threat scores (<http://tau.ac.il/~yair1/ABMT.html>). This toolbox was designed as an initiative to provide a standardized tool for the analysis of dot probe paradigm data and has been used in several studies to clean the data and quantify attention bias scores, including a study by the authors of the toolbox (Goldman, Shulman, Bar-Haim, Abend, & Burack, 2016), as well as several other studies (De Voogd et al., 2016; Fitzgerald, Rawdon, & Dooley, 2016; Fu, Taber-Thomas, & Pérez-Edgar, 2015; Thai, Taber-Thomas, & Pérez-Edgar, 2016). The tool removes trials with reaction times shorter than 150 ms, trials with reaction times longer than 2,000 ms, and error trials. For each trial type, z-scores are calculated and trials with scores above 2.5 are removed from the analysis. After the removal of trials, the average percentage of trials that remained ($M = 94.85$, $SD = 4.31$, range = 82.5–99.1) was similar to the suggested amount of 94% (Abend et al., 2014). The threat bias score was calculated by subtracting the mean reaction time on congruent trials (in which the probe appeared behind the angry face) from incongruent trials (in which the probe appeared behind the neutral face). A positive threat bias score reflects a bias towards threatening stimuli (the angry face) and captures increased orientation toward the threatening stimuli, disengaging attentional allocation to threat, or both (Salemink, van den Hout, & Kindt, 2007). The behavioral results were similar to other studies using this paradigm with a pediatric sample (Fitzgerald et al., 2016; Pine et al., 2005; Troller-Renfree, McDermott, Nelson, Zeanah, & Fox, 2015). Additionally, we calculated attentional bias to happy stimuli by subtracting the mean reaction time on congruent trials (in which the probe appeared behind the happy face) from the mean reaction time on incongruent trials (in which the probe appeared behind the neutral face). A positive attentional bias to happy stimuli score would reflect an increased attentional allocation towards happy stimuli while a negative score would reflect attentional allocation away from the happy face to the neutral face. See Table 1 for a description of the behavioral performance from the dot probe paradigm.

Measurements of IQ, anxiety, and pubertal status

To examine the specificity of the results, we also measured child IQ, anxiety, and pubertal status to test them as possible confounds. We used the WASI (Wechsler, 2014) to examine child's IQ. For anxiety symptoms, we used the SCARED (Birmaher et al., 1997). Lastly, to measure pubertal status, we used the Petersen Physical Development Scale (Petersen, Crockett, Richards, & Boxer, 1988). Refer to Table 1 for more information about IQ, anxiety, and pubertal status.

MRI acquisition

T1-weighted MPAGE (magnetization prepared rapid gradient-echo) images were acquired using a 3T Siemens Magnetom Tim Trio scanner with a 32-channel phase-array coil. The MPAGE sequence acquired high resolution images with the following parameters: 192 axial slices each at 1.00-mm thick, TR = 2,530 ms, TE = 1.64 ms, skip = 0 mm, flip angle = 7°, FOV = 256 mm and voxel size = 1.0 x 1.0 x 1.0 mm.

Structural image processing

Visual inspection was conducted for each image to check for excessive motion artifacts, such as “ringing,” using a 4-point visual scale: for example, 1 = no motion; 2 = mild motion; 3 = moderate motion; 4 = severe motion. According to this framework, scans scoring a 1 have little or no detectable motion artifact (51.4% of the sample); a score of 2 has mild but detectable bands of motion (37.1% of the sample). A score of 3 is considered moderate as far as detectable motion and can be included in the data analysis (8.6% of the sample) (Blumenthal, Zijdenbos, Molloy, & Giedd, 2002). One participant scored a 4 on the rating scale in which motion artifact is extreme; this participant was excluded reducing the sample size from 35 to 34 participants. Several studies have used these rating scales for quantifying motion artifact in both adult and pediatric samples (Lin et al., 2012; Lyall et al., 2015; Schweren et al., 2016; Wang et al., 2017; Zhang et al., 2015). Furthermore, the motion scores were not associated with INR, maternal education, and attentional bias to threat scores.

Volumetric segmentation of the images was conducted using the Freesurfer Image Analysis Suite 5.3 (<http://surfer.nmr.mgh.harvard.edu/>). This method has been demonstrated to be appropriate for pediatric images (Ghosh et al., 2010), and several studies have used the Freesurfer pipeline to segment hippocampal and amygdala volumes in a similar age range as the current sample (Geller et al., 2009; Ghassabian et al., 2014; Nardelli, Lebel, Rasmussen, Andrew, & Beaulieu, 2011; Pagliaccio et al., 2014; Teicher, Anderson, & Polcari, 2012). We carefully examined the segmentation accuracy for each structure for each participant using a similar 4-point rating skill (1 = very accurate; 2 = accurate; 3 = less accuracy; 4 = severe problems with accuracy). Based on the ratings of the segmentation, accuracy no participants were excluded as no segmentation scored a 4, indicating severe problems with the accuracy; images scoring a 3 (only 2 participants) were included in the study based on the recommendations of the rating scale (Blumenthal et al., 2002). No images scoring a 4, indicating extremely poor segmentation, were included in the analysis.

The specifics of the procedure for the automatic segmentation of the subcortical structures have been previously documented (Fischl et al., 2002). The automated pipeline begins with motion and intensity nonuniformity correction in the data followed by affine transformation using the MNI305 atlas and intensity normalization. Images are skull stripped, and an automatic subcortical segmentation computes volumetric data for subcortical structures, including the amygdala and hippocampus. For the analysis of the amygdala, hippocampus, we used the calculation of gray matter volume from the “aseg” output in Freesurfer. However, because Freesurfer does not provide a “ventrolateral prefrontal cortex” volumetric measurement, we combined the gray matter volumes calculated for the pars opercularis, pars orbitalis, and pars triangularis. This method has been used in other studies to provide a volumetric measurement of the vIPFC (Ding et al., 2015; Vijayakumar et al., 2014). For the post hoc analysis of the specificity of the results, we also calculated gray matter volume for the precentral gyrus, basal ganglia, and lateral occipital gyrus. For the precentral gyrus and lateral occipital gyrus volume, we used the gray matter volume calculated by the automatic segmentation and output in “aseg.” Freesurfer automatic segmentation does not have an explicit segmentation for the basal ganglia; however, we calculated the basal ganglia volume by taking the sum of the volume of the caudate, putamen, and globus pallidus (Hutcherson et al., 2014; Qiu et al., 2009; Wyciszkievicz & Pawlak, 2014).

Regional gray matter analysis: regression models

After conducting quality control on the segmented images from Freesurfer, volumetric information from the subcortical structures were transferred into SPSS (Statistical Package for the Social Sciences, IBM) for analysis. Based on our *a priori* hypothesis, the analysis focused on the volumes of the hippocampus, amygdala, and vIPFC. Hippocampal and amygdala volumes were examined for outliers using a protocol designed for outlier detection for Freesurfer volumetric analysis (<http://enigma.loni.ucla.edu/protocols/>), consistent with other studies (Guadalupe et al., 2014; Stein et al., 2012; Wang et al., 2017). Based on these criteria, no participants' data for the hippocampus, amygdala, or vIPFC was detected as an outlier. It has been discussed that controlling for age and sex is critical when studying the relationship between family income and gray matter volume (Brito & Noble, 2014), and total gray matter volume is associated with both age and sex (Gur et al., 1999; Taki et al., 2011). Total gray matter volume was calculated during the processing pipeline (retrieved from the “aseg” output) and reflects the sum of the gray matter volume in the left cortex, right cortex, subcortical regions, and cerebellum.

Therefore, to test the relationships between INR, amygdala/hippocampal/vIPFC volume, and threat bias, we used separate multiple regressions for each hypothesis and controlled

for age, sex, race/ethnicity, and total gray matter volume. Similarly, we used separate multiple regressions to test the association between maternal education, amygdala/hippocampal/vIPFC volume, and threat bias, which controlled for age, sex, race/ethnicity, and total gray matter volume and a False Discovery Rate (FDR) correction of $q < 0.05$. For these regressions, covariates were all entered in the same block, because we did not have a specific *a priori* reason to use a stepwise regression, and this procedure may introduce bias (Harrell, 2001). However, we have included the regression results using a stepwise elimination processes (see the [Supplementary Material](#)). To further examine the specificity of the INR versus maternal education results, we conducted a multiple regression in which INR, maternal education, and threat bias were simultaneous predictors of the gray matter volumes. We also used a Williams' test (Wilcox & Tian, 2008) to examine whether there was a statistically significant difference between the correlation between INR and our hypothesized brain region's volume and maternal education and the hypothesized region's volume. Furthermore, we used an additional Williams' test to examine if there was a significant difference between the associations between INR and threat bias and maternal education and threat bias. These tests were implemented using R's “psych” package (Revelle, 2014).

Results

Demographic variables

Income-to-needs ratio did not differ by child sex or child race/ethnicity ($ps > 0.05$). INR was correlated with age ($r = 0.34$, $p < 0.05$) for the sample; the older participants in the sample tended to have a higher INR. INR was not significantly correlated with total gray matter volume or intracranial volume. Maternal education also did not differ by child sex and did not differ by child ethnicity ($ps > 0.05$). There was no significant correlation between maternal education and child age, total gray matter volume, or total intracranial volume ($ps < 0.05$). The time interval between the home visit and MRI visit was not correlated with INR nor threat bias scores. There was a significant correlation between maternal education and the interval between the home visit and lab visit ($r = 0.41$, $p < 0.05$). Age, sex, and ethnicity were not significantly related to the attentional bias to threat scores. There was a positive association between INR and maternal education ($r = 0.42$, $p < 0.05$). In the post hoc analyses, we examined the specificity of the results to INR by including child IQ, anxiety symptoms, and pubertal status in the models. There was a significant correlation between INR and child IQ ($r = 0.050$, $p < 0.01$) but not a significant correlation between INR and anxiety symptoms (as measured by the SCARED) and pubertal status ($p < 0.05$). There was a significant correlation between maternal education

and child IQ ($r = 0.60$, $p < 0.0001$) and significant correlation between maternal education and anxiety symptoms ($r = -0.45$, $p < 0.01$); the correlation between maternal education and pubertal status was not significant ($p > 0.05$).

SED and volumes of *a priori* brain regions

A multiple regression with INR as a regressor and participant age, sex, and total gray matter volume as covariates revealed a significant regression equation ($F(4, 29) = 7.04$, $p < 0.001$) with an R^2 of 0.49. There was a significant relationship between INR and left hippocampal volume ($\beta = 0.61$, $p < 0.0001$, $f^2 = 0.96$; Figures 1 and 2a). A similar regression model revealed a significant regression equation for the relationship between the INR and right hippocampal volume ($F(4, 29) = 4.66$, $p < 0.01$) with an R^2 of 0.39. The regression indicated that higher INR was associated with higher right hippocampal volume ($\beta = 0.39$, $p < 0.05$, $f^2 = 0.63$; Figure 2b). For the left amygdala (Figure 2c), the association with INR was not significant ($p > 0.05$). The regression equation for the right amygdala was significant, ($F(4, 29) = 5.91$, $p < 0.01$) with an R^2 of 0.44. Therefore, higher INR was associated with higher right amygdala volume ($\beta = 0.41$, $p < 0.01$, $f^2 = 0.78$). There was not a significant relationship between INR and left ($p > 0.05$) or right ventrolateral prefrontal cortex ($p > 0.05$). Scatter plots of the relationship between raw INR and the raw gray matter volumes for the hippocampus and amygdala are available as Supplementary Figure 2.

A multiple regression with maternal education as a regressor and participant age, sex, and total gray matter volume did not find a significant relationship between maternal education for left hippocampal volume ($p > 0.05$), right hippocampal volume ($p > 0.05$), left amygdala volume ($p > 0.05$), right

amygdala volume ($p > 0.05$), left vIPFC ($p > 0.05$), or right vIPFC ($p > 0.05$).

Associations among SED, brain volumes, and threat bias scores

As the associations between maternal education and brain volumes were not significant, we focused our analysis on INR. First, we examined the relationship between INR and threat bias scores on the dot probe paradigm. We used a multiple regression controlling for participants' age, and sex and INR was significantly related to threat bias ($\beta = -0.39$, $p < 0.05$, $f^2 = 0.32$) despite a regression equation that was not significant ($F(3, 30) = 1.93$, $p > 0.05$). A multiple regression controlling for the sex, age, and total gray matter volume of the participants was used to examine the association between hippocampal volumes and threat bias. The regression equation was significant $F(4, 29) = 3.63$, $p < 0.05$, and an $R^2 = 0.33$ threat bias was associated with left hippocampal volumes ($\beta = -0.42$, $p < 0.05$, $f^2 = 0.49$). Therefore, lower left hippocampal volume was associated with increased attentional bias to threatening faces on the affective dot probe paradigm (see Figure 3a for the partial regression plot controlling for age, sex, and total gray matter volume; see Supplementary Figure 2 for the scatter plot of the relationship between raw hippocampal volumes and raw threat bias scores). The non-significant F test suggests that there is a better fitting model for data. However, to keep consistent with the other regression models we included the same covariates. While mediation testing is not suggested for cross-sectional data (Maxwell & Cole, 2007), we tested the mediation in an exploratory analysis to be followed up with future longitudinal data (see Supplementary Material). While we cannot establish directionality, we provide a path diagram of the main results of the study, e.g. the associations between INR, left hippocampal volumes, and threat bias (Figure 3b).

There was no significant relationship between threat bias scores and volume in the right hippocampus, bilateral amygdala, or bilateral vIPFC. We also examined the relationship among INR, brain volumes, and attentional bias to happy stimuli scores using the same covariates and found no significant association.

Testing the specificity of SED results

First, as several separate regressions were used, we corrected for multiple testing using the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) treating INR models and maternal education models as separate analyses. We used a False Discovery Rate (FDR) correction of $q < 0.05$. At this threshold, all the results included in section 3.2 and 3.3 remained significant except for the relationship between INR and threat bias (Benjamini-Hochberg $p = 0.057$).

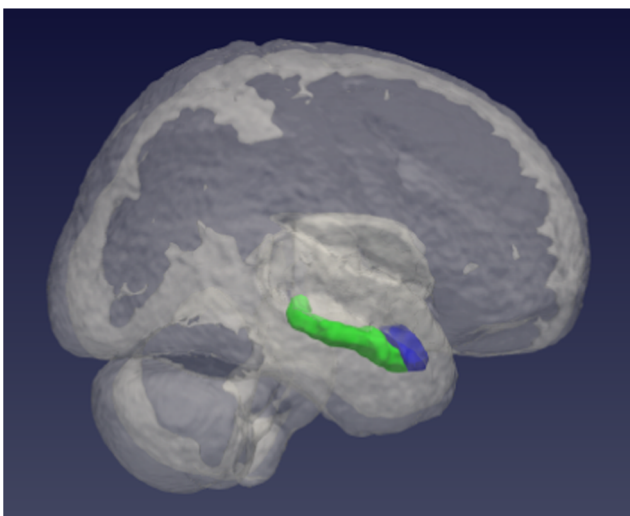


Fig. 1 Example of the automatic segmentation of the amygdala (blue color) and hippocampus (green color)

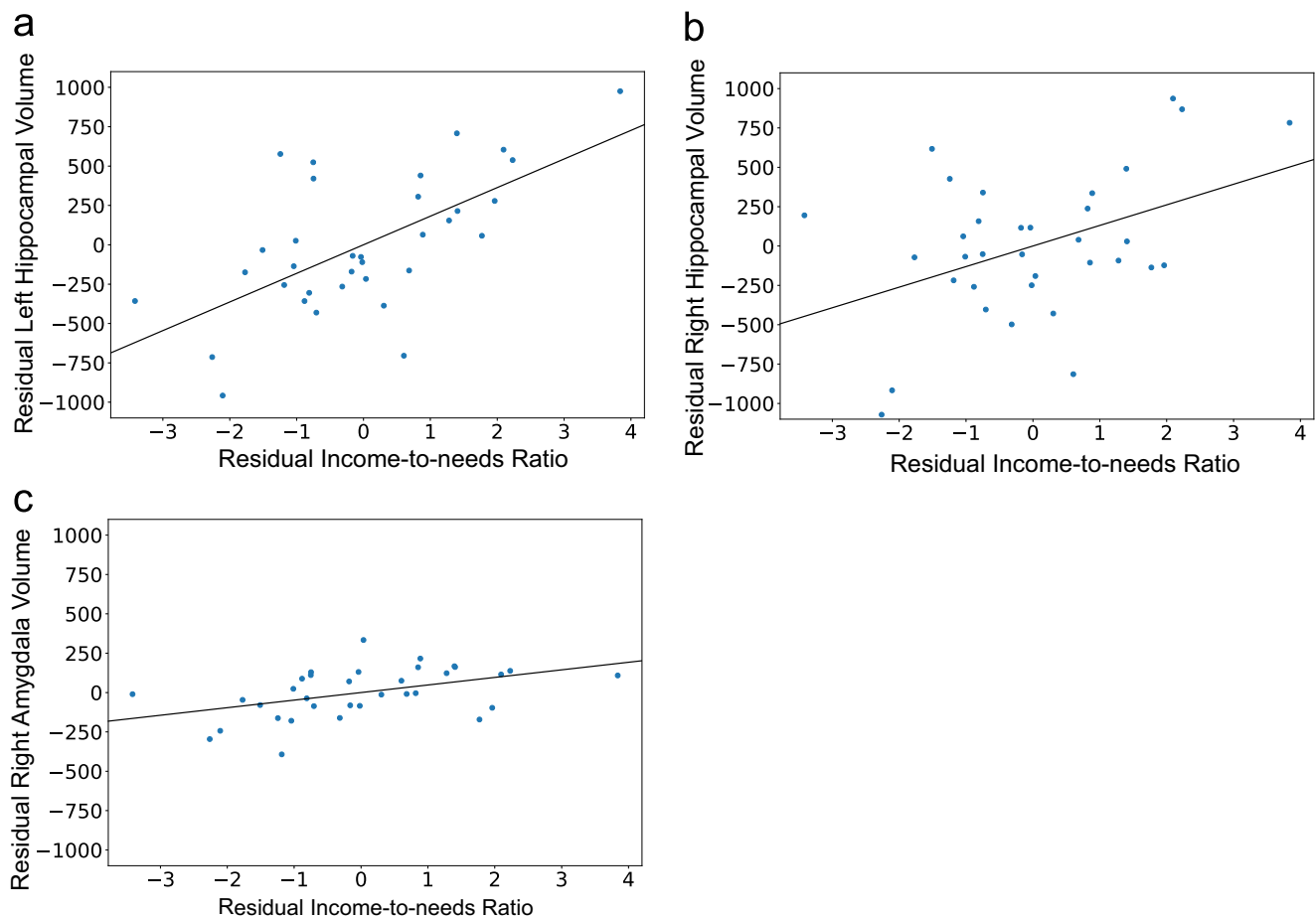


Fig. 2 (a) Partial regression plot of the relationship between residual income-to-needs ratio (INR) and residual left hippocampal volumes. (b) Partial regression plot of the relationship between residual INR and residual right hippocampal volumes. (c) Partial regression plot of the relationship between residual INR and residual right amygdala

volumes. For all the figures, the values reflect residuals from the models with age, sex, and total gray matter volume as covariates. Scatter plots of the raw data can be found in the Supplementary Material (Supplementary Figure 1)

Second, we conducted each multiple regression using INR, maternal education, and attentional bias to threat scores as simultaneous predictors. In a multiple regression, including INR, maternal education, threat bias scores, age, sex, and total gray matter volume, INR was significantly associated with the left hippocampus ($\beta = 0.56$, $p < 0.01$, $f^2 = 1.22$) and right hippocampus ($\beta = 0.48$, $p < 0.05$, $f^2 = 0.75$). INR was not significantly associated with the left amygdala ($p > 0.05$) and significant for the right amygdala ($\beta = 0.40$, $p < 0.05$, $f^2 = 0.88$). Consistent with the main analysis findings, for the left and right vLPFC, INR was not significant ($ps > 0.05$). Maternal education and threat bias scores were not significantly associated with gray matter volume for each region of interest ($ps > 0.05$).

Third, we used a Williams' test to examine if there was a significant difference between two correlations (INR and brain structure and maternal education and brain structure). The Williams' test indicated that there was a significant difference among the correlations between INR and left hippocampal volume and between maternal education and left

hippocampal volume ($t = 2.2$, $p < 0.05$). The Williams' test indicated that there was a difference at a trend level in the right hippocampus ($t = 1.94$, $p = 0.06$). The Williams' tests for the bilateral amygdala were not significant ($ps > 0.05$). Therefore, particularly in the left hippocampus, a region that is also associated with threat bias, we had the strongest evidence that INR but not maternal education was associated with smaller volume. We also used a Williams' test to examine whether there was a significant difference amid the correlations between INR and threat bias and maternal education and threat bias. The Williams' test indicated that the correlations were not significantly different ($p > 0.05$).

Also, as an exploratory analysis to test the specificity of the results, we examined the relationship between INR and volumes of the precentral gyrus, lateral occipital gyrus, and basal ganglia using multiple regressions controlling for age, sex, and total gray matter volume. We specifically tested regions that we did not expect to have an association with INR. Consistent with our hypothesis, INR was not associated with gray matter volumes for the precentral gyrus, lateral occipital

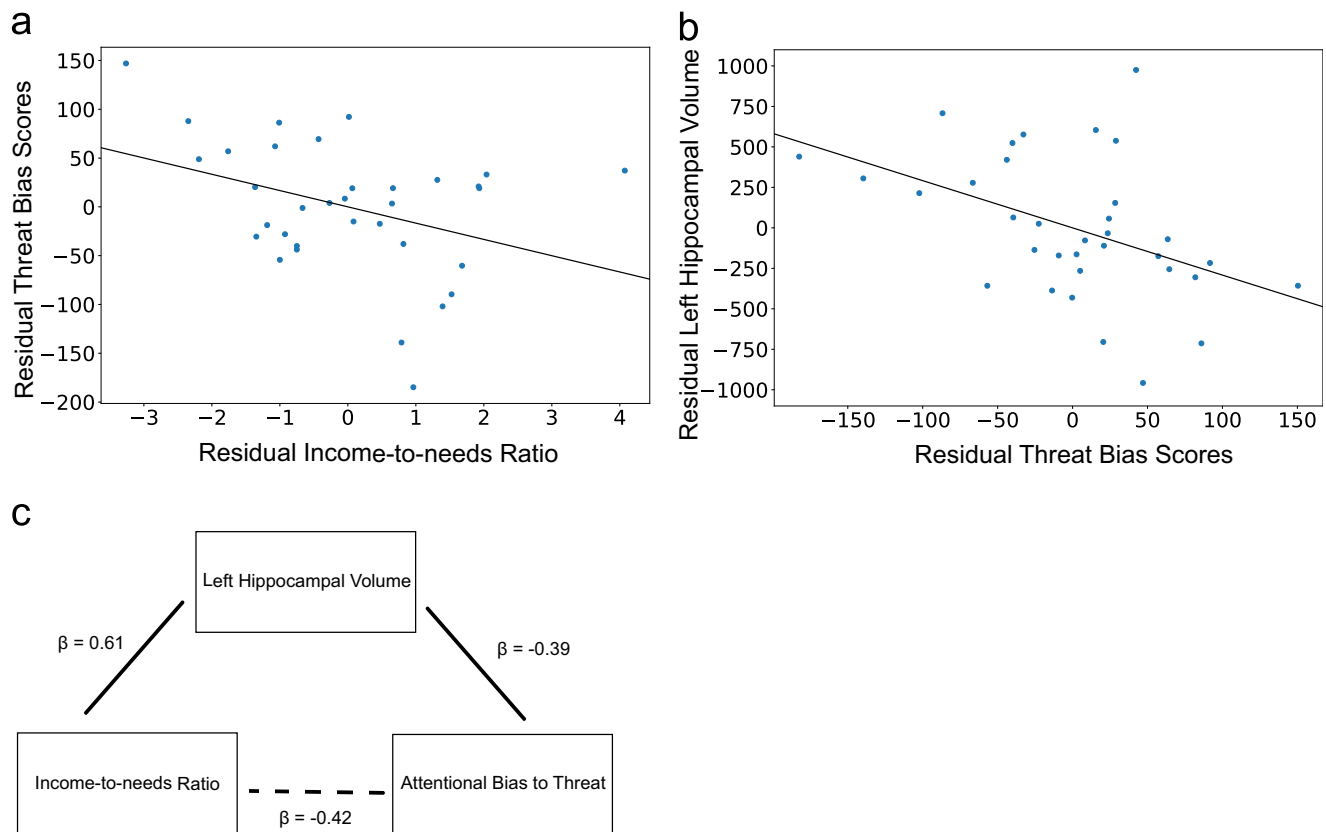


Fig. 3 (a) Partial regression plot of the relationship between residual INR and residual threat bias scores controlling for age and sex. (b) Partial regression plot of the relationship between residual attentional bias to threat scores and residual left hippocampal volumes. The values reflect residuals from the model with age, sex, and total gray matter volume as covariates. A scatter plot of the raw data can be found in the

Supplementary Material (Supplementary Figure 2). (c) A path diagram of the main findings of the study. The solid line indicates significant associations ($p < 0.05$) controlling for age, sex, and total gray matter volume. The dotted line indicates a relationship that did not survive correction for multiple comparisons ($q < 0.05$). *Indicates that this relationship did not survive multiple comparisons correction

gyrus, or basal ganglia volume ($ps > 0.05$). These exploratory analyses confirm the specificity of the results to the hippocampus and amygdala (by demonstrating it is not a global effect) and provide evidence for future studies of the specific relationship between INR and gray matter volume in reward processing regions.

Fourth, we ran a post hoc multiple regression with child's IQ included as a covariate. This regression also included sex, age, and total gray matter volume as covariates. INR remained significant for the left hippocampus ($\beta = 0.62$, $p < 0.001$, $f^2 = 0.96$) and right hippocampus ($\beta = 0.42$, $p < 0.05$, $f^2 = 0.63$). Consistent with the other models, the left amygdala was not significant ($p > 0.05$); however, the association remained for the right amygdala ($\beta = 0.45$, $p < 0.01$, $f^2 = 0.85$). Despite not surviving the multiple comparisons correction in the main analysis, the association between INR and threat bias remained significant with IQ included in the model along with sex and age ($\beta = -0.41$, $p < 0.05$, $f^2 = 0.19$). The association between left hippocampal volume and threat bias score remained significant when age, sex, and total gray matter volume and IQ were included as covariates ($\beta = -0.42$, $p < 0.05$, $f^2 = 0.51$).

Fifth, we conducted an additional post hoc multiple regression including SCARED (Birmaher et al., 1997) scores (a measure of pediatric anxiety symptoms) as a covariate in addition to age, sex, and total gray matter volume. In this model, INR remained significant for the left hippocampus ($\beta = 0.65$, $p < 0.001$, $f^2 = 1.00$), right hippocampus ($\beta = 0.45$, $p < 0.05$, $f^2 = 0.72$), and right amygdala ($\beta = 0.45$, $p < 0.05$, $f^2 = 0.85$). Consistent with other models, the left amygdala was not significant ($p > 0.05$). The relationship between INR and threat bias was not significant but trending when including SCARED scores, age, and sex in the model ($\beta = -0.39$, $p = 0.0501$, $f^2 = 0.19$). The association between left hippocampal volume and threat bias remained significant when SCARED scores, age, sex, and total gray matter volume were included as covariates ($\beta = -0.41$, $p < 0.05$, $f^2 = 0.49$).

Lastly, we conducted an additional post hoc regression to include pubertal status as measured by the Petersen Physical Development Scale (Petersen et al., 1988) as a covariate. In the model that included pubertal status, age, sex, and total gray matter volume, INR remained significant for the left hippocampus ($\beta = 0.62$, $p < 0.001$, $f^2 = 1.12$), right hippocampus (β

$= 0.40, p < 0.01, f^2 = 0.96$), and right amygdala ($\beta = 0.41, p < 0.01, f^2 = 0.78$). Similarly, the left amygdala was not significantly associated with INR ($p < 0.05$). The relationship between INR and threat bias remained significant when puberty status was included in the model ($\beta = -0.39, p < 0.05, f^2 = 0.66$) despite not surviving the correction for multiple comparisons in the main analysis. The association between left hippocampal volume and threat bias scores remained significant when pubertal status, age, sex, and total gray matter volume were entered as covariates ($\beta = -0.43, p < 0.05, f^2 = 0.61$). Therefore, the main results largely independent of the child's IQ, current anxiety symptoms, and puberty status.

Discussion

In this study, we address the following research questions: 1) Is SED related to gray matter volume in the amygdala, hippocampus, and ventrolateral prefrontal cortex? 2) Are SED and gray matter volumes in the hippocampus, amygdala, and ventrolateral prefrontal cortex related to higher attentional bias to threat? For our first research question, we found that lower income-to-needs ratio was associated with lower gray matter volume in the bilateral hippocampus and right amygdala but not in the vlPFC. Additionally, we found that lower INR was associated with greater attentional bias to threat and lower left hippocampal volume was associated with greater attentional bias to threat. Overall, these findings extend the current knowledge on SED-related variations in brain structure and their relation to risks for negative emotional outcomes. We provide evidence of a relationship between the left hippocampus and attentional bias to threat, a risk marker for affective disorders, such as anxiety. Future studies examining the specific functional role of the hippocampus in attentional bias to threat in the case of childhood SED and the relationship between structure and function in this context are needed.

Our hippocampal findings are consistent with several studies that have reported positive associations between family income and gray matter volume (Johnson et al., 2016). We extended the existing literature by finding the associations in middle childhood. Studies across the lifespan reported a relationship between family income and gray matter volume with these effects present in samples as young as infancy (Hair et al., 2015), to middle childhood to early adulthood (Hanson et al., 2015; Jednoróg et al., 2012), into middle (Butterworth, Cherbuin, Sachdev, & Anstey, 2011) and late adulthood (Staff et al., 2012). While the association was stronger in the left hippocampus for our study, we find support for a relationship between family income and bilateral hippocampal volume.

We extend the understanding of the association between family income and hippocampal development by examining a behavioral risk marker for psychopathology. Our study suggests a positive relationship between income-to-needs ratio

and left hippocampal volume and a negative relationship between left hippocampal volume and attentional bias to threat. Additionally, we found that lower INR was associated with greater attentional bias to threat; however, this finding should be interpreted with caution, because it did not survive the multiple comparisons threshold. The finding is consistent with other studies that have found childhood adversity in the form of physical abuse to be related to increased attentional bias to threatening faces (Pollak & Tolley-Schell, 2003). However, a recent study found that children from families experiencing low income were more likely to have an attentional bias away from, not toward, threat (Raver et al., 2017). In this study, negative images included various threatening information, including animals, objects, and situations. Additionally, stimuli were presented for 250 ms, whereas the paradigm of the current study includes only threatening faces, which were presented for 500 ms. The differences in the study designs may contribute to the inconsistent findings as attentional bias toward or away from threats is highly sensitive to these design factors (Cisler, Bacon, & Williams, 2009; Koster, Crombez, Verschuere, & De Houwer, 2004; Matlow, Gard, & Berg, 2012). It has been demonstrated that both anxious and nonanxious children have significant attentional bias to threat; however, nonanxious children learn to inhibit this bias with age and anxious children do not (Kindt, Brosschot, & Everaerd, 1997; Kindt & Van Den Hout, 2001). These findings could explain the individual differences observed in our sample such that children experiencing low family income with large attentional biases to threat may have difficulties inhibiting attentional allocation to threat, whereas some children experiencing low family income may have no attentional bias to threat or attentional bias away from threat. Thus, attentional bias to threat often is more clearly observed in children at risk for developing psychopathology. For example, behaviorally inhibited (BI) children showed increased attentional bias to threat and social withdrawal compared with non-BI children in adolescence (Pérez-Edgar, Bar-Haim, et al., 2010). It is noteworthy that the mean reaction times between threat and happy trials were similar. However, there was no significant association between the hippocampus, amygdala, or vlPFC for the happy trials ($ps > 0.05$). This supports the specificity of the results to attentional bias to threat as opposed to the degree of which the faces had affective expressions (happy or threat). Thus, the regression analyses may suggest the specific associations among INR, hippocampal volume, and attentional bias to threat.

While the amygdala is more traditionally thought to play a role in attentional bias to threat, our results suggest the morphometry of the hippocampus also may be involved in threat bias. Activity in the hippocampus has been associated with attentional bias to threat; specifically, it has been associated with deficits in disengagement from threat towards neutral stimuli (Price et al., 2014). It has been hypothesized that the

hippocampus in a network of regions, including the amygdala and prefrontal cortex, is involved in distinguishing new information regarding threat from previously learned information (Milad & Quirk, 2012). Further studies will be needed to examine the structure-function relationship of the hippocampus in attentional bias to threat. However, we add further evidence to the body of literature that also suggest a direct link between the structure of the hippocampus and attentional bias to threat (Cha et al., 2016; Fani et al., 2013; Grupe et al., 2016).

Like the hippocampal volumes, for the right amygdala in our sample, lower INR was associated with lower, not greater, gray matter volume. This finding replicates the positive relationship found between INR and amygdala volume as similar results were observed at age 10 years (Barch et al., 2016). The finding is consistent with a study that found that children experiencing low SES (ages 9–15 years) had smaller left amygdala volumes than comparison children (Hanson et al., 2015). While INR was only associated with the right amygdala, any interpretations concerning the laterality of the finding will need larger sample sizes. However, in contrast to the hippocampus, we did not find a relationship between amygdala volume and threat bias. While abnormal functional activity patterns in the amygdala have strongly been associated with threat bias across several age groups and disorders (Bishop, 2008; Monk et al., 2008; Price et al., 2014; Roy et al., 2008), little is known about the specific link between amygdala structure and threat bias. In a study examining the structure of the amygdala, consistent with our findings, attentional bias to threat using a dot probe paradigm was not associated with amygdala gray matter volume (Carlson, Reinke, & Habib, 2009). To address the questions of the relationship between amygdala structure and function in threat bias, future studies are needed to examine the relationship among family income, amygdala structure, and threat bias, including both the neural measures of the morphometry and task-related functional activation.

Relationships between prefrontal cortex volume and family income have been previously reported (Hair et al., 2015; Hanson et al., 2013; Holz et al., 2015); however, we did not find a significant relationship between INR and vIPFC gray matter volume. This may be due to the relatively small parcellation of the prefrontal cortex we used as we had an *a priori* hypothesis of the vIPFC based on previous attentional bias to threat fMRI studies. While the functional activity of the vIPFC has been demonstrated in several studies of attentional bias to threat (Bishop, 2008; Monk et al., 2006; Monk et al., 2008), we also did not find evidence of a relationship between the gray matter volume of the vIPFC and attentional bias to threat. The null findings may be in part explained by the different developmental trajectories of subcortical and cortical development and a relationship between INR, the vIPFC gray matter, and threat bias, which may only be present when the

prefrontal cortex reaches maturity in early adulthood (Giedd et al., 1999). Future studies will be needed to examine the specific regions of the prefrontal cortex associated with INR in middle childhood as well as the contribution of function versus structure of the vIPFC in attentional bias to threat. We also note that all our findings should be interpreted with caution, because we should not conflate structure and function of the brain.

Studies of SED typically chose to focus on one indicator of socioeconomic status, such as family income or maternal education. However, this study chose to include both indicators. We acknowledge that socioeconomic status is a multidimensional construct in which INR and maternal education may be missing some of the complexity. For example, in some cases maternal education may play a moderating role between SED and child developmental outcomes (Augustine & Crosnoe, 2010; Hoff, 2003; Miller et al., 2011). Unfortunately, due to our small sample size, we could not conduct the moderation analysis. However, due to the mixed evidence reported concerning the direct effects of maternal education and brain morphometry (Hanson et al., 2011; Luby et al., 2013; Noble, Grieve, et al., 2012), we also examined its direct effect. We contribute to evidence suggesting a nonsignificant relationship between maternal education and gray matter volume in the hippocampus, amygdala, and prefrontal cortex (Hanson et al., 2011; Luby et al., 2013). Furthermore, we tested whether the correlation between INR and brain structure and maternal education and brain structure was significantly different. For the left hippocampus, we provided evidence of a significant difference between the correlations. This finding supports the hypothesis that INR and maternal education capture unique aspects of a child's environment and therefore may have different relationships with brain structure (Brito & Noble, 2014).

We further tested the specificity of our results in several different ways. First, we examined if the association between INR and hippocampal/amygdala volume was specific to these regions by also examining the relationship in brain regions that we did not hypothesize to be related to INR. We hypothesized INR would not be related to the volume of the precentral gyrus, basal ganglia, and lateral occipital gyrus. There was no significant association between INR and precentral gyrus or lateral occipital gyrus volume. This suggests the associations between INR and brain morphometry may be specific to certain regions (the hippocampus or amygdala) and may not be associated with brain structure globally. We did not find a significant correlation between INR and basal ganglia volume. Second, we provided post hoc regression analyses to indicate that the results were not driven by the children's IQ, anxiety symptoms as measured by the SCARED, or pubertal status.

While smaller hippocampal and amygdala volumes and increased attentional bias to threat are considered as negative

outcomes, we would like to discuss alternative explanations. First, from infancy to adolescence, hippocampal gray volume increases nonlinearly with its volume peaking from 9–11 years old (Raz et al., 2005; Uematsu et al., 2012; Voineskos et al., 2015). A similar pattern is observed for the amygdala with its volume peaking within the same age range (Payne, Machado, Bliwise, & Bachevalier, 2010; Uematsu et al., 2012). In more extreme cases of early adversity, such as maternal deprivation, amygdala functional connectivity to the prefrontal cortex has been shown to reach more mature, adult-like patterns earlier compared with children who had not experienced maternal deprivation (Gee et al., 2013). Therefore, our results for the smaller hippocampal and amygdala volumes in children experiencing low family income may reflect accelerated structural maturation (such as increased synaptic pruning) associated with exposure to early adversity. While the smaller volume may reflect increased synaptic pruning, it may not be adaptive regarding attentional bias to threat as smaller volumes were associated with greater threat bias scores. Animal studies suggest that short-term neuronal remodeling in the context of chronic stress is an adaptive function to protect the brain structure from excitotoxicity (McEwen, Eiland, Hunter, & Miller, 2012). However, this response to stress (shrinkage of dendrites in the CA3 region, and loss of spines in CA1 neurons) may have long-term consequences and promote maladaptive behaviors in response to stress in the future (Davidson & McEwen, 2012). However, we highlight that evidence from animal models suggests that dendritic remodeling associated chronic stress is not fixed and has shown to be reversible (McEwen, 2016), as well as amenable to interventions (Davidson & McEwen, 2012). It is important to note, however, that animal models cannot capture all aspects of the experience of SED (Hackman, Farah, & Meaney, 2010; Thapar & Rutter, 2015) and should always be interpreted with caution. However, currently they are useful to inform human studies about cause and effect relationships between SED and the brain (Perry et al., 2018).

Similarly, for children experiencing low family income, attention bias to threat to some degree may be adaptive to efficiently respond to possible dangerous situations in the environment (Sussman, Winkler, & Schröger, 2003). Therefore, it is critical to examine situations in which attentional bias to threat may be towards the extreme end and therefore a potential socioemotional risk marker for psychopathology. As suggested by biological embedding, differences in the quality of an individual's early environment may "sculpt" the development of the central nervous system, which then may impact cognitive, social, and behavioral development (Hertzman, 1999). For some children experiencing low income, the exposure to increased levels of family turmoil, violence in the home, and violent crime in the neighborhood may increase the allocation of attentional resources towards potential threats in the environment to respond quickly. According to the

theory of experiential canalization, living in a low-resource environment involves adaptations that have short-term benefits that may eventually lead to long-term costs (Blair & Raver, 2012). Neurobiological and psychological mechanisms (such as lower hippocampal volume and attentional bias to threat) may be protective by promoting short-term adaptations but can contribute to long-term dysregulation of stress mechanisms, which can have deleterious effects on resiliency to stress and outcomes, such as mental health (McEwen & Gianaros, 2010).

The findings should be considered bearing in mind the following limitations. First, the sample size of the current study was modest and will need replication in a larger sample size. We replicated findings from studies analyzing the relationship between INR and the hippocampus and amygdala; however, we will need to replicate the associations with attentional bias to threat in a large sample of children. Second, INR may influence the brain and emotional development through lack of cognitive stimulation in the home environment (Barry, Vervliet, & Hermans, 2015; Conger, Conger, & Martin, 2010; Lipina et al., 2013), toxins from the environment (Gray, Edwards, & Miranda, 2013; Liu & Lewis, 2014), or nutritional deprivation (Kant & Graubard, 2012). Thus, it is important for future studies to examine the role of these risk factors to understand further the environmental and biological pathways of the neural embedding of INR. Additionally, the study did not focus on paternal psychopathology. This aspect should be explored in the future as a potential confound or moderator of the relationship between SED and brain morphometry (Brown & Moran, 1997; Hackman et al., 2010; Spence, Najman, Bor, O'callaghan, & Williams, 2002). Furthermore, SED can co-vary with maltreatment, abuse, and neglect as well as parental substance abuse (Conger, Conger, & Martin, 2010; Herrenkohl & Herrenkohl, 2007; Trickett, Aber, Carlson, & Cicchetti, 1991). While the current study was limited in its ability to address the potential relations between the findings and these factors, future studies should investigate the unique contributions of the different risk factors for brain structural development. Third, we assessed the relationship between INR and brain structure based on the INR that was calculated for the last 12 months of the participant's life. While this is one of the most objective and commonly used methods to assess socioeconomic status, this measurement does not assess the chronicity of the exposure. Thus, it is unclear whether the variations in brain structure in the current study are associated with family income during the past year or family income since birth. To further examine the timing versus the chronicity of exposure, future studies are needed to assess the amount of time spent in low-income environments and its relationship to neural morphometry and attentional bias to threat.

Fourth, due to the cross-sectional nature of our data, we could not test whether left hippocampal volumes mediated the relationship between family income and attentional bias

to threat. While substantial biases in the parameters have been shown for cross-sectional mediation (Maxwell & Cole, 2007; Maxwell, Cole, & Mitchell, 2011), we provide evidence of a potential mediational model that will need to be followed up with a longitudinal study in which mediation can be accurately examined. Fifth, the stability of the dot probe paradigm has recently come into debate as some studies have demonstrated poor internal reliability and test-retest reliability (Kappenman, Farrens, Luck, & Proudfit, 2014; Price et al., 2015; Schmukle, 2005). Because we only measured the dot probe at one-time period, we could not assess the reliability of our estimates. There also are alternative methods for assessing attentional bias to threat scores using the dot probe (Price et al., 2015). These approaches will help to determine whether threat bias reflects an enhance orientation to nonneutral stimuli or a difficulty in disengagement from nonneutral stimuli. Replication of these findings could include eye-tracking to rule out possible location effects during the dot probe (a correspondence between the spatial location of the probe and the location of the participant's attention). Thus, it will be important that future studies will include multiple sessions of the dot probe to examine the reliability of the threat bias measure. Lastly, our analysis was limited by the atlas used by Freesurfer for the segmentation. We chose structures that we hypothesized would be associated with both SED and attentional bias to threat. Regarding attentional bias to threat, we could not capture all the structures that have been implicated in this task. For example, the dot probe has been shown to involve activity in multiple subcortical regions in the ascending reticular activity system (Pine, 2003; Price et al., 2013; Sara & Bouret, 2012). However, we could not examine these regions, because they were not adequately defined in the atlas used for segmentation. Future studies using manual tracing or automatic segmentation with an atlas that includes these regions will be critical to assess the potential relationship between these structures, INR, and threat bias. Additionally, while there have been studies of the relationship between family income and cortical thickness (Lawson, Duda, Avants, Wu, & Farah, 2013; Noble et al., 2015), we focused on gray matter volume, because subcortical morphometry and thickness measurements are not provided for these regions. We acknowledge the limitations of the correlational relationship between INR, gray matter volume, and threat bias. Future studies using an intervention or longitudinal approach will help to understand a mechanism of associations among socioeconomic status, brain structure, and socioemotional behavior in children. Future directions include examination of cortical thickness (focusing on the prefrontal cortex), functional activity (e.g., affective dot-probe fMRI), and structural connectivity (e.g., white matter organization) in and between these regions and its relationship to family income and attentional bias to threat. It will be critical to examine the functional connectivity between the amygdala and hippocampus as well as their

connectivity with other brain regions as altered connectivity patterns have been observed across several types of early adversity (Cisler et al., 2013; Gee et al., 2013; Sripada, Swain, Evans, Welsh, & Liberzon, 2014).

Conclusions

In the current study, we found a positive relationship between income-to-needs ratio and gray matter volume during middle childhood specifically in the bilateral hippocampus and right amygdala. Additionally, we observed an association between lower income-to-needs ratio and attentional biased responses to threatening faces on an affective dot probe, although this finding did not survive multiple comparison correction. Lastly, lower left hippocampal volumes were associated with greater attentional bias to threat. The main contribution of these findings is extending the current knowledge about the associations between family income-related variations in brain structure and neural and behavioral risk for socioemotional outcomes. Previous studies focus more on the associations between childhood SED, brain structure, and cognitive outcomes, such as executive function and academic performance. However, SED has been associated with elevated risks for negative socioemotional outcomes. Thus, the current study addresses the gap in the literature by demonstrating an environment—brain morphometry—behavior relationship that may play a role in the relationship between childhood SED and socioemotional difficulties.

Our findings may provide evidence of possible early socioemotional and neural risk markers for socioemotional difficulties for children living in families experiencing low income. Middle childhood is a developmental period in which symptoms of psychopathology arise, specifically anxiety and mood disorders (Feng, Shaw, & Silk, 2008; Shanahan, Calkins, Keane, Kelleher, & Suffness, 2014). Thus, it is critical to detect the relationship among environmental risks, brain morphology, and behavioral markers that have been associated with pediatric anxiety (Puliafico & Kendall, 2006) and internalizing symptoms (Hardee et al., 2013). While the data provide preliminary evidence for an association between INR, left hippocampal volume, and attentional bias to threat, future studies will be needed to examine this relationship in greater depth.

We acknowledge that the sample of children in this study did not have a current or past diagnosis of psychopathology. This was to reduce a confounding effect of psychopathology on the associations between SED and outcomes. This is likely to explain why the main findings of the study was independent of current anxiety symptoms. Attentional bias to threat has been well-researched in terms of predictive ability of anxious behavior later in development (Pérez-Edgar, Bar-Haim, et al., 2010a; Pérez-Edgar, McDermott, et al., 2010b; Pérez-Edgar

et al., 2011). Thus, caution is required for interpreting the results of the current study. The variation in the gray matter volume and attentional bias to threat suggest only potential risks for future psychopathology or subclinical symptoms. Our findings may help to support initiatives for preventative efforts to start earlier, such as middle childhood, when the amygdala and hippocampal structures may have increased vulnerability. Our results may elucidate a mediational pathway in which the structure of the left hippocampus mediates the relationship between INR and attentional bias to threat, which will need to be established using longitudinal data.

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