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Differential Associations of Distinct Forms of Childhood Adversity With Neurobehavioral Measures of Reward Processing: A Developmental Pathway to Depression

Meg J. Dennison
University of Washington

Maya L. Rosen
University of Washington, mrosen@smith.edu

Kelly A. Sambrook
University of Washington

Jessica L. Jenness
University of Washington

Margaret A. Sheridan
The University of North Carolina at Chapel Hill

See next page for additional authors

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Differential associations of distinct forms of childhood adversity with neurobehavioral measures of reward processing: A developmental pathway to depression

Meg J. Dennison[1], **Maya L. Rosen**[1], **Kelly A. Sambrook**[2], **Jessica L. Jenness**[3], **Margaret A. Sheridan**[4], and **Katie A. McLaughlin**[1]

[1]Department of Psychology, University of Washington

[2]Department of Radiology, University of Washington

[3]Department of Pediatrics, University of Washington

[4]University of North Carolina, Chapel Hill

Abstract

Childhood adversity is associated with altered reward processing, but little is known about whether this varies across distinct types of adversity. In a sample of 94 children (6 to 19 years), we investigate whether experiences of material deprivation, emotional deprivation, and trauma have differential associations with reward-related behavior and white-matter microstructure in tracts involved in reward processing. Material deprivation (food insecurity), but not emotional deprivation or trauma, was associated with poor reward performance. Adversity-related influences on the integrity of white-matter microstructure in fronto-striatal tracts varied across childhood adversity types, and reductions in fronto-striatal white matter integrity mediated the association of food insecurity with depressive symptoms. These findings document distinct behavioral and neurodevelopmental consequences of specific forms of adversity that have implications for psychopathology risk.

Childhood adversity is common. Population-based studies suggest that one-third to one-half of children have experienced some form of adversity by the time they reach adulthood (Green et al., 2010). Childhood adversity is one of the most potent risk factors for mental disorders (Green et al., 2010; McLaughlin, Greif Green, et al., 2012), highlighting the importance of characterizing how these experiences influence psychological and neurobiological development in ways that might increase risk for psychopathology. Disorders characterized by atypical reward functioning, such as depression, are common among youth and adults who have experienced childhood adversity (Green et al., 2010; McLaughlin, Greif Green, et al., 2012). Disruptions in reward processing are hypothesized to play a key role in these associations (Luking, Pagliaccio, Luby, & Barch, 2016). In the current paper, we examine the associations of three distinct forms of childhood adversity—

Corresponding Author: Katie A. McLaughlin, Associate Professor, University of Washington, Box 351525, Seattle, WA 98195, mclaughk@uw.edu.
DR. MEG JAYNE DENNISON (Orcid ID : 0000-0002-2289-5170)

trauma, caregiver neglect, and food insecurity—with reward processing and the structure of white matter tracts known to be involved in reward processing. Additionally, we investigate whether disruptions in reward-related pathways are a mechanism linking adversity with depressive symptoms.

Animal and human studies demonstrate that reward processing involves a complex set of psychological, behavioral and neurological processes that promote learning, encourage approach and consummatory behavior, and induce positive emotions, such as excitement during anticipation of rewards and satisfaction when experiencing them. These distinct components of reward processing have recently been formally organized into four conceptually coherent constructs, providing a systematic way of studying this complex set of processes (Olino, 2016). A*pproach motivation* involves the regulation of behaviors that result in reward achievement; *initial responsiveness* refers to feelings of liking or enjoying rewards; *sustained responsiveness* involves processes associated with satiety and cessation of reward-seeking; and, *reward learning* involves processes that determine the strength of associative learning following positive reinforcement. Systematic consideration of the distinct components of reward processing is instrumental to more clearly establishing mechanistic links between early life adversity and disorders characterized by atypical reward function.

Structural connectivity (i.e., white matter (WM) microstructure) between the striatum and PFC underlies many reward processing functions (Haber, Kim, Mailly, & Calzavara, 2006; Schultz, Tremblay, & Hollerman, 2000). Dopamine function within the mesolimbic pathway, involving dopaminergic projections from the mid-brain to the striatum, is involved in most, if not all, aspects of reward processing. Several prefrontal regions within the mesocortical dopamine pathway, which encompasses projections from the striatum to the prefrontal cortex (PFC), are central to reward processing. At least three WM tracts link the striatum and PFC: the anterior corona radiata connects the anterior cingulate with the striatum (Mori et al., 2008); the anterior limb of the internal capsule passes adjacent to the striatum and connects limbic regions with the PFC (Schmahmann, Smith, Eichler, & Filley, 2008); the external capsule connects the striatum with the medial and ventral prefrontal cortices (Schmahmann et al., 2008). Microstructural properties of these WM tracts are associated with behavioral and psychological indices of reward processing. For example, greater connectivity strength between striatal and PFC regions—measured as the number of structural projections reaching the striatum from PFC regions—has been positively associated with novelty seeking (Lei et al., 2014), and trait measures of reward dependence, a personality trait characterized by enhanced approach motivation (i.e., persistence in repeating actions associated with rewards) (Cohen, Schoene-Bake, Elger, & Weber, 2009). Further, higher levels of reward dependence are associated with reduced fractional anisotropy (FA)—a measure of the integrity of WM tracts—in prefrontal regions linked to the striatum (Bjornebekk, Westlye, Fjell, Grydeland, & Walhovd, 2012). Decreases in reward learning associated with healthy aging have been linked to decreased WM integrity in tracts linking the medial PFC to the ventral striatum (Samanez-Larkin, Levens, Perry, Dougherty, & Knutson, 2012). Finally, increased FA in the anterior corona radiata and the anterior limb of the internal capsule is positively associated with reward-related activation in ventral striatum in healthy adults (Koch et al., 2014). Together, these findings suggest that

differences in reward processing are associated with connectivity strength and microstructural properties of anatomical connections between reward processing regions, particularly fibers connecting the striatum with the PFC.

A fourth WM tract, the uncinate fasiculus, links the rostral part of the temporal lobe to the orbital and medial PFC, might also play a role in reward processing (Camara, Rodriguez-Fornells, & Munte, 2010). The uncinate fasciculus is a component of the circuit underlying recognition memory, and is implicated in cognitive tasks that are linked with emotional associations (Ghashghaei & Barbas, 2002). Camara and colleagues (2010) found that in healthy adults WM microstructure in the uncinate fasciculus correlates positively with individual differences in reward-related activation in the ventral striatum during a gambling task. Further, participants with greater blood-oxygen-dependent level (BOLD) signal change in the ventral striatum on loss versus gain trials also had higher uncinate fasciculus FA values (Camara et al., 2010), indicating a role for this WM structure in reward processing.

Childhood adversity is associated with altered reward processing at both behavioral and neural levels, although the pattern of findings varies across domains of reward processing and adversity type. For example, behavioral deficits in reward learning have been observed among maltreated children—defined as either abused or neglected (Hanson et al., 2017), but not adult women with childhood sexual abuse histories (Pechtel & Pizzagalli, 2013). Similarly, findings regarding approach motivation are also mixed: children exposed to institutional rearing show behavioral deficits in approach motivation in that they are less likely to alter their behavior in response to increasing rewards than children raised in family environments (Wismer Fries & Pollak, 2016), whereas adolescents with abuse histories do not show these deficits (Dennison et al., 2016). Maltreated children—defined as either abused or neglected—also fail to modulate their behavior in response to reward value (Guyer et al., 2006).

At the neural level, emotional neglect—but not other forms of abuse or neglect—is associated with a blunted developmental trajectory of functional activation in the ventral striatum to the receipt of reward across adolescence (Hanson, Hariri, & Williamson, 2015), indicating altered development of initial responsiveness to rewards following neglect. A similar pattern has been observed in children exposed to institutionalization in early childhood (Goff et al., 2013). Adults who experienced child abuse exhibit weaker responses in the left pallidum and putamen during anticipation of monetary reward (Dillon et al., 2009). Similarly, childhood poverty is associated with reduced activation in the striatum and thalamus during reward anticipation in adults (Boecker et al., 2014). Thus, multiple forms of adversity involving social and cognitive deprivation are associated with blunted reward responses. However, contrary findings show exposure to child abuse is associated with *increased* striatal reactivity to positive social cues among adolescents (Dennison et al., 2016), and childhood poverty has also associated with elevated insula, pallidum and putamen activation during reward delivery (Boecker et al., 2014). Understanding these mixed findings remains difficult without systematically examining the effects of distinct types of adversity on different components of reward processing.

One possible explanation for these discrepant findings relates to variability in the types of adversity examined across studies. Conceptual models argue that diverse forms of childhood adversity have distinct consequences of on affective, neural, and cognitive development (McLaughlin & Sheridan, 2016), which in turn may differentially mediate risk for the development of disorders commonly associated with adversity, including depression. McLaughlin (2016) defines childhood adversity as an environmental event or series of events that are severe or prolonged and that "are likely to require significant adaptation by an average child and that represent a deviation from the expectable environment" (p. 4). These include experiences of deprivation and threat. Deprivation involves the *absence* of expected inputs from the environment (i.e., caregiver neglect, poverty, institutionalization, food insecurity), whereas experiences of threat (i.e., trauma) involves the *presence* of unexpected inputs that represent significant threats to physical integrity or well-being of the child (i.e., exposure to violence, and physical, sexual or emotional abuse) (McLaughlin, 2016). Recent empirical studies directly comparing experiences reflecting threat and deprivation have confirmed that the developmental consequences of these experiences are at least partially distinct in the domains of emotional processing, and cognitive control (Lambert, King, Monahan, & McLaughlin, 2016). We are unaware of prior work that has attempted to disentangle distinct influences of these different forms of adversity on reward processing. We do so in the current report.

Maturation of WM microstructure is highly protracted, with ongoing development throughout childhood into late adolescence (Lebel & Beaulieu, 2011), suggesting that WM development may be particularly susceptible to postnatal environmental influences. There is rapidly emerging evidence that childhood adversity impacts the development of WM microstructure across a number of brain regions (Bick, Zhu, et al., 2015; Choi, Jeong, Polcari, Rohan, & Teicher, 2012; Ugwu, Amico, Carballedo, Fagan, & Frodl, 2015), and that adversity-related WM differences may also be related to specific types of adverse experiences (Choi et al., 2012). For example, Choi et al. (2012) showed that witnessing domestic violence in childhood was associated with reduced FA in the visual limbic pathway during young adulthood. Less evidence has linked childhood adversity specifically with altered development of fronto-striatal WM structures. Recent work suggests that institutional rearing is associated with global alterations in WM tracts, including in regions involved in reward processing such as the anterior corona radiata and the external capsule (Bick, Zhu, et al., 2015).

Given the relevance of reward processing as a potential mechanism underlying risk for psychopathology following childhood adversity (Luking et al., 2016), understanding how such experiences impact the development of WM tracts that support reward processing may help identify neurobiological mechanisms that confer elevated risk for psychopathology in children exposed to adversity. We hypothesize that disruptions in neural circuits underlying reward processing might be a key mechanism linking childhood adversity with depression. Consistent with this hypothesis, blunted developmental increase in ventral striatum response to reward across adolescence has been identified as a mechanism linking emotional neglect with depression (Hanson et al., 2015). With regard to WM microstructure, a recent study found that reduced structural integrity in the external capsule and uncinate fasciculus were associated with depressive symptoms in children, and that microstructure of the external

capsule mediated the link between institutional rearing and depressive symptoms (Bick, Fox, Zeanah, & Nelson, 2015). The degree to which WM integrity in fronto-striatal tracts plays a role in the association of other forms of childhood adversity with depression is unknown.

In the current study we examine the unique associations of distinct forms of adversity with reward processing, measured at behavioral and neural levels, in children and adolescents and test whether alterations in reward processing mediate the relationship between adversity and depressive symptoms. We measured three forms of adversity to capture dimensions of both threat and deprivation: trauma, neglect and food insecurity. Trauma exposure, an indicator of threat, was operationalized as exposure to physical abuse, sexual abuse, or domestic violence, each of which reflects serious threats to the physical integrity of the child. Experiences of deprivation were operationalized as two separate measures: caregiver neglect and food insecurity. Caregiver neglect reflects failure of a caregiver to act in ways that are necessary to meet the basic needs of a child. Caregiver neglect reflects not only an absence of provision for a child's physical needs but also an absence of expected, positive social and emotional inputs from a caregiver, including sensitive and responsive caregiving and appropriate supervision and support. Food insecurity differs from caregiver neglect in that it is an indicator of extreme material but not social or emotional deprivation, whereby the child fails to consistently experience one of the most fundamental forms of positive reinforcement (i.e., food). Although research into the psychological impacts of food insecurity is much more limited than abuse and neglect, the experience of food insecurity is common (Coleman-Jensen, Rabbitt, Gregory, & Singh, 2016) and childhood exposure is associated with risk for mood disorders, even after controlling for extreme poverty (McLaughlin, Green, et al., 2012). Given that food is a very strong behavioral reinforcer, and the reinforcing qualities of food are in part a dopamine-mediated phenomenon (Epstein & Leddy, 2006), it is possible that the chronic absence of food or unpredictability of access to food may influence reward processing independent of nutrition-related effects on cognitive function (Kar, Rao, & Chandramouli, 2008), which in turn creates unique risk for depression.

Behavioral measures of reward processing were obtained using a child-friendly version of the monetary incentive delay task, which provided indices of approach motivation. Given the mixed findings regarding the effects of adversity on different aspects of the PVS, we chose to focus solely on behavioral indices of approach motivation, particularly given evidence that neural deficits in approach motivation is associated with risk for depression (Olino et al., 2014). Indeed, preliminary evidence suggests that multiple forms of adversity influence approach motivation (Boecker et al., 2014; Dillon et al., 2009; Guyer et al., 2006; Pechtel & Pizzagalli, 2013; Wismer Fries & Pollak, 2016), although we are unaware of studies that have tested for independent effects of different types of adversity on approach motivation.

White matter microstructure in four white matter tracts: the anterior limb of the internal capsule, the anterior corona radiata, the external capsule, and the uncinate fasciculus, were included in our analysis based on evidence that they connect striatal regions associated with reward processing to PFC regions in the mesocortical dopaminergic system (Schmahmann et al., 2008) and have previously been implicated in reward processing (Camara et al., 2010; Koch et al., 2014; Lei et al., 2014; Lin et al., 2012). We examined each hemisphere

separately due to longstanding evidence of frontal brain lateralization in reward processing (Harmon-Jones, Gable, & Peterson, 2010).

With respect to reward behavior, we predicted that exposure to adversity involving deprivation (i.e., caregiver neglect and food insecurity) would be associated with both poorer overall performance on the reward task and reduced sensitivity to reward value, indicating deficits in approach motivation. This prediction stems from the consistent evidence for blunted approach motivation following early deprivation (e.g., Hanson et al., 2015; Wismer Fries & Pollak, 2016) and less consistent findings following trauma (e.g., Dennison et al., 2016; Pechtel & Pizzagalli, 2013). Second, we expected deprivation-related adversity to be associated with reduced integrity of fronto-striatal WM tracts across a greater number of WM tracts than trauma. Third, we expected that all types of adversity would be associated with increased depressive symptoms and that depression symptoms would be associated with both decreases in reward processing behavior (Morris, Bylsma, Yaroslavsky, Kovacs, & Rottenberg, 2015) and reduced FA in fronto-striatal WM tracts (Zhu et al., 2011). Finally, we expected that associations between deprivation-related adversity and depression symptoms would be mediated by both behavioral measures of reward processing and reduced FA in fronto-striatal WM tracts. A schema of the proposed model is depicted in Supplemental Figure S1.

Methods

Participants

A mixed community/clinic sample of 94 children and adolescents aged 6 to 19 years (Mean = 13.57, SD = 3.47 years; 48.9% female) and one of their parents or caregivers participated. Of these, 52 without MRI contraindications (e.g. orthodontic braces) and who were at least 8 years old, were invited to complete an MRI assessment (Mean = 14.49, SD = 2.72 years; 49.0% female). The smaller size of the MRI sample was based on funding constraints. The sample was recruited in Seattle, WA between February 2014 and February 2015. Youths were recruited at schools, after-school and prevention programs, medical clinics, and in the general community. Sample characteristics are depicted in Table 1. The Institutional Review Board at the University of Washington approved all procedures. Participants were compensated and written informed consent was obtained from legal guardians, while youths provided written assent.

Measures

Childhood Adversity—Child abuse and domestic violence, indicators of trauma exposure, were assessed using two validated measures: the Childhood Trauma Questionnaire (CTQ) (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997), and the Childhood Experiences of Care and Abuse (CECA) interview (Bifulco, Brown, & Harris, 1994). The CTQ is a 28-item scale that assesses the frequency of physical, sexual, and emotional abuse during childhood and has good convergent and discriminant validity (Bernstein et al., 1997). The abuse sub-scales exhibited good internal consistency in this sample (α = .909). The CECA assesses multiple aspects of caregiving experiences, including physical and sexual abuse; we modified the interview to ask parallel questions about witnessing domestic violence (i.e.,

directly observing violence directed at a caregiver). Inter-rater reliability for maltreatment reports is excellent, and validation studies suggest high agreement between siblings on maltreatment reports (Bifulco, Brown, Lillie, & Jarvis, 1997). Participants who reported physical abuse, sexual abuse, or exposure to at least two incidents of domestic violence during the CECA interview or who had a score on the physical or sexual abuse subscales of the CTQ above a validated threshold (Walker et al., 1999) were classified as abused. A total of 40.4% of the sample (n=38) were trauma-exposed.

Caregiver neglect was assessed using an 8-item self-report measure assessing the frequency of neglectful behaviors that is embedded in the CECA interview (Bifulco, Bernazzani, Moran, & Jacobs, 2005). This measure was completed separately in reference to neglectful behaviors on the part of each caregiver for children living with two caregivers. We elected to use this measure rather than the emotional neglect subscale of the CTQ as this measure more closely aligns with accepted definitions of neglect (Straus & Kantor, 2005) by assessing neglectful behaviors (e.g., “She would leave me unsupervised before the age of 10”) as compared to the CTQ which focuses largely on appraisals (e.g., “My family was a source of strength and support”). Participants who reported levels greater than predefined cut-off scores (Bifulco et al., 2005) were classified as neglected. The neglect subscales exhibited acceptable internal consistency in this sample (α = .69 for child report on the mother and α = .84 for child report on the father). We selected the highest score for either parent to determine the overall neglect score, which was then turned into a binary score according the previously established cut off scores linked to optimal sensitivity and specificity (Bifulco et al., 2005).

Food insecurity in the past 12 months was assessed using a set of 4 items drawn from the short form of the U.S. Department of Agriculture’s Food Security Scale (Blumberg, Bialostosky, Hamilton, & Briefel, 1999), these four items constitute a validated measure of food insecurity that has been used in epidemiological surveys of youth psychopathology (e.g., the National Comorbidity Survey Replication – Adolescent Supplement) (McLaughlin, Green, et al., 2012). Children and their parent completed two dichotomous items indicating whether they had ever been hungry but did not eat because they could not afford enough food and whether they had ever eaten less than they thought they should because there was not enough money to buy food. Two additional items assessed how often adolescents and parents did not have enough money to buy food and could not afford to buy balanced meals in the past 12 months.

Depressive Symptoms—Depression symptoms were measured using the Child Depression Inventory (CDI) (Kovacs, 1992). The CDI has good internal consistency, test-retest reliability, and discriminant validity (Kovacs, 1992). The CDI demonstrated good reliability in this sample (α=0.87).

Reward processing task—The reward processing task was a child-friendly version of the monetary incentive delay (MID) task that includes cartoon animals that children are told are piñatas (Helfinstein et al., 2013). The task is depicted in Figure S2. Each piñata contains a variable number of stars (0, 1, 2, or 4). Children are told to “whack” the piñata as quickly as possible to earn the stars inside, and that the number of stars they earn during the task will

determine the size of the reward they receive at the end. On each trial, children make a speeded response to a target in order to earn the stars inside the piñata. Each trial is composed of three stages: anticipation, response, and feedback. In the anticipation stage, children see a cue indicating the size of the potential reward for that trial. The piñata is partially revealed at the top of the screen; the number of stars inside the piñata is visible, but children cannot yet hit it. In the response stage, children can earn the stars for that trial by responding quickly once the target appears. The piñata drops to the middle of the screen and children push a button to hit the piñata. In the outcome stage, children see feedback indicating whether or not their response was fast enough to receive the reward. For successful trials (i.e., hits), the piñata cracks open and the stars are deposited in a basket at the bottom of the screen. On unsuccessful trials (i.e., misses), children see the intact piñata swinging to the side of the screen with the stars inside. The task was designed to be visually appealing and engaging for children. In order to incentivize performance, at the start of the task, all children were told they would receive up to $10 based on their performance. Upon completion, all children received $10 irrespective of performance.

Prior to the task, participants played a practice round with 22 trials, and average reaction time (RT) was calculated for each participant. During the task, the piñata was displayed during the cue phase for a pre-specified range of durations calibrated based on the participant's RT during the practice round. As a result, participants were required to respond within a narrow window calculated based on their RT, consistent with prior work (Helfinstein et al., 2013). This was done to make the task equally challenging for all children at the beginning of the task, and was particularly necessary due to the large age range of the sample. However, once the task commenced, display time was no longer manipulated based on the participant's performance during the task, which meant that each child had the opportunity to improve their performance throughout the task. During the task, the cue appeared for 1500 ms, followed by a cue-free anticipatory period that varied between 1000 and 2000 ms. The target appeared for a variable period of time, followed by a delay period with a duration such that the target period and delay period combined to a total of 1500 ms. Finally, the feedback appeared for 1500 ms. The task consisted of six task runs of 22 trials each, for a total of 132 trials. Trials were divided evenly between the four incentive levels for a total of 33 trials at each incentive level. One child did not complete the task and data for two subjects was removed from the analyses due to lack of responses on any of the trials, indicating that the task was not completed as directed.

Image Acquisition and Processing—Diffusion tensor imaging was performed on a 3.0-T scanner (Phillips Achieva) with a 32-channel sensitivity-encoding (SENSE) head coil using a single-shot echoplanar imaging sequence (TR=8165ms, TE=75ms, flip angle=90°, FOV=256×256mm, 72 slices, in-plane voxel size=2mm^3). Diffusion-weighted images were acquired along 64 non-collinear and non-coplanar directions with a b value of 1000 s/mm^2 and 1 image with a b value of 0 s/mm^2.

DTI pre-processing including skull-stripping and correction for distortion due to eddy currents in FSL and registration using non-linear symmetric diffeomorphic transformation in Advanced Normalization Tools (ANTS) (Avants, Epstein, Grossman, & Gee, 2008). Head motion and eddy current correction were conducted with the 'eddy' tool in FSL, which uses

the diffusion direction and weighting of each volume to model the diffusion signal. Two subjects with artifacts in more than 10% gradient directions, motion greater than 2.5 SD of the group mean, and temporal signal-to-noise (TSNR) ratio less than 2.5 SD of the group mean were excluded. The diffusion tensor was calculated per voxel using conventional reconstruction methods in FSL's dtifit. From these maps, fractional anisotropy (FA) was calculated.

To extract FA values in our 4 tracts of interest, we used a standardized protocol developed by the ENIGMA consortium; this protocol is described in detailed elsewhere (Jahanshad et al., 2013). Briefly, FA images were nonlinearly registered to the ENIGMA-DTI target brain using FNIRT. The data were then processed using a modified version of FSL's tract-based spatial statistics (TBSS) (Smith et al., 2006) to project individual FA values on the hand-segmented ENIGMA-DTI skeleton mask rather than the TBSS skeleton. After extracting the skeletonized WM and the projection of individual FA values, ENIGMA tract-wise regions of interest, derived from the Johns Hopkins University (JHU) WM parcellation atlas (Mori et al., 2008), were transferred to extract the mean FA across the full skeleton and average FA values for the four WM tracts for each hemisphere, for a total of 8 tracts of interest. The whole brain average FA values were calculated to include all voxels in the ENIGMA-DTI skeleton. The protocol, target brain, ENIGMA-DTI skeleton mask, source code and executables are all publicly available (http://enigma.ini.usc.edu/ongoing/dti-working-group/).

Statistical Analysis

Our goal was to identify unique associations of each type of adversity (trauma, caregiver neglect, and food insecurity) with reward processing, WM microstructure and depression symptoms. As such, all three adversity measures were simultaneously included in all models. This follows recommendations for examining unique contributions of distinct dimensions of adversity (McLaughlin & Sheridan, 2016). A linear transformation (square root) was applied to the CDI scores due to skew. We used linear regression to explore associations between our three adversity measures and two behavioral indicators of reward processing. First, we measured approach motivation using the total number of stars earned on the piñata task. Consistent with the definition of approach motivation as a multi-faceted construct involving processes that regulate the direction and maintenance of approach behavior, we conceptualized the total number of stars gained on the task as capturing a child's ability to attend to reward cues throughout the task and make accurate behavioral responses to them; that is, to continue to regulate their behavior to successfully approach and engage with reward. A second measure of approach motivation was constructed by examining residualized change in reaction time to high-reward trials (i.e., 4 stars) compared to no-reward trials (i.e., 0 stars), averaged across all trials in the task. This construct measures the degree to which a child modulates their behavior in response to reward value —a measure that has been used in both child and adult studies of reward processing (Pizzagalli et al., 2009; van Hulst et al., 2015). Next, we tested direct associations between adversity types and FA in the anterior corona radiata, anterior limb of the internal capsule, external capsule, and uncinate fasiculus, separately by hemisphere (Figure 1). Then, we tested direct associations between depression symptoms with adversity measures, behavioral

measures of reward processing, and white-matter microstructure. Finally, where we observed significant associations between adversity and reward processing and depression (i.e., a and b paths) we used mediation to explore indirect effects (Hayes, 2009). These models were used to determine whether behavioural and/or neural measures of reward processing were underlying mechanisms that explain (i.e., mediate) associations between childhood adversity and depression symptoms. All indirect effects were tested using bootstrapped standard errors (1000 draws) in the Lavaan package in R. In all models, sex and age were included as covariates. The false discovery rate method described by Benjamini and Yekutieli (2001) was used to correct for multiple comparisons within each analysis pathway. Analyses were completed in R Version 3.3.1, for Macintosh, using the Lavaan package. Finally, we conducted ancillary analyses to explore whether adversity moderated the development of reward processing by examining the interaction of age and adversity to predict reward behavior and FA in the eight regions of interest—given the exploratory nature of these analyses we did not control for multiple comparisons and detailed findings are reported in Supplemental Materials S4.

Missing data—Full information maximum likelihood (FIML) was used to estimate missing data. Data were not missing at random (Little's MCAR test $p<.05$). This was unsurprising given that younger children in the sample were not eligible to complete an MRI scan, and missingness on FA values brain ROIs was related to age, $t(73.8) = 3.2$; $p=.002$. FIML data estimation approaches are reasonable even if missingness is non-ignorable provided correlates of missingness are included in the model (Graham, 2003); this was another reason why age was included as a covariate in all models.

Results

Descriptive Statistics

Significant co-occurrence was observed between trauma and neglect, $\chi^2(1) = 9.19$, $p = .002$, and between food insecurity and trauma, $\chi^2(1) = 4.63$, $p = .032$, but not food insecurity and neglect, $\chi^2(1) = 0.55$, $p = .46$. Means and standard deviations for age, reward and FA measures by exposure to adversity type are presented in Table 2. Bivariate correlations between reward outcome measures and FA values for the 8 ROIs show moderate positive associations ($.32 < r < .37$, $p < .05$) between FA in the right and left anterior limbs of the internal capsule and total number of stars gained on the reward task (Table S1). Age was associated with a greater number of total stars earned (B =1.90, $p<.001$, CI: 0.99, 2.81), faster RT to 4 star relative to 0 star trials (B= −2.67, $p<.001$, CI: −4.07, −1.27), and greater FA in the left (B=.004, $p<.001$, CI: 0.002, 0.006) and right (B=.003, $p=.001$, CI: 0.001, 0.005) anterior limbs of the interior capsule. Age was also positively associated with depressive symptoms (B=.07, $p=.045$, CI: .002, .147), see Figure S3.

Adversity and depression

When examined as separate predictors, both food insecurity (B=.58, $p=.042$, CI: 0.02, 1.15) and trauma (B=.55, $p=.030$, CI: 0.05, 1.04) were associated with greater depressive symptoms. When controlling for other forms of adversity, caregiver neglect was associated with greater depressive symptoms (B=.68, $p=.023$, CI: .09, 1.26), see Figure 2.

Adversity and reward behavior

After controlling for other types of adversity, food insecurity was associated with lower reward performance, as indicated by a smaller total number of stars earned (B=–11.47 p=.001, CI: –18.43, −4.50), but trauma and caregiver neglect were not associated with reward performance, see Figure 2. Adversity was not associated with any differences in modulation of RT to rewarded trials relative to unrewarded trials.

Adversity and white matter microstructure

After controlling for other types of adversity, trauma was associated with reduced FA in the left external capsule (B= −.015, p<.001, CI: −.024, −.006). Food insecurity was associated with reduced FA in the left anterior limb of the internal capsule (B= −.016, p=.008, CI: −0.012, −0.004) and greater FA the left uncinate (B= .041, p=.006, CI: 0.012, 0.070). Caregiver neglect was also associated with greater FA in the left uncinate (B=0.038, p=.012, CI: .008, .067), see Figure 3.

Reward behavior and depression

Greater number of stars earned on the reward task was associated with fewer depression symptoms (B= −0.017, p=0.049, CI:−.033, 0.0001), although not after controlling for multiple comparisons using the false discovery rate method described above. Change in RT was not associated with depression symptoms (B=.001, p=.88, CI: −.011, .013).

White-matter microstructure and depression

Depression symptoms were associated with reduced FA in the right and left anterior limbs of the internal capsule (B=–24.3, p=.003, CI: −40.6, −8.1; B= −26.5, p<0.001, CI: −41.8, −11.1); the right and left anterior corona radiata (B=–19.8, p=.002, CI: −32.1, −7.5; B= −17.1, p=.009, −30.0, −4.2); and the left external capsule (B=–26.8, p=.011, CI: −47.6, −6.1). See Figure 4.

Adversity and the development of reward behavior and white-matter microstructure

Adversity did not moderate the development of reward behavior (p's all <.05). Trauma exposure moderated the development of the left ALIC (B=−.004, p = .037), such that age related increases in FA observed among children without trauma were not observed among those with trauma (See Supplement S4).

Mediation models

Given the pattern of findings, two indirect effect models were tested: first we examined whether the association between food insecurity and depression was explained by FA in the left anterior limb of the internal capsule, and, second, whether the association between trauma and depression was explained by FA in the left external capsule. Before we tested the indirect effects, a linear transformation was applied to the FA value for the anterior limb of the internal capsule due to large differences in observed variances. First, we found that FA in the left anterior limb of the internal capsule indirectly explained the association between food insecurity and depression, as demonstrated by confidence intervals for this indirect effect not containing zero, b= 0.41, CI: 0.038, 0.928. The association between trauma

exposure and depression was not explained by FA in the left external capsule (b=.159, CI:–.151, .568).

Discussion

In this study we show that food insecurity, but not trauma or caregiver neglect, predicts poor performance on a reward processing task. We further show that different forms of childhood adversity exhibit distinct associations with WM microstructure in tracts linking the striatum and PFC. Specifically, childhood trauma was associated with reduced integrity of WM microstructure in the external capsule, whereas food insecurity was associated with reduced WM microstructure integrity in the left anterior limb of the internal capsule. In contrast, both food insecurity and caregiver neglect were associated with *increased* WM microstructure integrity in the left uncinate fasciculus. The association between food insecurity and depression was mediated by FA in the anterior limb of the internal capsule. These findings suggest that different types of childhood adversity exert unique effects on biobehavioral indices of reward processing, which confer risk for depression, highlighting the importance of considering distinct forms of adversity independently.

Food insecurity was associated with poor performance on the reward task and reduced FA in the left anterior limb of the internal capsule, providing support for our hypothesis that material deprivation is associated with deficits in reward processing at both behavioral and neural levels. Our finding that children who experienced food insecurity obtained fewer stars on the task, but did not exhibit differences in modulation of RT to rewarded trials, indicates greater deficits in aspects of approach motivation associated with accurate responses—while children who experienced food insecurity also reacted faster to rewarded trials, this increased motivation did not facilitate orienting or approach behaviors that drive accurate and consistent responding to increase overall performance. Given that approach motivation is influenced by previous learning history (Hollerman, Tremblay, & Schultz, 1998), our findings could suggest material deprivation early in life reduces exposure to formative learning experiences, creating generally weak stimulus-reward associations, triggering changes to the development of biobehavioral systems underpinning adaptive responses to reward in the future, particularly to expectancy of reward. Over time, associative learning creates connections between co-occurring stimuli or between a stimulus and response, and is mediated by coordinated cell assemblies whose synaptic connections are strengthened upon co-activation. Our neural findings are consistent with this idea: reduced FA in the anterior limb of the internal capsule suggests poorer connectivity between the striatum and PFC—regions whose coordinated activity is critical to the regulation and organization of approach behaviors based on prior learning (Haber et al., 2006; Schultz et al., 2000). Children raised in environments where material resources such as food are readily available are more likely to learn that behavioral responses to internal hunger cues will elicit rewards. In the context of food insecurity, behavioral responses to hunger are less likely to be reinforced by food rewards. Thus, when food is scarce, over time, the child learns to *expect* that the environment will not produce reinforcement, leading to reduced approach motivation. Our findings are consistent with a number of recent studies showing that environments characterized by the absence of positive reinforcement influence approach motivation. Children reared in institutions exhibit deficits in learning tasks that pair visual cues with

motivational significance, such that they do not alter behavioral responses to stimuli that are associated with reward as compared to typically developing children who are faster and more accurate in responding to rewarded stimuli (Wismer Fries & Pollak, 2016), and show reduced activation in the ventral striatum during reward anticipation and in response to positive cues (Goff et al., 2013). Finally, preliminary evidence from a recent rodent study showed that a developmental history of food insecurity is associated with altered behavioural sensitivity to reward and reductions in electrically evoked dopamine release compared to animals raised with stable access to food (Lin et al., 2017). Together, evidence supports the hypothesis that early deprivation is associated with reduced approach motivation, which may be driven by reduced expectancy of rewarding outcomes given prior learning history.

Although we have proposed a key role for associative learning during early life in the relationship between food insecurity and differences in reward processing, it is possible that other processes may explain this association. For example, food insecurity is likely to be coupled with nutritional deficiencies, which are known to impact brain development at both global and circuit levels, and exert differential effects based on developmental timing (Georgieff, 2007). Malnourishment may have lead to poorer performance on the reward task due to changes in physical and cognitive abilities that decrease the child's ability to maintain speed and attention independent of reward processing. Further research is required to disentangle the psychological and nutritional aspects of food insecurity to identify underlying mechanisms that predict poorer outcomes observed across multiple cognitive and affective domains (Kar et al., 2008).

Our finding that FA in the anterior limb of the internal capsule mediated the associations between food insecurity and depressive symptoms suggests a potential neurobiological mechanism and is broadly consistent with previous findings implicating this WM tract in the pathophysiology of depression. For example, whole brain studies have reported reduced FA in the left anterior limb of the internal capsule among adolescents with first-onset major depression (Zhu et al., 2011). Our findings are generally consistent with prior work indicating disruptions in the functional development of striatal circuitry is a mechanism linking deprivation-related adversity to depression (Goff et al., 2013; Hanson et al., 2015) and suggest that environmental deprivation shapes brain development to increase vulnerability for depression.

While caregiver neglect was associated with greater depressive symptoms, it was not significantly associated with reward processing as there was wide variability in performance in this group. Differences in processing of social versus non-social rewards may be involved. For example, Kohls and colleagues (2009) show that monetary reward is valued more highly than social reward in children and adolescents. In the context of caregiver neglect, the absence of a secure attachment with a primary caregiver may differentially hamper the development of response to social rewards, but have less impact on non-social reward. In the current study, we only considered non-social rewards in our task. While processing social rewards involves fronto-striatal systems, it also involves circuitry extending beyond these regions. Further studies are needed to more carefully examine the association between caregiver neglect and reward type (i.e., social and non-social), as well as the effects on brain

systems underlying social cognitive processes, which extend beyond the fronto-striatal system.

We observed an association between both measures of deprivation—food insecurity and caregiver neglect—with increased FA in the left uncinate fasiculus. Prior work on childhood adversity and the structural integrity of the uncinate fasiculus has produced mixed findings. Bilaterally reduced FA in the uncinate has been reported following institutionalization, a severe form of global deprivation (Govindan, Behen, Helder, Makki, & Chugani, 2010). Another study reported no association between institutionalization and WM microstructure in this region (Bick, Zhu, et al., 2015), and, in a community sample of adults, childhood adversity—which included measures of both threat and deprivation—was associated with greater FA in the left uncinate fasiculus (Ugwu et al., 2015), consistent with our finding. One difference between prior work reporting decreased FA and the current investigation is that children in prior studies were adopted into well-resourced families following institutionalization in infancy and early childhood. In the current investigation, the duration and timing of exposure to adversity is less clearly circumscribed. Such differences in exposure to deprivation, including timing and chronicity (and cessation) of exposure, may lead to different outcomes. Further, the current sample encompasses a wider and older age range than previous studies, which may also explain different effects, particularly given that development of the uncinate fasciculus continues throughout childhood into early adulthood (Lebel & Beaulieu, 2011).

Another hypothesis explaining increased rather than reduced WM integrity in the uncinate fasciculus may relate to accelerated development of connectivity between the amygdala and PFC following material and caregiver deprivation (Callaghan, Sullivan, Howell, & Tottenham, 2014). Work in rodents has shown that amygdala-PFC circuitry matures around the time pups begin to leave the nest (Landers & Sullivan, 2012), and it has been hypothesized that this biological event in humans coincides with individuation from a caregiver, and that early-life stress accelerates this process (Gee et al., 2013). In support of this, Gee and colleagues (2013) showed that early-life institutionalization was associated with earlier maturation of amygdala-PFC functional coupling. Anatomically, the uncinate fasciculus connects the anterior temporal lobe, including the amygdala, with the PFC. Our results are somewhat consistent with these findings, such that exposure to deprivation was associated with greater connectivity/axonal organization, between the amygdala and PFC, as indicated by greater FA in the uncinate fasciculus. We did not observe a similar pattern among children exposed to trauma, suggesting that this acceleration of amygdala-PFC circuitry may be specific to adverse environments characterized by deprivation, but not threat. The absence of material needs and caregiver input early in life may accelerate neurodevelopment in amygdala-PFC circuitry, potentially marking an ontogenetic adaptation to these particular forms of adversity. This biological adaption may act to promote early maturation to support greater autonomy from environments characterized by material and emotional deprivation.

Experiences of trauma were not associated with the two behavioral measures of reward processing but were associated with reductions in FA in the left external capsule, which did not mediate the relationship between trauma and depression symptoms. The behavioral

findings are consistent with previous findings in abused adolescents (Dennison et al., 2016), but inconsistent with reports of reduced approach motivation—assessed using an incentive-based decision task, among adult women with histories of childhood sexual abuse (Pechtel & Pizzagalli, 2013), highlighting the need for replication across multiple reward tasks. Reduced FA in the external capsule has been associated with childhood institutionalization (Bick, Zhu, et al., 2015); however, links to trauma have not been made previously. While institutionalization is typically characterized as an extreme form of deprivation, arguably the absence of a secure attachment with a primary caregiver may instigate, at least in part, similar physiological distress responses to those experienced by children exposed to abuse (Luecken & Lemery, 2004), potentially explaining the overlapping findings. While the external capsule links the striatum and PFC and has been linked to addiction problems (Lin et al., 2012), its precise function remains largely unknown, and is likely to be multifaceted (Schmahmann et al., 2008). This finding warrants replication in future research.

We report a complex pattern of findings regarding the effects of adversity on WM structure, such that different types of adversity were differentially associated with both increases and decreases in the integrity of specific WM tracts. The findings did not clearly support our hypothesis that deprivation would be associated with global reductions in FA (i.e., reduced FA in WM tracts) that threat. The specificity of our findings suggests that a global mechanism, such hormonal disruptions in the stress response, may be insufficient to explain these effects. Another possible mechanism involves early learning experiences, which, through neuroplastic processes of synaptic pruning, shape the organization of the developing brain. By its very nature, adversity, either in the form of threat or deprivation, is characterized by disruptions to expected learning experiences (McLaughlin, 2016). Here we have shown that specific experiences of adversity, which result in learning environments characterized by distinct reward contingencies, appear to uniquely affect the development of WM tracts linking key cortical and subcortical structures integral to reward processing.

Across all three types of adversity, differences in WM structure were isolated to the left hemisphere. These findings are consistent with a large literature on the lateralization of motivational processes in the PFC, which show that greater left, relative to right, frontal cortical activity is involved in approach-motivated affective states and reflects stable individual differences in approach motivation (Harmon-Jones et al., 2010). A recent study also showed this laterality effect is associated with behavioral indices of approach motivation; specifically that greater resting left PFC activation predicts greater effort expenditure for rewards (Hughes, Yates, Morton, & Smillie, 2015). Although we did not directly explore whether asymmetry in connectivity between the two hemispheres predicts reward-related behavior, our findings suggest a bias toward adversity-related differences in PFC connectivity in the left hemisphere. Further exploration of links between adversity, lateralization and reward processing may provide important insights into underlying mechanisms that link adversity to disorders characterized by disruptions to approach motivation.

Modulation of RT to cues that predicted reward was not associated with any form of adversity. This is consistent with previous reports in abuse-exposed adolescents who showed no differences from non-exposed adolescents in reaction time on a similar task (Dennison et

al., 2016), but differs from findings in maltreated children (i.e., both abused and neglected) who had faster, but invariant, RT when selecting reward contingencies than non-maltreated children (Guyer et al., 2006). Discrepant findings may be related to differences in age between the samples, such that deficits are observed in younger but not older children—the cross sectional developmental design in the current study may have reduced our ability to observe these more nuanced effects, such that larger developmental samples are required.

These findings should be considered in light of the following limitations. Due to limitations in sample size, we did not explore sex differences or the effects of puberty, in the effects of adversity on WM microstrucuture, which may be important due to evidence of sex-based differences in typically developing children and adults (Lebel & Beaulieu, 2011). Further, we did not have power to examine the effect of timing or duration of adversity exposure, which may differentially influence biobehavioral outcomes (Govindan et al., 2010). Due to our hypothesis regarding the role of fronto-striatal circuitry, we adopted a region of interest approach and did not do whole brain analysis—a data-driven approach may have highlighted other WM tracts outside those of interest. We did not examine measures of WM microstructure other than FA, although Koch et al. (2014) did not report associations between reward responsivity in the ventral striatum and axial and radial diffusivity. Given that our primary aim was to study the effects of distinct types of adversity using a multivariate approach, our sample size was not large enough to examine developmental effects of adversity on reward behavior or WM microstructure. Our cross-sectional rather than longitudinal design limits the capacity for our mediation analyses to describe causal processes. We did not examine differential effects of social and non-social reward (Kohls et al., 2009). Finally, the reward processing task did not include loss trials, and we only considered approach motivation and not other aspects of reward processing (Olino, 2016). While the finding that increased age predicted faster responses on reward trials relative to unrewarded trials (see supplement S3) is consistent with previous behavioral characterizations of the developing reward system using alternate reward tasks (Galvan et al., 2006), the measure of reward processing using the piñata task may vary from characterizations of reward processing using reward tasks that may tap into other aspects of the PVS. The development of novel reward tasks that allow for more comprehensive assessment of behavioral responses to reward that distinguish between the different aspects of the positive valence system will allow for more precise characterization of links between adversity and biobehavioral mechanisms that confer risk for psychopathology (for a recent example of a task examining stochastic learning effects, see Hanson et al., 2017).

This is the first study to consider the unique effects of three common and distinct forms of adversity on biobehavioral measures of reward processing using a multivariate approach. We observe distinct associations between different types of adversity and reward processing, highlighting the importance of parsing the unique effects of environmental experiences in order to understand underlying mechanisms that may confer risk for psychopathology. Our findings suggest that material deprivation, but not caregiver neglect or exposure to threat, is associated with deficits in non-social reward-related behavior reflective of approach motivation. We further showed that experiences of deprivation and threat exert unique influences the microstructural properties of reward-related regions within the developing brain, building upon a growing body of evidence that distinct adverse experiences shape

neurobiological development in specific and nuanced ways (McLaughlin & Sheridan, 2016). These alterations in neural development appear to be a neurobiological pathway that confers vulnerability to psychopathology. Our novel findings call for further longitudinal research to explore how alterations to reward processing following exposure to deprivation relate to the elevated risk for psychopathology observed in this vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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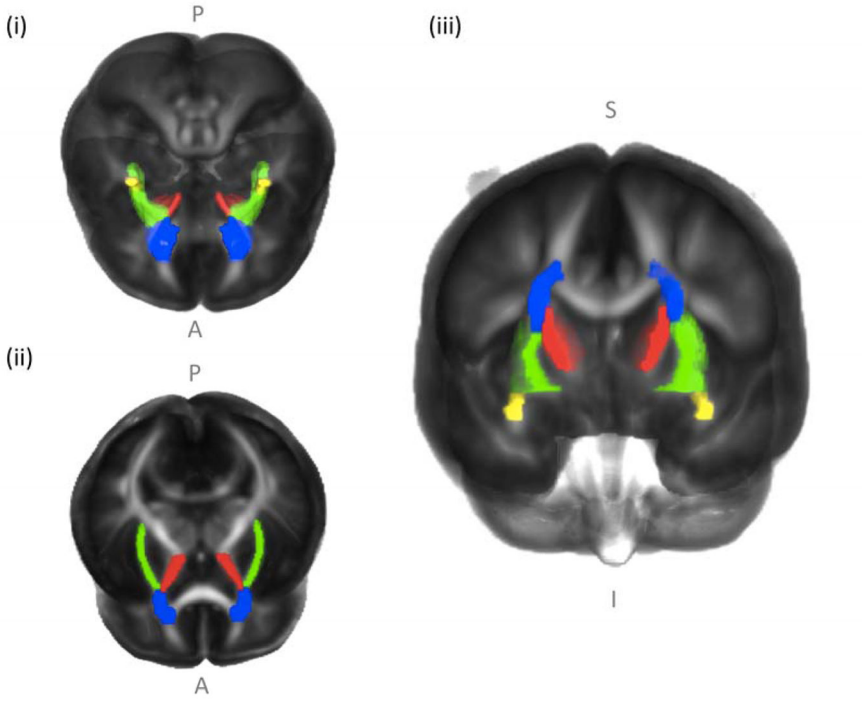

Figure 1.

Three views of the four white-matter fiber regions of interest delineated using tract-based spatial statistics. Views (i) and (ii) are inferior and superior transverse views respectively; (iii) provides a coronal view. Blue = Anterior corona radiata; Red = Anterior limb of the internal capsule; Green = External capsule; Yellow = Uncinate fasciculus. A =anterior, P = posterior, I = inferior, S = superior.

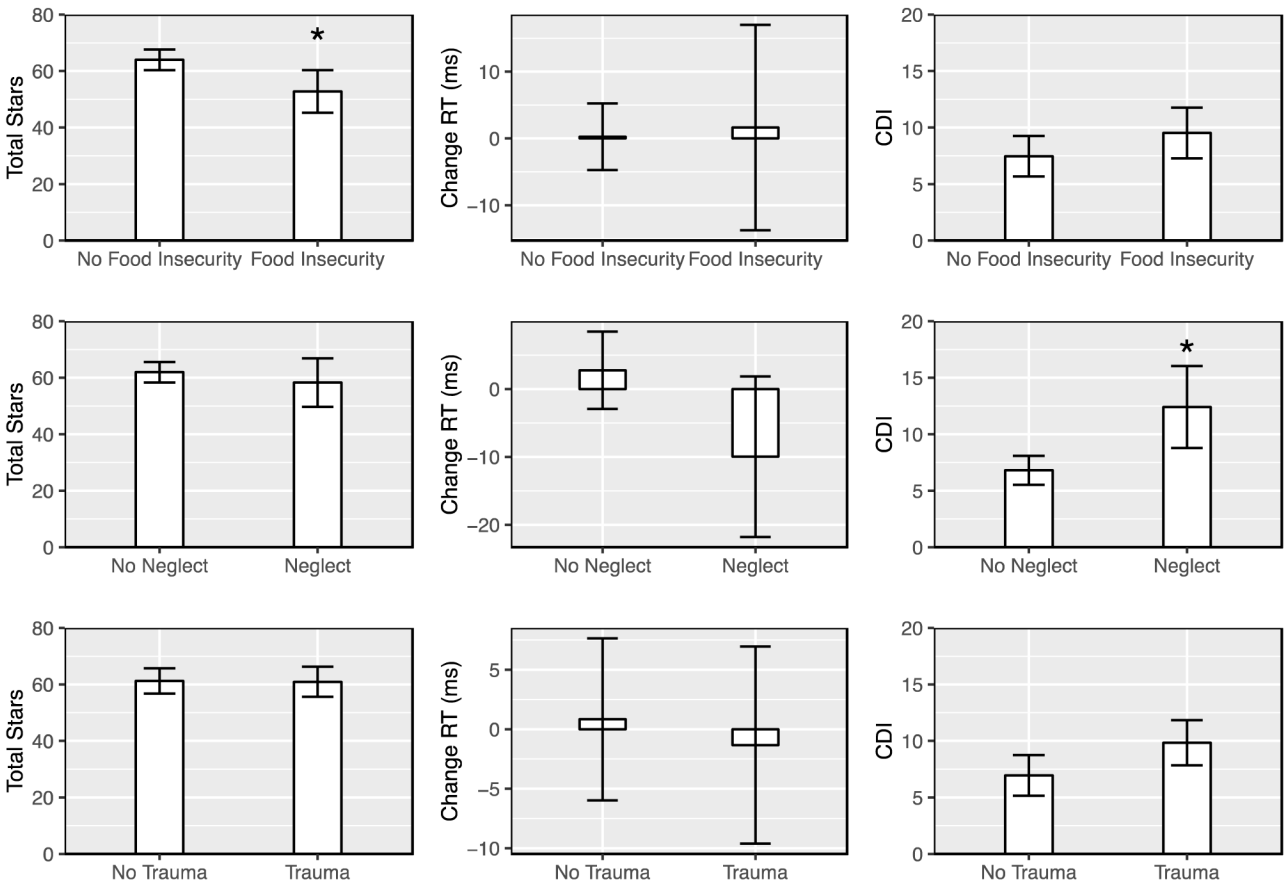

Figure 2.

Bar plots depicting means and 95% confidence intervals for the total number of stars, change in reaction time (RT) from 0 to 4 stars on the piñata task and depression symptoms (CDI) by food insecurity, neglect and trauma exposure. (*) Depicts significant difference between groups after controlling for sex, age and other forms of adversity and after corrections for multiple comparisons ($p<.05$ adjusted for the family-wise error rate). When analyzed independently, trauma and food insecurity were associated with greater depression symptoms ($p<.05$). Depicted means are not adjusted for covariates included in the regression models. Original data are presented for the CDI; statistical tests were conducted on transformed data.

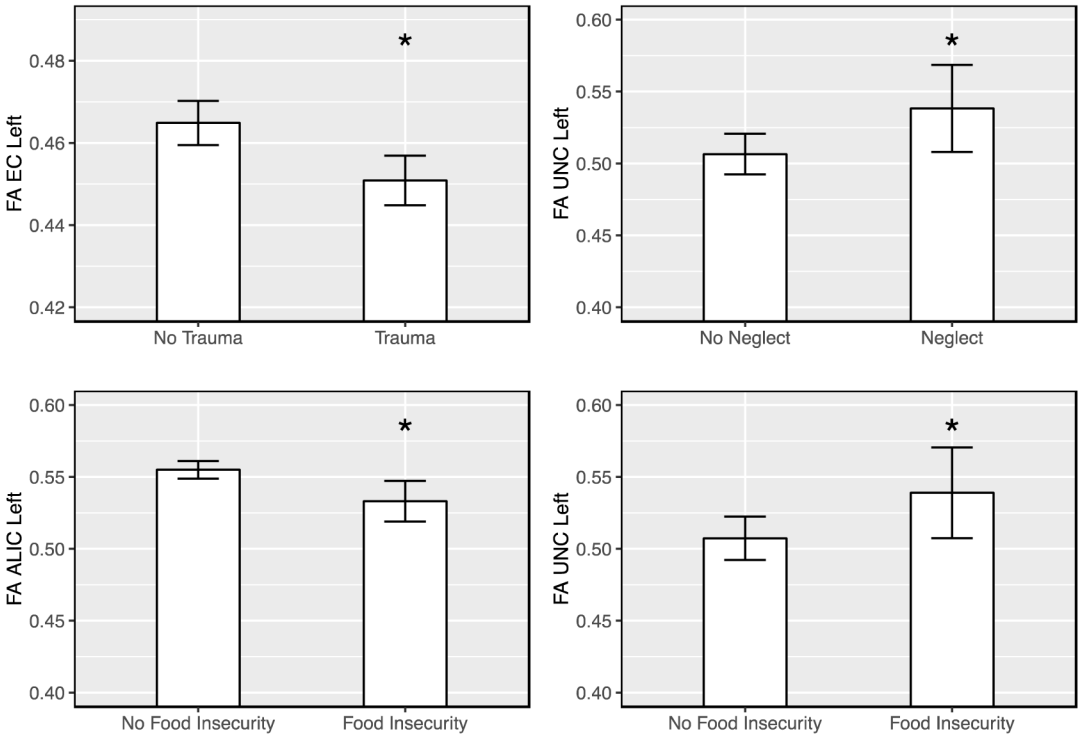

Figure 3.

Bar plots depicting means and 95% confidence intervals for fractional anisotropy in: the left external capsule (EC) by trauma (upper left panel), the left uncinate fasciculus (UNC) by neglect (upper right panel), the left anterior limb of the internal capsule (ALIC) by food insecurity (lower left panel), and, the left uncinate fasciculus by food insecurity (lower right panel). (*) Depicts significant difference between groups after controlling for sex, age and other forms of adversity and after corrections for multiple comparisons ($p<.05$ adjusted for the family-wise error rate). Depicted means are not adjusted for covariates included in the regression models.

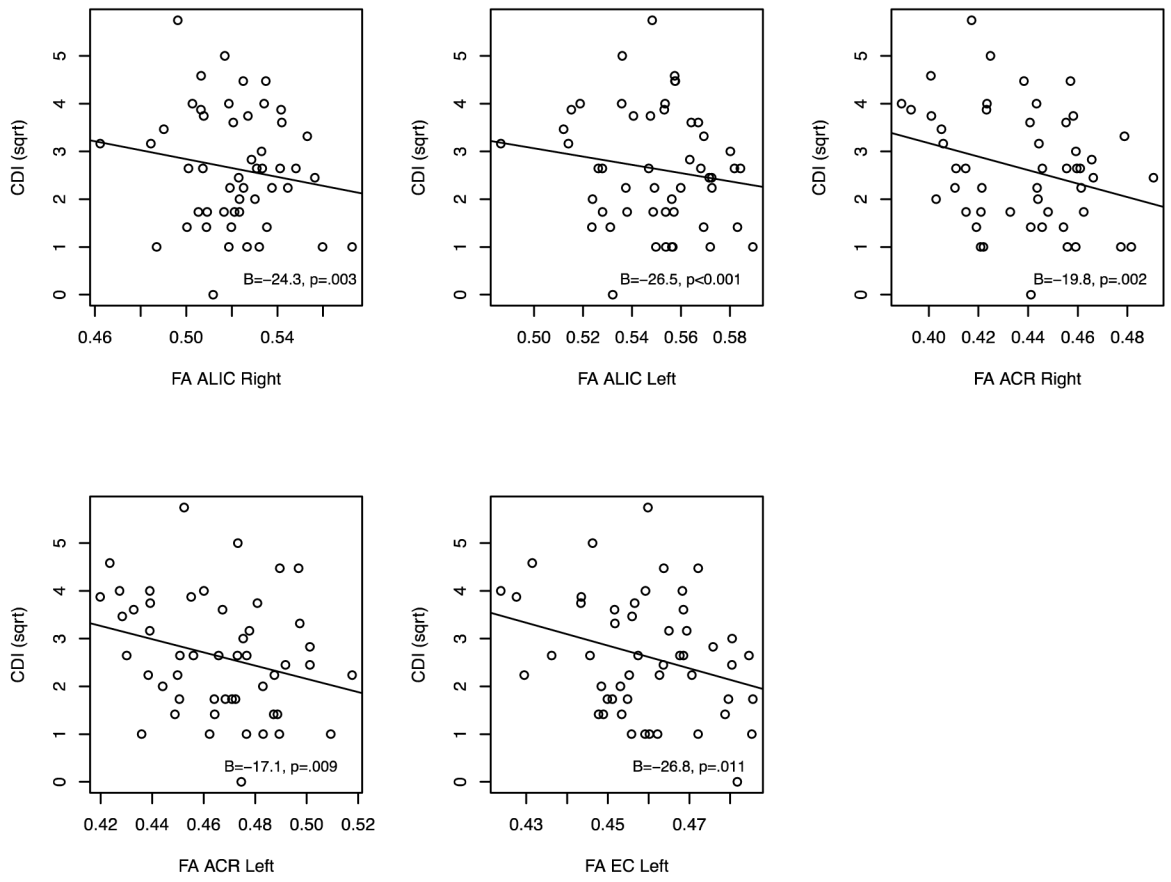

Figure 4.

Scatter plots depicting significant negative associations between white-matter microstructure and depression symptoms (Child Depression Inventory; CDI, depicted as square root). ALIC = Anterior limb of the internal capsule; EC = External capsule; ACR = Anterior corona radiata; UNC = Uncinate fasciculus. All depicted associations survive corrections for multiple comparisons.

Table 1

Sample characteristics

	%	N
Female	48.9	46
Race/Ethnicity		
White	51.1	48
Black	17.0	16
Hispanic	13.8	13
Asian	10.6	10
Biracial/Other	7.5	7
Parent education[a]		
High school or less	28.7	27
Associate degree	13.8	13
Bachelor degree	22.3	21
Graduate school	24.5	23
Trauma history	40.4	38
Neglect history	23.4	22
Food insecurity history[b]	26.6	25
Number of types of adversity experienced[b]		
None	42.0	37
1	28.4	25
2	23.9	21
3	5.7	5

[a] 7 parents did not provide their own education data

[b] Food insecurity measures were not reported for 6 participants

Table 2

Means and standard deviations for age, reward and fractional anisotropy measures by exposure to adversity type

	Adversity Type													
	Food insecurity				Neglect				Abuse				Total Sample	
	Absent		Present		Absent		Present		Absent		Present			
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Age	13.52	3.36	12.71	3.52	13.48	3.46	13.88	3.57	13.44	3.49	13.77	3.48	13.57	3.47
Total stars	64.0	14.3	52.8	17.5	62.0	15.2	58.3	18.9	61.3	16.3	60.9	16.0	61.1	16.1
RT 0 stars	248.9	50.0	275.7	50.4	257.1	45.1	251.3	72.6	246.2	50.3	271.1	51.3	255.8	51.8
RT 4 stars	243.3	41.6	257.2	54.8	250.1	45.3	237.8	47.2	243.6	44.7	252.5	47.5	247.2	45.8
CDI	7.46	7.13	9.52	5.44	6.81	5.46	12.41	8.17	6.95	6.73	9.84	6.08	8.12	6.60
FA Measures														
ALIC-R	0.523	0.019	0.515	0.024	0.521	0.021	0.526	0.019	0.522	0.023	0.523	0.017	0.522	0.021
ALIC-L	0.555	0.017	0.533	0.024	0.549	0.024	0.551	0.016	0.553	0.023	0.545	0.019	0.550	0.022
EC-R	0.420	0.015	0.414	0.013	0.418	0.016	0.415	0.013	0.420	0.016	0.412	0.012	0.417	0.015
EC-L	0.462	0.016	0.453	0.015	0.460	0.016	0.457	0.015	0.465	0.014	0.451	0.013	0.459	0.015
ACR-R	0.444	0.022	0.424	0.025	0.438	0.024	0.438	0.027	0.445	0.023	0.428	0.025	0.438	0.025
ACR-L	0.469	0.022	0.457	0.028	0.466	0.023	0.465	0.027	0.472	0.022	0.457	0.025	0.466	0.024
UNC-R	0.515	0.035	0.524	0.044	0.511	0.037	0.527	0.038	0.513	0.039	0.518	0.035	0.515	0.037
UNC-L	0.507	0.042	0.539	0.055	0.507	0.042	0.538	0.052	0.515	0.048	0.516	0.046	0.515	0.047

CDI = Total Children Depression Inventory score; RT = Reaction time; ALIC = Anterior limb of the internal capsule; EC = External capsule; ACR = Anterior corona radiata; UNC = Uncinate fasciculus; R= Right; L =Left.