**Identifying cognitive, affective, and developmental mechanisms linking threat and deprivation with adolescent psychopathology**

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**Abstract** (255/300 words)

Background:

Early-life adversity is strongly related to psychopathology over the life-course, but the mechanisms are complex and may depend on the nature of adversity experiences. In this prospective study, we examine the relationships between proposed cognitive, affective, and developmental mediators linking childhood threat and deprivation experiences to adolescent psychopathology and empirically identify the strongest mechanisms.

Methods:

The question was addressed in a community sample of 227 children from the Seattle metro area designed to reflect a diversity in income (mean child age 11.5±0.5 years, 48.5% female). Candidate mechanisms included attention bias to threat, implicit emotion regulation, theory of mind, fear learning, pubertal timing, inhibitory control, language ability, reasoning ability, and reward sensitivity. Using a high-dimensional mediation approach, we examined the joint significance of mediating pathways linking threat and deprivation to psychopathology to determine which pathways emerge after controlling for all phenotypes predictive of psychopathology.

Results:

Blunted reward sensitivity was a significant mediator of the prospective relationship between threat and internalizing psychopathology, explaining 15.3%, 95% CI (3.3%,38.9%) of this association after controlling for age, sex, poverty chronicity, maternal depression, and pubertal timing. While deprivation was a significant independent predictor of both psychopathology dimensions, none of the cognitive, affective, and developmental candidate mediators were significant.

Conclusion:

In a small, but well-characterized community sample, we determined that reward sensitivity is mediates the prospective association between early-life threat experiences and adolescent internalizing psychopathology. Further investigation into the impact of interventions that bolster reward sensitivity are warranted in large representative samples.

**1. Introduction**

Adversity experienced early in life is a well-established predictor of psychopathology, explaining roughly 30% of the liability for lifetime psychiatric disorders (Kessler et al., 2010; McLaughlin et al., 2012). Early-life adversity is defined as a circumstance, either chronic or singular but severe, that constitutes a deviation from a nurturing environment conducive to normative development and likely requires adaptation on behalf of an average child (McLaughlin, 2016). Adversity is, however, not monolithic. The dimensional model of adversity proposes that adversity can be conceptualized across dimensions of experience that share common features including threat—which involves harm or threat of harm to the child’s physical integrity, and deprivation—which involves reduced social or cognitive stimulation. The dimensions of threat and deprivation have been argued to influence cognitive, affective, and neural development in ways that are at least partially distinct (McLaughlin & Sheridan, 2016; McLaughlin et al., 2021; McLaughlin et al., 2014; Sheridan & McLaughlin, 2014).

Numerous mechanisms have been proposed to link threat and deprivation with psychopathology. A growing body of literature explores disruptions in executive functioning, emotion regulation, social information processing, pubertal timing, and fear learning as mechanisms linking early-life adversity to later psychopathology (Colich et al., 2020; McLaughlin et al., 2020; McLaughlin et al., 2021). Recent studies focus on validating the dimensional model for adversity and psychopathology and determining whether experiences of threat and deprivation influence psychopathology via shared versus distinct mechanisms.

Alterations in social information processing, emotion regulation, and pubertal timing have been proposed as mechanisms linking threat with psychopathology (McLaughlin et al., 2020; McLaughlin & Lambert, 2017). Biases in social information processing linked to threat experiences encompass heightened sensitivity to anger cues, attribution of a wider range of interactions to hostility, and greater attention devoted to threatening stimuli. Enhanced threat detection and greater attention bias to threatening stimuli have been shown to mediate the relationships between abusive and threatening early-life experiences and psychopathology transdiagnostically (Pollak et al., 2000; Shackman et al., 2007; Weissman et al., 2019). Children exposed to trauma demonstrate reduced fear extinction and have a lower skin conductance response to stimuli paired with aversive stimuli versus unpaired stimuli during conditioning compared to children who have not been exposed to trauma, mediating trauma’s impact on externalizing psychopathology (McLaughlin et al., 2016). Poor accuracy on cognitive and affective theory of mind tasks was reported as a link between violence exposure in childhood and the development of externalizing behaviors (Heleniak & McLaughlin, 2020). Excessive rumination, a maladaptive emotion regulation strategy, was shown to mediate the relationship between child maltreatment and general psychopathology (Weissman et al., 2019). Underlying the influences of adversity on social information and emotion processing are potentially altered developmental trajectories captured by pubertal timing. Threatening experiences early in life have been demonstrated to accelerate pubertal timing, exacerbating psychopathology in adolescent girls (Colich et al., 2023; Colich et al., 2020; Hamlat et al., 2019; Platt et al., 2017).

Executive functioning, a complex domain that includes language ability, reasoning ability, memory, and inhibitory control, has been repeatedly implicated as a connection between deprivation experiences and psychopathology over the life-course. Significant indirect effects of institutional rearing, parental neglect, caregiver change, and financial difficulties were found with respect to internalizing and externalizing psychopathology via memory problems and inhibitory control (Carozza et al., 2022; McNeilly et al., 2021; Wade et al., 2020). Large longitudinal samples demonstrate that detriments in language ability in early childhood mediate deprivation’s impact on internalizing and externalizing psychopathology in adolescence (Miller et al., 2021; Miller et al., 2018).

The cited findings about cognitive, affective, and developmental mechanisms spanning the domains of social information processing, emotion regulation, fear learning, executive functioning, and biological aging are supported by neuroimaging data. A review of 109 imaging studies found divergent associations of threat and deprivation with structural and functional neurodevelopmental outcomes in children (McLaughlin, Weissman, et al., 2019). Exposure to threat, but not deprivation, is associated with reduced amygdala and hippocampal volume, as well as elevated activation in the amygdala in response to negatively-valenced stimuli (Brooks et al., 2014; Hanson et al., 2015; McLaughlin et al., 2016; David G. Weissman et al., 2020). These findings comport with threat having been found to sharpen emotional reactivity, enhance threat detection, and increase attention bias to threat. Experiences of deprivation, but not threat, are associated with the structure of frontoparietal cortical regions, in line with deprivation’s associations with executive functioning (Mueller et al., 2010). Findings about early life adversity and striatal reward circuits are less clear but suggest that deprivation and threat may each influence reward sensitivity, although potentially in divergent ways (Dennison et al., 2016; Goff et al., 2013; Hanson et al., 2016; Mehta et al., 2010).

We propose an exploratory analysis of a prospective study to determine which theorized mediating mechanisms from a likely correlated set emerge as jointly significant mediators of the relationships between childhood threat and deprivation and psychopathology in adolescence. We apply a novel statistical approach to explore this question in data with dimensional measures of threat and deprivation, a broad assessment of candidate mediating phenotypes, and an assessment of internalizing and externalizing psychopathology in adolescence.

**2. Methods**

2.1 Study overview:

Data for this analysis was sourced from a longitudinal cohort study of children followed from early childhood to adolescence. The study recruited 306 dyads of 3-year-old children and their mothers from the Seattle metropolitan area. The aim of the study was to examine cognitive and neurobiological development in relation to socioeconomic status, cumulative family risk, and parenting behaviors. Families were recruited to obtain diversity in income at the start of the study. Children with developmental disabilities and lack of English proficiency were excluded. This sample has been followed across numerous assessments in childhood and adolescence (Lengua et al., 2015; Lengua et al., 2020; Zalewski et al., 2012).

We included 227 mother-child dyads who provided data when the children were between 10.9 and 13.0 years of age (M=11.5, SD=0.5). Participating children and their mothers provided retrospective information on threat and deprivation experiences and the children underwent behavioral tasks and structural and functional MRI assessments to capture cognitive, affective, and developmental phenotypes. Psychopathology was assessed at this point and again at a follow-up assessment conducted approximately 2 years later, when the children were between 13.1 and 15.1 years of age (M=13.7, SD=0.4). Chronicity of poverty and maternal depression symptoms were measured at early childhood assessments (between ages 3 and 6) and used to control for confounding of the relationships between adversity and subsequent cognitive, affective, developmental, and psychopathology outcomes. Chronicity of poverty was defined as the number of visits out of four when the participating child’s family income was at or below 1.5 times the national poverty line (to account for higher living expenses in the Seattle metro area). Maternal depression was captured by the maximum score on the Center for Epidemiologic Studies Depression Scale (CES-D) across the four early childhood visits (Radloff, 1977). The sample was 48.5% female, with 38.1% having experienced poverty at some point in childhood. Early childhood maternal CES-D depression symptom scores ranged from 12 to 56 (M=23.9, SD=7.6).

2.2 Measures:

*2.2.1. Threat and deprivation experiences:*

Both threat and deprivation experience measures were constructed using multi-informant methods. Higher values on both measures convey greater experience. Algorithms used to construct the threat and deprivation measures have been preregistered (<https://osf.io/6yf4p/>) and described in detail in a recent publication (Weissman et al., 2022).

The continuous threat experiences variable is a composite of the count of distinct types of violence, the frequency, and the severity of violence experienced. Up to 5 types of interpersonal violence - physical abuse, sexual abuse, domestic violence, witnessing a violent crime, or being a victim of a violent crime – could be endorsed either by the child or the parent if reported on the UCLA PTSD Reactions Index (Steinberg et al., 2004; Steinberg et al., 2013). Physical abuse, sexual abuse, and domestic violence could be additionally endorsed by the child on the Childhood Experiences of Care and Abuse Interview (CECA) or by the parent on the Juvenile Victimization Questionnaire (JVQ) (Bifulco et al., 1994; Finkelhor et al., 2005). Frequency of violence exposure was measured by the summed frequency ratings of witnessing or experiencing violence on the Violence Exposure Scale for Children-Revised instrument (VEX-R) (Raviv et al., 2001; Raviv et al., 1999). Severity of violent exposures was measured by the physical and sexual abuse subscales of the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1997; Kaufman Kantor et al., 2004). The count, frequency, and severity of violence experiences were each standardized to mean of 0 and standard deviation of 1 and averaged to create the composite threat experience variable.

The continuous deprivation composite measure comprises domains of cognitive, emotional, and physical deprivation. Cognitive deprivation was measured using maternal responses on the Home Observation Measurement of the Environment-Short Form (HOME-SF) instrument (Mott, 2004). The 19 cognitive stimulation items on the HOME-SF (including the presence of learning materials in the home, the child’s engagement with activities outside the home, the degree of parent-child interaction, and parental scaffolding of the child learning, among others) were counted and reverse-scored so higher scores reflect greater cognitive deprivation. Emotional deprivation is the average of standardized scores on emotional neglect subscales of the CECA and Multidimensional Neglectful Behavior Scale (MNBS) (Bifulco et al., 1994; Kaufman Kantor et al., 2004). Lastly, physical deprivation is the standardized average of a food insecurity score, measured by parental report on the four-item Household Food Insecurity Scale, the child-reported physical needs subscale score of MNBS, and the child-reported physical neglect subscale score of the CTQ (Bernstein et al., 1997; Kaufman Kantor et al., 2004). The continuous overall deprivation experiences measure is the average of cognitive, emotional, and physical deprivation composites.

*2.2.2. Candidate mediators:*

Candidate mediators of threat and deprivation’s relationships with adolescent psychopathology were scoped from a review of emotional, social, cognitive, and neurobiological mechanisms that mediate the effects of childhood adversity and psychiatric sequelae in youth (McLaughlin, 2020), the conceptual model of the pathways linking threat with psychopathology (McLaughlin et al., 2020), and the review of potential intervention targets to prevent adverse psychiatric consequences of childhood deprivation and threat experiences (McLaughlin, DeCross, et al., 2019). The available phenotypes cover the domains of attention bias to threat, implicit emotion regulation, theory of mind, fear conditioning, pubertal timing, inhibitory control, language ability, reasoning ability, and reward sensitivity. See **Table 1** for a summary of the 15 variables considered grouped by domain.

*Attention bias to threat* was captured by the difference in reaction times to neutral versus angry faces displayed by the visual dot-probe task (Amin et al., 2004; Steinberg et al., 2013). Greater values signify shorter response times to angry rather than neutral expressions. Each trial consisted of a pair of facial expressions from the same actor, displayed side-by-side, with a left- or right-pointing arrow appearing in place of one of the faces. The participating child was instructed to press the corresponding arrow key on a keyboard to identify behind which face the arrow flashed. The task consisted of 16 practice trials, then two experimental blocks of 80 trials each, where each trial began with a central fixation point displayed for 500ms, then the pair of faced displayed for 500ms, and finally the arrow displayed for 500ms. On trials where the participant correctly pressed the button, reaction times were averaged and compared by expression type. Faster reaction times to correctly identify the arrow behind angry faces rather than neutral faces signaled greater attention bias to threat.

*Implicit emotion regulation* was captured by several metrics from the emotional Stroop task (Ben-Haim et al., 2016; Egner et al., 2008; Etkin et al., 2006). Each trial consisted of an image with a happy or fearful facial expression displayed with the word “happy” or “fear” overlaid over the image. In congruent trials, the emotional valence of the face matched the label displayed, whereas in incongruent trials, the emotion label was inconsistent with the facial expression, and required the child to correctly identify the valence of the facial expression despite a conflicting label. We used three measures of implicit emotion regulation derived from this task. Using only trials with correctly identified facial expressions, we contrasted reaction times on incongruent versus congruent trials with fearful faces and happy faces separately. We also included a variable for adaptation to emotional conflict. Faster reaction times are expected on incongruent trials that are preceded by incongruent trials rather than congruent trials, since cognitive control over emotional conflict is expected to be elicited. Adaptation to emotional conflict was operationalized as the difference in reaction times on incongruent trials that were preceded by congruent trials versus reaction times on incongruent trials preceded by incongruent trials (Kim et al., 2021). Higher values on this contrast signal greater adaptation to emotional conflict.

*Theory of mind* was measured with a Theory of Mind task, adapted from a previously implemented task to detect differences between cognitive and affective theory of mind dimensions (Heleniak & McLaughlin, 2020; Schlaffke et al., 2015). Cartoons depicting vignettes of cooperation or cooperation to deceive were shown to children who were asked to predict the conclusion of each story and respond to questions about the story. Of the twelve vignettes, four involved two characters cooperating to achieve a common goal, four depicted a story where the two characters deceived each other, and in the remaining four, the two characters together deceived a third character. The vignettes were displayed in experimental blocks with each of three types of stories displayed in random order. Each block began with a set of instructions corresponding to cognitive theory of mind, affective theory of mind, or physical causality conditions. Cognitive theory of mind represents the ability of participants to understand thoughts, beliefs, and intentions of the characters in the cartoon while affective theory of mind gages whether the children can accurately interpret the emotional state of the characters. Average accuracy metrics on cognitive and affective theory of mind trials were recorded.

*Fear learning* was measured by the difference in the amplitude of skin conductance response (SCR) during the early acquisition phase of a block design fear conditioning and extinction task that has been adapted to the early adolescent population (Shechner et al., 2015). SCR was captured by electrodermal activity and calculated using standard procedures (Braithwaite et al., 2013). A blue square and orange diamond were conditioned stimuli. In the initial sequence, the first 10 trials presented the blue square with no aversive reinforcement – the CS- block. Next, 10 trials presented the orange diamond and 8 of the 10 were paired with an aversive sound – the US block. Next, 10 trials showed the orange diamond without the aversive stimulus – the CS+ block. After the initial sequence (of which blocks 2 and 3 were considered pre-acquisition), 9 stimulus blocks (3 reinforced US, 3 non-reinforced CS+ blocks, and 3 CS- blocks) were shown in random order in sets of 3. The difference in SCR on CS+ trials versus CS- trials in the first set of 3 blocks after the pre-acquisition set, corrected for pre-acquisition conductance, was used to capture fear learning.

*Pubertal timing* was assessed using the Tanner staging method (Marshall & Tanner, 1969, 1970). Children were shown sex-specific line drawings conveying stages of development of sexual characteristics (breasts for girls, testes/scrotum/penis for boys, and pubic hair for both). Pubertal timing was the average of the two sex-specific ratings.

*Inhibitory control*, an executive functioning ability to suppress a prepotent response to achieve a longer-term goal, was measured using two tasks. NEPSY Circles & Squares task tested the children’s reaction time on “inhibit” and “switch” tasks (Brooks et al., 2009). The participants were shown a series of circle and square shapes, with some of them shaded in, and asked to read through the shapes to establish a baseline reaction time. In the “inhibit” trials, the participants were asked to say the opposite of the shape presented, regardless of whether it was shaded in or blank. In the “switch” trial sequence, they are asked to say the opposite of the shape if it was blank, and the true shape if it was shaded in. Greater differences in reaction times on “inhibit” and “switch” trial sequences relative to baseline indicate poorer inhibitory control. Stroop task measured the ability of the participating children to accurately read words for colors, even if the color with which the word is presented didn’t match, with greater accuracy conveying greater inhibitory control (Stroop, 1935).

*Language ability and reasoning ability* were measured using the Wechsler Abbreviated Scale of Intelligence (WASI) task (Wechsler, 1999). Language ability was measured with the t-score on the WASI vocabulary subtest. The vocabulary subtest was designed to measure word knowledge and verbal concept formation. Reasoning ability was measured with the t-score on the WASI matrix reasoning subtest, which gages fluid intelligence, broad visual intelligence, classification and spatial ability, knowledge of part–whole relationships, simultaneous processing, and perceptual organization.

Lastly, *reward sensitivity* was assessed using the Piñata task, a child-friendly version of a monetary incentive task (Helfinstein et al., 2013). Animal-shaped piñatas with stars depicted inside appeared on the screen, and the participating children are asked to “whack” each piñata as quickly as possible once it dropped to the middle of the screen by pressing the spacebar on a keyboard. Each piñata was previewed as having 0, 1, 2, or 4 stars inside before it was dropped. If the piñata was hit before it dropped to the middle of the screen, no stars were earned. The stars were earned if the spacebar was pressed within a response window (between 250ms and 300ms after the piñata dropped to the middle of the screen). Earned stars accumulated in a basket at the bottom of the screen. The participating children were told that they will be awarded $10 if they earn enough starts, but ultimately, all children were awarded the $10. The participants were given 22 trials to practice at the start, during which baseline response times were recorded. The task consisted of 132 trials overall, with 6 runs of 22 trials each. The trials were evenly split by reward level with 33 trials each displaying 0, 1, 2, and 4 stars. The total earned stars and the contrast in average reaction times on no-reward (0-star) versus high-reward (4-star) trials measured reward sensitivity, with greater total stars and a greater reaction time contrast conveying greater reward sensitivity.

--- Table 1 here ---

*2.2.3. Psychopathology symptoms*:

Internalizing symptoms of depression, anxiety, and post-traumatic stress disorder (PTSD) were measured with total scores on child-reported Children’s Depression Inventory-2 (CDI), Screen for Child Anxiety Related Emotional Disorders (SCARED), and UCLA PTSD Reaction Index, respectively (Birmaher et al., 1997; Kovacs, 2011; Steinberg et al., 2004). Externalizing psychopathology outcomes were constructed using the maximum of child and parent reports on attention problem, rule-breaking, and aggression subscales of the Youth Self-Report (YSR) and the Child Behavior Checklist (CBCL) (Achenbach, 1991; Liu et al., 1997). We focused on latent internalizing and externalizing psychopathology outcomes, constructed using a confirmatory factor analysis performed in MPlus Version 8.1 (Muthén & Muthén, 2017) on deciles of scores for depression, anxiety, PTSD, attention problem, rule-breaking, and aggression. The algorithm for internalizing and externalizing composites has been previously described (D. G. Weissman et al., 2020) and is outlined in the Appendix.

2.3. Statistical analysis:

For the 227 participants with data at the early adolescence visit, we imputed missing values on covariates, exposures, mediators, and outcomes using hot-deck imputation (Ono & Miller, 1969). We reported proportions of missing values and distributions of key variables in **Table A.1** in the Appendix.

We examined the mediator space using the 3-stage high-dimensional mediation algorithm executed implemented by the ‘HIMA’ R package (Zhang et al., 2016). Stage 1 uses sure independent screening to select candidate mediators that are most strongly individually associated with the outcome, selecting *d=[2n/log(n)]* variables with the largest coefficients, where n is the sample size (Fan & Lv, 2008). In our analysis, Stage 1 is not applicable given that *d* = *[2\*227/log(227)] =* 84 is far greater than the 15 mediators considered. Stage 2 is a minimax-concave penalty (MCP) regularized regression to jointly evaluate all candidate mediators selected by the screening, identifying significant predictors of the outcome from a correlated set. Stage 3 is joint significance testing, requiring that both the exposure-mediator and mediator-outcome relationships are statistically significant, with a family-wise type I error rate of 5% maintained by the implementation of the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995). All exposure, candidate mediator, and outcome variables involved in this analysis were continuously measured and standardized to mean 0 and standard deviation 1 to facilitate interpretable comparisons of effect sizes.

We evaluated the main and mediated associations of threat and deprivation with internalizing and externalizing adolescent psychopathology outcomes. Exposure-mediator and exposure-outcome relationships were adjusted for age at baseline, biological sex, chronicity of poverty, and the severity of the mother’s depression symptoms in the child’s early life. Mediator-outcome models were additionally adjusted for both adversity types. In a sensitivity analysis for the HIMA procedure, exposure-mediator and exposure-outcome models for threat were also adjusted for deprivation and models for deprivation were adjusted for threat to account for unmeasured common causes of adversity. We also examined identified relationships stratified by sex in supplementary materials.

Lastly, for any significant mediator, we estimated its indirect effect on the outcome, quantifying the impact of increasing the mediator phenotype to the level it would naturally take on if the aversity measure was increased by a standard deviation. For indirect effects and proportions mediated, we used bootstrapping to calculate standard errors using the CMAverse package in R (Shi et al., 2021; Valeri & Vanderweele, 2013).

**3. Results**

*3.1 Pairwise associations*

Correlations among the variables under study are reported in **Tables 2** and **3**. Significant associations are evident among candidate mediators from different domains. Greater attention bias to threat is positively associated with language and reasoning ability, as well as accuracy on the Stroop task (an inhibitory control marker) and total stars earned on the reward sensitivity task. The two reward sensitivity metrics, while not correlated with each other, are significantly correlated with facets of executive functioning, including inhibitory control and reasoning ability. Accuracy on cognitive theory of mind trials is crudely associated with language ability. We see that cognitive, affective, and developmental phenotypes theorized to mediate the relationships between threat and deprivation are not exclusively correlated within the domains of social information processing, emotion regulation, fear learning and executive functioning. We see relationships across domains, underscoring the complexity of mechanisms we are examining.

--- Tables 2 and 3 here ---

**Table 4** summarizes the results of the HIMA analysis. After adjustment for age, biological sex, poverty chronicity, and severity of maternal depression in early life, the standardized associations between adversity dimensions and psychopathology outcomes remained similar to the pairwise correlations shown in **Table 2**, with deprivation’s association with internalizing symptoms becoming more pronounced (β = 0.34, 95% CI (0.20,0.48)) and threat’s association with externalizing symptoms diminishing slightly (β = 0.31, 95% CI (0.18,0.44)). The contrast in reaction times on no-reward versus high-reward trials (a measure of reward sensitivity) and pubertal timing were retained as having non-zero associations with internalizing symptoms by the MCP-regularization step of the HIMA algorithm. Greater reward sensitivity emerged as protective against internalizing symptoms (standardized β = -0.15, 95% CI (-0.27,-0.03)), and accelerated pubertal timing as predictive of greater internalizing symptoms (standardized β = 0.19, 95% CI (0.06,0.32)). However, the only significant association between adversity and the retained candidate mediator phenotypes was between threat and reward sensitivity, with a 1-SD increase in threat experiences associated with a 0.20 standard deviation decrease in reward sensitivity on average (95% CI (-0.33,-0.07)).

A similar set of phenotypes was selected as mutually predictive of adolescent externalizing symptoms. Pubertal timing and an alternative measure of reward sensitivity (total stars earned during the piñata task) were retained in the regularized regression. Accelerated pubertal timing was predictive of greater externalizing symptoms in adolescence (standardized β = 0.21, 95% CI (0.08,0.34)), and greater reward sensitivity was associated with diminished adolescent externalizing symptoms (standardized β = -0.19, 95% CI (-0.31,-0.07)). Neither threat nor deprivation was significantly associated with any of the phenotypes selected as predictive of externalizing symptoms.

In a sensitivity analysis, when the exposure and mediator models in the HIMA procedure for threat were additionally adjusted for deprivation, the reward sensitivity mediating pathway connecting threat and internalizing symptoms remained significant, and no new mediating pathways were found. Interestingly, the overall association of threat with internalizing symptoms diminished with the addition of deprivation in the model for this outcome, with a 1-SD increase in threat resulting in a 0.16-SD increase in internalizing symptoms (95% CI (0.02,0.29)), down from β=0.22, 95% CI (0.09,0.36). Please refer to **Tables A.2 in the Appendix** for results with mutual adjustment for the other type of adversity.

--- Table 4 here ---

--- Figure 1 here ---

**Figure 1** highlights the identified mediating pathway for threat and internalizing symptoms via reward sensitivity. Threat is associated with significantly lower reward sensitivity, and in turn, diminished reward sensitivity is associated with greater internalizing symptomatology after controlling for age, sex, poverty experiences, and maternal depression symptoms. If the reaction time contrast on no- versus high-reward tests were set to the natural value it would be expected to have if threat is increased by 1 standard deviation, internalizing symptoms would be expected to increase by 0.04 standard deviations, 95% CI (0.01,0.08), p-value=0.01. A 1-standard deviation increase in threat is expected to increase internalizing symptoms by 0.22 standard deviations, and reward sensitivity is estimated to explain 15.29%, 95% CI (3.31%,38.91%) of the association with threat. Additional adjustment for pubertal timing does not meaningfully alter the results.

**4. Discussion**

In this application of a high-dimensional mediation algorithm to a community sample with longitudinally measured accounts of childhood threat and deprivation exposures, 15 cognitive, affective, and developmental phenotypes, and adolescent internalizing and externalizing symptom measures, we found that the empirically strongest mediating pathway connecting threat to internalizing psychopathology is through reward sensitivity. Specifically, threat is associated with significantly lower reward sensitivity, as measured by the contrast in reaction time on no-reward versus high-reward piñata trials, which is in turn associated with greater internalizing symptomatology during adolescence. Accelerated pubertal timing and diminished reward sensitivity significantly predicted greater adolescent internalizing and externalizing symptoms. No significant mediating mechanisms were identified for the relationship between deprivation and psychopathology.

*4.1. Reward processing mechanism*

Facets of reward processing, including sensitivity to reward value, have been consistently implicated in psychopathology, such as major depression, bipolar disorder, anxiety, and externalizing behaviors (Alloy et al., 2016; Cardoso Melo et al., 2022; Nusslock & Alloy, 2017). Costello’s seminal work identified that anhedonia and a reduction in reward’s effectiveness are critical in the etiology of major depression (Costello, 1972). A recent meta-analysis indeed found small but consistent associations between childhood adversity and impaired reward processing – specifically deficits in reward learning and valuation – and confirmed that dimensions of reward processing contribute to the relationship between adversity and psychopathology (Oltean et al., 2022). A review investigating neurobiological vulnerability to onset and severity of depression underscores consistent findings of blunted reward-related striatal activity in fMRI and EEG studies (Toenders et al., 2019). Fewer studies have investigated specific relationships between dimensions of adversity and reward sensitivity, and the evidence has not been definitive, with some studies finding that reward sensitivity moderates the relationships between threat and psychopathology, while others finding suppression of threat’s impact on adolescent depression through dampened reward sensitivity (Dennison et al., 2016; Kasparek et al., 2020; Sheridan et al., 2018).

*4.2. Complexity of candidate mechanisms*

We found that theory of mind, inhibitory control, language and reasoning ability, and reward sensitivity were crudely associated with early life adversity. Only one marker of inhibitory control differed in its association with threat and deprivation. Otherwise, if significant crude associations were found, they were consistent in direction and magnitude between threat and deprivation. We demonstrated the complexity in cognitive and affective phenotypes that are theorized to mediate the relationships between adversity domains and psychopathology over the course of development. Several cross-domain associations emerged. Attention bias to threat was associated with inhibitory control, language, and reasoning abilities. Total stars earned on the piñata task, one of the reward sensitivity measures, was significantly associated with inhibitory control measured using the Stroop task but was not associated with the alternative reward sensitivity measure from the same task – the contrast in reaction time to no-reward versus high-reward trials. This underscores the utility of regularization methods to identify jointly significant mediators among this complex set of interrelated phenotypes.

*4.3. Potential differences by sex*

Unlike in other studies, pubertal timing was not associated with greater threat exposure in this sample (Colich et al., 2020; Platt et al., 2017; Sumner et al., 2019). When we stratified the HIMA results by biological sex, however, we saw an interesting contrast - threat slightly advanced pubertal timing for boys in this sample but slowed it down for girls, although the associations were underpowered (see Appendix **Table A.3**). In fact, the emergence of pubertal timing as a significant predictor of internalizing symptomatology in the total sample appears to be driven by girls. Despite the indication that threat may be slowing pubertal timing among girls in this population, girls who were advanced in their pubertal development relative to their peers had greater liability for internalizing psychopathology compared to boys who were advanced for their age.

Another surprising finding in this study was that threat was less strongly associated with adolescent internalizing psychopathology than deprivation. It has been a consistent finding that traumatic experiences – exuding harm or a threat of harm to the individual’s physical well-being – approximately double the risk of developing psychopathology in adolescence and the impact does not attenuate over the lifecourse (Kessler et al., 2010; Lewis et al., 2019; McLaughlin et al., 2012). In sex-stratified analyses, we see that threat has a greater influence on both types of adolescent psychopathology among girls (**Appendix** **Table A.3**), but girls experienced lower levels of threat in this sample relative to boys (**Appendix Table A.4**). Given that the prevalence of internalizing psychopathology among biologically male versus female adolescents is generally lower, it’s possible that the observed dampening of threat’s association with internalizing disorders stems from the confluence of these factors (Hankin et al., 1998; Van de Velde et al., 2010).

*4.4. Strengths and limitations*

This study has important strengths. The community-based longitudinal study included dimensional constructs of adverse experiences from multiple informants (mother and child). All candidate mediators selected for the analysis (with the exception of pubertal timing) were measured with tasks, greatly reducing the concern for finding a mediating pathway solely because of correlation of errors that would be expected if exposures, mediators, and outcomes were all collected via self-report. The candidate mediators captured the domains of attention bias to threat, emotion regulation, theory of mind, fear learning, pubertal timing, inhibitory control, language and reasoning ability, and reward sensitivity. We demonstrated that cognitive, affective, and developmental phenotypes assessed in this analysis are correlated across domains as well as within domains, making the HIMA approach a useful tool for discerning mediator constructs most strongly relating threat and deprivation to adolescent psychopathology.

There are also notable limitations to our approach. Deep phenotyping like what was done in this study is seldom possible in large samples. Thus, grappling with a small sample size, we addressed the paucity of power with an analytic approach designed to deal with high-dimensional data to detect the statistically evident mediating pathways. However, such approaches are prone to identifying large effect sizes and favoring relationships with low error variance, but potentially missing biologically relevant small-to-modest effects (Marek et al., 2022). We also did not consider possibly non-linear relationships or complex interactions between candidate mediators due to a lack of statistical power.

**5. Conclusion**

A confirmation of diminished reward sensitivity as an impactful precursor of internalizing psychopathology associated with early life experiences of threat is required for our findings to be conclusive. If, indeed, reward sensitivity emerges as an early sign of adolescent psychopathology, intervention strategies can be implemented to bolster valuation of rewards and behavioral sensitivity to reward value among children and adolescents with a history of traumatic and threatening experiences. Validated self-rated scales such as Monetary Choice Questionnaire, Behavioral Activation System (BAS) scale, and Reward Responsiveness (RR) scale are available to facilitate the exploration of reward sensitivity as a modifiable early marker of internalizing psychopathology in larger, more representative studies (Carver & White, 1994; Kirby & Petry, 2004; Van Den Berg et al., 2010).

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