**An empirical assessment of cognitive, affective, and developmental mechanisms by which threat and deprivation impact adolescent psychopathology.**

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**Abstract** (249 words)

Early life adversity is a major predictor of psychiatric dysregulation over the lifecourse, but the mechanisms are likely complex and differential depending on the type of adversity experienced. This analysis strives to empirically determine the most salient mediating phenotypes connecting childhood threat and deprivation experiences to internalizing and externalizing symptoms in adolescence. Candidate mediating phenotypes considered covered the domains of attention bias to threat, emotion regulation, theory of mind, fear conditioning, pubertal timing, language and reasoning ability, inhibitory control, and reward sensitivity. High-dimensional mediation analysis (HIMA), combining minimax concave penalty and joint significance testing, was used to identified individual phenotypes linking deprivation and threat to psychopathology. We additionally determined latent mediating profiles to examine if threat and deprivation have at least partially differential mechanisms with respect to adolescent psychopathology. We found that threat most strongly predicted externalizing symptoms while deprivation predicted lower self-reported internalizing symptoms via diminished language ability. Three latent mediator profiles emerged, separating a subgroup with considerably dampened theory of mind and fear conditioning and a subgroup with lower executive functioning from a reference subgroup. Threat and deprivation significantly interacted, with greater threat experiences particularly strongly decreasing the odds of belonging to the reference subgroup at lower levels of deprivation. The latent mediator profiles, however, were not associated with psychopathology after adjustment for early-life poverty and maternal depression. In summary, threat exerts strong impact on theory of mind and executive functioning markers and deprivation’s impact on internalizing symptoms is suppressed by diminished language ability in this population.

**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 and psychopathology proposes that threat (harm or threat of harm) and deprivation (lack of social or cognitive stimulation and nurturing support) influence cognitive, affective, and neurodevelopmental phenotypes in ways that are at least partially distinct (McLaughlin & Sheridan, 2016; McLaughlin et al., 2014; Sheridan & McLaughlin, 2014).

Mechanisms by which early life adversity impacts psychopathology are poorly understood. A growing body of literature explores facets of emotion regulation, social information processing, and fear learning as candidate mediating phenotypes that connect adversity to the development of psychopathology. Excessive rumination, a maladaptive emotion regulation strategy, has been shown to mediate the relationship between child maltreatment and general psychopathology (Weissman et al., 2019). Poor accuracy on cognitive and affective theory of mind tasks was reported as a link between violence exposure in childhood and development of externalizing behaviors (Heleniak & McLaughlin, 2020). Lower reward sensitivity likely mediates the relationship between cognitive deprivation and depression but suppresses the impact of maltreatment on depression in adolescents (Dennison et al., 2016; Sheridan et al., 2018). Pollak et al experimentally showed that neglected children have a difficult time differentiating emotional valence of facial expressions, whereas children who experienced abuse were considerably better at detecting anger (Pollak et al., 2000). Maltreatment was shown to predict attention bias to threat in younger adolescents, mediating the relationship of maltreatment and general psychopathology longitudinally (Weissman et al., 2019). Shackman et al demonstrated mediation of the relationship between physical abuse and child-reported anxiety by increased attention allocated to anger cues (Shackman et al., 2007). Children exposed to trauma take longer to differentiate between paired and unpaired conditioned stimuli (reduced fear extinction) and have a lower skin conductance response to paired stimuli during conditioning compared to children who have not been exposed to trauma. Fear conditioning and fear extinction were identified as mediators of trauma’s impact on externalizing psychopathology (McLaughlin et al., 2016).

Detriments in executive functioning and accelerated biological aging have also been implicated as potential precursors to psychopathology that are affected by threat and deprivation. Executive functioning is a complex domain that includes language ability, reasoning ability, memory, and inhibitory control. Significant indirect effects of deprivation (such as institutional rearing and low socioeconomic status) were found with respect to internalizing and externalizing psychopathology via memory problems and inhibitory control (Wade et al., 2020), (McNeilly et al., 2021). Detriments in language ability were found in several large longitudinal samples to mediate deprivation’s impact on internalizing and externalizing psychopathology in adolescents (Miller et al., 2018), (Miller et al., 2021). Lastly, threatening experiences early in life predict accelerated pubertal timing, which exacerbates externalizing symptoms (Colic et al., 2020).

These findings about cognitive, affective, and developmental mechanisms spanning the domains of emotion regulation, social information processing, 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, predicts reduced amygdala and hippocampal volume, as well as elevated activation in the amygdala to negatively-valenced stimuli. These findings comport with threat having been found to enhance threat detection, attention bias to threat, and sharpen emotional reactivity. Experiences of deprivation, but not threat, are associated with the volume and function of frontoparietal cortical regions, suggesting deprivation’s likely effects on executive functioning. Findings about the relationships between early life adversity and striatal reward circuits are less clear but suggest that deprivation and threat may impact reward sensitivity in divergent ways.

In summary, there is a complex and growing literature in support of the dimensional model of adversity and psychopathology. We propose an analysis that looks at a large set of candidate mediator phenotypes simultaneously and utilizes penalized regression techniques to empirically identify characteristics with strongest indirect pathways linking threat and deprivation to adolescent psychopathology. The novelty of this analysis is the availability of detailed threat and deprivation accounts and a comprehensive assessment of cognitive, affective, and developmental phenotypes that have been proposed as precursors to psychiatric disorders. We hypothesize that threat and deprivation have at least partially distinct mechanisms of impact with respect to adolescent psychopathology. Learning about such mechanisms can help inform efforts to prevent psychiatric disorders in the population.

**Methods**

Study overview:

Data for this analysis was sourced from a longitudinal cohort study that recruited 306 dyads of 3-year-old children and their mothers from the Seattle metropolitan area to assess the mechanisms through which socioeconomic status, cumulative family risk, and parenting behaviors impact the function of the hypothalamic-pituitary-adrenal (HPA) axis in children (Zalewski et al., 2012). From the original cohort, 227 mother-child dyads were recruited into a second phase of data collection when the children were between 10.9 and 13 years of age. The main aim of the second phase of the study was to examine the associations of childhood threat and deprivation experiences, characterized in detail using a multi-informant approach, with the neural architecture governing emotion regulation and cognitive control of the developing adolescents.

Chronicity of poverty and reports of the mother’s depressed mood were captured from 4 early childhood assessments (between ages 3 and 6) to control for confounding of the relationships between adversity and subsequent outcomes. Chronicity of poverty was defined as the number of visits out of 4 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 CES-D score across the four pre-baseline visits. At the baseline assessment of the second phase of data collection, 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 outcomes were collected at a follow-up assessment conducted approximately 2 years post-baseline.

Key constructs:

*Deprivation and threat exposures*:

The continuous deprivation 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). 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) were counted and reverse-scored so higher scores reflect greater cognitive deprivation. Emotional deprivation is a standardized composite of scores on emotional neglect subscales of the Childhood Experiences of Care and Abuse Interview (CECA) and Multidimensional Neglectful Behavior Scale (MNBS) (Bifulco et al., 1994; Kaufman Kantor et al., 2004). Lastly, physical deprivation is the standardized composite of food insecurity, measured by a 4-item household food insecurity scale, and physical neglect subscales of MNBS and the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1997; Kaufman Kantor et al., 2004). The continuous overall deprivation metric is the average of cognitive, emotional, and physical deprivation composites.

The continuous threat exposure variable is an average of (a) the count of distinct types of violence experienced (b) the standardized frequency of violence and (c) the standardized composite of physical and sexual abuse severity. A participating child could endorse up to 5 types of violence exposure, captured by CECA and the UCLA PTSD Reactions Index: physical abuse, sexual abuse, domestic violence, witnessing a violent crime or being a victim of a violent crime (Bifulco et al., 1994; Steinberg et al., 2004). Frequency of violence exposure was measured by the Violence Exposure Scale for Children-Revised instrument (VEX-R) (Raviv et al., 1999). Severity of violent exposures was measured by the physical and sexual abuse subscales of the CTQ (Bernstein et al., 1997).

Higher values on the deprivation and threat measures convey greater levels of exposure. Algorithms used to construct the deprivation and threat measures have been detailed in a pre-registration found here: <https://osf.io/6yf4p/>.

*Candidate mediators:*

Candidate mediators of the impact of deprivation and threat on psychopathology were scoped from a review of neurodevelopmental mechanisms that mediate the effects of childhood adversity and psychiatric sequelae in youth (Sheridan & McLaughlin, 2020), the conceptual model of the pathways linking the effects of threat on 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 comprehensively cover the domains of attention bias to threat, emotion regulation, theory of mind, fear conditioning, pubertal timing, language ability, reasoning ability, inhibitory control, and reward sensitivity. Except for pubertal timing, these phenotypes were objectively captured by tasks rather than questionnaires, minimizing the influence of shared method variance on the identification of indirect effects.

Attention bias to threat was captured by the difference in reaction times to neutral vs angry faces displayed by the Dot Probe task (Amin et al., 2004). Each trial consisted of a pair of faces of different emotional valence and a brief flash of a dot behind one of them. The participating child was instructed to press a button to identify behind which face the dot flashed – faster reaction times to correctly identify the dot behind angry faces rather than neutral faces signaled greater attention bias to threat.

Emotion regulation was captured by several metrics from the Emotional Stroop task (Ben-Haim et al., 2016). In congruent trials, the emotional valence of the face matched the emotion label displayed, whereas in incongruent trials, the emotion label was inconsistent with the facial expression, and required the child to correctly read the label despite a distracting conflicting visual stimulus. To capture emotion regulation, we used the difference in reaction times incongruent vs congruent trials with fearful faces and happy faces (correct trials only). We also included a variable for adaptation to emotional conflict, operationalized as the difference in reaction times on incongruent trials that were preceded by congruent trials vs reaction times on incongruent trials preceded by incongruent trials (Kim et al., 2021).

Cognitive and affective theory of mind was measured with a Theory of Mind task <CITE>. Cartoons depicting stories of cooperation or cooperation to deceive were shown to children who were asked to predict the conclusion of each story. Cognitive theory of mind represents their ability 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. Accuracy on cognitive and affective theory of mind trials was recorded.

Fear conditioning was measured by the skin conductance response (SCR) captured during the first block of the acquisition phase of the fear conditioning task (Shechner et al., 2015). Greater SCR is expected on trials where the neutral stimulus is coupled with an aversive stimulus (loud sound) as opposed to when an alternative neutral stimulus is not coupled with any aversive signal.

Pubertal timing was assessed using the Tanner staging method (Marshall & Tanner, 1969, 1970). Children were shown sex-specific pictographs 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.

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.

Inhibitory control, an executive functioning ability to suppress a prepotent response to achieve a longer-term goal, was measured using several tasks. NEPSY Circles & Squares task tested the children’s reaction time on “inhibit” and “switch” tasks (Brooks et al., 2009). The Stroop task measured the ability of the participating children to accurately read words for colors, even if the color with which the words are presented doesn’t match, with greater accuracy conveying greater inhibitory control (Stroop, 1935). Additionally, reaction times and accuracy on the Go/No-Go task were recorded for clicking a button when presented with “Go” stimuli (a set of specific shapes) and withholding clicking when other shapes were presented (Verbruggen & Logan, 2008).

Lastly, reward sensitivity was assessed using the Piñata task, a child-friendly version of a monetary incentive task (Helfinstein et al., 2013). A piñata appears on the screen with 0, 1, 2, or 4 stars inside, and the participating children are asked to “whack” the piñata as quickly as possible once the piñata drops to the middle of the screen. The stars are earned if the response is sufficiently quick. The total earned stars and the contrast in reaction times on no-reward (0-star) vs high-reward (4-star) trials measure reward sensitivity, with greater total stars and a greater reaction time contrast conveying greater reward sensitivity.

Overall, 19 variables capture cognitive, affective, and developmental characteristics hypothesized to mediate the relationships between adverse experiences and adolescent psychopathology. A summary of the constructs, measurement tools, and specific metrics can be found in Appendix **Table A.2**.

*Psychopathology outcomes*:

Internalizing and externalizing psychopathology were captured using continuous t-scores from the parent-reported Child Behavioral Checklist (CBCL) and self-reported Youth Self Report (YSR). The internalizing psychopathology outcomes cover anxious/depressed symptoms, depression, somatic complaints, social problems and thought problems. Externalizing psychopathology includes attention problems, rule-breaking behavior, and aggressive behavior syndromes (Achenbach, 1991, 2001).

Analysis methods:

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

We first ran an exploratory analysis of the mediator space using the 3-stage high-dimensional mediation algorithm executed using 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)]* largest effects for the outcome, where n is the sample size (Fan & Lv, 2008). In our analysis, Stage 1 is not applicable given that *d* = 84 is far greater than the number of mediators considered. In the Stage 2, a minimax-concave penalty (MPC) regularized regression is run to consider all candidate mediators selected by the screening, identifying mediators from a correlated set with non-null associations with the outcome. Stage 3 is joint significance testing, requiring that both the exposure-mediator and mediator-outcome relationships are significant at the two-sided 0.05 level.

We evaluated the main effects of threat and deprivation on the 4 adolescent psychopathology outcomes, and ran the HIMA algorithm for outcomes with significant main effects associated with each adversity type. 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, 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.

In an additional analysis, we looked at the candidate mediator space holistically by building latent mediator profiles (LMPs). We compared models with 1 to 9 possible latent profiles, and across 14 Gaussian multivariate mixture model types with various combinations of distribution, volume, shape, and orientation parameters (Scrucca et al., 2016). We chose the mixture model type that minimized the Bayesian Information Criterion (BIC). The LMPs identified clusters in the cognitive, affective, and developmental phenotypes and facilitated a comprehensive appraisal of potential mechanisms linking adverse early life experiences with adolescent psychopathology.

Multinomial logistic regression models were run to characterize the relationships between threat and deprivation experiences and the odds of belonging to the fitted LMP. The relationships between the adversity exposures, LMPs, and internalizing and externalizing psychopathology outcomes at follow-up were estimated using linear regressions. We reported 95% confidence intervals for all associations. Imputation was carried out using PROC SURVEYIMPUTE in SAS 9.4 () and the analysis was run using R version 4.2.1 (Team, 2022)

**Results**

The data was imputed to reconstruct the sample of 227 children for whom detailed characterization of early life adversity, candidate mediating phenotypes, and psychiatric outcomes were collected. Overall sample statistics and proportions of missing data across the key study variables are summarized in **Table A.1** in the Appendix. The average age of the participating children was 11.47 (SD=0.48) at baseline and 14.XX at follow-up. The sample was 48.5% female, with 38.1% having experienced poverty at some point in early childhood. Maternal CES-D depression symptom scores ranged from 12 to 56 (mean=23.94, SD=7.55). Approximately 84% reported having threatening experiences, while all children had at least some deprivation experiences. Adversity types were modestly correlated (Pearson correlation 0.32). Positive univariate correlations were observed between threat and self- and parent-reported externalizing disorders, while deprivation was correlated with self-reported internalizing and externalizing symptoms. Correlations between exposures, candidate mediators, and adolescent psychopathology outcomes are reported in **Table 1**.

--- Table 1 here ---

In models adjusted for age, sex, poverty chronicity, and maternal depression severity in early life (**Table 2**), threat is strongly associated with greater parent- and self-reported externalizing but not internalizing symptoms. A 1-standard deviation increase in the severity of threat experiences increases the externalizing t-score by 2.16 points 95% CI (1.04,3.28) for parent-reported symptoms and by 2.52 points 95% CI (1.22,3.82) for self-reported symptoms. Deprivation was strongly associated with self-reported internalizing and externalizing psychopathology, but neither parent-reported outcome. Increasing deprivation severity by 1 standard deviation increased internalizing t-scores by 2.74 points 95% CI (1.22,4.25) and 2.62 points 95% CI (1.21, 4.02) for self- and parent-reported symptoms, respectively. The magnitudes and statistical significance of these relationships persisted when the main effects of each adversity type were adjusted for the severity of the other.

--- Table 2 here ---

In **Table 1**, we show that most candidate mediator variables had the same direction of correlation with threat and deprivation, and the strongest correlations were with metrics of theory of mind, language and reasoning ability, and reward sensitivity. Appendix **Table A.3** shows the correlations among the candidate mediator phenotypes. Language and reasoning ability were positively associated with attention bias to threat (coefficients of 0.22 and 0.20, respectively) and correlated in opposing ways with accuracy and reaction times on inhibitory control metrics. The ability to earn more stars on the Piñata reward sensitivity task was positively associated with various aspects of executive functioning, including language and reasoning ability and accuracy on inhibitory control tasks. In short, many of the candidate mediator phenotypes cited in the literature as individual mechanisms conveying the impact of adversity on psychopathology were interrelated in this population.

*HIMA*

The HIMA algorithm’s MCP-regularization stage identified greater inhibitory control (accuracy on “No-Go” trials), slower pubertal timing, and greater reward sensitivity (total stars earned in the Piñata task) as protective factors for parent-reported externalizing psychopathology. Tanner pubertal stage was also retained in relation to self-reported externalizing symptoms. Language ability, reward sensitivity, and Tanner stage were retained as predictors of self-reported internalizing symptoms. Parent-reported internalizing psychopathology was not modeled using HIMA given that it proved not to have significant relationships with either threat or deprivation in this population.

Only language ability emerged as jointly significantly related to both deprivation and self-reported internalizing symptoms. A 1-standard deviation (SD) increase in deprivation severity decreases language ability by 0.17 of an SD on average (95% CI (-0.31,-0.03)). Contrary to prior findings, diminished language ability decreased self-reported internalizing symptoms, with a 1-SD decrease in language ability reducing the internalizing t-score by 1.07 points in expectation (95% CI (-2.03, -0.10)). Prior work by Miller and colleagues has identified language ability as a significant mediator, conveying the impact of greater deprivation on greater internalizing symptomatology (Miller et al., 2021; Miller et al., 2018). In this sample, with additional adjustment for Tanner stage and reward sensitivity, language ability emerged as a suppression mechanism of deprivation’s effect on internalizing symptomatology. Slower pubertal timing and dampened reward sensitivity did not reach significance at the 2-sided alpha level of 0.05, but trended towards significance, with joint p-values for the indirect effects of 0.0684 and 0.0970, respectively. While the impacts of slower pubertal timing and increased reward sensitivity were strongly associated with lower self-reported internalizing psychopathology (-1.85, 95% CI (-3.19,-0.52) and -1.41, 95% CI (-2.52,-0.29), respectively), their relationships with deprivation did not reach the significance threshold. A 1-SD increase in deprivation severity is associated with a 0.12-stage drop in the Tanner score (95% CI (-0.26,0.01)) and a 0.12-SD drop in the reaction time difference on no-reward vs high-reward Pinata trials (95% CI (-0.27,0.02)). There is a suggestion that slower pubertal timing may serve as another suppression mechanism, and detriments in reward sensitivity may mediate deprivation’s impact on internalizing symptoms, but larger samples are needed to explore these relationships. **Figure 1** summarizes the HIMA findings with respect to deprivation and self-reported internalizing psychopathology.

--- Figure 1 here ---

Inclusion of threat as a covariate in deprivation models for the mediators and outcomes resulted in the dilution of the relationship between deprivation and reward sensitivity but did not change the results for Tanner stage and language ability. In summary, an empirical selection of mediator phenotypes for adversity and psychopathology using HIMA only identified likely pathways for deprivation with respect to self-reported internalizing symptoms. Given a type-I error rate of 0.05, detriments in language ability emerged as the only significant suppression mechanism of deprivation’s impact on internalizing symptoms.

*LMPs*

We next explored the candidate mediators holistically by constructing latent mediator profiles (LMPs). The Gaussian mixture model with the lowest BIC was VVI,3 – a model with 3 clusters, a diagonal distribution, variable volume and shape, and coordinate orientation (details on this approach provided in (Scrucca et al., 2016)). **Figure 2** shows the contrasts in average values of the candidate mediator phenotypes, standardized to have mean 0 and standard deviation 1 in the overall sample. The 20 individuals grouped in Profile 2 have markedly lower cognitive and affective theory of mind, and diminished fear conditioning. This subgroup of children is also at earlier pubertal stages, and has lower adaptation to emotional conflict, and diminished inhibitory control. The 115 individuals in Profile 1 contrast with the 92 children in Profile 3 on executive functioning – particularly reasoning and language ability, and poorer performance on inhibitory control markers such as accuracy on the Stroop task. **Table 3** shows that children in Profiles 1 and 2 (particularly Profile 2) have greater experiences of poverty and maternal depression in early life, and experience more threat and deprivation. Profile 2 is drastically different from Profiles 1 and 3 with respect to biological sex, with only 20% reporting female biological sex compared to 50% and 52% in Profiles 1 and 3, respectively. There are subtle differences in the distributions of adolescent psychopathology by LMP – those who are in Profiles 1 and 2 have greater parent-reported externalizing symptoms, but no other significant crude associations are apparent.

--- Figure 2 here ---

--- Table 3 here ---

**Table 4** summarizes the multinomial logistic regression models relating threat and deprivation with LMPs. Adjusted for age and sex, a 1-SD increase in threat increases the odds of being in Profiles 1 and 2 by 61% and 69%, respectively. Deprivation is associated with a greater likelihood of being in Profile 2, relative to the reference Profile 3 (OR 1.69, 95% CI (1.05, 2.72)). Putting both adversity exposures into the model diminishes the associations but reveals a significant multiplicative interaction with respect to the odds of being in either Profile 1 or 2 relative to the reference Profile 3 (p-values 0.0103 and 0.0236, respectively). Greater experiences of one adversity exposure diminish the strength of the association with the other adversity exposure. Specifically, the impact of threat on the odds of being in Profiles 1 or 2 relative to 3 is strongest at lower levels of deprivation. The odds of having lower executive functioning (Profile 1) are 2.12 times higher (95% CI (1.31,3.78)) with a 1-SD increase in threat when deprivation is fixed at the average value in the population, but only 1.49 times higher (95% CI (1.01,2.19)) when deprivation is increased by 1-SD relative to the average. A similar pattern is evident with respect to threat’s impact on the odds of being in Profile 2 relative to Profile 3 at varying levels of co-occurring deprivation. The odds of being in Profile 2 are elevated slightly by increases in deprivation when threat is held at the sample’s average, but the association does not reach significance.

--- Table 4 here ---

Lastly, Table 5 shows the relationships between LMPs and adolescent psychopathology outcomes. Having lower executive functioning (Profile 1) is associated with a 3.11-point increase in parent-reported externalizing symptoms (95% CI (0.72,5.51)) when adjusted for age and sex only, but the association dissipates when adversity exposures, early-life poverty, and maternal depression are taken into account (OR 1.40, 95% CI (-0.96,3.76)).

--- Table 5 here ---

Ultimately, we learn from this cohort that deprivation’s impact on internalizing symptoms is suppressed by diminished language ability and that threat exerts strong impact on theory of mind and executive functioning markers, particularly when deprivation exposure is low.

**Discussion**

In this analysis, we show that the consequences of threat and deprivation with respect to cognitive, affective, developmental, and ultimately psychiatric outcomes are quite complex. After accounting for age, biological sex, experiences of poverty, and maternal depression severity in the child’s early life, threat was strongly associated with both parent- and self-reported externalizing psychopathology, but not associated with internalizing symptoms. Conversely, deprivation was associated with both self-reported internalizing and externalizing psychopathology, but neither parent-reported outcome.

ADDITIONALLY MENTION:

* Emphasize the longitudinal nature of the data, the availability of covariates well established to predict both adversity and psychiatric outcomes, the detailed assessment of threat and deprivation, a comprehensive coverage of candidate mediator phenotypes, many of which were measured objectively with tasks, and a multi-informant record of adolescent psychopathology
* In contrast to the majority of the literature available, threat was not associated with adolescent internalizing symptomatology. Experiences of abuse, threat of harm – such as neighborhood violence – or general maltreatment in early life are strong predictors of psychopathology across the board. In this sample, 16% reported no threatening experiences at all, and only few had reported high levels of threat. This may be due to the reluctance of the participants to report such experiences, or other sources of measurement
* Discuss why language ability may have a reverse association with internalizing symptoms in the population – in contrast to established literature. It’s not just because reward sensitivity and Tanner stage are controlled for – the crude correlations with internalizing outcomes are also positive.
* Raise the point that Tanner stage was a significant predictor of all assessed adolescent psychopathology outcomes – important to continue to assess mechanisms tying differences in pubertal timing to psychiatric dysregulation
* Overall limitations:
  + Small sample size
  + Retrospective assessment of adversity collected at the same time as the assessment of candidate mediator phenotypes
  + Challenge in conceptualizing what a 1-SD increase in threat and deprivation really means, since the composite measures are so complex.
* Overall strengths:
  + Thoughtful study design – purposefully recruited children from the spectrum of socioeconomic backgrounds. One third of the original cohort were living below the poverty line during recruitment, another third were in lower middle class, and the remaining third were middle class and above.
  + Availability of key confounders, including the chronicity of poverty and maternal depression in the participating child’s early life
  + Multi-informant detailed adversity assessment
  + Comprehensive assessment of candidate mediating phenotypes with tasks rather than questionnaires (aside from Tanner) - **­**lower impact of shamed method variance because most of the candidate mediators are task-measured

**Tables and Figures**

Table 1: Correlations between key variables

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Adversity | | Internalizing | | Externalizing | |
|  | Threat | Deprivation | CBCL | YSR | CBCL | YSR |
| Threat | 1 |  | 0.14 | 0.06 | 0.30 | 0.27 |
| Deprivation | 0.32 | 1 | 0.10 | 0.20 | 0.15 | 0.28 |
| AB: Attention bias threat | -0.01 | -0.02 | 0.04 | 0.03 | -0.05 | 0.02 |
| ER: Adaptation to emotional conflict | 0.03 | 0.05 | -0.01 | -0.02 | -0.04 | 0.01 |
| ER: Stroop - fear | -0.12 | 0.08 | -0.03 | 0.05 | -0.01 | -0.05 |
| ER: Stroop - happy | -0.05 | -0.03 | 0.07 | 0.02 | 0.03 | -0.04 |
| ToM: Accuracy on affective trials | -0.13 | -0.19 | -0.03 | 0.01 | -0.07 | -0.08 |
| ToM: Accuracy on cognitive trials | -0.17 | -0.18 | -0.03 | -0.02 | -0.09 | -0.09 |
| FC: Skin conductance response to CS+ vs CS- | 0.08 | 0.02 | 0.07 | -0.02 | 0.10 | 0.10 |
| PT: Tanner stage | -0.05 | -0.09 | -0.03 | 0.16 | 0.09 | 0.13 |
| AL: Language ability | -0.14 | -0.26 | 0.09 | 0.09 | -0.05 | -0.02 |
| AR: Reasoning ability | -0.18 | -0.13 | -0.11 | -0.05 | -0.17 | -0.02 |
| IC: Reaction time on inhibit trials | 0.14 | -0.01 | -0.01 | -0.01 | 0.04 | 0 |
| IC: Reaction time on switch trials | 0.09 | 0.04 | 0.03 | 0.06 | 0.09 | 0 |
| IC: Accuracy on Stroop task | -0.10 | -0.02 | 0 | 0.05 | -0.09 | -0.03 |
| IC: Accuracy on 'Go' trials | -0.13 | -0.03 | -0.05 | 0.06 | -0.11 | -0.06 |
| IC: Accuracy on 'No-Go' trials | 0.06 | -0.04 | -0.11 | -0.03 | -0.16 | -0.01 |
| IC: Reaction time on accurate 'Go' trials | 0.14 | 0.03 | 0.02 | -0.01 | 0.02 | 0.03 |
| IC: Reaction time on inaccurate 'No-Go' trials | 0.02 | 0.10 | 0.06 | -0.01 | 0.06 | 0 |
| RS: Reaction time on high- vs low-reward trials | -0.16 | -0.07 | -0.04 | -0.19 | 0.02 | -0.16 |
| RS: Total stars | -0.04 | -0.08 | -0.1 | 0.03 | -0.29 | -0.14 |
| CBCL Internalizing t-score |  |  | 1 | 0.41 | 0.49 | 0.17 |
| YSR Internalizing t-score |  |  |  | 1 | 0.08 | 0.41 |
| CBCL Externalizing t-score |  |  |  |  | 1 | 0.41 |
| YSR Externalizing t-score |  |  |  |  |  | 1 |

AB=Attention bias to threat; ER=Emotion regulation; ToM=Theory of Mind; FC=Fear conditioning; PT=Pubertal timing; AL=Language ability; AR=Reasoning ability; IC=Inhibitory control, RS=Reward sensitivity

Table 2: Associations between adversity and adolescent psychopathology outcomes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | CBCL Internalizing | YSR  Internalizing | CBCL Externalizing | YSR Externalizing |
| Coefficientb  (95% CI) | Coefficientb (95% CI) | Coefficientb  (95% CI) | Coefficientb  (95% CI) |
| Threata | 1.09  (-0.27,2.46) | 0.83  (-0.62,2.27) | 2.16 (1.04,3.28)\*\*\* | 2.52 (1.22,3.82)\*\*\* |
| Deprivationa | 0.70  (-0.77,2.18) | 2.74 (1.22,4.25)\*\*\* | 0.70  (-0.55,1.94) | 2.61 (1.21,4.02)\*\*\* |
| a Adjusted for age, sex, poverty chronicity, maternal depression  b Coefficient for a 1-SD increase in adversity  p-value \*<0.1, \*\*<0.05, \*\*\*<0.01 | | | | |

Figure 1: High-dimensional mediation analysis results for deprivation and self-reported internalizing symptoms

Diagram

Description automatically generated

p-value \*<0.1, \*\*<0.05, \*\*\*<0.01

Figure 2: Latent mediator profiles (LMPs)

Chart, line chart

Description automatically generated

AB=Attention bias to threat; ER=Emotion regulation; ToM=Theory of Mind; FC=Fear conditioning; PT=Pubertal timing; AL=Language ability; AR=Reasoning ability; IC=Inhibitory control, RS=Reward sensitivity

Table 3: Distributions of child characteristics by LMP

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristic | Profile 1:  Below average executive | Profile 2:  Below average ToM, SCR | Profile 3: Reference | p-value |
| n | 115 | 20 | 92 |  |
| Age, baseline | 11.47 (0.48) | 11.28 (0.33) | 11.51 (0.49) | 0.148 |
| % Female biological sex | 0.50 (0.50) | 0.20 (0.41) | 0.52 (0.50) | 0.027 |
| Chronicity of poverty, early childhood | 0.88 (1.39) | 1.55 (1.70) | 0.83 (1.31) | 0.100 |
| Maternal depression, early childhood | 25.43 (7.96) | 26.45 (10.78) | 21.53 (5.26) | <0.001 |
| Threat, standardized | 0.12 (1.10) | 0.31 (1.03) | -0.22 (0.81) | 0.016 |
| Deprivation, standardized | 0.06 (0.98) | 0.45 (1.27) | -0.17 (0.93) | 0.025 |
| CBCL internalizing t-score | 52.02 (11.04) | 52.55 (8.24) | 49.70 (9.65) | 0.222 |
| CBCL externalizing t-score | 49.99 (8.83) | 49.00 (9.29) | 46.83 (8.44) | 0.035 |
| YSR internalizing t-score | 50.57 (10.56) | 51.45 (8.42) | 49.34 (10.99) | 0.598 |
| YSR externalizing t-score | 48.01 (10.81) | 48.70 (7.14) | 46.33 (9.12) | 0.394 |

Table 4: Associations between adversity and latent mediator profiles

|  |  |  |  |
| --- | --- | --- | --- |
|  | Coefficient for: | Profile 1: Below average executive | Profile 2: Below average ToM, SCR |
|  |  | OR(95% CI) relative to Profile 3 | OR(95% CI) relative to Profile 3 |
| Model 1a: Threat, age, sex | Threat | 1.61(1.09,2.39)\*\* | 1.69(1.01,2.81)\*\* |
| Model 1b: Deprivation, age, sex | Deprivation | 1.29(0.96,1.74)\* | 1.69(1.05,2.72)\*\* |
| Model 1: Threat, deprivation, age, sex | Threat | 1.53(1.02,2.28)\* | 1.47(0.86,2.51) |
| Deprivation | 1.17(0.86,1.59) | 1.55(0.94,2.56)\* |
| Model 2: Model 1, with interaction between threat and deprivation | Interaction p-values | 0.0103 | 0.0236 |
| Threat @ average deprivation | 2.22(1.31,3.78)\*\*\* | 2.50(1.25,4.98)\*\*\* |
| Threat @ 1SD above average deprivation | 1.49(1.01,2.19)\*\* | 1.45(0.84,2.51) |
| Deprivation @ average threat | 1.10(0.80,1.51) | 1.54(0.92,2.58) |
| Deprivation @ 1SD above average threat | 0.74(0.46,1.18) | 0.89(0.46,1.75) |
| Model 3: Model 2, adjusted for poverty chronicity & maternal depression | Interaction p-values | 0.0194 | 0.0300 |
| Threat @ average deprivation | 2.12(1.22,3.69)\*\*\* | 2.38(1.16,4.88)\*\* |
| Threat @ 1SD above average deprivation | 1.46(0.98,2.16)\* | 1.41(0.99,2.01)\* |
| Deprivation @ average threat | 1.03(0.72,1.48) | 1.31(0.74,2.30) |
| Deprivation @ 1SD above average threat | 0.71(0.35,1.45) | 0.77(0.46,1.28) |
| p-value \*<0.1, \*\*<0.05, \*\*\*<0.01 | |  |  |

Table 5: Associations between latent mediator profiles and adolescent psychopathology outcomes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Internalizing | | Externalizing | |
|  | Coefficient for: | CBCL | YSR | CBCL | YSR |
|  |  | Coefficient  (95% CI) | Coefficient  (95% CI) | Coefficient  (95% CI) | Coefficient  (95% CI) |
| Model 1: Latent mediator profiles, age, sex | Profile 1: Below average executive vs Reference profile | 2.34 (-0.48,5.16) | 1.31 (-1.59,4.22) | 3.11 (0.72,5.51)\*\* | 1.67 (-1.05,4.39) |
| Profile 2: Below average ToM, SCR vs Reference profile | 3.27 (-1.83,8.37) | 2.82 (-2.42,8.07) | 1.78 (-2.54,6.11) | 2.17 (-2.74,7.09) |
| Model 2: additionally adjusted for threat, deprivation | Profile 1: Below average executive vs Reference profile | 1.78 (-1.07,4.63) | 0.84 (-2.13,3.82) | 2.24 (-0.11,4.58)\* | 0.50 (-2.12,3.13) |
| Profile 2: Below average ToM, SCR vs Reference profile | 2.38 (-2.76,7.52) | 2.13 (-3.14,7.4) | 0.52 (-3.71,4.75) | 0.15 (-4.58,4.88) |
| Model 3: additionally adjusted for chronicity of poverty, maternal depression | Profile 1: Below average executive vs Reference profile | 0.78 (-2.10,3.65) | 0.74 (-2.25,3.73) | 1.40 (-0.96,3.76) | 0.49 (-2.21,3.2) |
| Profile 2: Below average ToM, SCR vs Reference profile | 1.59 (-3.51,6.68) | 1.93 (-3.37,7.24) | -0.25 (-4.43,3.93) | 0.12 (-4.67,4.91) |
| p-value \*<0.1, \*\*<0.05, \*\*\*<0.01 | |  |  |  |  |

**Appendix Tables**

Table A.1: Overall sample characteristics and proportions missing

|  |  |  |
| --- | --- | --- |
| Characteristic | Overall | % Missing |
| n | 227 |  |
| Age, baseline, mean(SD) | 11.47 (0.48) | 0 |
| Female biological sex, n(%) | 110 (48.5) | 0 |
| Chronicity of poverty, early childhood, mean(SD) | 0.92 (1.40) | 7.5 |
| Ever poverty, early childhood, n(%) | 80 (38.1) | 7.5 |
| Maternal depression, early childhood, mean(SD) | 23.94 (7.55) | 0 |
| Threat, mean(SD) | 0.01 (0.77) | 0 |
| Any threat, n(%) | 191 (84.1) | 0 |
| Deprivation, mean(SD) | 0.01 (0.71) | 0 |
| AB: Attention bias threat, mean(SD) | -4.91 (35.02) | 5.3 |
| ER: Adaptation to emotional conflict, mean(SD) | 8.07 (126.39) | 6.6 |
| ER: Stroop - fear, mean(SD) | -7.40 (88.52) | 6.6 |
| ER: Stroop - happy, mean(SD) | -5.31 (85.37) | 6.6 |
| ToM: Accuracy on affective trials, mean(SD) | 0.91 (0.10) | 10.6 |
| ToM: Accuracy on cognitive trials, mean(SD) | 0.79 (0.10) | 10.6 |
| FC: Skin conductance response to CS+ vs CS-, mean(SD) | 0.18 (0.19) | 15.4 |
| PT: Tanner stage, mean(SD) | 2.21 (0.85) | 15 |
| AL: Language ability, mean(SD) | 60.06 (8.98) | 0 |
| AR: Reasoning ability, mean(SD) | 55.56 (9.27) | 0 |
| IC: Reaction time on inhibit trials, mean(SD) | 5.02 (4.17) | 18.9 |
| IC: Reaction time on switch trials, mean(SD) | 26.64 (8.89) | 18.9 |
| IC: Accuracy on Stroop task, mean(SD) | 0.33 (0.09) | 10.6 |
| IC: Accuracy on 'Go' trials, mean(SD) | 0.91 (0.09) | 24.2 |
| IC: Accuracy on 'No-Go' trials, mean(SD) | 0.63 (0.16) | 24.2 |
| IC: Reaction time on accurate 'Go' trials, mean(SD) | 491.41 (41.60) | 24.2 |
| IC: Reaction time on inaccurate 'No-Go' trials, mean(SD) | 418.97 (40.64) | 24.2 |
| RS: Reaction time on no- vs high-reward trials, mean(SD) | -28.98 (56.85) | 7.5 |
| RS: Total stars, mean(SD) | 59.82 (14.47) | 7.5 |
| CBCL internalizing t-score, mean(SD) | 50.96 (10.38) | 9.7 |
| YSR internalizing t-score, mean(SD) | 50.35 (10.57) | 12.3 |
| CBCL externalizing t-score, mean(SD) | 48.29 (8.73) | 9.7 |
| YSR externalizing t-score, mean(SD) | 47.45 (9.88) | 12.3 |

AB=Attention bias to threat; ER=Emotion regulation; ToM=Theory of Mind; FC=Fear conditioning; PT=Pubertal timing; AL=Language ability; AR=Reasoning ability; IC=Inhibitory control, RS=Reward sensitivity

Table A.2: Candidate mediator constructs and how they are measured

|  |  |  |  |
| --- | --- | --- | --- |
| **Construct** | **Measurement tool** | **Tool type** | **Variable(s)** |
| 1. Attention bias to threat (AB) | Dot Probe task | Behavioral task | • Difference in reaction times on accurate trials with neutral faces vs angry faces |
| 2. Emotion regulation (ER) | Emotional Stroop task | Behavioral task | • Adaptation to emotional conflict - the difference in reaction times on incongruent trials that were preceded by congruent trials and reaction times on incongruent trials preceded by incongruent trials • Difference in reaction time on incongruent vs congruent correct fear trials • Difference in reaction times on incongruent vs congruent correct happy trials |
| 3. Theory of mind (ToM) | Theory of Mind task | Behavioral task | • Accuracy on affective and cognitive trials |
| 4. Fear conditioning (FC) | Fear conditioning task | Physiologic response | • Difference between skin conductance response to CS+ and CS- in the first acquisition block of the task, adjusted for baseline conductance |
| 5. Pubertal timing (PT) | Tanner staging | Self-report | • Mean of testes/scrotum/penis & pubic hair development stages for biologically male participants and mean of breast and pubic hair development stages for biologically female participants |
| 6. Language ability (AL) | Wechsler Abbreviated Scale of Intelligence | Behavioral task | • T-score on the vocabulary subset |
| 7. Reasoning ability (AR) | Wechsler Abbreviated Scale of Intelligence | Behavioral task | • T-score on the matrix reasoning subset |
| 8. Inhibitory control (IC) | NEPSY Circles and Squares task | Behavioral task | • Reaction times relative to baseline on "inhibit" tasks • Reaction times relative to baseline on "switch" tasks |
| Stroop task | Behavioral task | • Accuracy on all trials |
| Go/No-Go task | Behavioral task | • Accuracy on "Go" trials • Accuracy on "No-Go" trials • Reaction time on accurate "Go" trials • Reaction time on inaccurate "No-Go" trials |
| 9. Reward sensitivity (RS) | Pinata task | Behavioral task | • Difference in reaction time on no-reward (0-star) trials and reaction time on high-reward (4-start) trials  • Overall performance (total stars earned) |

Table A.3: Correlations among candidate mediators

Chart

Description automatically generated

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