**Methods**

Study overview:

Data for this analysis was sourced from a longitudinal cohort study that recruited 306 dyads of 36-month-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 approximately 11 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.

Participants completed a 3-session baseline assessment at age of 10.9-13.0 and provided survey data on the history of threat and deprivation experiences, demographics, home environment, and psychological symptomatology. At baseline, the children additionally underwent behavioral tasks and structural and functional MRI assessments to capture emotional, cognitive, and developmental characteristics at the brink of adolescence. Child and parent survey measures, behavioral tasks, and components of the MRI assessment conducted at the baseline assessment are summarized in **Table A.1** in the Appendix. A follow-up psychological assessment was conducted approximately 2 years post-baseline. Of the 227, 14 participants did not provide any follow-up data.

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 the development of 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 et al., 2019). The chosen variables comprehensively covered 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.

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 displayed 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 on incongruent vs congruent trials with fearful faces and happy faces. 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 the 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 could accurately interpret the emotional state of another character. Accuracy on cognitive and affective theory of mind trials were 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 <CITE>. 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 <CITE>. Children were shown sex-specific pictographs conveying stages of development of sexual characteristics (pubic hair for both, breasts for girls, and testes/scrotum/penis for boys). Tanner pubertal development stage was constructed as the average of the two sex-specific sexual characteristic ratings.

Language ability and reasoning ability were measured using the Wechsler Abbreviated Scale of Intelligence (or WASI) task.(Wechsler, 1999) Language ability was measured with the t-score on the WASI vocabulary subtest. The vocabulary subtest is 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 of the letters with which color words are presented don’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 was sufficiently quick. The total earned stars and the contrast in reaction times on high-reward (4-star) and non-reward (0-star) trials measure reward sensitivity, with greater total stars and a greater reaction time contrast conveying greater reward sensitivity.

Overall, 19 variables capture emotional, cognitive, 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 **Table 1**.

*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 outcome covered anxious/depressed symptoms, depression, somatic complaints, social problems and thought problems. Externalizing psychopathology included attention problems, rule-breaking behavior, and aggressive behavior syndromes. <CITE>.

*Covariates:*

Exposure-outcome and exposure-mediator relationships are adjusted for age at baseline, biological sex, chronicity of poverty in early childhood (the count of years the child lived in a low-income household between the ages 3 and 6), and the severity of the mother’s depression symptoms in the child’s early life (maximum score on the CES-D reported over 4 early-life data collection waves). We additionally adjusted the threat models for deprivation and vice-versa, to account for unmeasured common causes of adversity. Relationships between mediators and outcomes were additionally adjusted for the baseline income-to-needs ratio. Finally, randomized intervention analogues were computed to adjust for baseline child psychiatric symptoms, a confounder of the mediator-outcome relationship that is likely affected by the adversity exposures. <CITE randomized interventional analogues>. Baseline child psychiatric symptoms were captured with the maximum of the self-reported overall problem score from the youth self-report (YSR) and parent-reported overall problem score from the CBCL.

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 among those with complete vs incomplete data in **Table A.2** in the Appendix.

We first ran a latent profile analysis to group participants according to their values on standardized candidate mediator variables. We compared models with 1 to 9 possible latent profiles, and across 14 Gaussian multivariate mixture models 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 Criteria. The identified latent mediator profiles identified clusters in the correlated cognitive, affective, and developmental phenotypes and facilitated a comprehensive analysis 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 latent mediator profile. The relationships between the adversity exposures, latent mediator profiles, and internalizing and externalizing psychopathology outcomes at follow-up were estimated using linear regressions. We reported 95% confidence intervals and two-sided p-values.

Natural direct and indirect effects, as well as the proportion of the effects of threat and deprivation mediated by the latent phenotype profiles were estimated using the causal mediation framework outlined by Valeri & Vanderweele <CITE>. We allowed for an interaction between the adversity exposures and latent profile mediators, and having ruled it out, simplified the models. Estimation of causal mediation quantities was conducted using imputation of counterfactual quantities and standard errors were bootstrapped.

**Results**

**Table 1: Summary of candidate mediator construct domains and measures**

|  |  |  |  |
| --- | --- | --- | --- |
| **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 high-reward (4-start) trials and reaction time on no-reward (0-star) trials • Overall performance (total stars earned) |

**Figure 1: Latent mediator profiles**

Chart, line chart

Description automatically generated

**Table 2: Distributions of child characteristics by latent mediator profile**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristic | Profile1: 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 |
| Maternal depression, early childhood | 25.43 (7.96) | 26.45 (10.78) | 21.53 (5.26) | <0.001 |
| Chronicity of poverty, early childhood | 0.88 (1.39) | 1.55 (1.70) | 0.83 (1.31) | 0.100 |
| Income-to-needs ratio, baseline | 3.43 (1.74) | 2.58 (1.62) | 3.98 (1.81) | 0.003 |
| Threat experiences, standardized | 0.12 (1.10) | 0.31 (1.03) | -0.22 (0.81) | 0.016 |
| Deprivation experiences, 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 |

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