**Aim 1:** **To investigate whether the deprivation and threat domains of adversity experienced in childhood impact adolescent psychopathology through empirically discernable emotional, cognitive, and developmental mediation mechanisms.** **(1a)** To characterize which precursor phenotypes convey the strongest indirect effects of threat and deprivation **(1b)** To determine if the effect of threat is mediated by the same set of mechanisms overall and in subgroups determined by the level of co-occurring deprivation, and vice versa. *We hypothesize that mechanisms of effects of threat and deprivation on adolescent psychopathology will differ, and that depending on the severity of the other, each type of adversity will have heterogeneous total and indirect effects.*

Introduction

Examining modifiable mediators of the relationship between early-life adversity (ELA) and psychiatric outcomes is an important step towards alleviating the burden of adolescent-onset psychopathology. Adversity experienced in childhood is a well-established predictor of psychiatric sequelae proximally and longitudinally, explaining roughly 30% of the liability for lifetime psychiatric disorders.1,2 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.3 ELA is, however, not monolithic. McLaughlin and Sheridan proposed the dimensional model of ELA, dissecting adverse experiences into those of threat (harm or threat of harm) and deprivation (lack of social or cognitive stimulation and nurturing support).4-6 Neurodevelopmental outcomes reflect discrepant consequences of experiencing threat and deprivation, two domains of ELA as specified by McLaughlin & Sheridan’s dimensional model of adversity and psychopathology (DMAP).4-6

A review of 109 imaging studies found divergent impacts of threat and deprivation on structural and functional neurodevelopmental outcomes in children.7 Experiences of deprivation, but not threat, have been found to impact the volume and function of frontoparietal cortical regions, suggesting deprivation’s likely effects on executive functioning. Exposure to threat, but not deprivation, was found to affect amygdala’s size and connectivity to the medial pre-frontal cortex, as well as the function of the salience network and hippocampal volume, explaining findings of threat’s impact on enhanced threat detection, attention bias to threat, and working memory. Findings about the relationships between ELA and striatal reward circuits were less clear but suggest that deprivation and threat may have divergent consequences.

Exploration of emotional, cognitive, and developmental metrics that reflect differences in structural and functional brain development precipitated by facets of ELA is a rapidly developing area of research. Most of the published analyses test mediation of threat and deprivation by one or a small set of interrelated phenotypes at a time using path analysis methods. The impact of threat, but not deprivation, on psychopathology has been shown to be mediated by enhanced threat detection, increased attention bias to threat, cognitive and affective theory of mind, fear conditioning, disruptions in automatic emotion regulation, and earlier onset of puberty.15,17-22 Experiences of deprivation, but not threat, were found to be mediated by language ability and aspects of executive functioning (inhibitory control, working memory, and reasoning ability).23-26 Given that many of these cited characteristics influence one another, and are not mutually accounted for in mediation analyses, estimates of indirect effects found in analyses focusing on one emotional, cognitive, or developmental mediator at a time should not be imbued with causal interpretation.

We propose an analysis that looks at a large set of objectively measured characteristics that have been previously cited to mediate the effects of threat, deprivation, or both, and utilize penalized regression techniques to empirically identify the mediators that convey the strongest indirect effects of threat and deprivation on adolescent psychopathology.

A critical task from an epidemiologic perspective is to establish which precursor phenotypes, measurable on a population scale and targetable with intervention, most saliently reflect biological changes precipitated by deprivation and threat. Ultimately, the completion of this analysis will add to our understanding of how emotional, cognitive, and developmental phenotypes are affected by adversity, and which constitute early signs of dysregulation that precipitates onset of psychopathology in adolescence.

Methods

C1.1 The Deprivation and Threat study overview

Deprivation and Threat is a longitudinal cohort study which initially recruited a sample of 306 dyads of 36-month-old children and their mothers from the Seattle metro area to assess the mechanisms through which socioeconomic status, cumulative family risk, and parenting behaviors impact the functioning of the hypothalamic-pituitary-adrenal (HPA) system of the children 27. The primary cohort was recruited into a second phase of data collection when the children were approximately 11 years of age. This extension cohort (N=227) provides exposure, mediator, and outcome data for the proposed analysis. Covariates such as chronicity of poverty in early childhood will be pulled in from the primary cohort’s data. The main aim of the second phase of data collection was to examine the effects of childhood threat and deprivation experiences, characterized in detail, on the neural architecture governing emotion regulation and cognitive control.

Participants of the extension cohort completed a 3-session baseline assessment (together T1) at the age of 10.9-13.0 at the time of the first session. All 227 completed the first session; of the 215 who completed the second session, 83.3% did so within 2 months of the first session and of the 183 who completed the third session, 79.23% did so within 3 months of the first session. At T1, recruited children and their parents provided survey data on demographics, home environment, and the child’s psychological symptomatology; the children additionally underwent behavioral tasks and structural and functional MRI assessments to capture emotional, cognitive, and developmental characteristics of the children in early adolescence. Child and parent survey measures, behavioral tasks, and components of the MRI assessment administered at each T1 session are summarized in **Table A.1** in the Appendix. At T2, approximately 2 years after T1, a follow-up psychological assessment was conducted. Of the original 227, 14 participants did not provide follow-up data. Data from T1 and T2, along with select pre-baseline covariates from the initial cohort’s data, will be utilized in this analysis to elucidate whether objectively measured mediators of the effects of threat and deprivation on adolescent psychopathology are empirically discernable.

C1.2 Key Constructs

*Deprivation and threat exposures*:

The continuous deprivation measure comprises domains of cognitive, emotional, and physical deprivation. Cognitive deprivation is measured using maternal responses on the Home Observation Measurement of the Environment-Short Form (HOME-SF) instrument.28 Cognitive deprivation is the count of 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 child learning), 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).29,30 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).30,31 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 violence exposures (b) the standardized frequency of violence and (c) the standardized composite of physical and sexual abuse severity as measured by the respective subscales of the CTQ.31 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.29,32 Frequency of violence exposure was measured by the Violence Exposure Scale for Children-Revised instrument (VEX-R).33 Severity of violent exposures was measured by the physical and sexual abuse subscales of the CTQ.31

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/>).

*Primary psychopathology outcomes*:

The primary outcome variables will be continuous measures of internalizing, externalizing, and general psychopathology. Internalizing psychopathology (INT for brevity in future references) comprises assessments of depression, anxiety, and post-traumatic stress disorder (PTSD) based on total scores on the Children’s Depression Inventory-2 (CDI), the Screen for Child Anxiety Related Emotional Disorders (SCARED), and the UCLA PTSD Reaction Index, respectively.32,34,35 Externalizing psychopathology (EXT for brevity in future references) was 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).36,37 A confirmatory factor analysis was performed using MPlus Version 8.138 on deciles of scores for depression, anxiety, PTSD, attention problem, rule-breaking, and aggression to arrive at the continuous INT and EXT latent factors. An additional higher-order general factor model with INT and EXT latent factors was run to construct P, a transdiagnostic measure of psychopathology referred to as the *p*-factor in literature.39 The algorithm for the construction of the outcome variables has been previously described by Weissman et al.40

*Secondary psychopathology outcomes*:

In secondary analyses, we will consider continuous scores for depression, anxiety disorders, PTSD, attention problems, rule-breaking behavior, and aggressive behavior, measured as described above, and standardized to have a mean of 0 and standard deviation of 1.

*Candidate mediators:*

Potential mediators of the effect of deprivation and/or 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 41, the conceptual model of the pathways linking the effects of threat on psychopathology,42 and the review of potential intervention targets to prevent aversive psychiatric consequences of childhood deprivation and threat experiences 43. In an effort to avoid undue weight that would likely be attributed by mediation models to self-reported psychosocial characteristics due to shared method variance 44, the majority of candidate mediators considered are task-measured. Exceptions are self-reported Tanner pubertal stage and fear conditioning measured via skin conductance during a task – both physiologic constructs. Potential mediators include threat detection, attention bias to threat, cognitive and affective theory of mind, fear conditioning, pubertal development, language ability, inhibitory control, working memory, reasoning ability, automatic emotion regulation, and reward reactivity. Empirical evidence that endorses these phenotypes as candidate mediators and hypotheses drawn from the evidence are provided in **Table A.2** in the Appendix.

*Covariates:*

Exposure-outcome and exposure-mediator relationships will be adjusted for age at the first T1 session, sex, chronicity of low income in early childhood (the count of years the child lived in a low-income household between the ages 3 and 6), threat (in deprivation models) and deprivation (in threat models). Relationships between mediators and outcomes will additionally be adjusted for income-to-needs ratio and psychiatric symptoms at T1.

C1.3 Missing data

To test the robustness of our findings, we will compare the results using multiple imputation (chain-linked equations) and full-information maximum likelihood estimation (FIML). Non-participation in the T2 psychopathology assessment may be informative – we will weigh the data using inverse probability of censoring weights to avoid bias due to selection.

C1.4 High-dimensional mediation analyses

Adversity exposures, objectively measured mediators, and psychopathology outcomes from 213 mother/child dyads (of 227, 93.8%) from the Deprivation and Threat study will be utilized in this analysis to elucidate whether mechanisms of effects of deprivation and threat on adolescent psychopathology are empirically discernable. Two statistical algorithms built to handle high-dimensional mediation problems will be used to answer the research question. All candidate mediators will be standardized to mean 0 and standard deviation 1 for all subsequent analyses.

First, we will conduct a high-dimensional mediation analysis using a procedure that combines sure independent screening, minimax concave penalized (MCP) regression modeling, and joint significance testing to identify the most salient of task-measured mediators of threat and deprivation as individual exposures, controlling for the other while assessing one as the primary exposure.45 In step 1 of the algorithm, sure independent screening eliminates candidate mediators that are not associated with the outcome.46 Step 2 produces MCP-regularized estimates of coefficients *β1,…,βp* – the coefficients for retained mediators in a joint model for the outcome that is adjusted for the exposure and confounders (refer to Box 1).47 Step 3 produces p-values that safeguard the family-wise error rate at 0.05 using Bonferroni and Benjamini-Hochberg joint significance testing procedures. This statistical approach, executed using the ‘HIMA’ R package, assumes that homogenous mediating mechanisms govern how the effect of an exposure is exuded on an outcome. Indirect effects are computed using the product method, given the following assumptions hold48:

1. Text

   Description automatically generatedThere is no unmeasured confounding of the exposure-outcome relationship
2. There is no unmeasured confounding of the exposure-mediator relationship
3. There is no unmeasured confounding of the mediator-outcome relationships
4. Exposure does not cause any of the mediator-outcome confounders
5. Parametric models (outlined in **Box 1**) are correctly specified
6. There are no exposure-mediator interactions

We will next test the hypothesis that there exist subgroups defined by severity of threat and deprivation exposure across which ELA mediating mechanisms are heterogeneous. To test this hypothesis of heterogeneous mediation, we propose to take one adversity type (deprivation or threat) as the primary exposure and build separate ‘HIMA’ mediation models within high vs low levels of the other exposure to isolate which intermediate phenotypes most saliently mediate the effect of the primary exposure.

Text

Description automatically generatedNext, we will utilize the a novel analysis framework laid out by Xue et al 49 that uses an iterative K-means and difference of convex-smooth gradient descent (DC-SmGD) algorithm to empirically examine heterogeneity of pathways mediating the effects of deprivation and threat. The algorithm takes a pre-specified number of subgroups (*H*) as an input, iteratively clusters observations, and detects mediating mechanisms within the clusters using the novel joint penalty on effects of both the exposure on the mediator and the mediator on the outcome, implemented using convex-smooth gradient descent. The linear structural equation model under heterogeneity, and the heterogeneous sequential ignorability for multiple mediators assumption (HSIMMA) that allows the identification of joint mediated and direct effects in subgroup *h* of 1,…,H, are presented in **Box 2**.

In simulation and in a real-world validation analysis of methylation and PTSD, DC-SmGD outperforms HIMA, finding previously established mediators where HIMA does not.49 The aim is to use a data-driven approach to determine subgroups for which an exposure (e.g. threat) has heterogeneous modes of action on psychopathology. We hypothesize that the effect of threat experienced at low levels of deprivation has a distinct set of mechanisms of action compared to the effects of comorbid threat and deprivation exposures, and congruently, that the effect of deprivation at low levels of threat has distinct mechanisms of action compared to the effects of comorbid threat and deprivation exposures. We are essentially aiming to characterize a Venn diagram of mechanisms relevant to each exposure separately and together. We hope that the empirically-driven identification of subgroups will roughly confirm the results of the high vs. low subgroup HIMA analysis.

C1.5 Potential challenges and alternative approaches

The biggest challenge in the proposed analysis is that the data comes from a small convenience sample, limiting statistical power and generalizability of the results. However, what this data lacks in the number of observations it makes up for by the comprehensive assessment of ELA and cognitive, emotional, and developmental phenotypes. Our use of penalized regression methods will help narrow in on the most powerful mediators from a correlated set. We recognize that including Tanner stage as a candidate mediator may seem incongruent with the other considered mediators. We are motivated to include this variable because a transdiagnostic model of risk and resilience in response to threatening experiences highlights it as one of the key mechanisms by which threat affects psychopathology.42 As a sensitivity analysis, we will remove Tanner stage as a candidate mediator.

Discussion

Analyses conducted for Aim 1 will be novel in two important ways. First, high-dimensional mediation methods will allow for the ranking of importance of correlated mediators, pointing out which emotional, cognitive, and developmental phenotypes from a correlated set most robustly connect childhood threat and deprivation exposures with psychiatric outcomes in adolescence. Second, a multiple mediator approach will build models for outcomes that include the exposure and a collection of relevant mediators, relaxing the assumption that any given mediator is independent of other characteristics impacted by the exposure and in turn impacting the outcome. The last in the set of four no-unmeasured confounding assumptions (listed in section C1.4 below) stipulates that no common cause of the mediator-outcome relationship is affected by the exposure if indirect effects are to be interpreted causally. In other words, it is required that mediators related to those already preconceived in the analysis are not simply conditioned on, because this blocks part of the natural direct effect of the exposure. Thus, conducting an analysis with a comprehensive set of candidate mediators and implementing a shrinkage method to identify those with the strongest indirect effects provides a guardrail against the violation of an assumption necessary for causal interpretation of mediated effects.

SUMMARY OF INTENT

The proposed work will first examine a rich set of characteristics previously found to mediate the relationships between deprivation and threat, two facets of early life adversity, and psychiatric outcomes over the lifecourse. We will then turn our focus to one mediator – earlier pubertal development – that has been shown to be differentially affected by deprivation and threat, and in turn predict elevated risk of psychopathology. One understudied mechanism by which earlier puberty may enact psychosocial harm is prematurely curtailed sleep. We will decompose the total effect of early puberty on adolescent depression symptoms into its natural direct effect and the natural indirect effect through weekday sleep duration. Lastly, we will use data from a natural experiment to explore the heterogeneity of effect of sleep duration on depression outcomes among high school students, with a two-pronged goal of learning about the etiology of depression and informing optimization of delaying high school start times to protect adolescent mental health.

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