Frontolimbic Resting-State Connectivity Mediates the Association Between Early Life Stress and Adolescent Psychopathology

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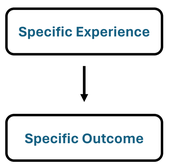
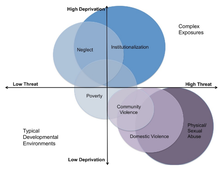
BACKGROUND

- Early environments exert **profound and lasting effects** on children's development and well-being.[1,2]
- Youth growing up in adverse conditions often experience **diverse forms of stress** including poverty, neglect, air pollution, and maltreatment.[3]
- This **multicollinearity** in early exposure has made it difficult to disentangle relations between specific stressors and outcomes, along with underlying psychobiological mechanisms.[4]
- **Frontolimbic functional brain connectivity** is one key pathway that may link early stress exposure and maladaptive developmental outcomes.[5,6]

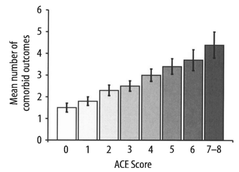
Taxonomic Models of Early Stress:



Specificity [7]



Dimensional [8]



Cumulative Risk [9]

How are various types of early stress differentially related to one another and to outcomes in a longitudinal sample of youth? Does functional connectivity between frontolimbic brain regions mediate these associations?

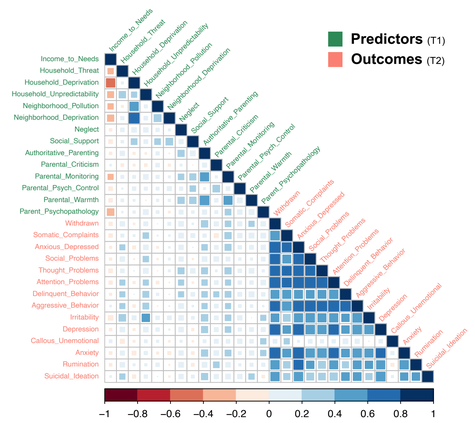
METHODS

- **Sample:** n=186 youth (M_{age}=11.33, 59%F) recruited from the community
- **Baseline (T1):** Traumatic Events Screening Inventory interview (TESI), household SES, parenting behavior, caregiver psychopathology, environmental pollution, neighborhood characteristics, and resting state fMRI scan
- **2-year follow-up (T2) :** self- and parent-reported measures of psychopathology and behavioral difficulties
- **Analyses:**
  - (1) Exploratory factor analyses conducted on measures of stress exposure in childhood and on measures of psychopathology in adolescence
  - (2) Linear regression among obtained latent factors
  - (3) Exploratory mediation analysis of frontolimbic functional connectivity

RESULTS

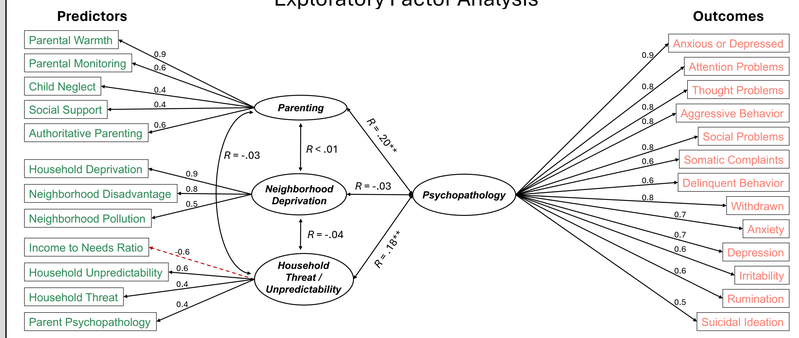
Early Life Stress and Psychopathology

#	Measure	Mean (SD)
[1]	Income to Needs Ratio	1.28 (0.56)
[2]	Household Threat (TESI)	1.18 (1.72)
[3]	Household Deprivation (TESI)	0 (0.72)
[4]	Household Unpredictability (TESI)	4.06 (3.21)
[5]	Neighborhood Pollution (CES)	4.24 (1.29)
[6]	Neighborhood Disadvantage (CES)	3.55 (1.71)
[7]	Child Neglect (MNBS)	2.71 (3.32)
[8]	Social Support (MSPSS)	2.42 (1.09)
[9]	Authoritative Parenting (PAQ)	23.49 (6.32)
[10]	Parental Criticism (PCS)	5.09 (3)
[11]	Parental Monitoring (PMC)	17.26 (4.39)
[12]	Parental Psychological Control (PPC)	20.92 (6.56)
[13]	Parental Warmth (PPC)	21.42 (7.54)
[14]	Parent Psychopathology (ASR)	32.76 (23.82)
[15]	Withdrawn (YSR)	3.24 (2.53)
[16]	Somatic Complaints (YSR)	2.3 (2.69)
[17]	Anxious or Depressed (YSR)	5.22 (5.48)
[18]	Social Problems (YSR)	3.05 (2.46)
[19]	Thought Problems (YSR)	3.23 (2.61)
[20]	Attention Problems (YSR)	5.1 (3.36)
[21]	Delinquent Behavior (YSR)	2.28 (2.17)
[22]	Aggressive Behavior (YSR)	6.81 (4.83)
[23]	Irritability (ARI)	3.35 (2.85)
[24]	Depression (CDI)	2.26 (2.52)
[25]	Callous & Unemotional Traits (ICU)	4.86 (3.54)
[26]	Anxiety (MASC)	19.76 (12.63)
[27]	Rumination (RRS)	19.82 (5.86)
[28]	Suicidal Ideation (SIQ)	6.33 (10.37)



Stress & Outcome Latent Factors

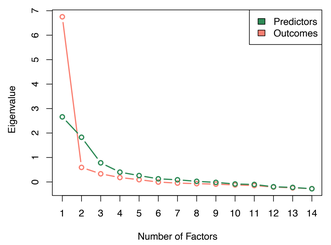
Exploratory Factor Analysis



- Measures of stress were reducible to 3 independent latent factors: '**Parenting**' (α=.58), '**Neighborhood Deprivation**' (α=.77), and '**Household Threat/Unpredictability**' (α=.62) – that were differentially associated with a single outcome factor: '**Psychopathology**' (α=.93)

Latent factors were computed by finding the minimum residual solution with varimax rotation. All factors with loadings >.4 were retained for estimation or factor scores. ** p<.001. PPC Control, PCS, and ICU variables did not load onto any latent factor and were subsequently excluded.

Scree Plot



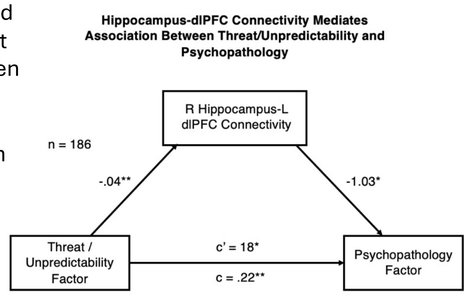
Predictor and Outcome Factors

- Regression analyses indicated that **Parenting** (b=.20, p=.003) and **Household Threat/Unpredictability** (b=.18, p=.007), but not **Neighborhood Deprivation** (b=-.003, p=.647), significantly predicted **Psychopathology.**
- Across all predictor factors, there were no main effects of Age or Sex, or a significant interaction with the predictor.

RESULTS

Household Threat/Unpredictability, Hippocampus-dlPFC Connectivity, and Psychopathology

- Mediation analyses yielded a significant indirect effect for the association between **Household Threat / Unpredictability** and **Psychopathology** through functional connectivity between the **right hippocampus and left dorsolateral prefrontal cortex** (b=.03, p=.036).



DISCUSSION

- Factor analyses of diverse measures of early stress yielded **three distinct factors**. Of these, Parenting and Household Threat/Unpredictability significantly predicted adolescent psychopathology.
- Given the single Psychopathology factor that emerged in our analysis, our results offer **mixed support for categorical models of adversity**, which generally posit distinct relations between classes of stress exposure and domains of adverse outcomes.
- We did, however, find evidence of **mechanistic specificity** in the relation between Household Threat/Unpredictability exposure and **frontolimbic functional connectivity**.
- In the future, researchers might conduct data-driven analyses to identify changes in brain circuitry that are associated with stress exposure. In addition, they might also implement **analytic strategies that are less dependent on co-occurrence** between stressors[10].
- In sum, our results suggest **broad dimensionality** in the relation between stress exposure and psychopathology, warranting further investigation of such dimensions, especially with respect to individual differences and their implications for intervention targets.

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