EARLY LIFE STRESS SETS THE STAGE

Socioemotional and Neurobiological Pathways to Health Problems from Childhood through Adolescence

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Wisconsin Study of Families and Work (WSFW)

- Longitudinal study of child development beginning in 1990

- Recruited 570 pregnant women & their partners from southeast Wisconsin; ~ 400 still participating

- 17 assessments, pregnancy to child age 18 years; multiple levels (social to biological), multiple reporters (parents, teachers, children), and multiple methods (questionnaire, observations, assays, brain imaging)

- Child socioemotional factors assessed beginning in infancy: parental stress (infancy to child age 15); child temperament (infancy to age 9) and cognitive style (age 9 to 18); extrafamilial relationships (teachers/peers; kindergarten thru high school); life events (birth to age 18)
WSFW (continued)

- Child neurobiological factors assessed beginning at age 4.5 years: cortisol (afternoon levels at age 4.5 years; diurnal patterns at ages 9, 11, 13, 15, 18; reactivity at ages 4.5, 7, 9 and 18); ANS reactivity (subsets of children at ages 7 and 9); brain imaging (subsets of adolescents at ages 15 and 18); DNA (ages 15 and 18)

- Mental health symptoms and social and academic functioning assessed 10 times, from kindergarten to age 18 (psychiatric diagnoses on subsets of adolescents at ages 15 and 18)

- Other health behaviors and outcomes (e.g., atopic disorders, sleep behaviors/problems, BMI/obesity, substance use/abuse) assessed at multiple times during salient developmental periods
Sample characteristics at recruitment (1990)

- Mother’s mean age = 29 (range 20 – 43)
- Father’s mean age = 31 (range 20 – 55)
- 95% married
- 40% first-time mothers
- 90% Caucasian
- Family income, median = $45,000 (range $7,500 – over $200,000)
What is the biggest finding?

The powerful and persistent long-term effects of early life stress (ELS) on a variety of health outcomes, and the processes by which this occurs.
**Definition of early life stress (5 domains)**

- **Maternal depression symptoms (CES-D)**
  
  “I felt that I could not shake off the blues even with help from my family or friends”

- **Marital conflict/family anger**
  
  concerned about “arguing or fighting”; “we blame one another for family troubles”

- **Maternal negative parenting**
  
  “I often feel angry with my child”

- **Maternal role overload**
  
  feel “pulled apart by conflicting obligations”

- **Financial stress**
  
  “how much difficulty meeting monthly payments on household bills”
Roadmap

• Developmental timing effects of ELS: Infancy as a sensitive period

• ELS sets up mediational chains, or linkages, through later socioemotional and neurobiological factors to the development of childhood and adolescent health problems

• ELS and child biological sensitivity to context also play important moderating roles
Developmental timing effects
Timing effect of maternal depression on child mental health symptoms in kindergarten

- OR=2.3
- OR=5.0

*Groups defined using symptom levels of clinic-referred children* 

*Essex, Klein, Miech, & Smider, 2001*
Socioemotional and neurobiological mediators in the pathways from ELS to mental health problems
## Potential risk factors in pathways to mental health symptom severity in grade 3

### Table. Potential Risk Factors for Symptom Severity and Directionality in Third Grade (Step 1)*

<table>
<thead>
<tr>
<th>Domain</th>
<th>Prenatal (Second Trimester/Birth)</th>
<th>Infancy (Ages 1, 4, and 12 mo)</th>
<th>Preschool (Ages 3½ and 4½ y)</th>
<th>School Transition (First Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child biology</td>
<td>Sex</td>
<td>Emotional reactivity and regulation:</td>
<td>Physical health:</td>
<td>Receptive language abilities</td>
</tr>
<tr>
<td></td>
<td>Gestational and perinatal</td>
<td>Approach-related negativity</td>
<td>Frequency of illness and</td>
<td>Academic competence</td>
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<tr>
<td></td>
<td>exposures (2)</td>
<td>Withdrawal-related negativity</td>
<td>No. of physician visits</td>
<td>School engagement</td>
</tr>
<tr>
<td></td>
<td>Birth complications (6)</td>
<td>Behavioral dysregulation</td>
<td>Chronic conditions</td>
<td>Prosocial behaviors</td>
</tr>
<tr>
<td>Child cognitive functioning</td>
<td></td>
<td></td>
<td></td>
<td>Social inhibition</td>
</tr>
<tr>
<td>Child emotions and behaviors</td>
<td>Parental age (3)</td>
<td>Paternal involvement (2)</td>
<td>Parental separation/divorce</td>
<td>Asocial behaviors</td>
</tr>
<tr>
<td></td>
<td>No. of children in household</td>
<td>Marital conflict (2)</td>
<td>Family expressed anger (2)</td>
<td></td>
</tr>
<tr>
<td>Family context</td>
<td>Family SES</td>
<td>Parental distress (3)</td>
<td>Maternal negative behaviors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Material family history of</td>
<td>(depression symptoms, role</td>
<td>toward child</td>
<td></td>
</tr>
<tr>
<td></td>
<td>psychopathology (4)</td>
<td>overload, parenting stress, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Material lifetime history of</td>
<td>financial stress)</td>
<td>Parental distress (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>depression</td>
<td></td>
<td>(same as infancy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parental depression symptoms (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School context</td>
<td></td>
<td></td>
<td></td>
<td>Teacher-child relationship (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Peer relations</td>
</tr>
</tbody>
</table>

Abbreviation: SES, socioeconomic status.

*Variables total 56; numbers in parentheses indicate the number of variables for each construct. No parentheses indicates only a single variable.

Essex, Kraemer, et al., 2006
Socioemotional risk factors and developmental pathways: Higher SES

Maternal history of MDD

Parental depression symptoms

Maternal family history of psycho-pathology

Family distress

Symptom severity

-0.17 ± 0.90

(n = 153)

Prenatal

Infancy

Preschool

School Transition

Grade 3

R = 0.475
R² = 0.226

R = 0.556
R² = 0.309

R = 0.626
R² = 0.392

R = 0.713
R² = 0.509

Essex, Kraemer, et al., 2006
Maternal distress

Maternal & child distress and dysregulation

Child social and academic impairment

Symptom severity

R = .301
R² = .091

R = .508
R² = .258

R = .603
R² = .364

(n = 223)

Essex, Kraemer, et al., 2006
Neurobiological mechanisms

- Genetics and epigenetics
- Hypothalamic-pituitary-adrenal (HPA) axis
- Autonomic nervous system (ANS)
- Pubertal hormones and development
- Brain structure and function
Developmental pathway from SES to mental health symptoms: Mediational role of the HPA axis (afternoon cortisol)

Socio-economic status

Early life stress

Afternoon cortisol (age 4½)

Mental health symptom severity, grade 1
(N=282)

Essex, Klein, Cho, & Kalin, 2002
Timing of early life stress and child cortisol at age 4.5 years

Both periods > Never; ** p = .004

Essex, Klein, Cho, & Kalin, 2002
Proposed neural mediating effect

Early life stress → Childhood HPA-axis functioning → Adolescent emotion regulation circuitry → Adolescent mental health problems
Correlation between cortisol at age 4.5 years and resting-state fcMRI to the left amygdala at age 18 years.

Connectivity between the left amygdala and vmPFC is significantly negatively associated with childhood cortisol ($R^2 = 0.38$, FDR-corrected $p = 0.01$).

This effect is driven entirely by females, represented by the magenta data points ($R^2 = 0.63$, FDR-corrected $p = .05$).

Burghy et al., 2012
Moderating effect of gender on the pathway from early life stress to childhood cortisol level to the adolescent brain

Chi² = 1.89, p > .05; RMSEA = .00; SRMR = .03; CFI = 1.00

* p < .05, ** p < .01

Burghy et al., 2012
Correlation of left amygdala-vmPFC rs-FC and concurrent anxiety symptoms in adolescent females

Partial correlation controlling for concurrent symptoms of depression and externalizing behaviors ($R^2 = 0.31$, $p = 0.004$).

Burghy et al., 2012
Moderating effect of gender on the pathway from child cortisol level to the adolescent brain to anxiety symptoms

* p < .05, ** p < .01  
Chi² = 9.95, p > .05; RMSEA = .11; SRMR = .04; CFI = 0.94
What might alter, or moderate, the pathways from ELS to mental health problems?

The importance of considering biological sensitivity to context
Biological sensitivity to context

• The idea that individuals with particular characteristics are more responsive to both adverse and supportive contextual influences, with negative outcomes under conditions of adversity and positive outcomes under conditions of support and protection (Boyce & Ellis, 2005)
• Similar to the notion of differential susceptibility (Belsky & Pluess, 2009)
• In our work, children’s biological sensitivity to context is operationalized as physiological responses (e.g., HPA-axis functioning, cardiovascular reactivity) and/or behavioral responses (e.g., temperamental disinhibition) to environmental conditions (e.g., paternal involvement, teacher–child relationship)
Early father involvement moderates biobehavioral susceptibility to mental health problems in middle childhood

Interaction of inhibition/disinhibition and father involvement.
Slope tests: father involvement low, $\beta = -.467$, $t_{110} = -3.478$, $p = .001$; father involvement high, not significant.

Boyce, Essex, et al., 2006
Biological sensitivity to context, early teacher–child relationship, and adolescent mental health problems

Inhibition/Disinhibition interacts with Grade 1 Teacher–Child Conflict (top panel) and Teacher–Child Closeness (bottom panel) to predict Grade 7 symptom severity, controlling for Grade 1 symptom severity

Essex, Armstrong, et al., 2011
Other potential neurobiological mechanisms
A central component of epigenetics (the expression of genes as opposed to the underlying sequence of DNA) is methylation, in which a chemical group attaches to parts of the DNA — a process that acts like a dimmer on gene function in response to social and physical environments.

Recent data (primarily animal studies) suggest that DNA methylation is involved in the modulation of genome function in response to early life experience (Szyf & Bick, 2013), which may be an important link to numerous disease processes.

DNA from buccal epithelial cells; Illumina array measures methylation within 27,578 cytosine-guanine dinucleotide (CpG) sites representing more than 50% of human genes; FDRs up to 20% were included. N=109
Early pubertal development in females

- Unhealthy weight gain (Bratberg et al., 2007)
- Early initiation of substance use (Dick et al., 2000)
- Early sexual initiation and pregnancy (Deardorff et al., 2005)
- Emotional and behavioral problems (Deardorff et al., 2007)
- Mortality from cardiovascular disease and breast cancer (Colditz & Frazier, 1995; Jacobsen et al., 2009)
The variation in initial and subsequent pubertal tempo (based on integrative puberty composite) as a function of sympathetic nervous system (SNS) reactivity (PEP) and parental supportiveness, controlling for sex. High versus low parental supportiveness only distinguishes pubertal tempo and timing in adolescents with high SNS reactivity.

Ellis et al., 2011
Summary and conclusions
• Early life stress has broad and enduring effects on child and adolescent health outcomes.

• Infancy appears to be a particularly sensitive period, suggesting the importance of early prevention efforts aimed at improving the early caretaking environment.

• However, later developmental periods may be especially important for understanding specific health-related problems (e.g., the family environment during the middle childhood period and early pubertal development).
• The socioemotional factors mediating the association of ELS and child and adolescent health outcomes (e.g., maternal depression, family relations, peer and teacher relations, child emotion reactivity and regulation) suggest potential targets for behavioral interventions.

• The neurobiological mechanisms underlying the association of ELS and child and adolescent health outcomes (e.g., HPA axis, neural functioning, DNA methylation, pubertal development) suggest potential targets for pharmacological as well as behavioral interventions.
• Children vary in their biological sensitivity to context, with those who are more sensitive being more susceptible to both positive and adverse environments.

• The identification and targeting of such children could increase the efficacy of prevention and intervention strategies aimed at improving the key contexts in which children develop.

• Overall, an understanding of the multiple pathways from ELS to health outcomes provides critical information on when, on what, and on whom to intervene.
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On the web

- psychiatry.wisc.edu/essexlab
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