The Childhood Roots of Adult Disease
Exploring the Biology and Psychology of Early Life Stress: Part III

Laura D. Kubzansky, PhD, MPH
Harvard School of Public Health
Center for the Developing Child Colloquium Series
April 15, 2008

Stress and the Toll It Takes on Health

“Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older”

Hans Selye

Toxic Stress and Emotional Problems

Stress

Experiences of discrimination
Exposure to violence
Social isolation
Inadequate resources
Chaotic neighborhoods
Financial strain

Post-traumatic Stress Disorder (6.8% lifetime prevalence, US)

Chronic Distress (range of severity)

Role of Emotion in Coronary Heart Disease

Disease-free
Incidence
Survival

Etiology
Behavior
Triggering
Progression

Depression and Incident CHD: Prospective Epidemiologic Studies

Meta analysis, 2002
Wenger, 2007
Mallon, 2002
Fasbinder, 2002
Wasserthiel-Smoller, 2004
Macari, 2006
Rowan, 2005
Empana, 2005
Egede, 2005
Wulsin, 2005
Sundquist, 2005
Empana, 2006
Kamphuis, 2006
Thurston, 2006
Boyle, 2006
Bohmeier, 2006
Sturmer, 2007

Relative Risk
Anxiety and Incident CHD: Prospective Epidemiologic Studies

Prospective Epidemiologic Studies

Boyle, 2006
Thurston, 2006
Ringback Weitoft, 2005
Albert, 2005
Nicholson, 2005
Yasuda, 2002
Eaker, 2005
Haines, 2001
Kubzansky, 1997
Vogt, 1994
Kawachi, 1994
Kawachi, 1994
Eaker, 1992
Haines, 1987

Anger and Incident CHD
Prospective Epidemiologic Studies

Prospective Epidemiologic Studies

Sturmer, 2006
Boyle, 2006
Eaker, 2004
Chang, 2002
Williams, 2001
Williams, 2000
Kawachi, 1996

Psychosocial vs. Conventional Risk Factors for Acute MI: The INTERHEART Study


Chronic Distress Indicates A Maladaptive Response Pattern

- Physiological coping mechanisms protect body from internal or external stress
- Designed to maintain biological homeostasis during environmental or physiological challenges (allostasis)
- Problems arise when the normal stress response...
  - occurs frequently
  - is not self-limited
  - recurs in response to repeated stressor of same type

Cardiovascular Effects of the Stress Response

From Kawachi et al. Am J Cardiol 1995; 75: 882-885

Anxiety and Heart Rate Variability

From Kawachi et al. Am J Cardiol 1993; 73: 682-685
**Progression of Atherosclerosis by Presence of Sustained Anxiety**

![Graph showing progression of atherosclerosis by presence of sustained anxiety in men and women.](image)

All p values < .07


---

**Acute Emotion and Cardiac Arrest**

- Triggering
- Acute myocardial stunning
- Voodoo death
- Fatal pleasures
- Tako-tsubo cardiomyopathy

---

**Time of onset of myocardial infarction (MI) after an outburst of anger (induction time)**

![Graph showing time of onset of myocardial infarction after an outburst of anger.](image)


---

**Tracing the Origins of (Mal)adaptive Processes: Early Roots of Disease**

- Emotions are functional – enable flexible response to ever-changing environment
- Importance of early life
  - Emotions are biologically basic
  - Emotional response patterns start early
  - Learning to regulate is a major developmental task with consequences for later development and adaptation
- Emotions have a significant neurobiological component

---

**FAR-REACHING EFFECTS OF EARLY LIFE STRESS**

- Impairs capacity to regulate emotion
- Fragile basis for later adaptation
- Chain of risk and cumulative damage

From Wittstein et al. NEJM 2005; 352:539-548
Childhood Emotional Tendencies and Adult Emotional Functioning

Adjusted for SES, sex, race/ethnicity

Childhood Emotional Tendencies and Adult Physical Health

Adjusted for SES, sex, race/ethnicity, child health
From Kubzansky et al., Under review.

The Neurobiology of (Mal)adaptive Emotion Response Patterns

• HPA axis and ‘stress’ hormones***
• Oxytocin, vasopressin
• Telomeres
• Gene X environment interactions
• Gene expression
• Brain function

Future Directions

1a. Can effects of early stress & distress be reversed or attenuated?

1b. How does critical period influence capacity for lifelong learning and plasticity?

Future Directions

2. What are neurobiological mediators?
   – Do biological alterations assessed in periphery provide meaningful information about effects of social stress on the brain?
   – Do early stress-related biological alterations predict subsequent adult health outcomes?
   – Does early stress impose cellular damage and increase rate of aging?

Future Directions

3. What is the role of epigenetic programming and genetic variation in the relationship between early life stress and health?
   – Identify epigenetically activated or silenced genes following early adversity, and their effect on development and health over the life course.
   – Consider impact of genetic variation in genes involved with cellular changes associated with early stress and accelerated aging.
Studying Early Life Stress:
A Cells to Society Approach

Link molecular / cellular information with higher level adaptational processes …
• Molecular mechanisms underlying effects of emotion response patterns
  – How do these get laid down over time?
  – Set up trajectories for future outcomes?
• Translate questions derived from population-based research into experimental studies
  – Elucidate mechanisms
  – Address concerns about reverse causality or spuriousness

Additional Resources

Unnatural Causes: Is Inequality Making Us Sick?
A documentary series on how social circumstances can get under the skin to make us ill.
http://www.unnaturalcauses.org/

RWJ report – FILL IN

WHO report – FILL IN
The Biological Toll of Early Psychosocial Deprivation

Charles A. Nelson III
Children’s Hospital Boston
Harvard Medical School

Context:
Biological Embedding and Developmental Programming
- Biological Embedding – how experience gets under the skin
- Developmental Programming – How pre- and postnatal events shape the life course

Examples of Developmental Programming
(Human and Animal)
- Association between
  - low birth weight + rapid weight gain and later cardiovascular disease and diabetes
  - early maltreatment and later depression and/or antisocial behavior
  - non-optimal maternal care and stress/anxiety in offspring (see next slide)

Stress causes neurons to change...
Which can alter brain function

Effects of Early Psychosocial Deprivation:
Rhesus Monkeys
- Work by Cameron et al. focused on “social bond disruption” in Rhesus monkeys
- Removed animals from their mothers at 1 week, 4 weeks, 12 weeks or 6 months of age.
- Examined variety of behavioral, neurological and genetic outcomes.

Effects on Behavior
- one week separated animals failed to develop social drive; also showed anxious behavior when approached socially by other monkeys; example:
  - animals showed less social contact and activity and more self-comforting behavior in some tasks (autistic-like behaviors).
- one month separated animals manifested other fearful behaviors (e.g., freezing); example:
  - These animals had overactive social drive, and sought constant social contact.
- Behavioral effects persisted through adulthood
Effects on Gene Expression

- Identified 1 gene (GUCY1A3) expressed in amygdala that differentiated 1 week vs. 1 week separated animals
- This gene was positively correlated with acute social comforting behavior and negatively correlated with self-comforting behavior.
- Because adult levels of this gene normally expressed by 1 week of age, this gene may contribute to altered phenotype associated with social bond disruption (via amygdala)

Intervention: Super Mom

- At different points in development, 1 week and 1 month separated animals cross fostered with “super mom” monkeys
- Results: those placed within a few months of separation recover; those placed later do not, or not as much

Conclusions

- Early social bond disruption in monkeys leads to behavioral changes
- Such changes likely mediated by changes in brain, which in turn likely mediated by changes in gene expression
- Hence important to look at epigenetic changes (e.g., see Meaney/Szyf)

Effects of Psychosocial Deprivation: Human Studies

- Bucharest Early Intervention Project:
  - Goal: to examine effects of early institutionalization on brain-behavioral development, and efficacy of foster care as intervention for early institutionalization

What characterizes life in an institution?

...isolation
Experimental Design

- Three groups targeted for study:
  - Institutionalized Group (IG)
  - Foster Care Group (FCG; began life as IG, then randomly assigned to foster care)
  - Never Institutionalized Group (NIG)
- Following baseline, children examined at 9, 18, 30, 42 and 54 months.

Institutionalized Children showed...

- Diminished IQ (mean IQ=~73)
- Impaired language (comparable to IQ)
- High rate of attachment disorders and indiscriminate behavior
- Exceptionally high rate of mental health problems (particularly anxiety)
- Reductions in brain activity (see next slide)

Efficacy of foster care intervention

**BRAIN, COGNITIVE, AND LANGUAGE FUNCTION**

- IQ, EEG improve if child placed <2 years
- Language improves if child placed <15-18 months
- Reduction in disorders of attachment and indiscriminate behavior (if placed before 22 months)

Efficacy of Foster Care (Con’t)

**MENTAL HEALTH**

- Reduction in attachment problems
- Reduction in anxiety (45% to 20%) and depression (8% to 4%)
- But, **NO** reduction in ADHD (20-25% in IG and FCG) or other “externalizing” problems
- Girls suffer less than boys and girls benefit from foster care more than boys
- **Timing of intervention has no impact on mental health recovery**
Social Bond Disruption/Psychosocial Deprivation: Summary

- History of profound early psychosocial deprivation associated with myriad of behavior, neurological and physical sequelae...in both monkeys and humans
- Placement in families (humans)/with super moms (monkeys) leads to dramatic improvements in many domains but appears to be sensitive period for recovery

Biological Mechanism?

- Changes in brain circuitry coupled with changes in gene expression (epigenetic changes) that occur at sensitive or critical developmental stages.
- Some biology can be worked out in primates (human and monkey) but animal (e.g., rodent) model essential

Next Steps

- What is the biological toll of early psychosocial deprivation?
- Goal: To examine
  - Oxidative stress
  - Epigenetic changes
  - Immune function?
  - Telomere length/telomerase activity (next slide)

Caregiver Stress and Accelerated Aging: Telomere Length and Telomerase Activity

- Oxidative stress
- One decade of accelerated aging
- Also, telomere shortening reported with diabetes and CVD

Overall Agenda

- Examine biological sequelae of early psychosocial deprivation
- Examine sensitive periods in altering biological sequelae of deprivation
- Examine associations and causal links among biological, neurological and behavioral outcome measures

The End