Epigenetic effects of early childhood adversity and psychosocial stress

PAS State of the Art Plenary 2013

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W. Thomas Boyce has documented that he has no financial relationships to disclose or conflicts of interest to resolve.
Social partitioning of child health and development (Chen et al, 2002)

Poor children sustain higher rates of acute, chronic and disabling diseases

Poor children have higher cumulative CHD morbidity throughout adulthood

• Conventional mediators of risk (smoking, cholesterol, obesity, BP, etc.) fail to account fully for the SES-health association

• What are then the mediators of social disparities in health?
Socioeconomic partitioning of stressors and adversities

Evans & English, 2002

Poverty

Middle Income

Density
Housing problems
Noise
Family turmoil
Violence
Pervasive differences
in the experiences of everyday life
Variability in developmental outcomes by adversity and SES

Variability may be better explained by individual differences in sensitivity to both positive and negative environments.
1. **Corticotropin releasing hormone (CRH) system**
2. **Locus coeruleus-norepinephrine (LC-NE) system**
Individual differences in biological reactivity to psychological challenge

- Measures of autonomic (LC-NE) and adrenocortical (CRH) reactivity to highly standardized laboratory stressors
  - Impedance cardiography
  - Salivary cortisol
- Broad and reliable individual variability in magnitude and patterns of response
- Internalizing behavior problems
- Respiratory illnesses
- Injury incidence
- Violent injuries in macaques
- Memory for stressful events

- Differential sensitivity to social contexts

Maskrosbarn (Sw): dandelion child
Orkidebarn: orchid child
Supportive

Stressful

Social context

Temperament & behavior (Belsky et al)

CRH and LC-NE systems (Boyce et al)
Differential susceptibility to rearing experience: the case of childcare
(Pluess, Belsky (2009) J Child Psychol Psychiatry)

- Children with high temperamental negativity had either the lowest or highest teacher-reported behavior problems, contingent upon childcare quality
- Child with low negativity relatively unaffected by childcare quality
**Early exposures to microbial products confer protection against atopic diseases.**

**CD14 receptor allelic variation x endotoxin load interaction**

*T* allele diminishes or amplifies sensitization depending on endotoxin exposure

BDNF gene Met allele carriers show highest or lowest basal cortisol expression, depending upon family income

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**Bush, Boyce et al (2013)**

- BDNF Met carrier
- BDNF Val/Val

**Guerra, Martinez (2008)**

- Predicted probability for sensitization
- Endotoxin load (EU m⁻²)

- Early exposures to microbial products confer protection against atopic diseases.
- CD14 receptor allelic variation x endotoxin load interaction
- *T* allele diminishes or amplifies sensitization depending on endotoxin exposure
Temperament & behavior (Belsky et al)

CRH and LC-NE systems (Boyce et al)

• GxE interactions without account of how they happen

GxE (Bush, Martinez, Manuck, van Ijzendoorn et al)
Gene... Environment

THEN A MIRACLE OCCURS:

$G \times E$
Temperament & behavior (Belsky et al)

CRH and LC-NE systems (Boyce et al)

GxE (Bush, Martinez, Manuck, van IJzendoorn et al)

Chromatin modification by epigenetic marks
Risk Alleles of Gene X

Transcription complex

Transcription

mRNA

Translation

protein

Phenotype

Risk for maladaptive phenotype

But risk allele alone usually insufficient to produce maladaptive phenotype!
One possible mechanism is epigenetic.

Maladaptive phenotype only occurs with combination of risk alleles and environmental adversity.
Wisconsin Study of Families and Work
Essex, Boyce, Hertzman & Kobor, 2012

N = 570

Stress:
- depression symptoms
- expressed anger
- parenting stress
- role overload
- financial stress

Infancy

Preschool

Epigenetic profiling:
- Buccal epithelial cells
- Illumina microarray
- ~28,000 CpG sites in 
~14,000 gene promoters

N = 109
Epigenetic vestiges of early developmental adversity

(Essex, Boyce, Kobor, Hertzman et al (2012) Child Dev)

• Differential methylation of multiple CpG sites by parental stress in infancy and preschool

• Mothers’ stressors in infancy more related to differences in methylation for both girls and boys

• Fathers’ stressors in preschool associated with demethylation differences, primarily for girls

• All associations substantial in magnitude, with rho’s in the range of -.60 to .60
Gene-environment interplay

Differences in developmental phenotypes
**FKBP5** gene: four SNPs; produces an immunophilin that operates as chaperone protein to GR

- Alters GR function by decreasing binding and impeding translocation of receptor complex into nucleus
- Risk allele (G→A substitution) interacts with childhood trauma to increase risk of PTSD
- SNPs in **FKBP5** gene produce increased expression and thus diminished GR sensitivity and HPA dysregulation
PTSD Risk and the *FKBP5* Gene

**Risk Alleles of *FKBP5* Gene**

- Promoter
- Transcription complex
- Coding sequence
- Stop

**Transcription**

- mRNA

**Translation**

- *FKBP5*

- Glucocorticoid resistance
- HPA dysregulation

**Adulthood PTSD**
Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions


- Interaction of early trauma exposure and FKBP5 risk allele is a significant predictor of lifetime PTSD
- Consistent with differential susceptibility hypothesis, risk allele is protective in absence of trauma exposure
CRH and LC-NE systems

Temperament & behavior (Belsky et al)

Human metagenome (Slavich & Cole, et al)

CRH and LC-NE systems (Boyce et al)

GxE (Bush, Martinez, Manuck, van IJzendoorn et al)

Chromatin modification by epigenetic marks
A physical *nexus* of gene-environment interplay?
CONCLUSIONS

• Poor children sustain disproportionate burdens of adversity, stress and disease
• Even among poor children, however, there are important individual differences in susceptibility to adversity
• At multiple biological levels—ranging from group ecologies to individual epigenomes—highly reactive children show differential susceptibility to the effects of important, negative and positive social contexts
• GxE interactions appear to be mediated, at least in part, by epigenetic modifications of chromatin structure
• Epigenetic marks may thus constitute a physical nexus of gene-environment interplay
[These observations] suggest that many adult diseases should be viewed as developmental disorders that begin early in life and that persistent health disparities associated with poverty, discrimination, or maltreatment could be reduced by the alleviation of toxic stress in childhood.

Shonkoff, Garner et al (2011)

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