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

-Hans Selye
Stress science meets environmental epidemiology

- Stress exposures (external)
- Quantitative biochemical exposures / aging pathways (internal)
Sources of stress exposure and protection

**Exposures:**

1. **Stressful environments**
   - Low SES -- Noise, crime, low social capital

2. **Objective stressors**
   - Early (Prenatal, abuse/trauma)
   - Chronic stressors

3. **Perceived stress / threat**

**Protection:**

- Maternal care, social connection
- Health behaviors like exercise
The Exposome (partial)

- Pollution toxins
- Poor nutrition
- Substance use
- Health behaviors
- Home
- Neighborhood
- Social relationships
- Stressful events
- Trauma
- Psychological stress

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The Exposome refers to the entire ensemble of environmental exposures that affect an individual's health.
Similar challenges in stress research as environmental epi

• Small relative risks
  – low ‘penetrance’ bt exposure & phenotype
  – Individual variation in responses
• Multi-exposures / multipathway
  – Interactions (within E and G X E)
  – Lack of specificity of markers (vs. adducts)
• Exposures vary over time
  – Need indices of cumulative risk (wear/tear)
  – Need to measure sensitive periods (latent effects)
Roadmap

• How do stress exposures may become biologically embedded?
  1. Allostatic Load
  2. Telomeres
  3. Gene expression

• Critical periods for exposure?

• Interactions: The Stress “G X E”

• Social Exposure Measurement ideas
Adrenal glands

Kidneys
Stress exposures & Aging Pathways?

STRESS AROUSAL
ALLOSTATIC LOAD

Oxidative Stress
Impaired DNA repair
Impaired antioxidant defense

Cell aging (Telomeres)
Gene Expression
Biological Aging pathways:

Allostatic Load
ALLOSTATIC LOAD:
A multi-systems view of life course accumulation of biological wear/tear
An example of an AL Battery
The CARDIA study

• Cardiovascular
  – Heart Rate Variability
  – Blood Pressure

• Immune System
  – C-reactive protein
  – fibrinogen
  – interleukin-6

• Metabolic
  – waist circumference
  – Cholesterol, triglycerides
  – fasting glucose & insulin

• Stress Hormones
  – Urinary epinephrine
  – Urinary norepinephrine
  – Salivary cortisol
Allostatic Load & 7-yr Mortality in the MacArthur Successful Aging Study

p-trend <0.0001

Relative Risk

5

Seeman, et al, 2004, SSM
Social Relationships & Allostatic Load: CARDIA

Seeman et al

Social Ties***
Emotional Support***
Social Conflict***

1st  2nd  3rd  4th quartile
Allostatic Load & Social Environment:

**High load:**
- Low Socio-economic status (reviewed by Dowd et al, 2009)
- Low SES neighborhoods (Bird et al, 2009; Merkin et al, 2009)

**Low Load**
- Greater close social relationships, social integration, having a spouse (for men) (Seeman et al, 2004; Seeman et al, 2002)
Biological Aging pathways:

“Social Regulation of Gene Expression”
Hypothesis  
(Cole, Miller et al)

Given that chronic stress can promote inflammation and glucocorticoid resistance, can we see this at genomic level?

Prediction: High expression of genes with transcripts bearing response elements for NF-kB (vs. glucocorticoids).

Inflammatory signals will be overexpressed across transcriptome, whereas cortisol signals will be muted.
“A Functional Genomic Fingerprint of Chronic Stress in Humans: Blunted Glucocorticoid and Increased NF-KB Signaling”

Miller et al, Biolog Psychiatry, 2008
Altered pattern of Gene Expression in states of:

• Chronic caregiving stress (Miller et al, 2008)
• Loneliness (Cole et al, 2007)
• In adults, low early life SES (Miller et al, 2009)
• In children with asthma, low SES (NF-KB only) (Chen et al, 2009)
Biological Aging pathways:

Telomeres
Cell Aging: Telomeres Length

- **Telomeres**: non-coding sequences capping ends, serving as a “senescence clock” (Blackburn, 1978)
- **Telomerase**: enzyme that prevents telomere shortening, promotes cell resilience.

- “**Psychobiomarker**”: Linked to social status, perceived stress, depression, predictive of mortality (Epel, 2009, Current Directions)
TELOMERE Length CORRELATES WITH HEALTH SPAN AND DISEASE

- Longer telomeres correlate with increased years of healthy life ($\beta = 0.08 \pm 0.04$), $p < 0.03$)
- Shorter telomeres predict:
  - Lower 17-year survival from aggregate of all causes
  - 8.5 fold higher mortality rate from infectious disease
  - 3.2 fold higher mortality rate from heart disease

Rate of TLC predicts CVD death in elderly men

Those men with shortening (dashed line) had 3.0 times greater likelihood of death over the 12 years since the baseline blood draw, compared to those without telomere shortening (solid line).

Epel et al., Aging
TL is related to high perceived stress

Telomeres in the lowest and highest stress quartiles of the whole sample are compared. Controlling for age and body mass index: F(3, 27) = 12.8, p < .001

(Epel, 2004, PNAS)
Telomere Length covaries with exposure to a chronic stressor

Epel, Blackburn et al, 2004
Telomeres are shorter in those with childhood maltreatment

Tyrka et al, 2010
Telomeres track with stress!

Fig. 5: Change in TL by Change in Stress Group

-0.6
-0.4
-0.2
0
0.2
0.4

Increased stress Decreased/No change

Change in Perceived Stress

T(14) = 2.0, p < .03

Unpublished data
TL is impacted by lifestyle, environment

- Psychological stress
  - (Epel, Lin et al, 2004; Damjanovic et al, 2006; Simon et al, 2006; Parks et al, 2009)
- SES (Cherkas et al, 2006)
- Exercise
  - (Cherkas et al, 2006; Werner et al, 2009, Mirabello et al, 2009)
- Omega 3s in the blood
  - (Farzaneh-Far et al, 2010)
- Vitamins from supplements and food
  - (Xu et al, 2009; Mirabello et al, 2009)
Telomere maintenance: a master integrator?

- Life style / Behavioral / Interventions
- Diet, Mental states, Exercise, Medications
- Biochemical Stressors
- Genes

Risks for aging-related diseases/Poor immune function
- Mental disorders
- Cardiovascular disease
- Cancer
- Metabolic disease
Sensitive Periods for stress exposure

The Developmental Origins of Adult Disease
Definition of “Adverse Childhood Experience” (ACE) Scores

ACE score = number of categories endorsed (0-8)

- Emotional Abuse
- Physical Abuse
- Sexual Abuse
- Household Substance Abuse
- Household Mental Illness
- Mother Treated Violently
- Incarcerated Household Member
- Parental Separation

(Anda et al., 2005)
Early Adverse Events

Brain:
• Increased HPA axis response to stress
• Small hippocampal volume
• Vulnerability to depression

Body:
Greater incidence of major diseases
Possibly through epigenetic mechanisms

Reviewed in Shonkoff et al, JAMA, 2009
Low Maternal Nurturing (Rats) and Early Life Abuse (Humans) is Associated with Hyperactive Stress Responses in Adults

**Rats**

Weaver et al., 2005

**Humans**

Heim et al., 2005
Interactions

Exposures with Genes
Serotonin Transporter Genotypes:

s/s, s/l, l/l
Stressful Life Events Increase the Likelihood of Depression

Adapted from: Caspi et al., 2003
Likelihood of Depression as a Function of 5HTT Genotype

Stress Leads to Depression in “Vulnerable” Individuals

Adapted from: Caspi et al., 2003
Wait! Meta-analysis shows no consistency

interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression

AMeta-analysis

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Kung-Yee Liang, PhD
Lindon Eaves, PhD
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Context Substantial resources are being devoted to identify candidate genes for complex mental and behavioral disorders through inclusion of environmental exposures following the report of an interaction between the serotonin transporter linked polymorphic region (5-HTTLPR) and stressful life events on an increased risk of major depression.

Objective To conduct a meta-analysis of the interaction between the serotonin transporter gene and stressful life events on depression using both published data and individual-level original data.

Data Sources Search of PubMed, EMBASE, and PsycINFO databases through March 2009 yielded 26 studies of which 14 met criteria for the meta-analysis.

Study Selection Criteria for studies for the meta-analyses included published data on the association between 5-HTTLPR genotype (SS, SL, or LL), number of stressful life events (0, 1, 2, ≥3) or equivalent, and a categorical measure of depression defined by the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)

Risch et al, JAMA, 2009
Lead Exposure & Stress Reactivity

Pb & SNS reactivity  
(Gump et al, 2007)

Pb and cortisol reactivity  
(Gump et al, 2009)
Measurement of social stress exposures

Tier 1: Exposures (self report)
SES, Life events, chronic stressors, maternal
*Can be retrospective or current*

Tier 2: Perceived stress (Self report)
Response to stressors, impact and chronicity
*Must be tied closely to the event, daily monitoring*

Tier 3: Regulatory systems
Steady state set points & reactivity
Potential methodologies for measuring predictive power of exposome

• Population-based studies with nested design
  – Naturalistic “Burst design” (Nesselroade, 1991)
    • Repeated daily assessments within prospective longitudinal design (Tier 2—exp & response)
  – Standardized lab stressor assessments (Tier 3)
• Women of childbearing age, transmission of risk
Summary

• Stress is not only ‘in the head’
  – Embedded into our environment
  – Gets under the skin
  – Systemic & Molecular measures
    • Telomeres may be cumulative measure

• Key part of exposome
  – Complex additive and interactive effects
  – Can lead to better mechanistic understanding of both individuals and populations
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