The Brain on Stress

How the social environment “gets under the skin”
(Biological embedding over the lifecourse)

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1.0 Germs, Genes and the biomedical model (antibiotics – ie “magic bullets”)

2.0 Multiple risks and the biopsychosocial model (stress, health behaviors, social environment). George Engel Science 1977

3.0 Lifecourse Health Development (epigenetics, context sensitive genes, complex systems biology.)

Missing until now: an understanding of the central role of the brain, its plasticity and vulnerability in brain-body interactions.
Social environment and health
Central Role of the Brain

Protective and Damaging Effects of Stress Mediators

Social environment and health
Stressors

Environmental stressors (work, home, neighborhood)
Major life events
Trauma, abuse

Perceived stress
(threat, no threat)
(helplessness)
(vigilance)

Physiologic responses

Behavioral responses
(fight or flight)
(personal behavior—diet, smoking, drinking, exercise)

Individual differences
(genes, development, experience)

Allostasis

Adaptation

Allostatic load
Types of Stress

Positive Stress
- Exhilaration from a challenge that has a satisfying outcome
- Sense of mastery and control
- Good self esteem
- Healthy brain architecture

Tolerable Stress
- Adverse life events but good social and emotional support
- Sense of mastery and control
- Good self esteem
- Healthy brain architecture

Toxic Stress
- Adverse life events without adequate social and emotional support
- Exacerbated by chaos, abuse, neglect in childhood (ACE)
- Poor social and emotional support
- Unhealthy brain architecture
Social environment and health
Allostasis and allostatic load

Environmental stressors (work, home, neighborhood)

Individual differences (genes, development, experience)

Perceived stress (threat, no threat) (helplessness) (vigilance)

Major life events

Trauma, abuse

Behavioral responses (fight or flight) (personal behavior—diet, smoking, drinking, exercise)

Physiologic responses

Allostasis

Adaptation

Allostatic load
Stress, allostasis and allostatic load

**STRESS**

Many targets for cortisol

**Cortisol**

Acute - enhances immune, Memory, energy replenishment, Cardiovascular function

Chronic - suppresses immune, Memory, promotes bone Mineral loss, muscle wasting; Metabolic syndrome

CRH

AVP

ACTH

Subarachnoid Space

Superior Cerebral Vein

Superior Sagittal Sinus

Achoroid

A.G. - Arachnoid Granulation

Aqueduct of Sylvius

C.C.M. - Cisterna Cerebella-Medullaris

C.I. - Cisterna Interpeduncularis

C.P.L.V. - Choroid Plexus of Lateral Ventricles

C.P.V.3 - Choroid Plexus of 3rd Ventricle

C.P.V.4 - Choroid Plexus of 4th Ventricle

C.S. - Cisterna Superior

D. - Dura Mater

F.L. - Foramen of Luschka

F.M. - Foramen of Magendie

G.C.V. - Great Cerebral Vein

I.F. - Interventricular Foramen (Monro)

S.A.S. - Subarachnoid Space

S.C.V. - Superior Cerebral Vein

S.S.S. - Superior Sagittal Sinus

A.G. - Arachnoid Granulation

S.C.V. - Superior Cerebral Vein

C.P.L.V. - Choroid Plexus of Lateral Ventricles
Mediators of stress and adaptation
NETWORK OF ALLOSTASIS

CNS function
- Cortisol
- DHEA
- Sympathetic
- Parasympathetic

Metabolism
- Inflammatory cytokines
- Anti-inflammatory cytokines
- Oxidative stress

Cardiovascular function

Immune function

Biphasic and non-linear; CO-MORBIDITY

Dysregulation by
- unhealthy lifestyle, toxic chemicals
- feed into network of allostasis
  (eg elevated inflammation, cortisol)
Social environment and health

Health-related behaviors
What we often mean by “stress” is being “stressed out”!

Feeling overwhelmed, out of control, exhausted, anxious, frustrated, angry

What happens to us?

HEALTH-RELATED BEHAVIORS

Sleep deprivation

Eating too much of wrong things, alcohol excess, smoking

Neglecting regular, moderate exercise

All of these contribute to allostatic load

Psychosocial stress is a major factor
Social environment and health
Central Role of the Brain

Lasting effects of the “lived experience” of each individual
McEwen and Getz
Remodeling of neural architecture
In adult as well as developing brain

Dendrites
Shrink and expand

Synapses
Disappear and are replaced

Neurogenesis
Continues in some brain areas
The Human Brain Under Stress
Three Key Brain Areas Under Investigation

Prefrontal cortex
Decision making, working memory, self regulatory behaviors: mood, impulses
Helps shut off the stress response

Hippocampus
Memory of daily events; spatial memory; mood regulation
Helps shut off stress response

Amygdala
Anxiety, fear; aggression
Turns on stress hormones and increases heart rate
Epigenetics
Biological Embedding

“above the genome”

Refers to the gene-environment interactions that bring about the phenotype of an individual.

- Modifications of histones - unfolding/folding of chromatin to expose or hide genes
- Binding of transcription regulators to DNA response elements on genes
- Methylation of cytosine bases in DNA without changing genetic code
- MicroRNA’s – regulate mRNA survival and translation

Effects can extend to next generation
Examples: obesity; parental behavior
http://www.pbs.org/wgbh/nova/sciencenow/3411/02.html

Effects of “non-shared” experiences – eg identical twins
Diverse Mechanisms of Adrenal Steroid Action

Endocannabinoid (eCB)
Glucocorticoid (GC)
Glucocorticoid receptor (GR)

MANY CO-MEDIATORS
Summary: Stress – Good and Bad
Role in Synaptic Function, Adaptive Plasticity and Damage

**Synaptic functions: enhancement**
- Synaptic transmission.
- Long-term potentiation.
- Learning - re: self-preservation

**Synaptic functions: suppression**
- Synaptic transmission.
- Long-term potentiation.
- Learning - less-important things

**Adaptive plasticity ***:**
- Suppression of neurogenesis.
- Mediates dendritic remodeling.

**Loss of resilience**
- Neurochemical distortion
- Impaired remodeling and lack of recovery from stress

**Damage potentiation:**
- Mediates excitotoxicity in seizures, stroke, & head trauma

Adrenal steroids and excitatory amino acids modulate both limbs of inverted U

***Chronic stress: how much protection vs. destabilization?***
Metabolic hormones enter and affect the brain

- Fat hormone
  - Leptin
    - 16 kD
    - Excitability
    - Memory
    - Mood
- Gut hormone
  - Ghrelin
    - 3.5 kD
    - Memory
    - Spines
- Liver hormone
  - IGF-1
    - 7.6 kD
    - Neurogenesis
    - Neuroprotection
- Pancreas hormone
  - Insulin
    - 5.8 kD
    - Glucose transporter
    - Neuroprotection

Metabolic syndrome – affects adolescent as well as adult brain and cognition

Yau...Convit Pediatrics 2012 “Obesity and metabolic syndrome and functional and structural brain impairments in adolescence”
Stress causes neurons to shrink or grow
....but not necessarily to die

Control

Chronic stress

Prefrontal Cortex And Hippocampus

Control

Chronic stress

Amygdala OFC
Plasticity and vulnerability in amygdala and PFC

Amygdala overactive in anxiety and depression

Timed glucocorticoid elevation reduces PTSD symptoms

Effective treatment of chronic anxiety can reduce amygdala volume

Overactive amygdala and underactive PFC input – early CVD

PFC is impaired by perceived stress and circadian disruption

In a study on medical students, high perceived stress associated with reduced cognitive flexibility and reduced functional connectivity within a circuit involving PFC. These alterations are reversible after a vacation.
Social environment and health
Central Role of the Brain

BIOLOGICAL EMBEDDING
Reactive alleles
Epigenetic modifications – transgenerational via DNA and behavior
Biological Embedding
Early Life Experiences

Low socioeconomic status
Poor language skills and executive function
and other effects on learning ability
Hart and Risley “Meaningful Differences”

Chaos in home
- Greater helplessness and distress, poor self regulatory behavior
- Obesity, elevated blood pressure and cardiovascular reactivity

Lasting effects of early life adversity on body fat accumulation, systemic inflammation and poor dental health
Gary Evans, Andrea Danese and Dunedin study, Miller, Chen and Cole

Abuse and neglect; ACE
Impaired lifelong physical and mental health; CVD, metabolic syndrome;
Depression, substance abuse Shorter lifespan
Felitti and Anda; Caspi and Moffitt

“Risky families” – cold, unsupportive, neglect
Many same consequences but not as extensively studied
This may be an increasing problem with ongoing financial and other concerns
Shelley Taylor
Lifecourse Health Development: Past, Present and Future

Neal Halton • Kandyce Larson • Michael Lu • Ericka Tullis • Shirley Russ

THE CHALLENGE – FIND INTERVENTIONS
that “OPEN WINDOWS OF PLASTICITY”
and change brain structure and function

Regular physical activity
Increased hippocampal volume and PFC blood flow
and improved executive function and memory

Mindfulness-Based Stress Reduction
Reducing anxiety decreases amygdala volume

Social support and integration
Experience Corps for elderly volunteers
Improved executive function, PFC blood flow and overall health
Meaning and purpose (eudaimonia)
FOR DISCUSSION
(IF NEEDED)
Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo

- Time course - hours
- Dexamethasone - reduces spine turnover;
- CORT restores
- MR - spine formation and elimination
- GR - spine formation

Higher CORT promotes elimination over formation

In adults as well as in young

All accessible cortical regions

Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance

Conor Liston1,2, Joseph M Cichon1, Freddy Jeanneteau3, Zhengping Jia4, Moses V Chao1 & Wen-Biao Gan1

Nature Neuroscience 2013
Regulation of gene expression:  epigenetics

Stress activates a **core set of genes** but not always in the same direction depending on stress history.

Chronic stress **increases the gene response** to an acute novel stressor.

**Recovery** from chronic stress **alters the pattern** of gene expression.

Acute stress and CORT injection produce some, but minimal, overlap: ie. “stress” is not just CORT and vice versa.

Acute stress activates a **“protective response”** to repress potentially disruptive genetic elements; this response is **diminished** with repeated stress and with aging.

**Individuals with similar genomes** differ in **vulnerability** to stressors and certain gene responses appear to predict that vulnerability.

**Epigenetic factors early in life** appear to be involved.
# Adverse Childhood Experiences (ACE)

ACE FOUND AT ALL SES LEVELS

LASTING EFFECTS ON BRAIN ARCHITECTURE

**Table 10-1. Categories of Adverse Childhood Experiences**

<table>
<thead>
<tr>
<th>Abuse, by Category</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological (by parents)</td>
<td>11%</td>
</tr>
<tr>
<td>Physical (by parents)</td>
<td>28%</td>
</tr>
<tr>
<td>Sexual (anyone)</td>
<td>22%</td>
</tr>
<tr>
<td>Neglect, by Category</td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>15%</td>
</tr>
<tr>
<td>Physical</td>
<td>10%</td>
</tr>
<tr>
<td>Household Dysfunction, by Category</td>
<td></td>
</tr>
<tr>
<td>Alcoholism or drug use in home</td>
<td>27%</td>
</tr>
<tr>
<td>Divorce or loss of biological parent &lt;18</td>
<td>23%</td>
</tr>
<tr>
<td>Depression or mental illness in home</td>
<td>17%</td>
</tr>
<tr>
<td>Mother treated violently</td>
<td>13%</td>
</tr>
<tr>
<td>Imprisoned household member</td>
<td>5%</td>
</tr>
</tbody>
</table>

**The Lifelong Effects of Adverse Childhood Experiences**

> When children are exposed to adversity, their brains are changed in ways that can lead to lifelong changes in behavior and health. By understanding these effects, we can better support children and their families. (Adapted from Felitti, 1998)
ACE in Wisconsin by Income: not just the poor!

Figure 10. Household Income and ACEs

Adverse Childhood Experiences in Wisconsin: Findings from the 2010 Behavioral Risk Factor Survey
Child Abuse Prevention Fund
Some reported brain effects of early life adversity

(Biological Embedding – can they be “reversed” or at least “compensated”?)

Lower SES
- disrupted white matter structure and increased systemic inflammatory tone
- lower volumes of gray matter, tissue in both the frontal and parietal lobes.
- slower trajectories of growth during infancy and early childhood associated with the emergence of disruptive behavioral problems.
- decreased prefrontal cortical gray matter volume - subjective SES ladder;

Lower childhood SES
- adults with lower family income at age 9 exhibited reduced ventrolateral and dorsolateral prefrontal cortex fMRI activity and failure to suppress amygdala activation during effortful regulation of negative emotion at age 24.
- In contrast to childhood income, concurrent adult income was not associated with neural activity during emotion regulation

Prolonged maternal depression for a decade - increased amygdala volume in children.
The Human Hippocampus Under Stress

Contextual, episodic, spatial memory
Mood regulation – target of depression

Hippocampus ATROPHIES in:
• Major depression
• Type 2 diabetes
• Post-traumatic stress disorder
• Cushing’s disease

ALSO as a result of:
• Chronic stress
• Chronic jet lag
• Lack of exercise
• Chronic inflammation
Hippocampus increases in size with:

- Regular exercise
- Intense learning
- Anti-depressant treatment
Obesity and Metabolic Syndrome and Functional and Structural Brain Impairments in Adolescence

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**KEY WORDS**

metabolic syndrome, adolescence, obesity, diffusion tensor imaging, brain abnormalities, cognitive performance, hippocampal volumes, fractional anisotropy

**ABBREVIATIONS**

BP—blood pressure
CRP—C-reactive protein
CSF—cerebrospinal fluid

**WHAT’S KNOWN ON THIS SUBJECT:** Despite the dramatic rise in prevalence of metabolic syndrome (MetS) among children and adolescents, and that MetS is associated with cognitive and brain impairments among adults, no data on the impact of MetS on the brain exist in children.

**WHAT THIS STUDY ADDS:** It provides the first data on the impact of MetS on brain in adolescence. We show reductions in cognitive function and brain structural integrity in nondiabetic adolescents with MetS, thus suggesting that even pre-clinical metabolic illness may give rise to brain complications.

Yau...Convit  Pediatrics 2012 “Obesity and metabolic syndrome and functional and structural brain impairments in adolescence”