Toxic Stress and Brain Development
Understanding Resilience

“Resilience is the ability to achieve a successful outcome in the face of adversity” National Scientific Council on the Developing Child

Bruce S. McEwen, Ph.D.
Alfred E. Mirsky Professor
The Rockefeller University
But we don’t fully understand what it is . . . and how our bodies defend us.

How does all of this stress “get under our skin”?

What does it do to our brain and body? And what can we do about it?
Types of Stress

Positive Stress

• Exhilaration from a challenge that has a satisfying outcome
• Sense of mastery and control
• Good self-esteem
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Tolerable Stress
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Toxic Stress – lack of sense of control
• Poor social and emotional support
• Compromised brain architecture due to early life adversity
• Context-sensitive genotype makes it worse
Conditions/Experiences that “Get Under the Skin” and Dysregulate Physiology

HEALTH DAMAGING BEHAVIORS from being “stressed out”!

• Diet: quality and quantity of food
• Lack of physical activity
• Alcohol
• Smoking

Loneliness

Circadian disruption: jet lag, shift work, sleep deprivation

Ugly, noisy, polluted neighborhood; lack of green space

ALL HAVE EFFECTS, WHETHER OR NOT CALLED “STRESS”
The Brain as a Primary Organ of Stress
Perception and Response

Environmental stressors
(work, home, neighborhood)

Individual differences
(genes, development, experience)

Major life events

Perceived stress
(threat / no threat; helplessness; vigilance)

Physiologic responses

Allostasis

Allostatic load

Trauma, abuse

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

Adaptation

Allostasis and allostatic load: What keeps us alive can also kill us!

The Same Mediators that Allow Us to Adapt Also Cause Damage When Overused and Out of Balance
We Need Cortisol to Stay Alive!

Many targets for cortisol

**Acute** - enhances immunity, memory, energy replenishment, cardiovascular function

**Chronic** - suppresses immunity, memory; promotes bone mineral loss, muscle wasting, metabolic syndrome
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Circadian Rhythm of Cortisol

Morning wakening (gets us going for the day)

A FLAT RHYTHM IS BAD NEWS!

Elevation at night causes obesity and can promote diabetes

- Accelerating Activity
- Decelerating Activity
- Wind Down
- Physical Repair
- Psychological Repair
Wisdom of the Body – If oscillations stop, learning and performance suffers.

Regular Oscillations in Cortisol Levels Promote Dendritic Spine Turnover

(Dr. Conor Liston, Weill Cornell)

Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo

Conor Liston and Wen-Biao Gan

Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance

Conor Liston, Joseph M Cichon, Freddy Jeanneteau, Zhengping Jia, Moses V Chao & Wen-Biao Gan
Stress-related metabolic changes contribute to multiple disorders.
Multi-morbidity

<table>
<thead>
<tr>
<th>Condition</th>
<th>0 other disease</th>
<th>1 other disease</th>
<th>2 other diseases</th>
<th>3+ other diseases</th>
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<td>Renal disease</td>
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<td>Hypertension</td>
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<td>Obesity</td>
<td>893</td>
<td>1350</td>
<td>1149</td>
<td>1509</td>
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</table>

*Multimorbidity in the Norwegian HUNT3 population (48.000)*

Tomasdottir, Getz ... McEwen, et al., 2014
The Brain as a Primary Organ of Stress
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- Environmental stressors (work, home, neighborhood)
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Allostasis and allostatic load: What keeps us alive can also kill us!

Remodeling of Neural Architecture

Dendrites
Shrink and expand

Synapses
Disappear and are replaced

Neurogenesis
Continues in some brain areas
Hippocampus: Target for Stress!
Gateway to discovering hormone actions on the cognitive and emotional brain (1968)

Receptors for glucocorticoids

Adrenal steroid receptors in hippocampus
Steroid autoradiography

Cortisol has biphasic effects on memory and neuron excitability
Important role in mood regulation
Wear and tear over the lifetime: aging, dementia
Dendrites in Hippocampus
Shrink with Chronic Stress But Neurons Do Not Die!

Control

Chronic stress

Magarinos AM, McEwen BS, 1995
Chronic Stress Inhibits Birth of New Neurons

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

- Neurogenesis recovers after chronic stress and is accelerated by physical activity
The Human Hippocampus Under Stress

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

Causes of hippocampus atrophy:
- 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 size **INCREASES** with:

- Regular exercise
- Intense learning
- Anti-depressant treatment
Regular Moderate Exercise
Enlarges the Hippocampus

You are never too young or too old to benefit!!

Exercise training increases size of hippocampus and improves memory

Kirk L. Erickson¹, Michelle W. Voss², Ruchika Shaurya Prakash³, Chandramallika Basak⁴, Amanda Szabo⁵, Laura Chaddock², Jennifer S. Kim², Susie Heo², Heloisa Alves³, Siobhan M. White⁶, Thomas R. Wojcicki⁶, Emily Mailey⁶, Victoria J. Vieira⁶, Stephen A. Martin⁶, Brandt D. Pence⁶, Jeffrey A. Woods⁶, Edward McAuley⁶, and Arthur F. Kramer²,³,¹

Hippocampus

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<th>Baseline</th>
<th>6-months</th>
<th>1-year</th>
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<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Volume (mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
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[Graph showing changes in hippocampus volume over time]
Regular physical activity is the most important behavior that we can do to maintain brain and body health.
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
Chronic stress causes neurons to shrink or grow.

**Prefrontal Cortex & Hippocampus**
- Impaired memory, mood, self-regulation

**Amygdala**
- Increased anxiety and vigilance
Stress, Glucocorticoids and the Basolateral Amygdala

Chronic stress - expansion of dendrites; increased spine density; increased anxiety

Acute traumatic stressor
- delayed increase in spine density
- delayed increase in anxiety
- can be prevented by CORT elevation during or right after trauma

In humans
CORT elevation during or after trauma reduces PTSD symptoms

Shona Chattarji
Prefrontal cortex - stress and aging

Medial PFC neurons - dendrite shrink with chronic stress

Orbitofrontal cortex neurons – dendrite expand with chronic stress

Recovery of dendrites impaired with aging

Jason Radley, Conor Liston, Erik Bloss

In a study on medical students, high perceived stress - associated with reduced cognitive flexibility - reduced functional connectivity involving PFC.

These alterations are reversible after a vacation.

John Morrison

Conor Liston, B.J. Casey
Social Environment and Health

- Environmental stressors (work, home, neighborhood)
- Individual differences (genes, development, experience)
- Major life events
- Perceived stress (threat / no threat; helplessness; vigilance)
- Physiologic responses
- Allostasis
- Trauma, abuse
- Behavioral responses (fight or flight; personal behavior – diet, smoking, drinking, exercise)
- Allostatic load
- Adaptation

Role of Early Life Stress
Developmental Issues for Children

Chaos in Home

- Greater helplessness and distress, poor self-regulatory behavior
- Brain development: prefrontal cortex development is altered
- Obesity, elevated blood pressure, and cardiovascular reactivity

Adverse Childhood Experience – Abuse, Neglect, Poverty

- Increases depression, substance abuse, antisocial behavior, cardiovascular disease, obesity
- Brain structure is altered for greater vigilance and anxiety
The Three D’s of Insulin Resistance

- Dementia
- Diabetes
- Depression

The Human Brain Under Stress
Developmental effects on hippocampus

Hippocampus
Contextual, episodic, spatial memory

Is smaller in
- Poverty
- Low self esteem
- Risk for PTSD

Amygdala
Hippocampus
The Human Brain Under Stress
Developmental effects on amygdala

Amygdala
- Emotion, fear, anxiety,
- Aggression
- Larger and more active in depression, anxiety disorders
- Larger in children living with a depressed mother
The Human Brain Under Stress
Developmental effects on prefrontal cortex

Prefrontal cortex
Decision making, working memory,
Self regulatory behaviors: mood, impulses
Underdeveloped with chaos of poverty, early life abuse

Amygdala
Hippocampus
"WE CANNOT ROLL BACK THE CLOCK!"

Changing the direction of the life course

From Halfon et al 2014

Positive vs Negative Direction

[Diagram showing stages of life course with various factors affecting health development]
PREVENTION
NURSE-FAMILY PARTNERSHIP

BEGINNING WITH TRUST, ENDING WITH EXTRAORDINARY OUTCOMES.
NURSE-FAMILY PARTNERSHIP® IS A COMMUNITY HEALTH PROGRAM THAT TRULY CHANGES LIVES – FOR GENERATIONS TO COME.

260,000+ FAMILIES SERVED

42 STATES

5X $ RETURN
Every $1 invested in NFP saves $5.70 in future costs

https://www.nursefamilypartnership.org/about/

https://developingchild.harvard.edu/science/national-scientific-council-on-the-developing-child/
Looking to the Future

The adult brain shows plasticity and we are only beginning to recognize its potential!

Dendrites
Shrink and expand

Synapses
Disappear and are replaced

Neurogenesis
Continues in some brain areas
PREVENTION OF HIPPOCAMPAL SHRINKAGE AND DEPRESSIVE BEHAVIOR

7 weeks of intensive intervention at age 11
Protection evident at age 25!!!
INTERVENTIONS TO PROMOTE RESILIENCE 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)
Structural plasticity of the social brain: Differential change after socio-affective and cognitive mental training

Sofie L. Vaalk, Boris C. Bernhardt, Fynn-Mathis Trautwein, Anne Böckler, Philipp Kanske, Nicolas Guizard, D. Louis Collins, Tania Singer

C Overall cortical thinning in retest controls over 9-month period

D Module-specific training-related cortical thickness increases

E Average cortical thickness change in module-specific clusters for all cohorts
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Robert Paul Juster

**Neuroimmune and inflammation Program**
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**Adelaide Acquaviva**
Maryse Aubourg
Halina Korsun

**HOPE FOR DEPRESSION RESEARCH FOUNDATION**
MacArthur Research Network for Socioeconomic Status and Health; National Scientific Council for the Developing Child