The Resilient Brain: Epigenetics, Stress and the Lifecourse

And how the social and physical environments gets "under the skin"

"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 and Head, Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology,
The Rockefeller University, NY, NY, USA

I declare that I have no potential conflicts of interest

We All Experience "Stress"

But we don't fully understand what it is . . . and how our bodies defend us.

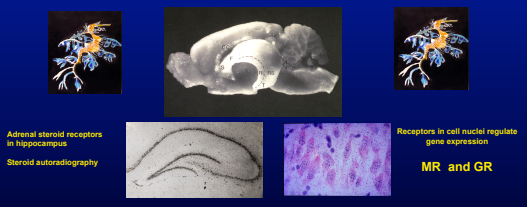
How does all of this stress "get under our skin"?

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

Hippocampus: Target for Stress!

Gateway to discovering hormone actions on the cognitive and emotional brain (1968)

Receptors for glucocorticoids



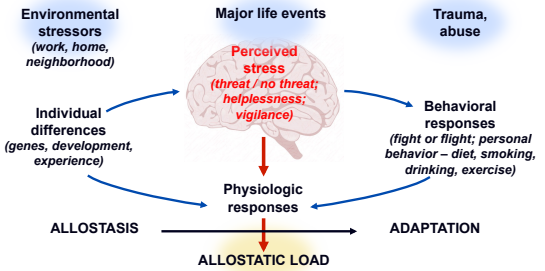
Cortisol has biphasic effects on memory and neuron excitability

Important role in mood regulation

Wear and tear over the lifetime: aging , dementia

The Brain as a Primary Organ of Stress

Perception and Response



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

McEwen, *New England Journal of Medicine* 1998

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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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*

Adaptation to Experiences

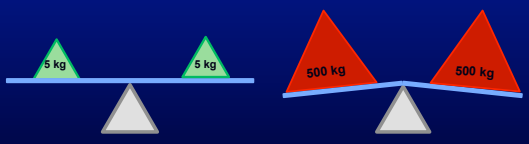
"allostasis"

Allostasis, the active process that promotes adaptation, emphasizes anticipation, prediction

Sterling, P., Eyer, J., 1988. Allostasis: A New Paradigm to Explain Arousal Pathology, in: Fisher, S., Reason, J. (Eds.), Handbook of Life Stress, Cognition and Health. John Wiley & Sons, New York, pp. 629-649.

Sterling, P., 2014. Homeostasis vs allostasis: implications for brain function and mental disorders. JAMA Psychiatry 71, 1192-1193.

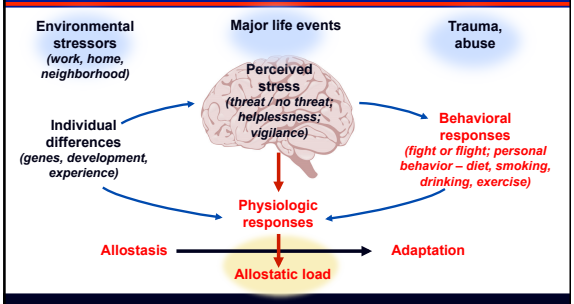
The Same Mediators that Allow Us to Adapt Also Cause Damage When Overused and Out of Balance



Allostatic Load

The Brain as a Primary Organ of Stress

Perception and Response



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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

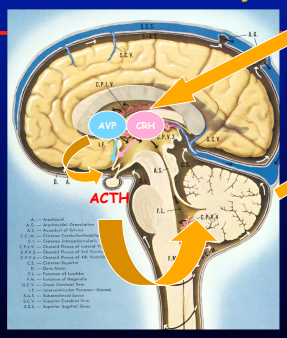
Circadian disruption: jet lag, shift work, sleep deprivation

Ugly, noisy, polluted neighborhood; lack of green space

ALL HAVE EFFECTS, WHETHER OR NOT CALLED "STRESS"

We Need Cortisol to Stay Alive!

STRESS



Many targets for cortisol

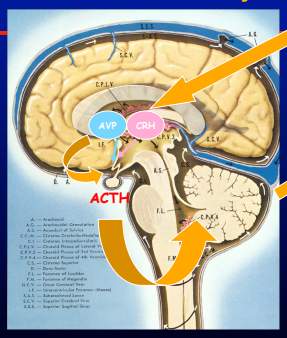
Cortisol

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

Chronic - suppresses immunity, memory; promotes bone mineral loss, muscle wasting, metabolic syndrome

We Need Cortisol to Stay Alive!

STRESS



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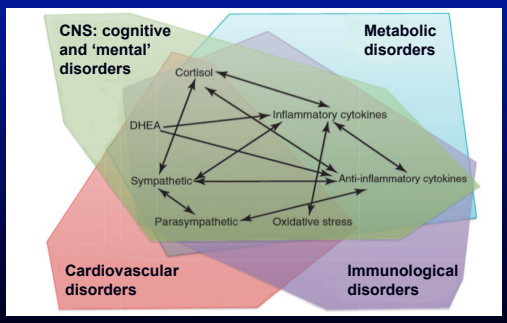
More than Cortisol

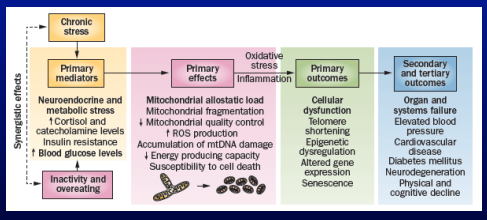
Mediators of Allostasis and System-wide Effects



Stress-related metabolic changes contribute to multiple disorders.

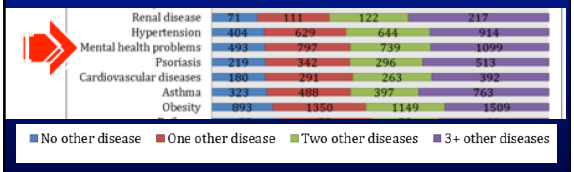
Mitochondrial allostatic load

Martin Picard, Robert-Paul Juster and Bruce S. McEwen



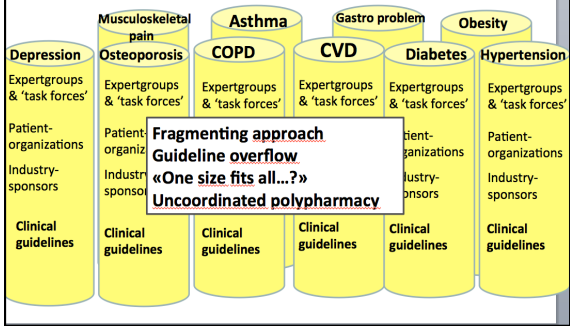
The stress–disease cascade and mitochondrial allostatic load. Allostatic load is a pathophysiological process in which multisystem biological dysregulation caused by chronic stress synergizes with unhealthy behaviours.

Multi-morbidity



Multimorbidity in the Norwegian HUNT3 population (48.000)
Tomasdottir, Getz ... McEwen, et al., 2014

«SILO MEDICINE»



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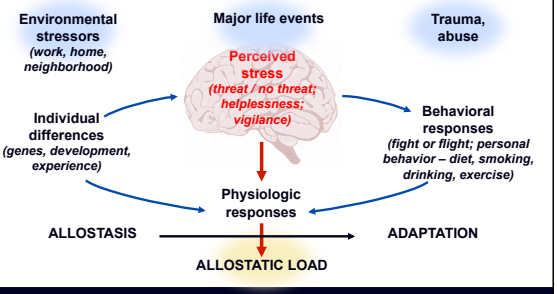

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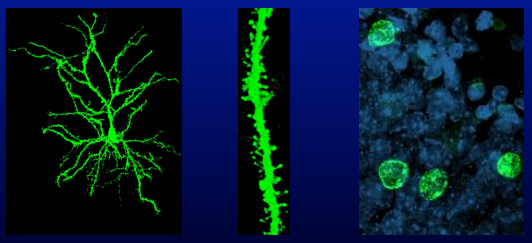
Remodeling of Neural Architecture

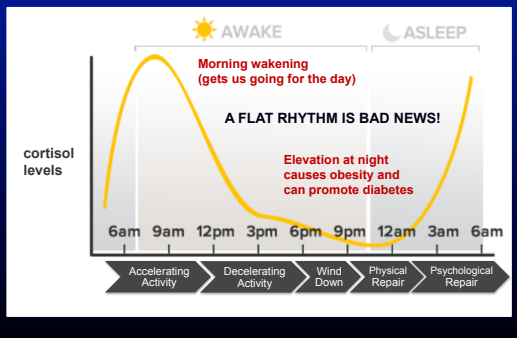


Dendrites
Shrink and expand

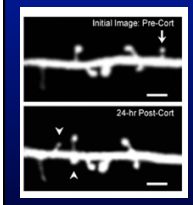
Synapses
Disappear and are replaced

Neurogenesis
Continues in some brain areas

Circadian Rhythm of Cortisol



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[4,5] and Wen-Biao Gan[4,5]

Wisdom of the Body **– If oscillations stop, learning and performance suffers.**

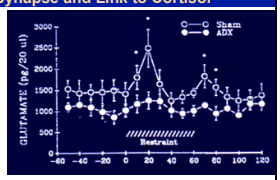
Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance

Conor Liston[1,2], Joseph M Cichon[1], Freddy Jeanneteau[3], Zhengping Jia[4], Moses V Chao[1] & Wen-Biao Gan[1]

The Stressed Glutamatergic Synapse and Link to Cortisol

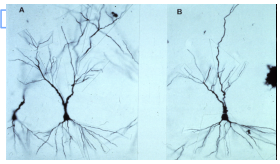
Stress induces strong elevation of extracellular glutamate levels that is dependent on adrenal glands

Mineralocorticoid receptors are indispensable for nonngenomic modulation of hippocampal glutamate transmission by corticosterone



Lowy M,Gault L,Yamamoto BK,'93

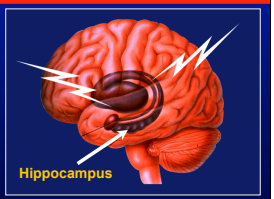
Chronic stress effects on dendritic remodeling are blocked by blocking NMDA receptors, as well as blocking adrenal steroid synthesis

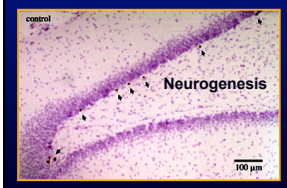


Chronic Stress Inhibits Birth of New Neurons

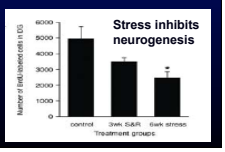
Hippocampus

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



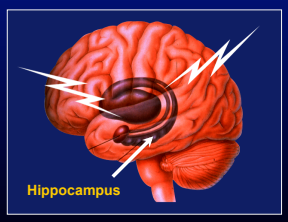


- Neurogenesis recovers after chronic stress and is accelerated by physical activity



The Human Hippocampus Under Stress

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

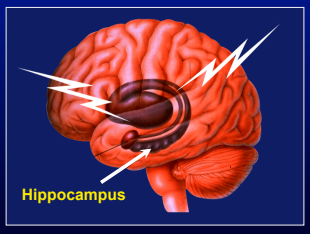


Causes of hippocampus *ATROPHY* :
- Major depression
- Type 2 diabetes
- Post-traumatic stress disorder
- Cushing's disease

ALSO as a result of:
- Chronic stress
- Chronic jet lag
- Lack of exercise
- Chronic inflammation

The Human Hippocampus Under Stress
The Positive Side of the Story

Hippocampus size *INCREASES* with:
- Regular exercise
- Intense learning
- Anti-depressant treatment

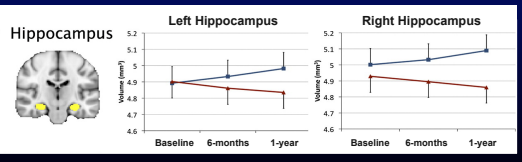


Regular Moderate Exercise Enlarges the Hippocampus

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

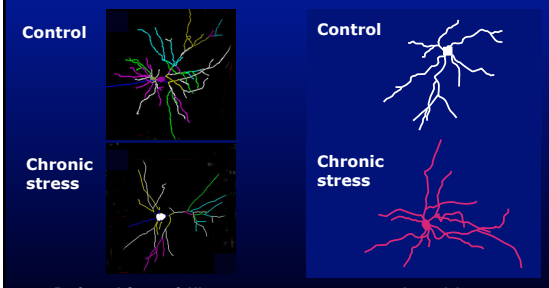
Exercise training increases size of hippocampus and improves memory

Kirk I. Erickson[a], Michelle W. Voss[b,c], Ruchika Shaurya Prakash[d], Chandramallika Basak[e], Amanda Szabo[f], Laura Chaddock[b,c], Jennifer S. Kim[b], Susie Heo[b,c], Heloisa Alves[b,c], Siobhan M. White[f], Thomas R. Wojcicki[f], Emily Mailey[f], Victoria J. Vieira[f], Stephen A. Martin[f], Brandt D. Pence[f], Jeffrey A. Woods[f], Edward McAuley[b,f], and Arthur F. Kramer[b,c,1]



Regular physical activity is the most important behavior that we can do to maintain brain and body health.

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

Shona Chattarji

In humans

CORT elevation during or after trauma reduces PTSD symptoms

Prefrontal cortex - stress and aging

Medial PFC neurons - dendrite shrink with chronic stress

Orbitofronal cortex neurons – dendrite expand with chronic stress

Recovery of dendrites impaired with aging

Jason Radley, Conor Liston, Erik Bloss

John Morrison

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

These alterations recover - after a vacation.

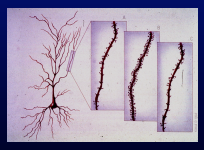
Conor Liston, B.J. Casey

Sex Hormone Action and Sex Differences in the Brain

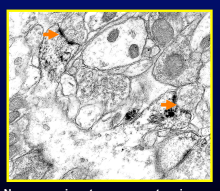
The entire brain has receptors for sex hormones in both male and female

Many of these receptors mediate non-genomic effects on cytoskeleton, neurotransmitter release, mitochondrial function.

Sex differences involve not only hormonal programming but also X and Y chromosomes and mitochondrial DNA inherited from the mother



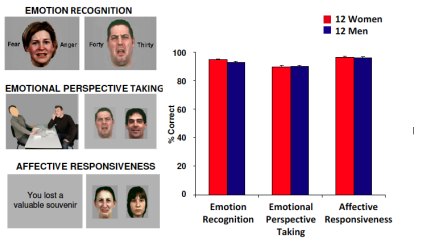
Synapse turnover in estrous cycle



Non-genomic estrogen receptors in synapses

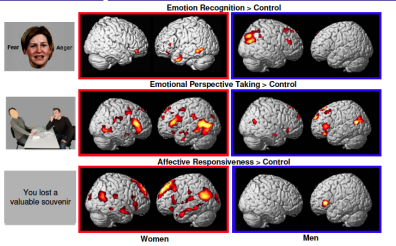
Men and women do equally well on this test….

Measurement of Empathy



Derntl, Finkelmeyer, Eickhoff, Kellermann, Falkenberg, Schneider & Habel, PNEC, 2010

Measurement of Empathy



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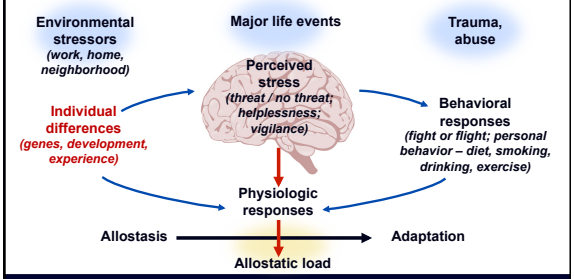
Social Environment and Health



Role of Early Life Stress

Developmental Issues for Children

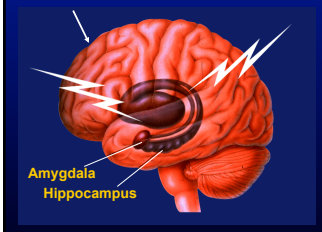
Chaos in Home

- 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 Human Brain Under Stress
Developmental effects on hippocampus

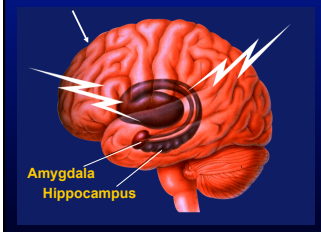


Hippocampus

Contextual, episodic, spatial memory

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

The Human Brain Under Stress
Developmental effects on amygdala



Amygdala

Emotion, fear, anxiety, Aggression

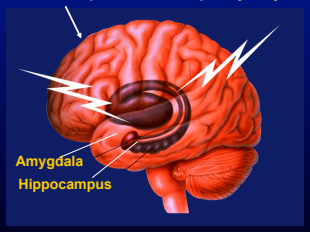
Larger and more active in depression, anxiety disorders

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

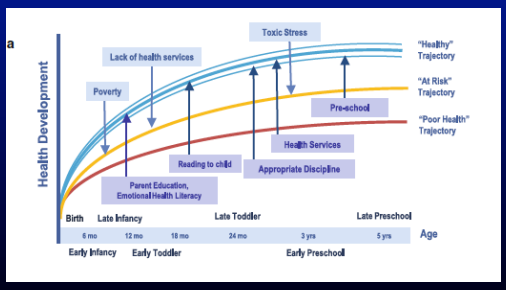


"WE CANNOT ROLL BACK THE CLOCK!"

Changing the direction of the life course

From Halfon et al 2014

Positive vs Negative Direction



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
Erickson, Kramer and colleagues Proc Natl Acad Sci U S A. 2011 108:3017-22

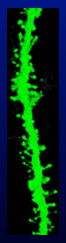
Mindfulness-Based Stress Reduction
Reducing anxiety decreases amygdala volume
Holzel …Lazar. Soc Cogn Affect Neurosci. 2010 5:11-17 .

Social support and integration
Experience Corps for elderly volunteers
Improved executive function, PFC blood flow and overall health
Carlson, Erickson, Kramer, Seeman, Fried, J Gerontol A Biol Sci Med Sci. 2009 64:1275-82.
Meaning and purpose (eudaimonia)

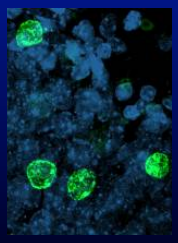
Looking to the Future

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

Stress Colleagues and Collaborators

Leiden University
- Nicole Datson
- Ron de Kloet

Medical College of Wisconsin
- Cecilia Hillard

- Paolo de Angelis
- Josh Kogan
- Hilary Lambert
- Gordon Petty
- Todd Rubin
- Dani Zelli

- Adelaide Acquaviva
- Maryse Aubourg
- Halina Korsun

Neuroimmune and inflammation Program
- Dr. Karen Bulloch

The stress group
- Benedetta Bigio
- Nicole Bowles
- Lisa Eiland
- Jason Gray
- Matt Hill
- Richard Hunter
- Ilia Karatsoreos
- Yoav Litvin
- Jordan Marrocco
- Melinda Miller
- Carla Nasca
- Constantine Pavlides
- Ana Pereira

Weill/Cornell
- Kevin Bath
- B.J. Casey
- Francis Lee
- Conor Liston
- Teri Milner

NYU
- Joe Ledoux

Stanford University
- Natalie Rasgon

Columbia University
- Martin Picard
- Robert Paul Juster

Mt. Sinai Schl Med
- Erik Bloss
- Deena Goldwater
- Patrick Hof
- John Morrison
- Jason Radley
- Rebecca Shansky

National Centre for Biological Sciences (Bangalore)
- Sumantra Chattarji
- Rajnish Rao

MacArthur Research Network for Socioeconomic Status and Health;

National Scientific Council for the Developing Child