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

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?

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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Types of 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

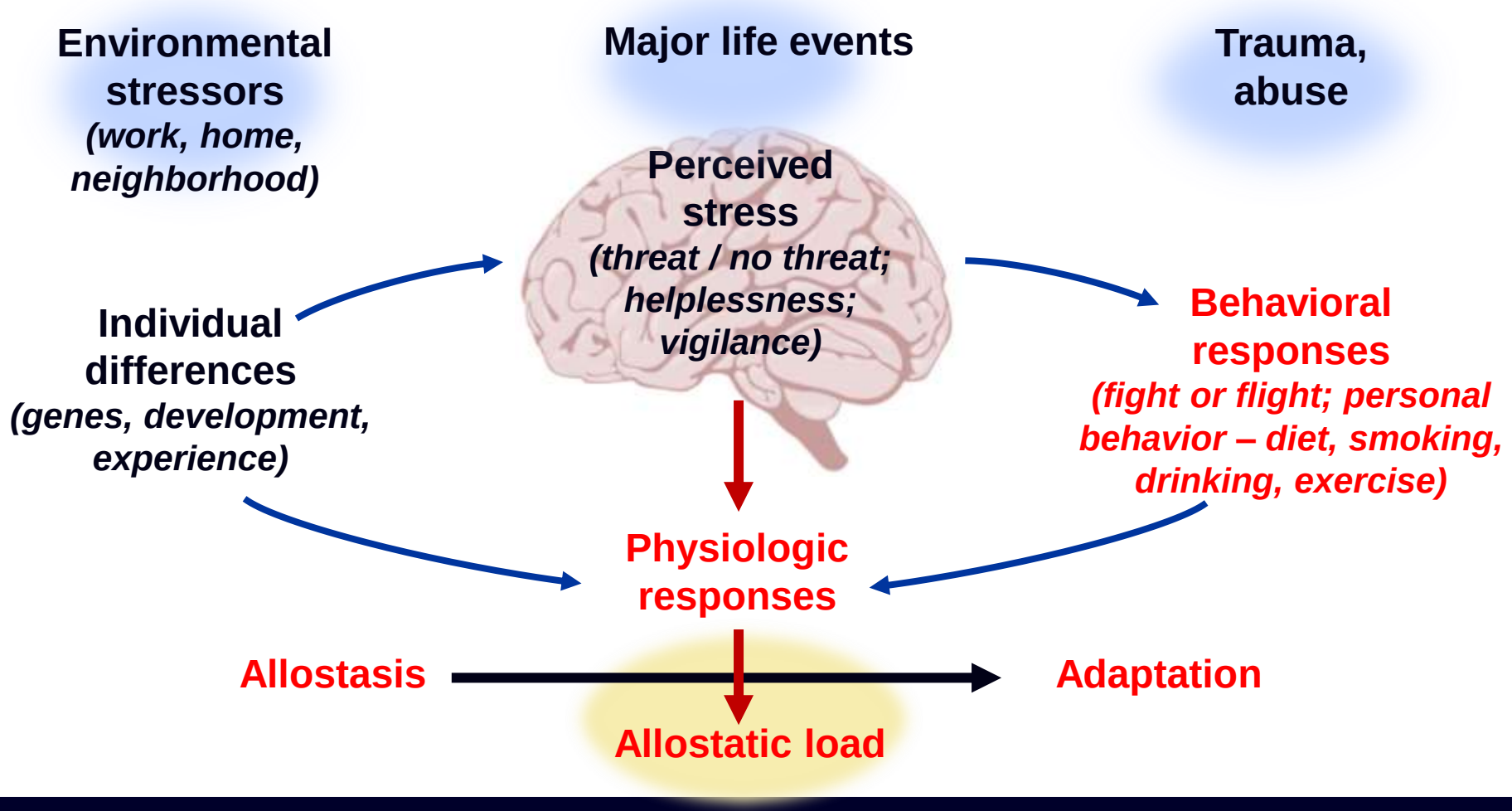
Circadian disruption: jet lag, shift work, sleep deprivation

Ugly, noisy, polluted neighborhood; lack of green space

ALL HAVE EFFECTS, WHETHER OR NOT CALLED "STRESS"

The Brain as a Primary Organ of Stress

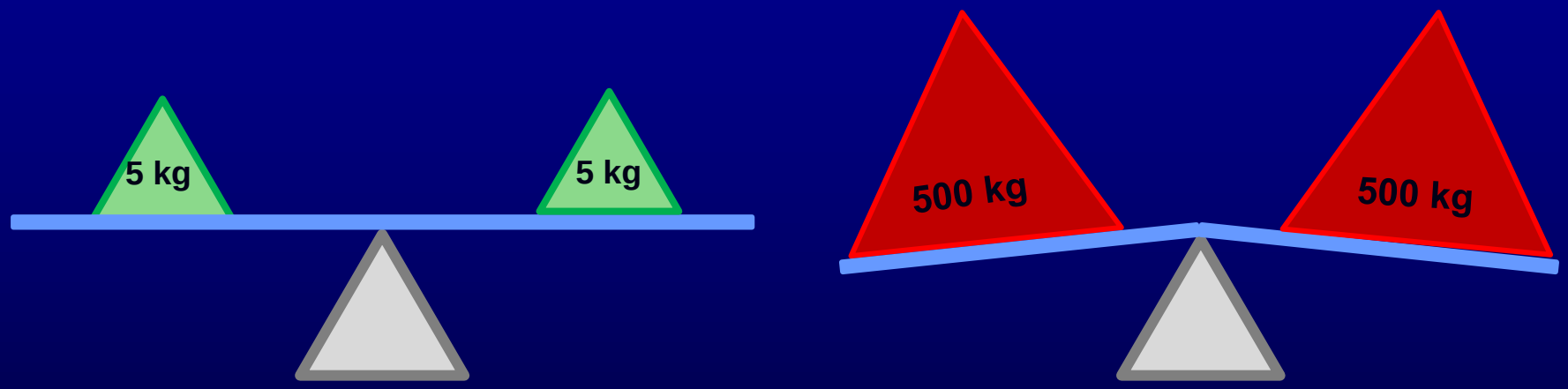
Perception and Response



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

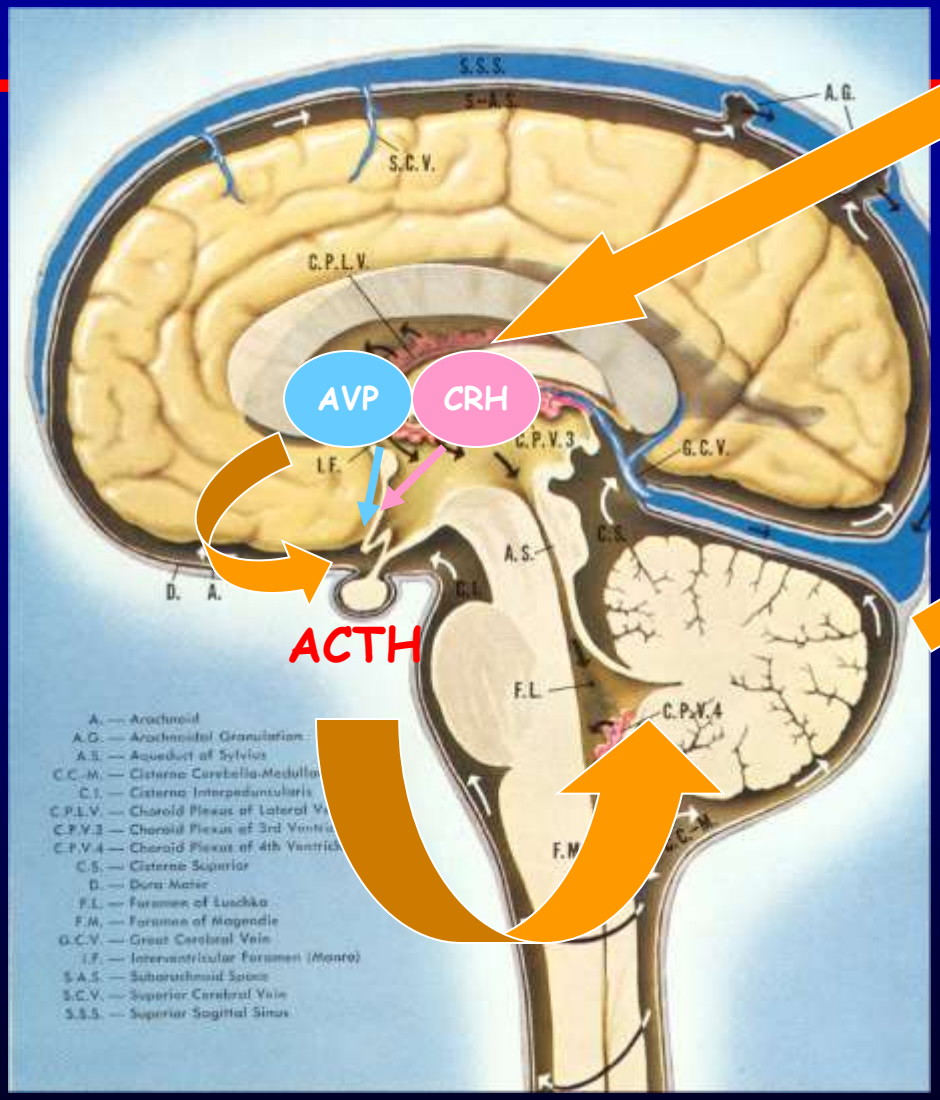
McEwen, *New England Journal of Medicine* 1998

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



Allostatic Load

We Need Cortisol to Stay Alive!



STRESS

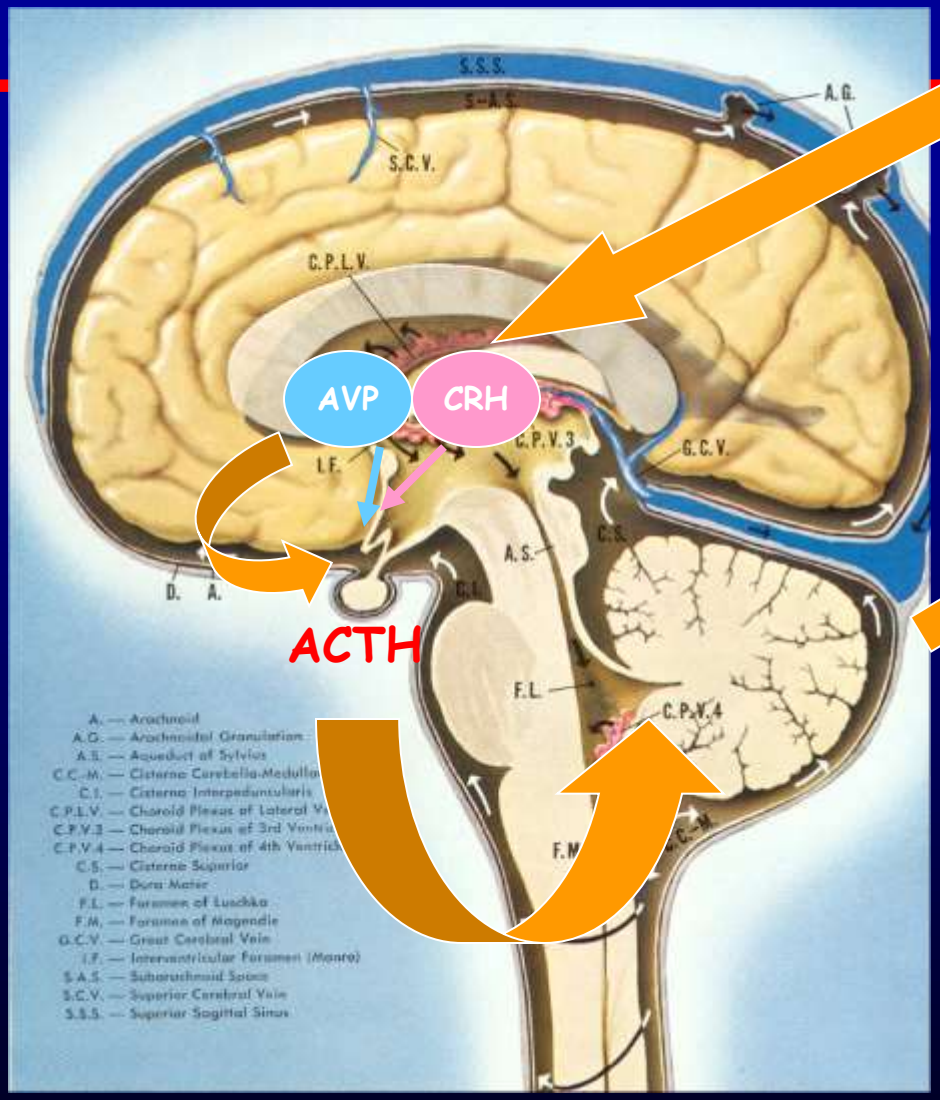
Many targets for cortisol

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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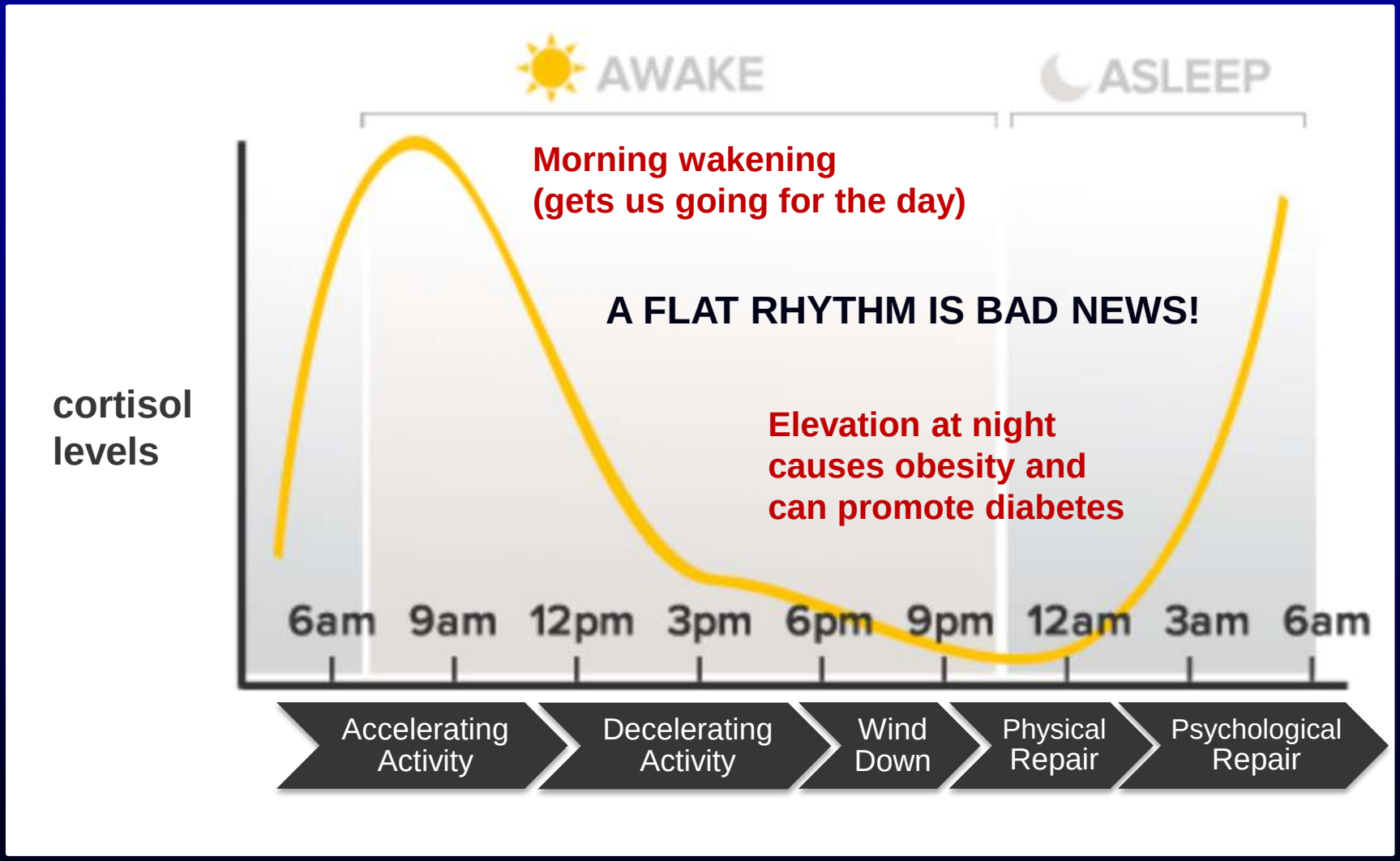
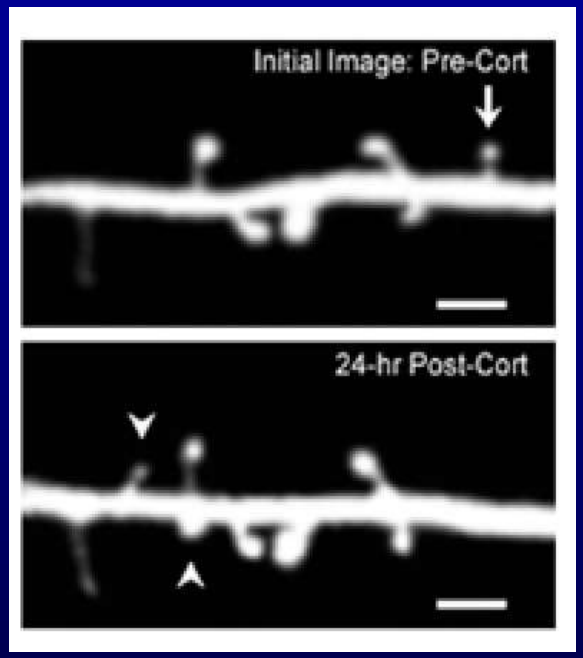
Circadian Rhythm of Cortisol



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[a,b,1] and Wen-Biao Gan[a,1]

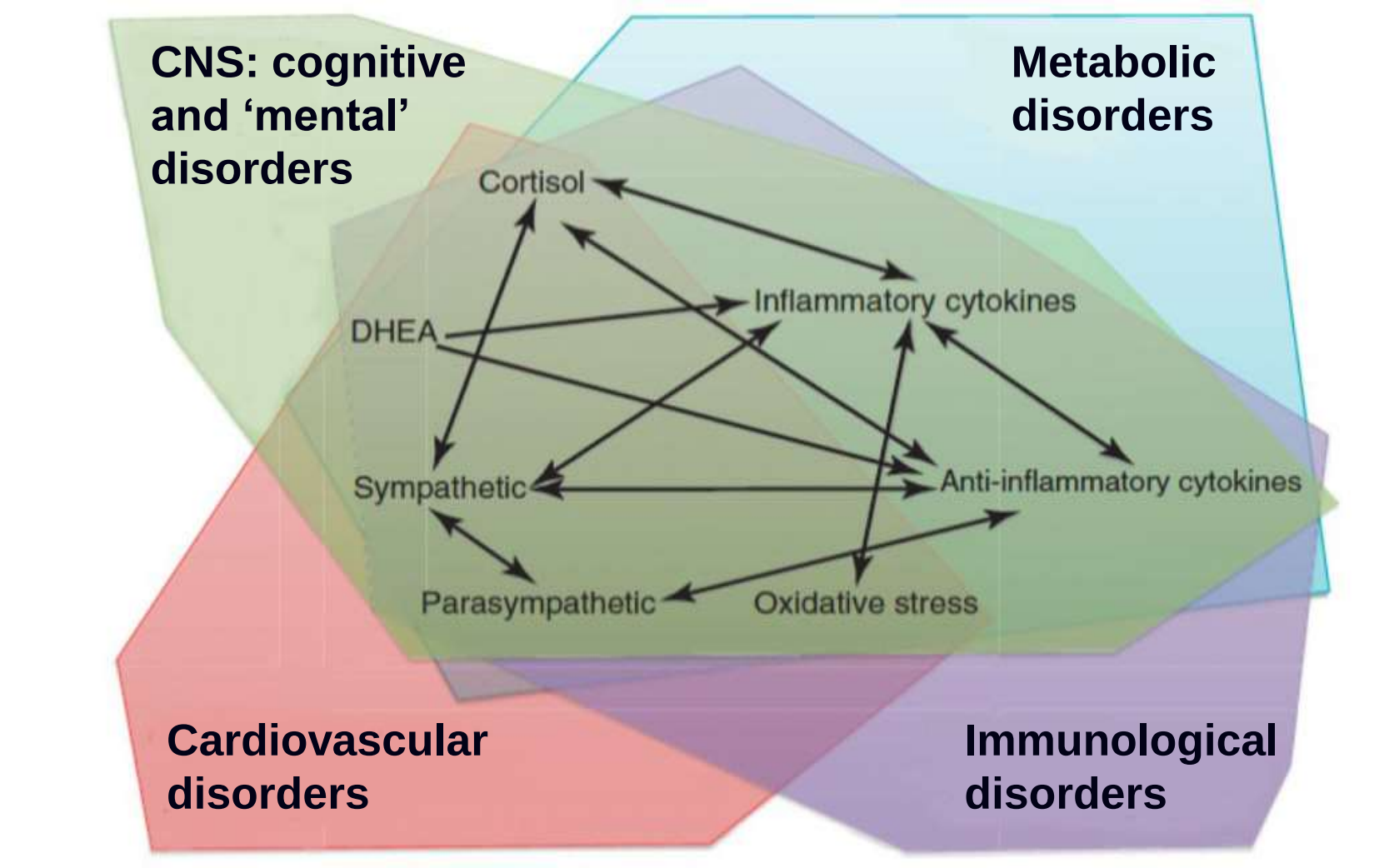
***Wisdom of the Body* – If oscillations stop, learning and performance suffers.**

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]

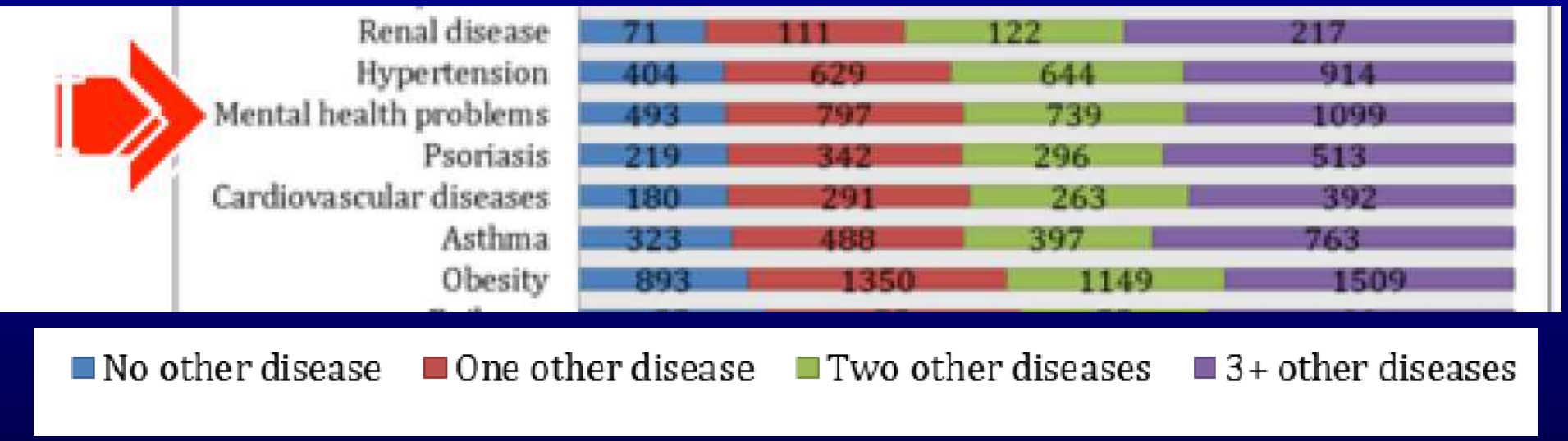
More than Cortisol

Mediators of Allostasis and System-wide Effects



Stress-related metabolic changes contribute to multiple disorders.

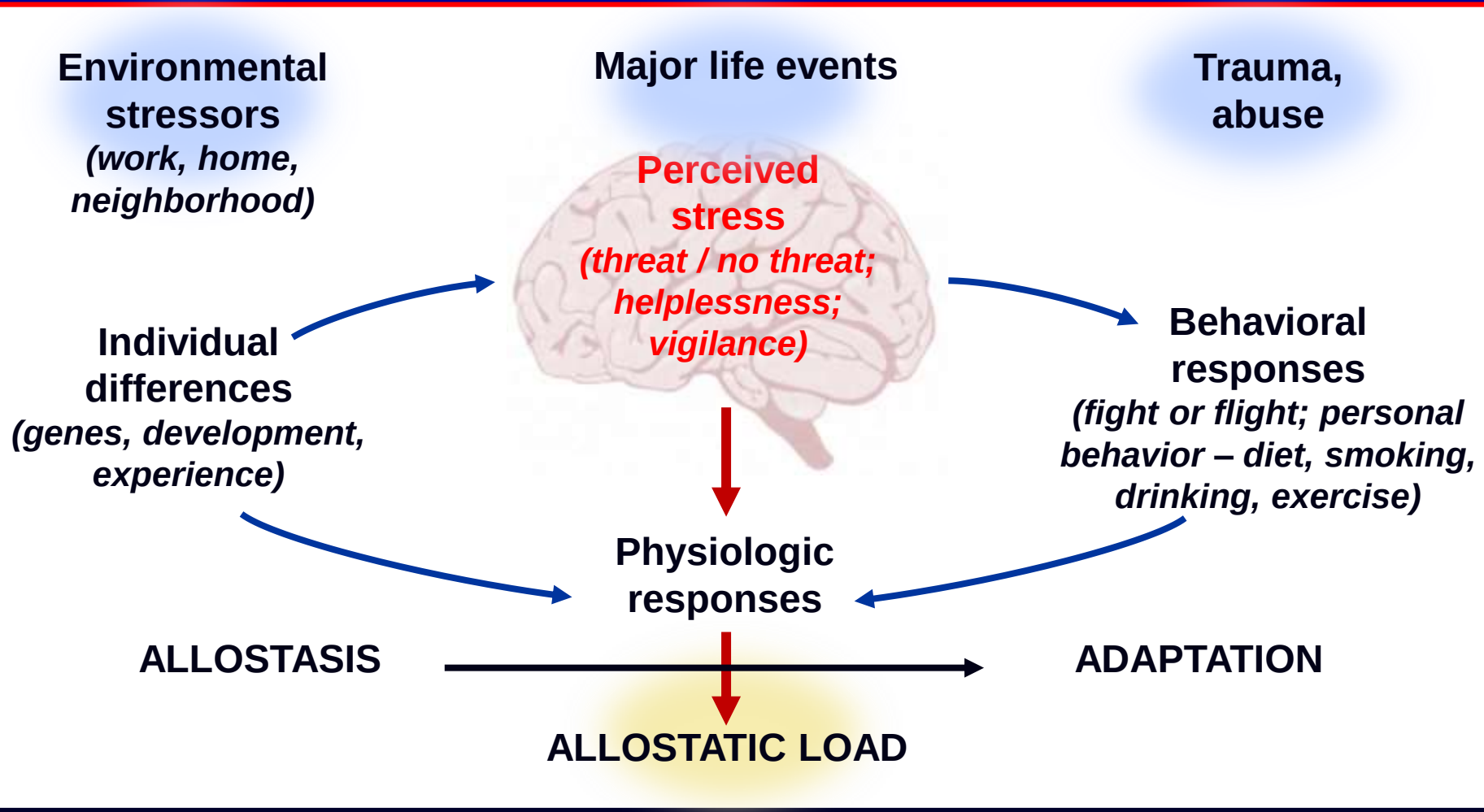
Multi-morbidity



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

The Brain as a Primary Organ of Stress

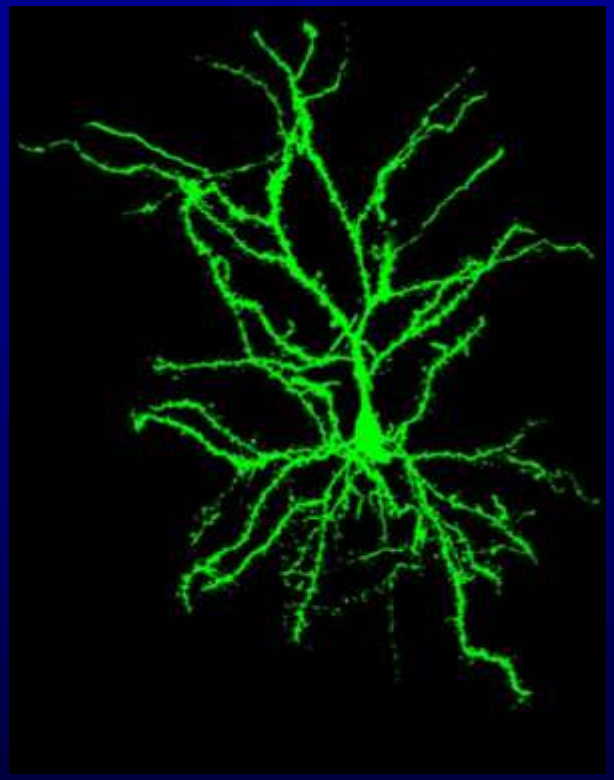
Perception and Response



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

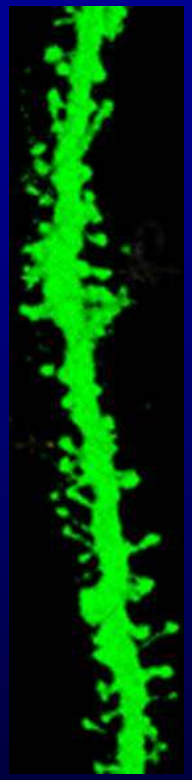
McEwen, *New England Journal of Medicine* 1998

Remodeling of Neural Architecture



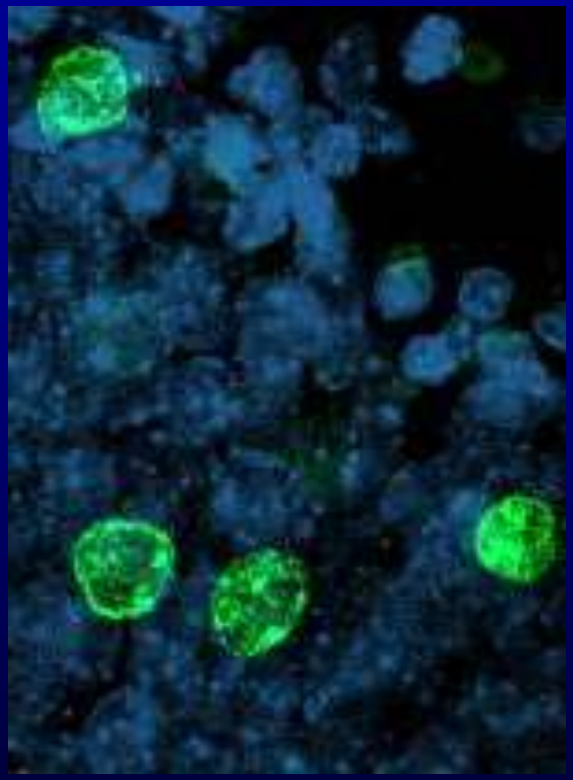
Dendrites

Shrink and expand



Synapses

Disappear and are replaced



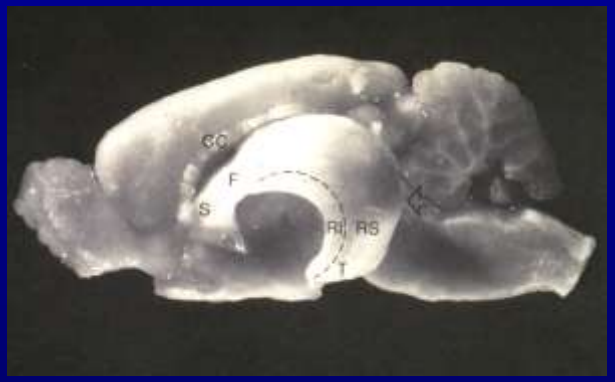
Neurogenesis

Continues in some brain areas

Hippocampus: Target for Stress!

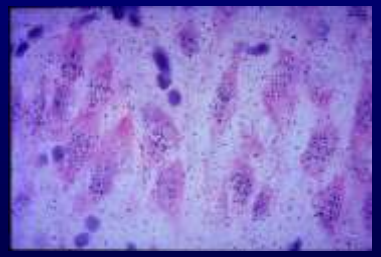
Gateway to discovering hormone actions on the cognitive and emotional brain (1968)

Receptors for glucocorticoids



Adrenal steroid receptors in hippocampus

Steroid autoradiography



Receptors in cell nuclei regulate gene expression

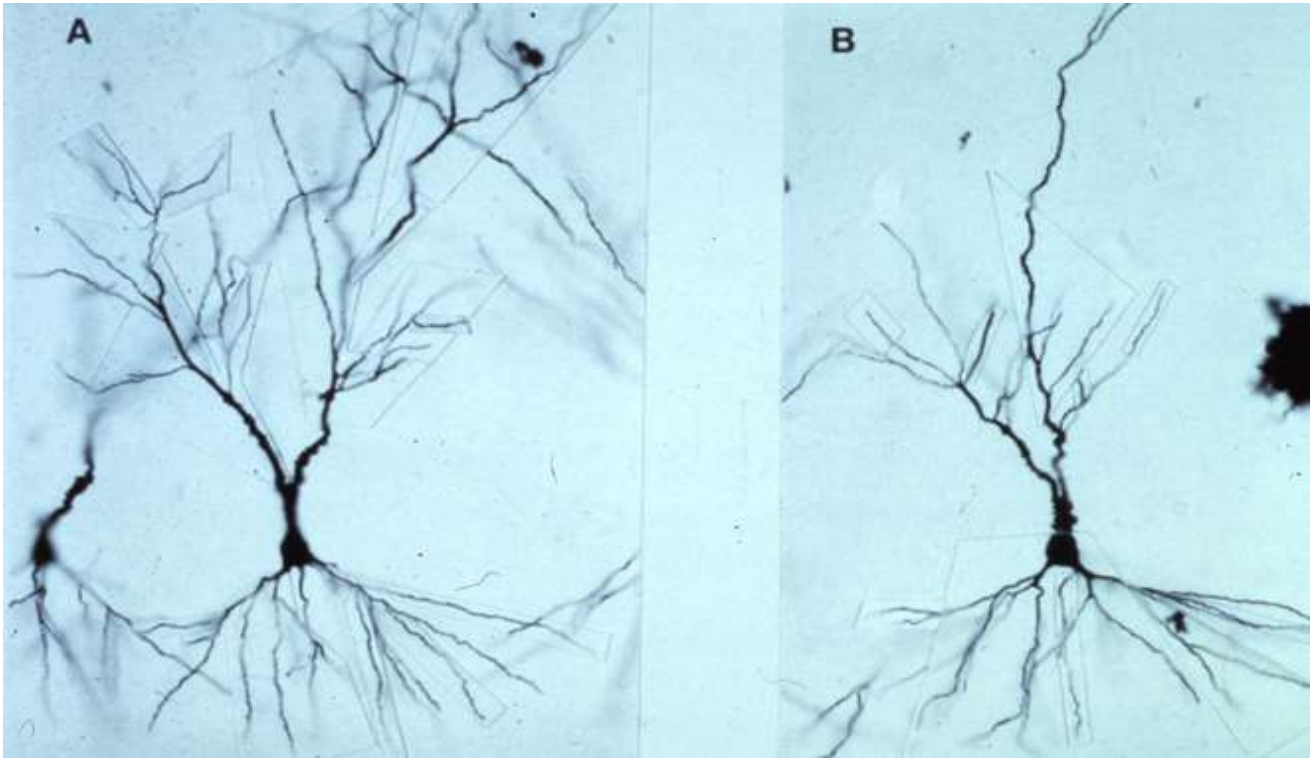
MR and GR

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!



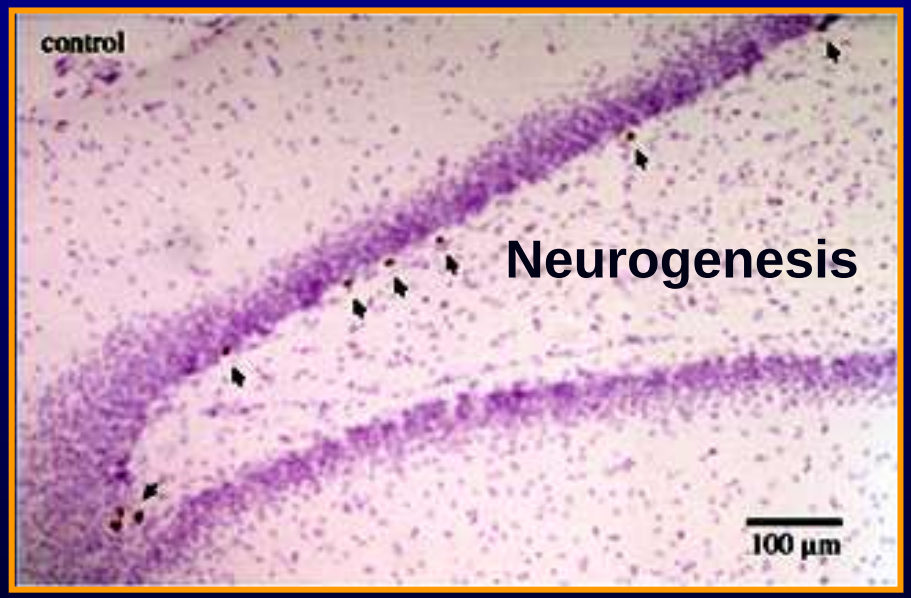
Control **Chronic stress**

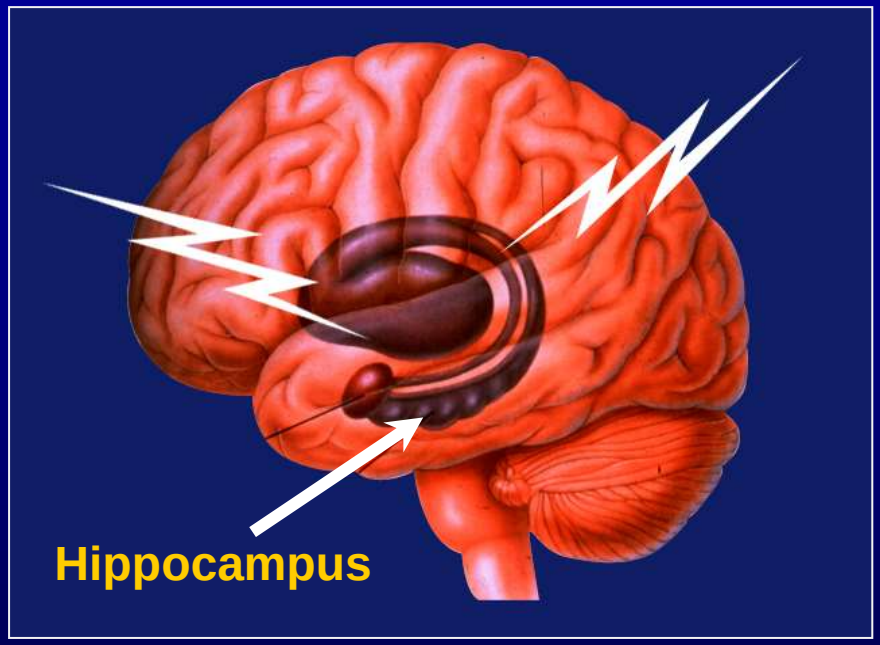
Magarinos AM, McEwen BS, 1995

Chronic Stress Inhibits Birth of New Neurons

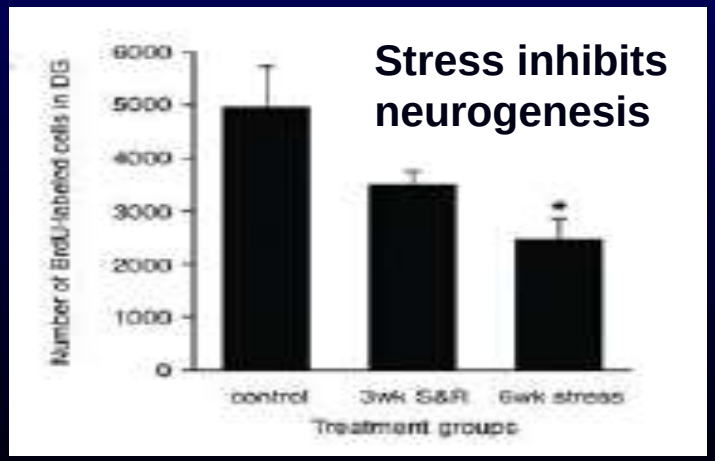
Hippocampus

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



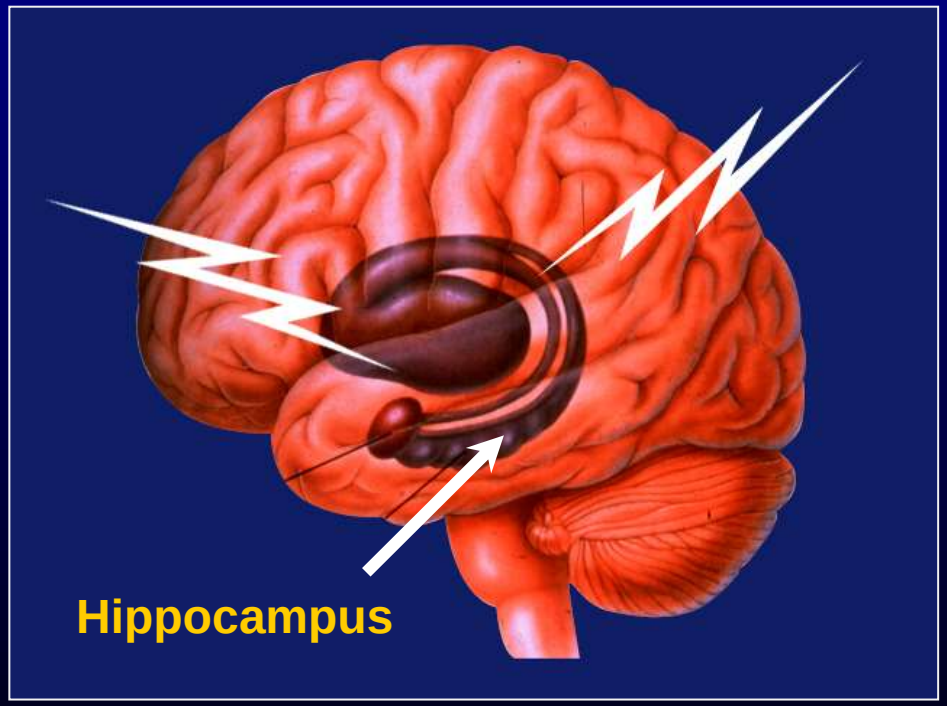


- Neurogenesis recovers after chronic stress and is accelerated by physical activity



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:**

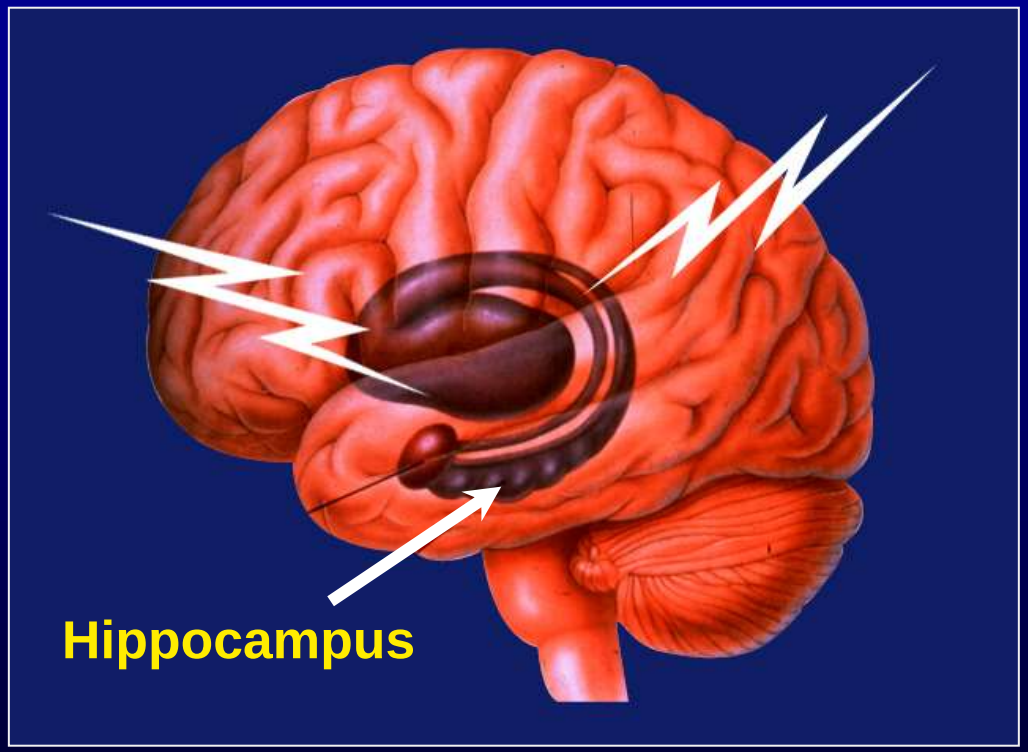
- Chronic stress
- Chronic jet lag
- Lack of exercise
- Chronic inflammation

The Human Hippocampus Under Stress

The Positive Side of the Story

Hippocampus size *INCREASES* with:

- **Regular exercise**
- **Intense learning**
- **Anti-depressant treatment**



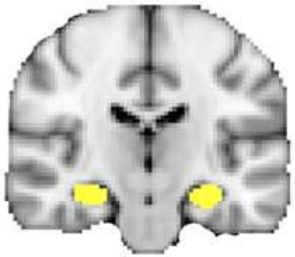
Regular Moderate Exercise Enlarges the Hippocampus

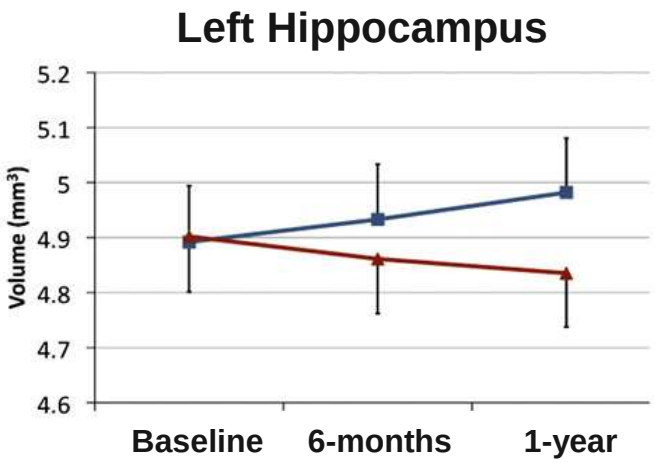
You are never too young or too old to benefit!!

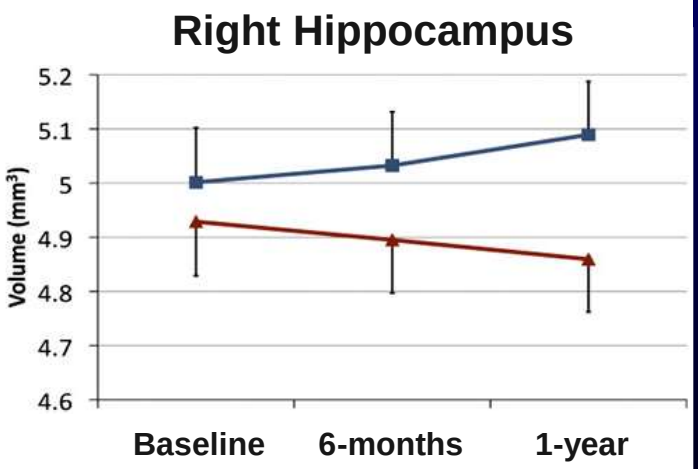
Exercise training increases size of hippocampus and improves memory

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]

Hippocampus







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

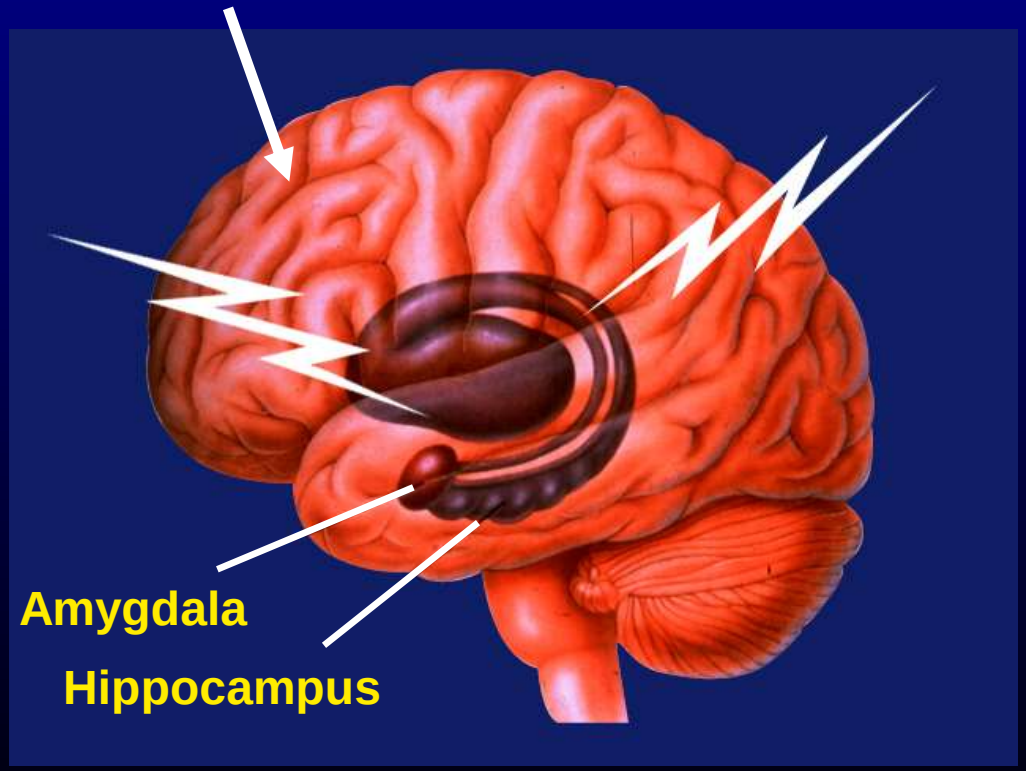
The Human Brain Under Stress

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

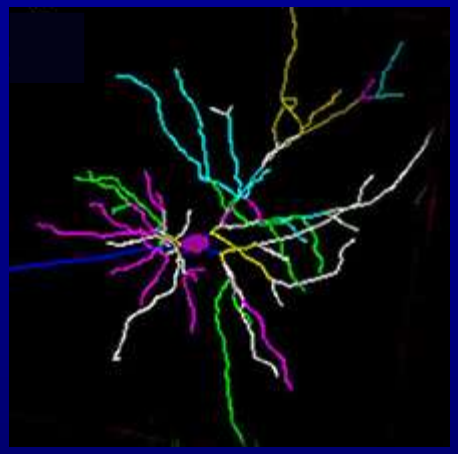
Amygdala

Anxiety, fear; aggression

Turns on stress hormones and increases heart rate

Stress Causes Neurons to Shrink or Grow

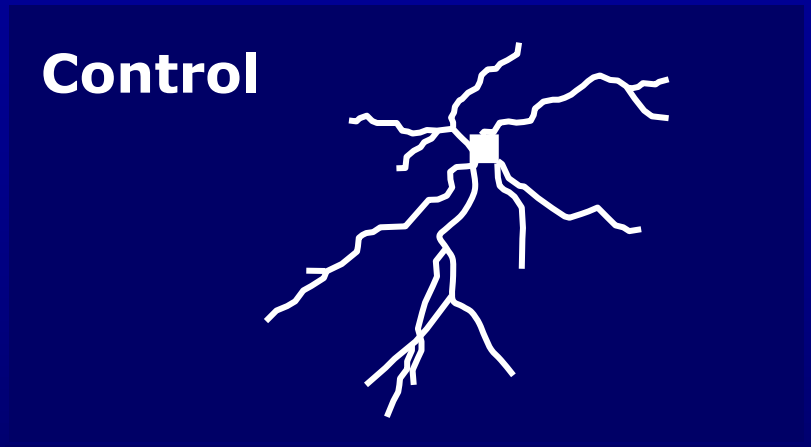
Control



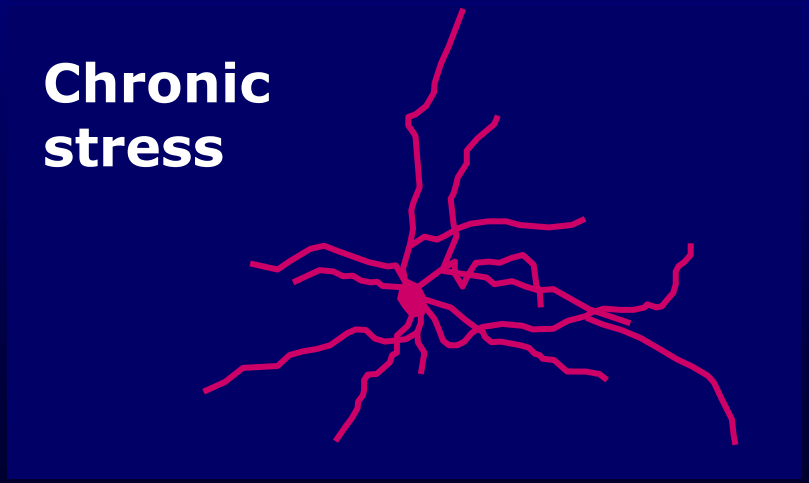
Chronic stress

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

Control



Chronic stress



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

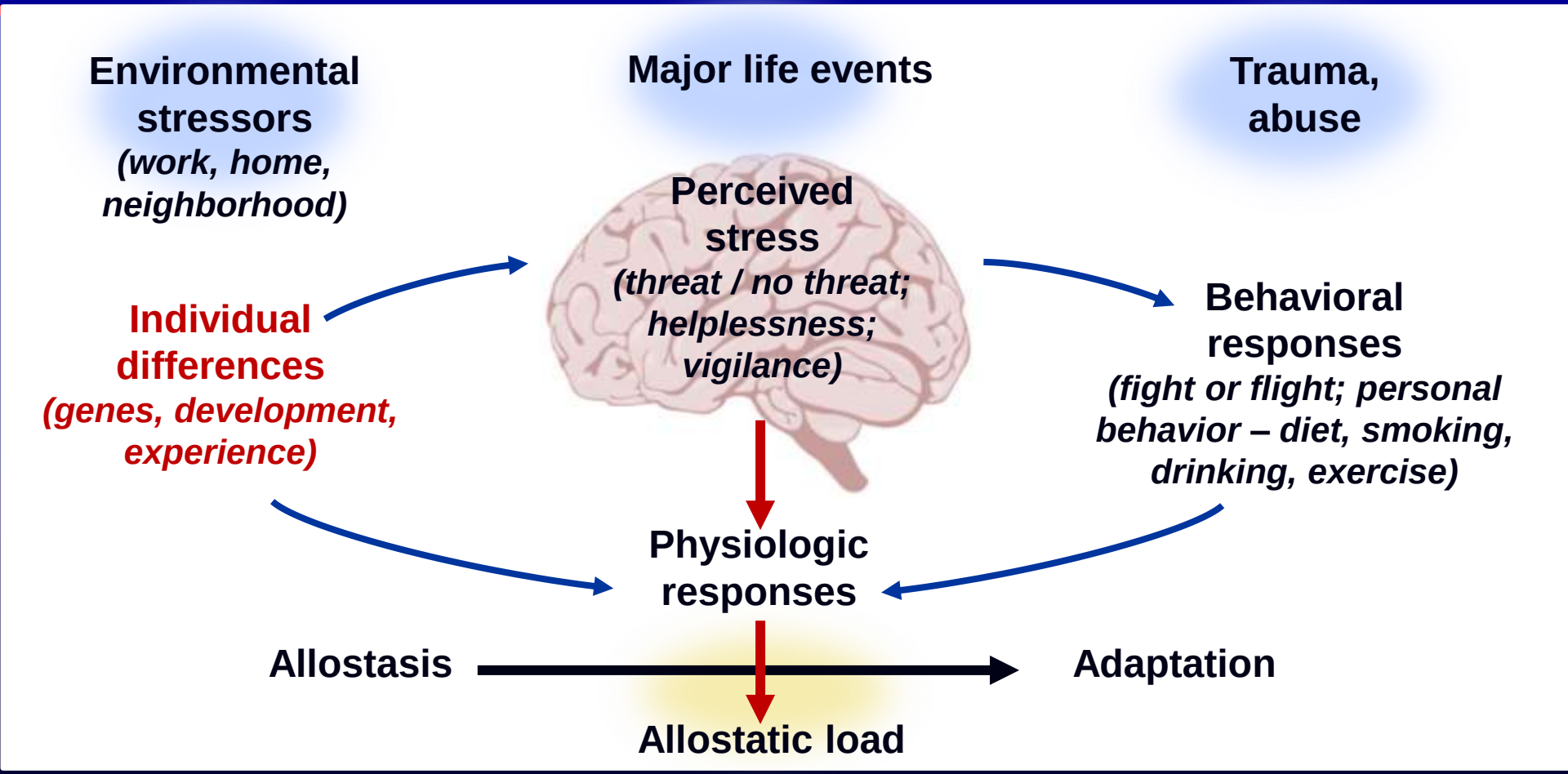
John Morrison

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

These alterations are reversible after a vacation.

Conor Liston, B.J. Casey

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

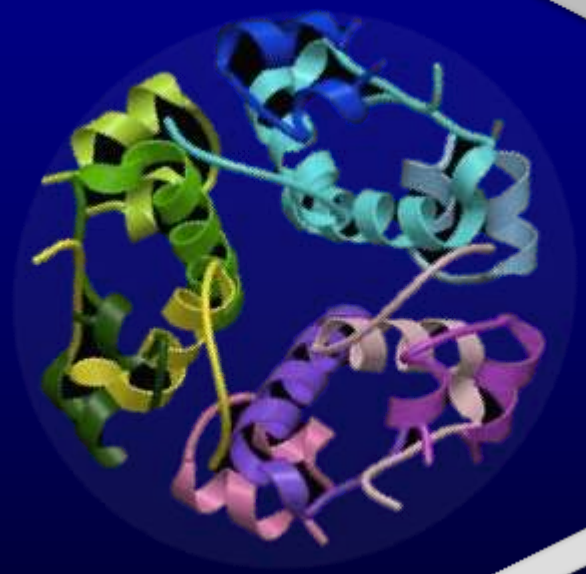
Adverse Childhood Experience – Abuse, Neglect, Poverty

- Increases depression, substance abuse, antisocial behavior, cardiovascular disease, obesity
- Brain structure is altered for greater vigilance and anxiety

The Three D's of Insulin Resistance

Dementia

- Ghasemi R et al. Mol Neurobiol. 2013.
- Morbelli S et al. J Nucl Med. 2013.
- Hokama M, et al., Cereb Cortex. 2013.



- Bewernick BH, et al. Dialogues Clin Neurosci. 2013
- Arlt S et al. Curr Alzheimer Res. 2013.
- Piccinni A et al. Int J Geriatr Psychiatry. 2012.

Diabetes

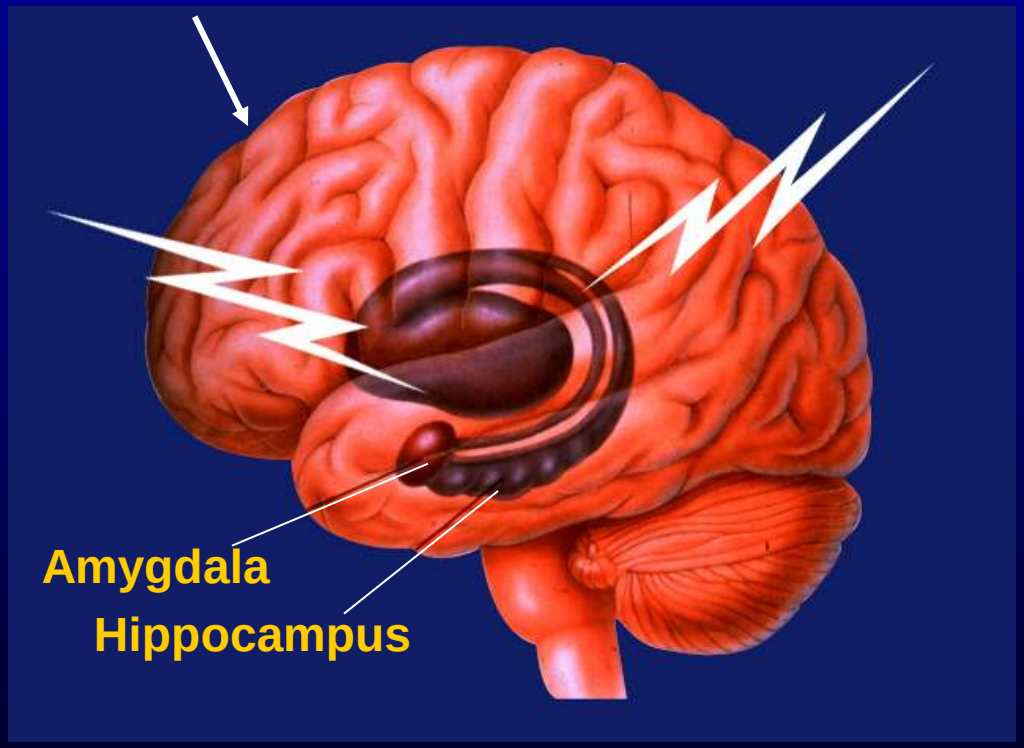
Depression

- Jakobsson J et al. Neuropsychopharmacology.2013.
- Kan C et al., Diabetes Care. 2013
- Akbaraly TN,et al., Diabetes Care. 2013.

Rasgon N, Jarvik GP, Jarvik L. Affective disorders and Alzheimer disease: a missing-link hypothesis. Am J Geriatr Psychiatry. 2001 Fall;9(4):44

The Human Brain Under Stress

Developmental effects on hippocampus



Hippocampus

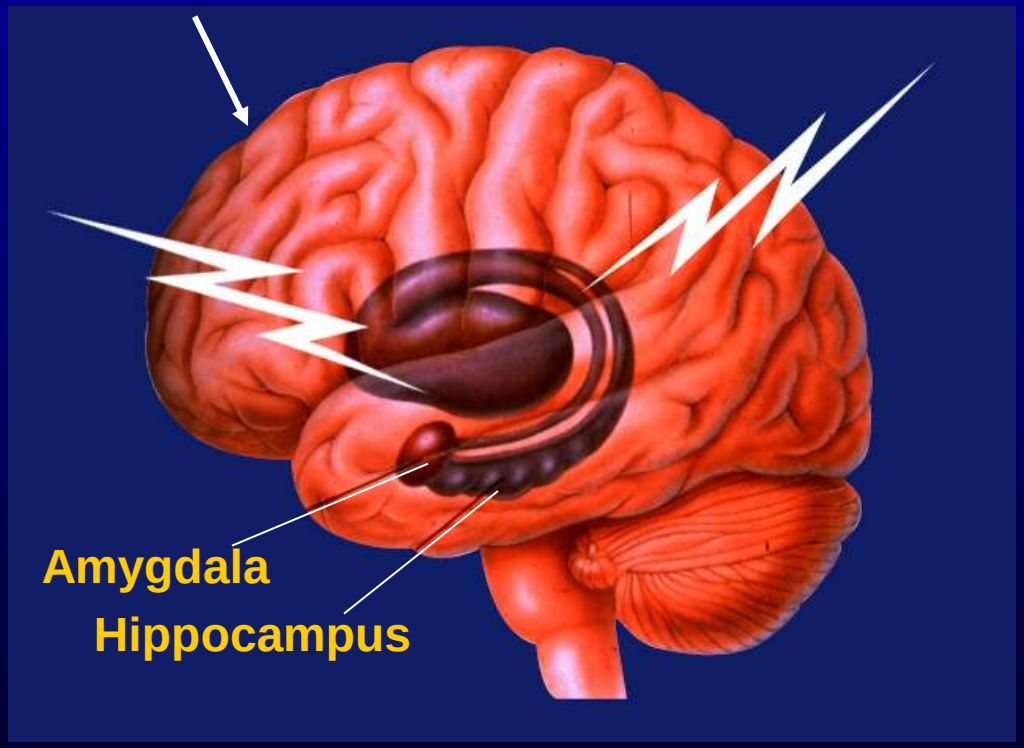
Contextual, episodic, spatial memory

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

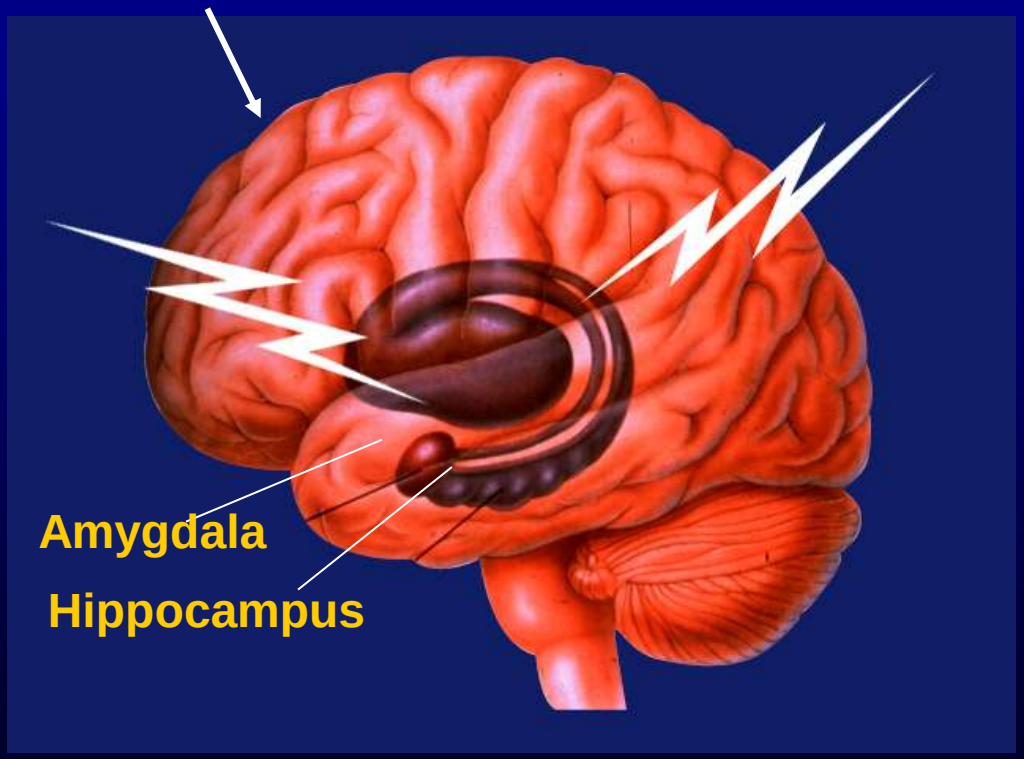
Larger in children living with a depressed mother

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

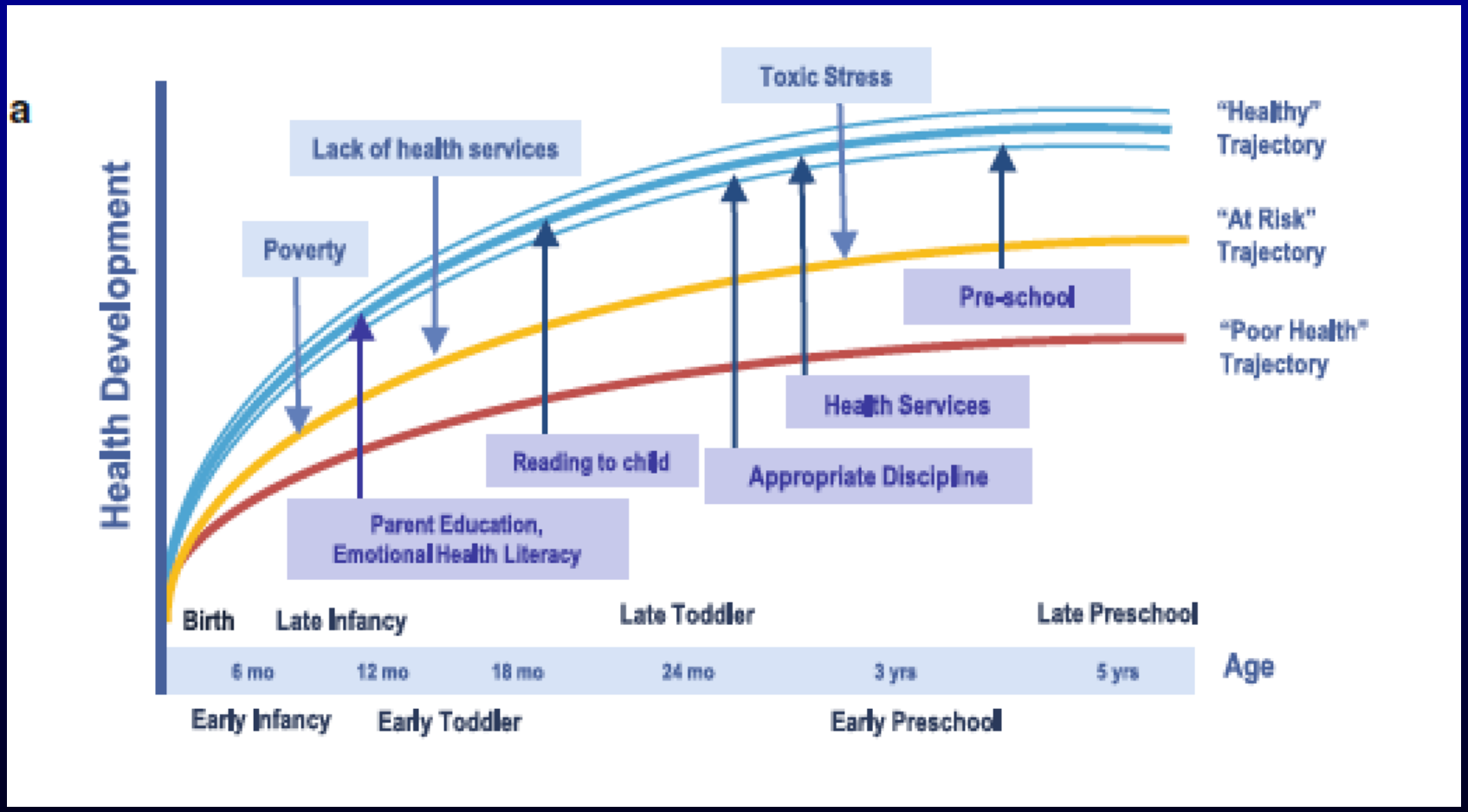


"WE CANNOT ROLL BACK THE CLOCK!"

Changing the direction of the life course

From Halfon et al 2014

Positive vs Negative Direction



PREVENTION

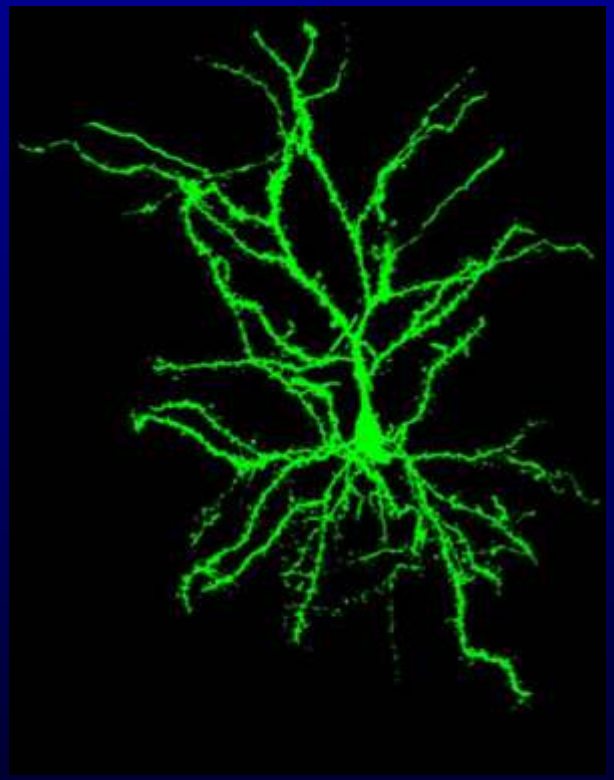
NURSE-FAMILY PARTNERSHIP

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

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

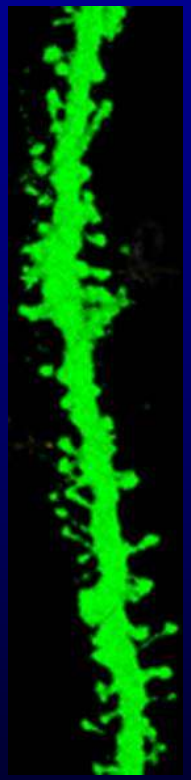
Looking to the Future

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



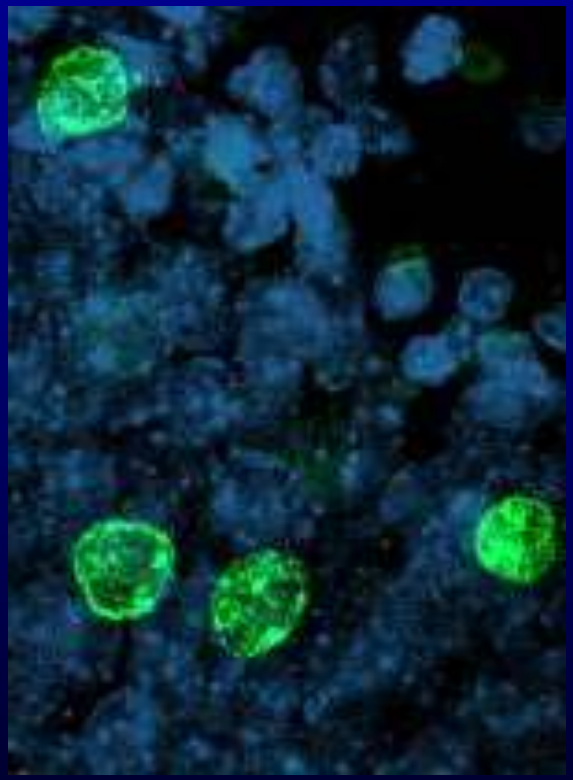
Dendrites

Shrink and expand



Synapses

Disappear and are replaced



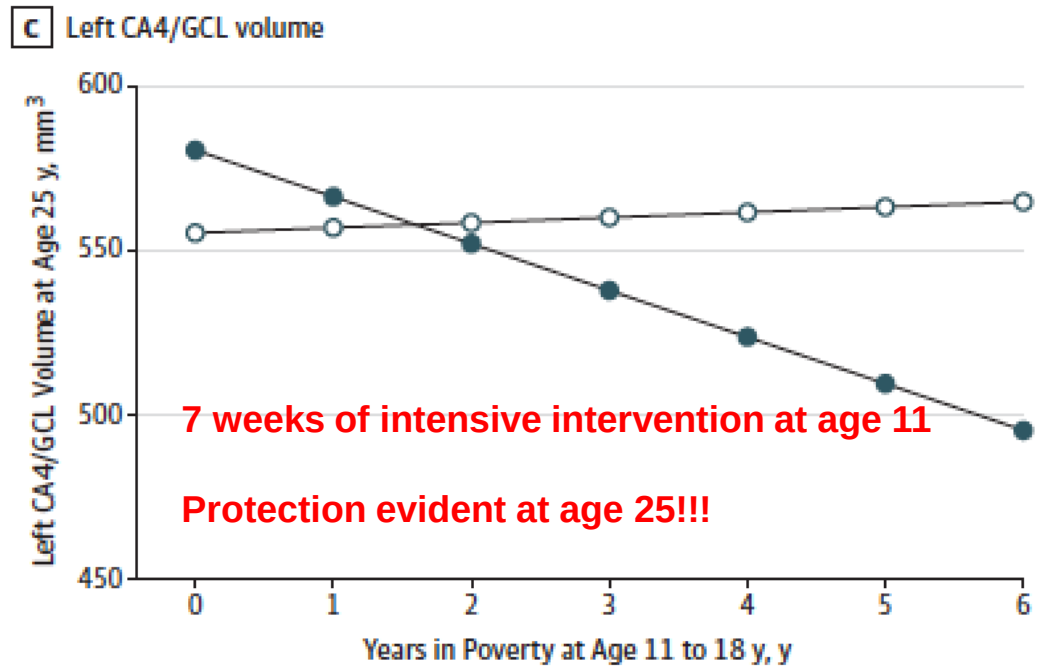
Neurogenesis

Continues in some brain areas

JAMA Pediatrics | Original Investigation

Protective Prevention Effects on the Association of Poverty With Brain Development

Gene H. Brody, PhD; Joshua C. Gray, PhD; Tianyi Yu, PhD; Allen W. Barton, PhD; Steven R. H. Beach, PhD; Adrianna Galván, PhD; James MacKillop, PhD; Michael Windle, PhD; Edith Chen, PhD; Gregory E. Miller, PhD; Lawrence H. Sweet, PhD



GCL indicates dentate gyrus; SAAF, Strong African American Families.

PREVENTION OF HIPPOCAMPAL SHRINKAGE AND DEPRESSIVE BEHAVIOR

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.

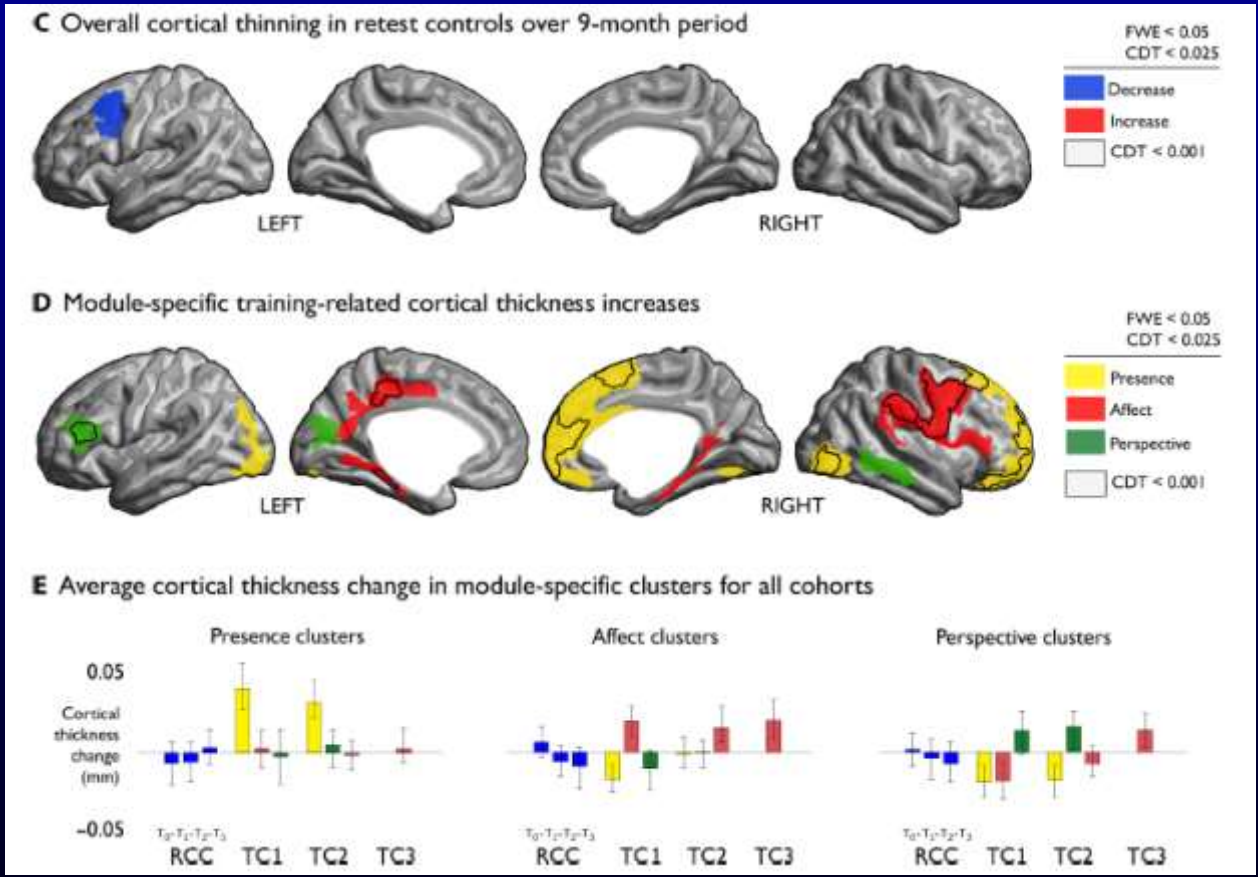
Meaning and purpose (eudaimonia)

SCIENCE ADVANCES | RESEARCH ARTICLE

BEHAVIORAL NEUROSCIENCE

Structural plasticity of the social brain: Differential change after socio-affective and cognitive mental training

Sofie L. Valk,[1] Boris C. Bernhardt,[1,2] Fynn-Mathis Trautwein,[1] Anne Böckler,[1,3] Philipp Kanske,[1,4] Nicolas Guizard,[2] D. Louis Collins,[2] Tania Singer[1*]



Colleagues and Collaborators

Leiden University

Nicole Datson
Ron de Kloet

Medical College of Wisconsin

Cecilia Hillard

Paolo de Angelis
Josh Dobbin
Nathaniel Einhorn
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
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Constantine Pavlides

Weill/Cornell

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Francis Lee
Conor Liston
Teri Milner
BJ Casey (YALE)

Columbia University

Martin Picard
Robert Paul Juster

Stanford University

Natalie Rasgon

Mt. Sinai Schl Med

Patrick Hof
John Morrison (UC Davis)
James Murrough
Eric Nestler
Ana Pereira
Scott Russo
Rebecca Shansky (Northeastern)

National Centre for Biological Sciences (Bangalore)

Sumantra Chattarji
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