THE SCIENCE THAT HEALS: THE NEUROBIOLOGY OF STRESS, TRAUMA, AND RESILIENCE

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College of Health Sciences
Marquette University

Beyond MU

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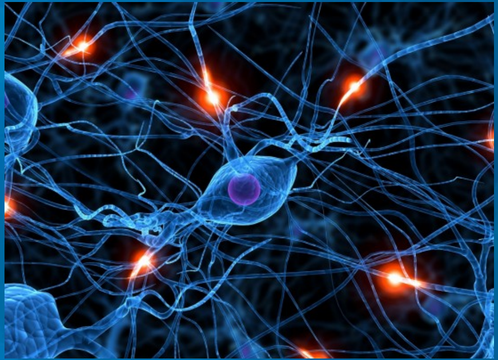
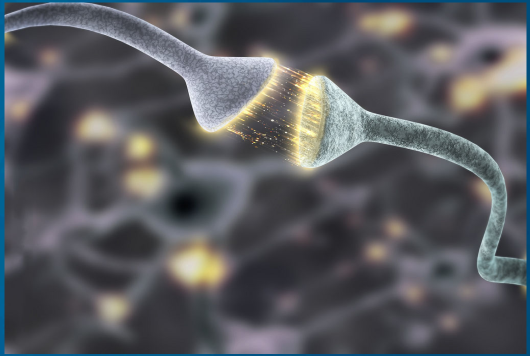
Quick Facts

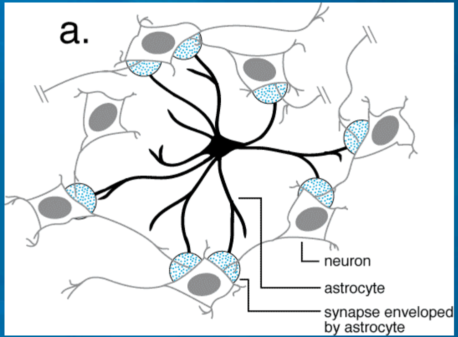
- The human brain contains an estimated <u>86 billion neurons</u>
- Each neuron forms up to 10,000 connections with other neurons; these connections are called <u>synapses</u>
- Synaptic communication involves > than 100 neurochemicals that act through > 1000 different receptors

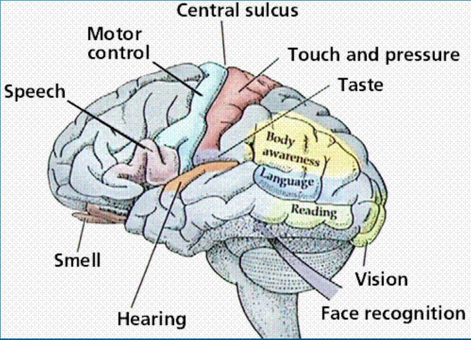




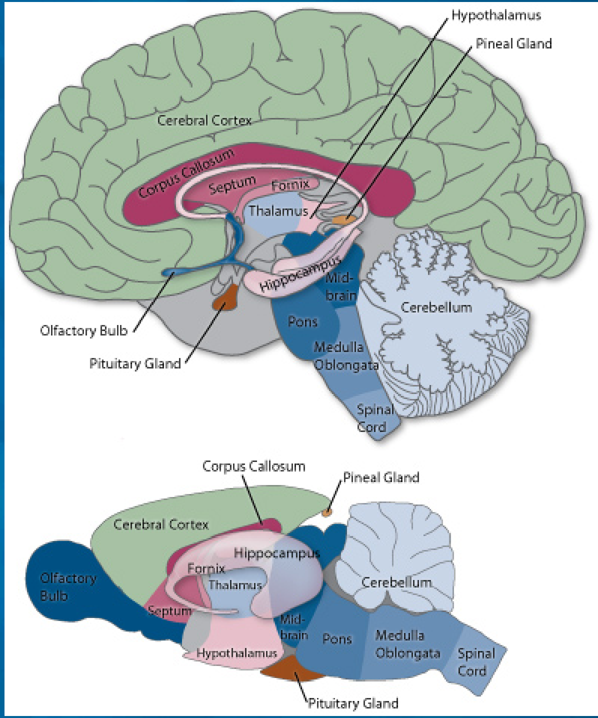
Quick Facts

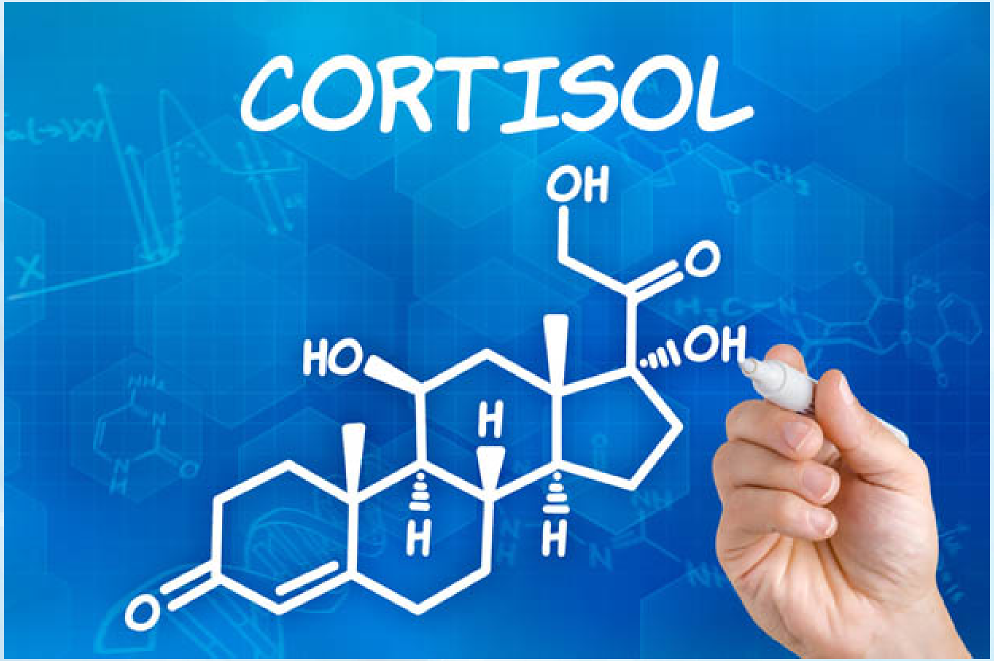
- Neurons work in close coordination with other cells types in the brain called astrocytes and form elaborate networks and systems that determine what we perceive and experience
- Many of the key neuronal pathways and chemical neurotransmitters involved in mental illness are coming into sharper focus





Homology Across Mammalian Species




CORTISOL
OH
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HO
OH
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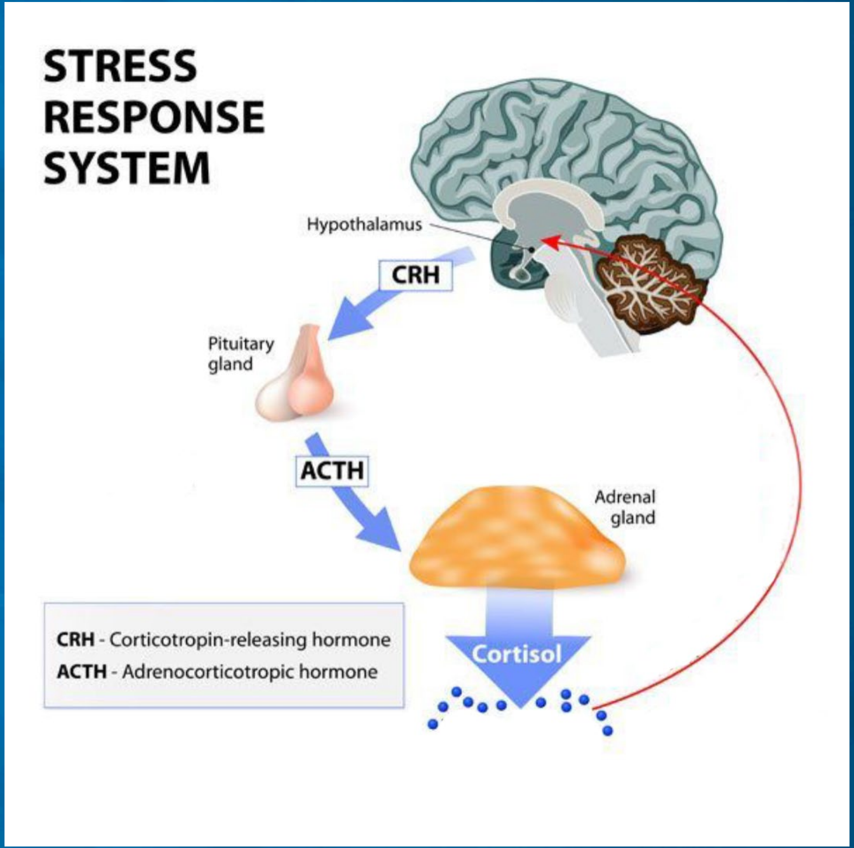
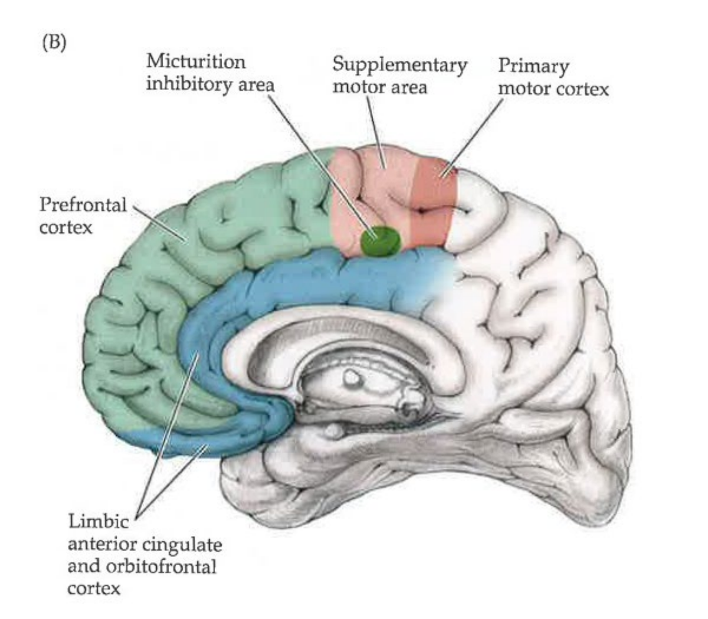
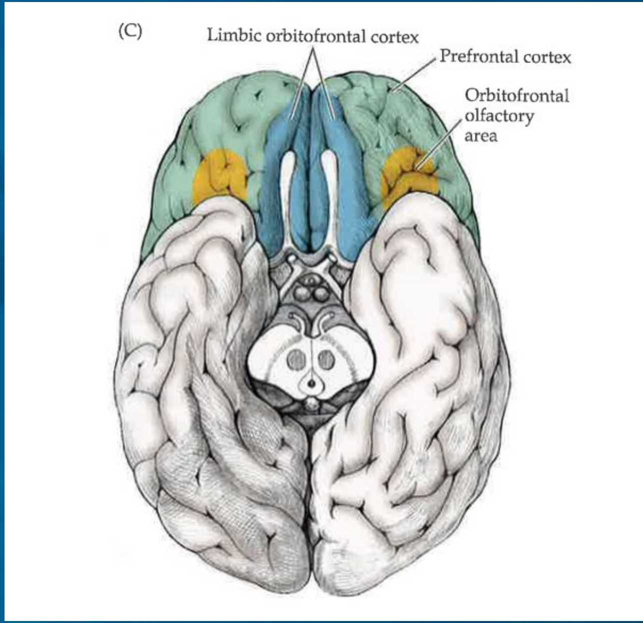

STRESS
RESPONSE
SYSTEM
Hypothalamus
CRH
Pituitary gland
ACTH
Adrenal gland
Cortisol
CRH - Corticotropin-releasing hormone
ACTH - Adrenocorticotropic hormone

Prefrontal Cortex

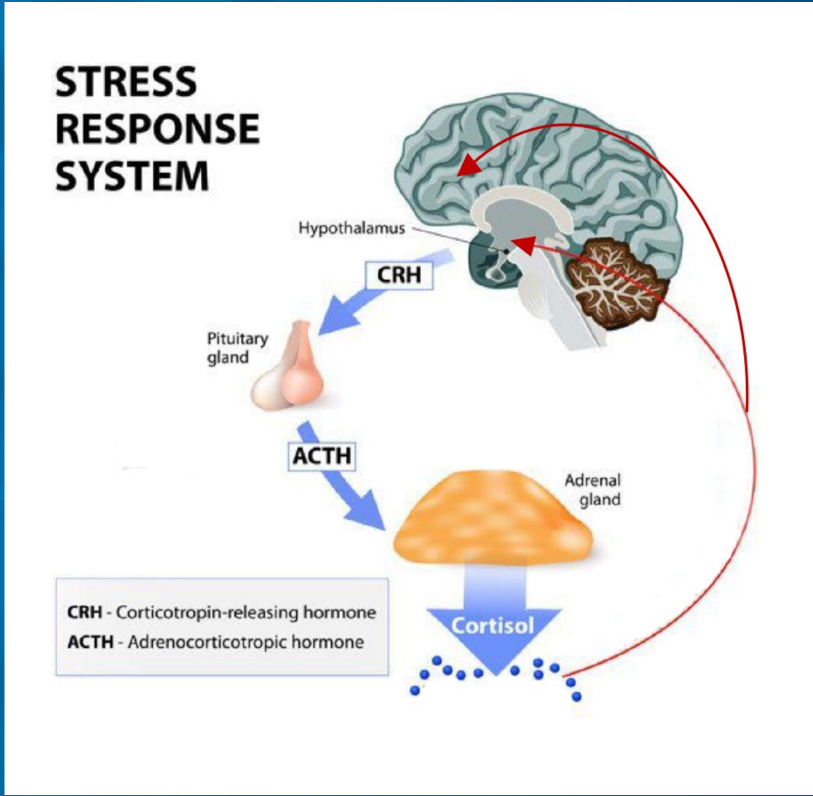




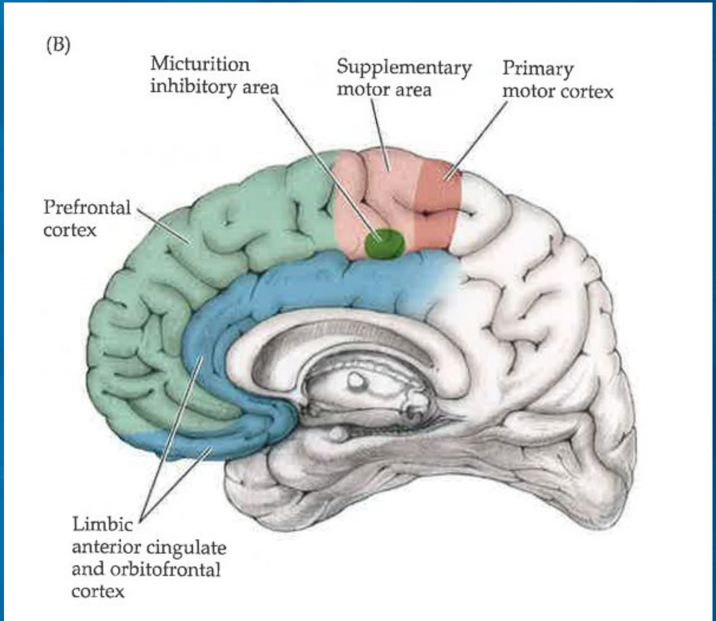
Prefrontal Cortex

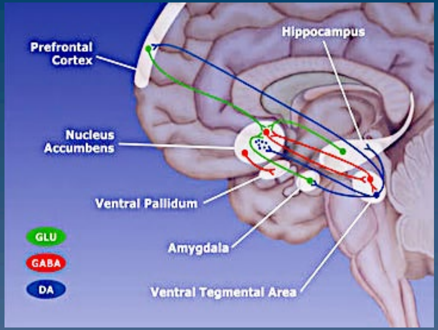
- Executive Function/ Decision Making
- Planning Complex Behavior
- Impulse Inhibition
- Predicting Future Consequences of Actions

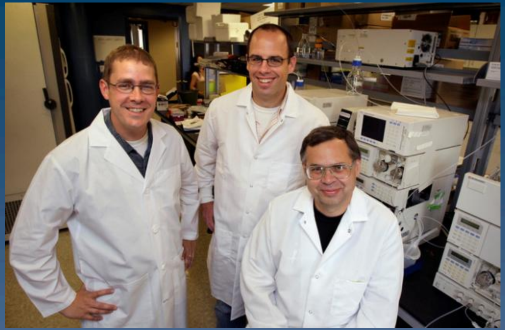
Prefrontal Cortex is Particularly Vulnerable to Glucocorticoids



Prefrontal Cortex is Among Last Brain Areas to Develop

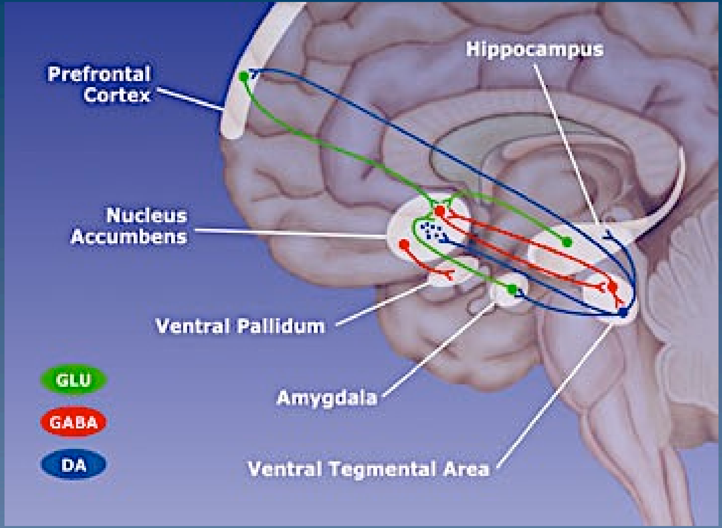


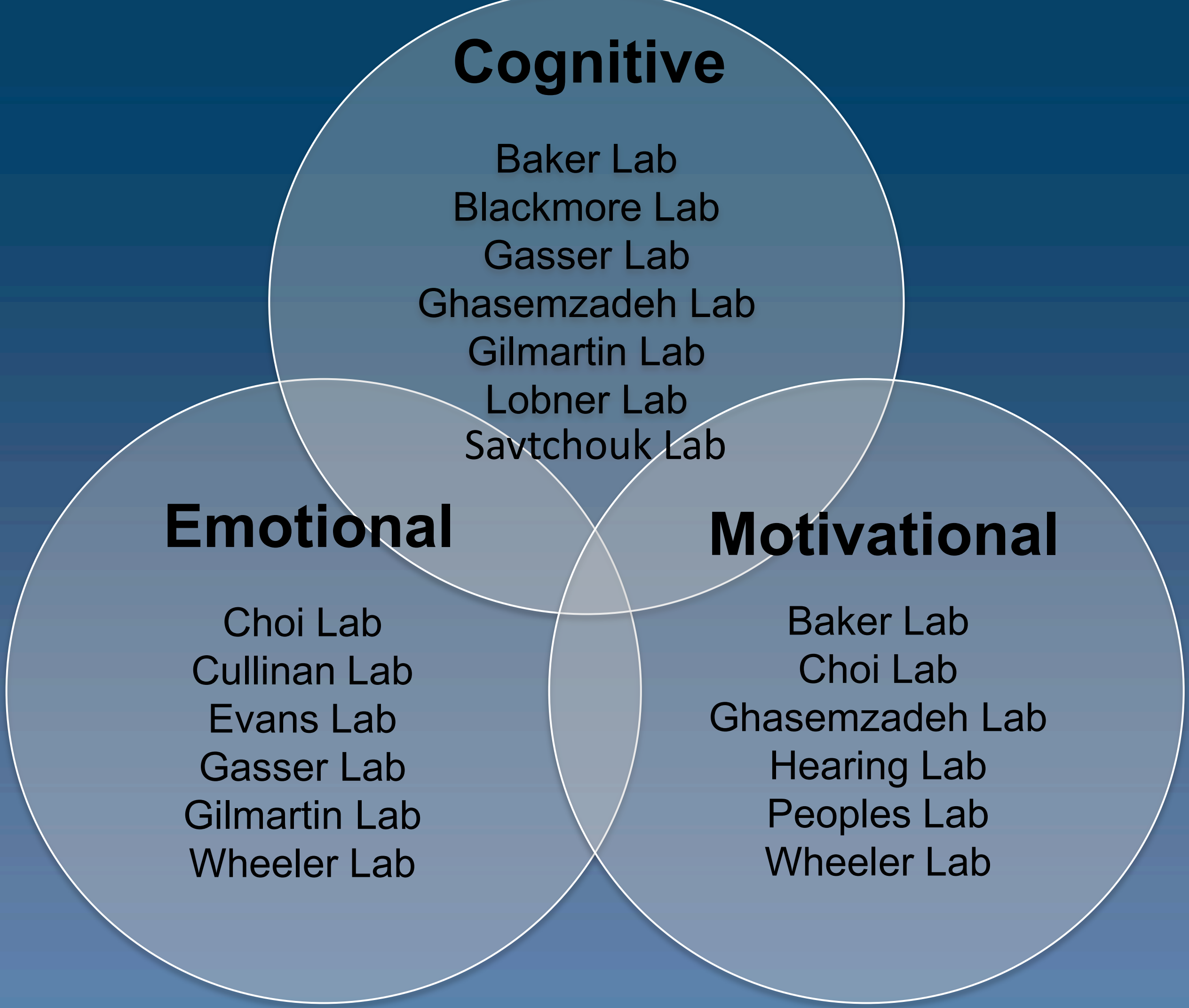


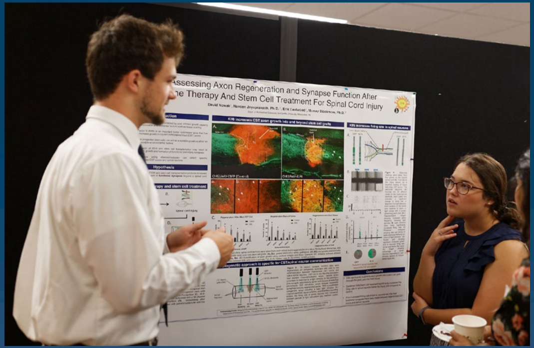


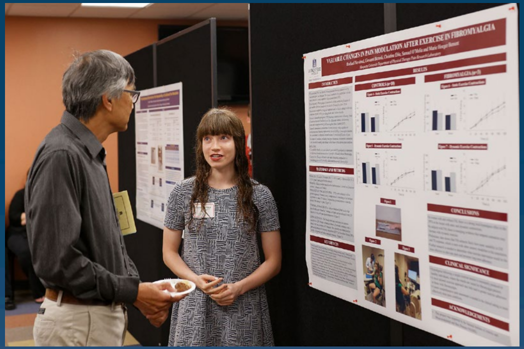
- >20 college neuroscientists working in funded research laboratories
- Particular strengths in neuroscience underlying neuropsychiatric disease and in motor control
- Promentis Pharmaceuticals, Inc. now has an IND in Phase III FDA clinical trial following >$31 million in venture capital investment

Cognitive – Emotional -- Motivational Brain Circuitries




Cognitive
Baker Lab
Blackmore Lab
Gasser Lab
Ghasemzadeh Lab
Gilmartin Lab
Lobner Lab
Savtchouk Lab
Emotional
Choi Lab
Cullinan Lab
Evans Lab
Gasser Lab
Gilmartin Lab
Wheeler Lab
Motivational
Baker Lab
Choi Lab
Ghasemzadeh Lab
Hearing Lab
Peoples Lab
Wheeler Lab





Summer Research Program

- Summer research program providing high impact experiences for undergraduate students
- 45-50 students across 23 faculty laboratories
- Large number of undergraduate students presenting at national scientific meetings and co-authors of publications

Billie and Michael Kubly

Eck Family Foundation

Dawne and Ray Manista

Kelly and Jim McShane

Michael Schmitz

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THE NEUROBIOLOGY OF STRESS, TRAUMA, AND RESILIENCE

Paul Gasser, Ph,D
Department of Biomedical Sciences
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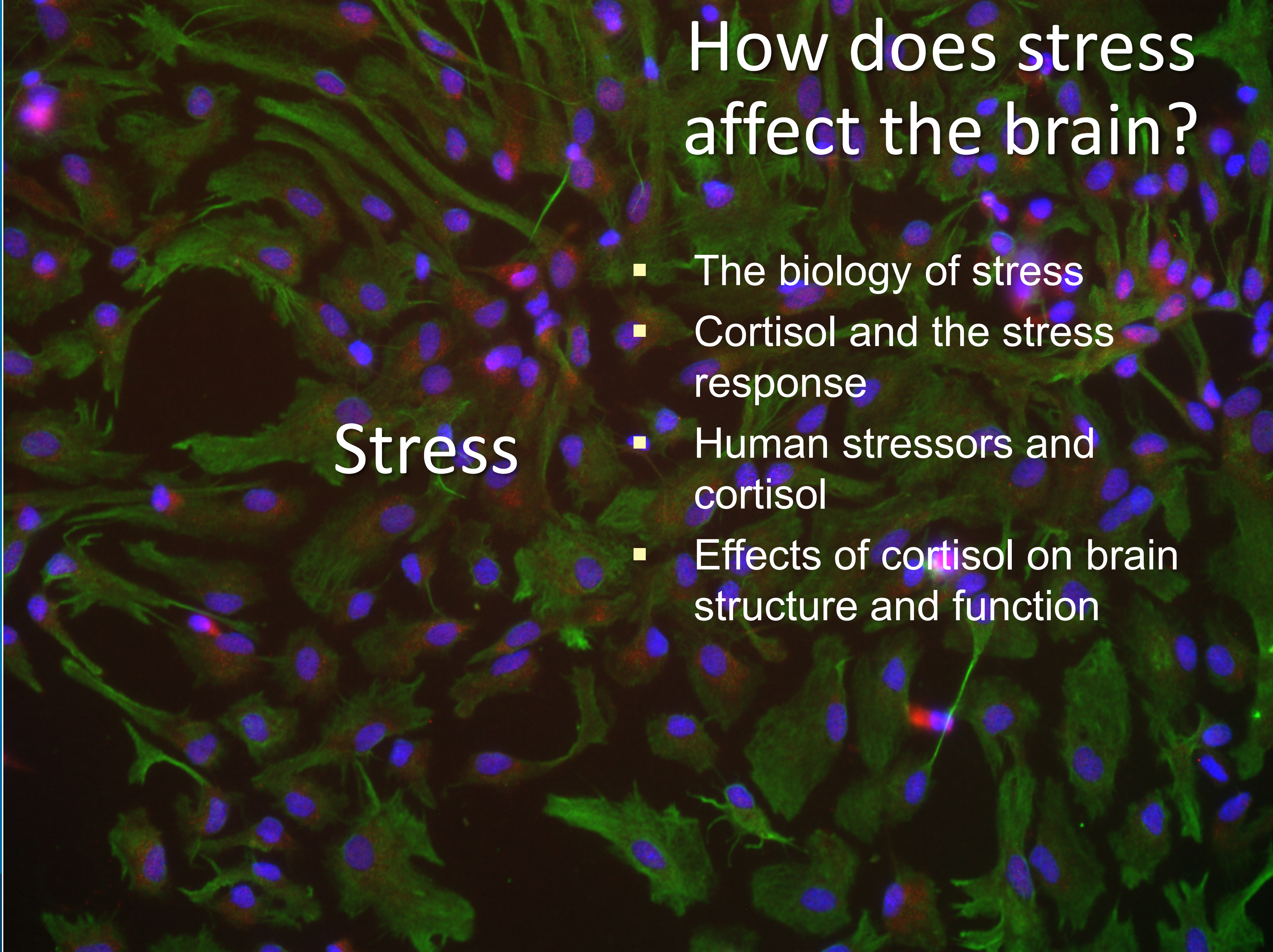


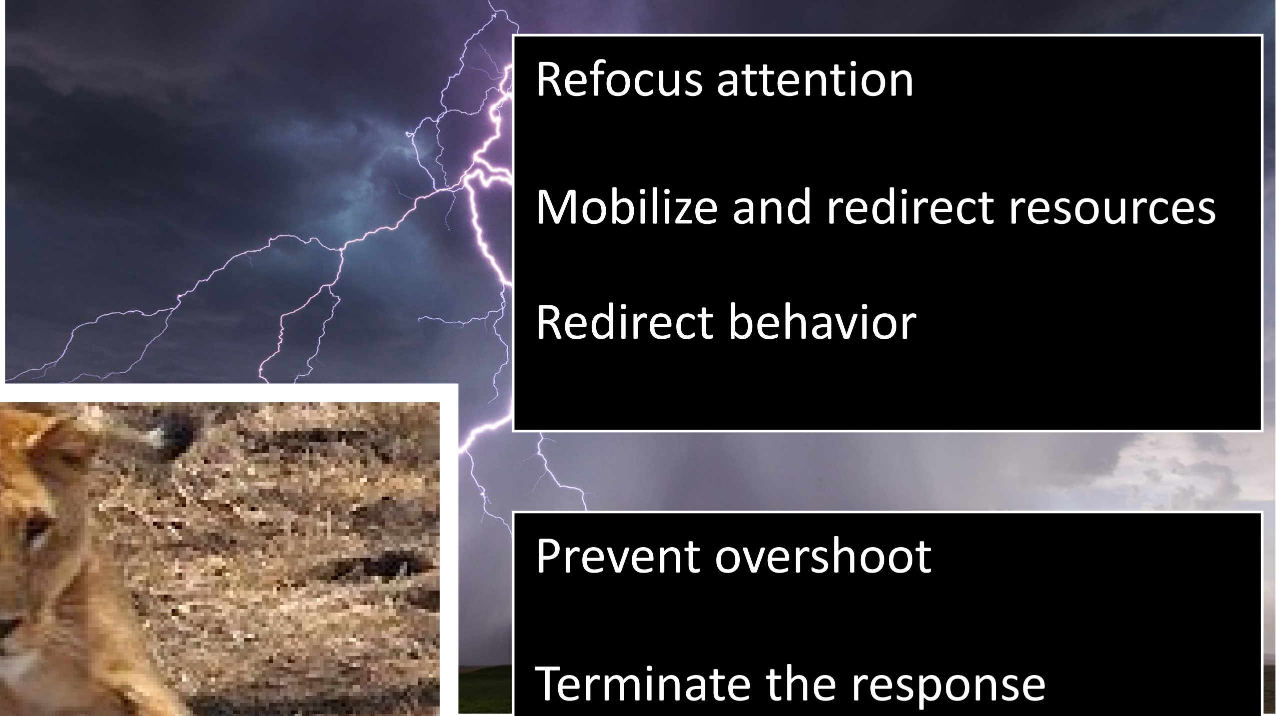
How does stress affect the brain?

Stress

- The biology of stress
- Cortisol and the stress response
- Human stressors and cortisol
- Effects of cortisol on brain structure and function

What is stress?

Getty Images – Brooke Mitchell



Refocus attention

Mobilize and redirect resources

Redirect behavior

Vivianne Diaz

Prevent overshoot

Terminate the response

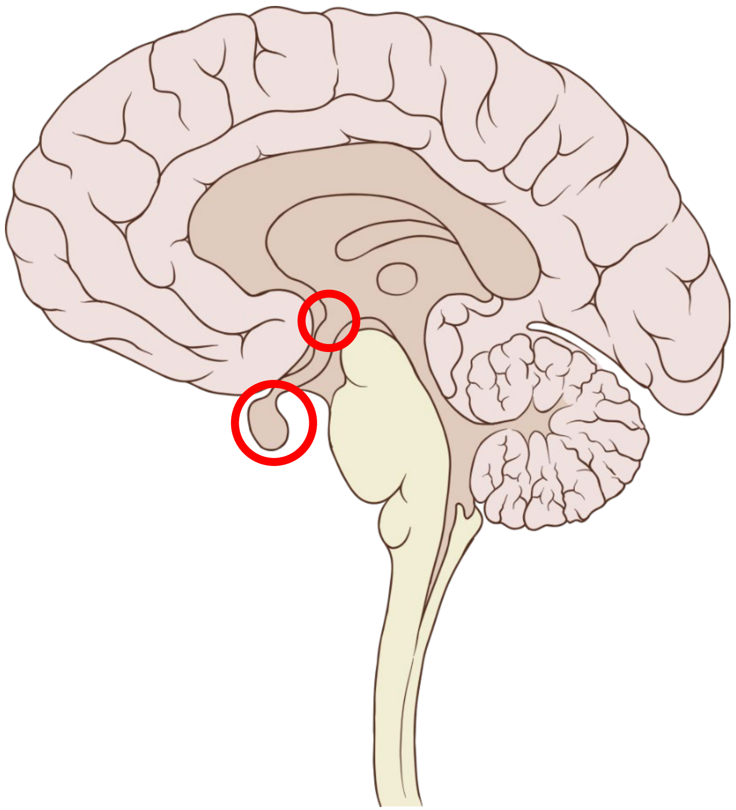
Promote recovery

Adapt/Prepare

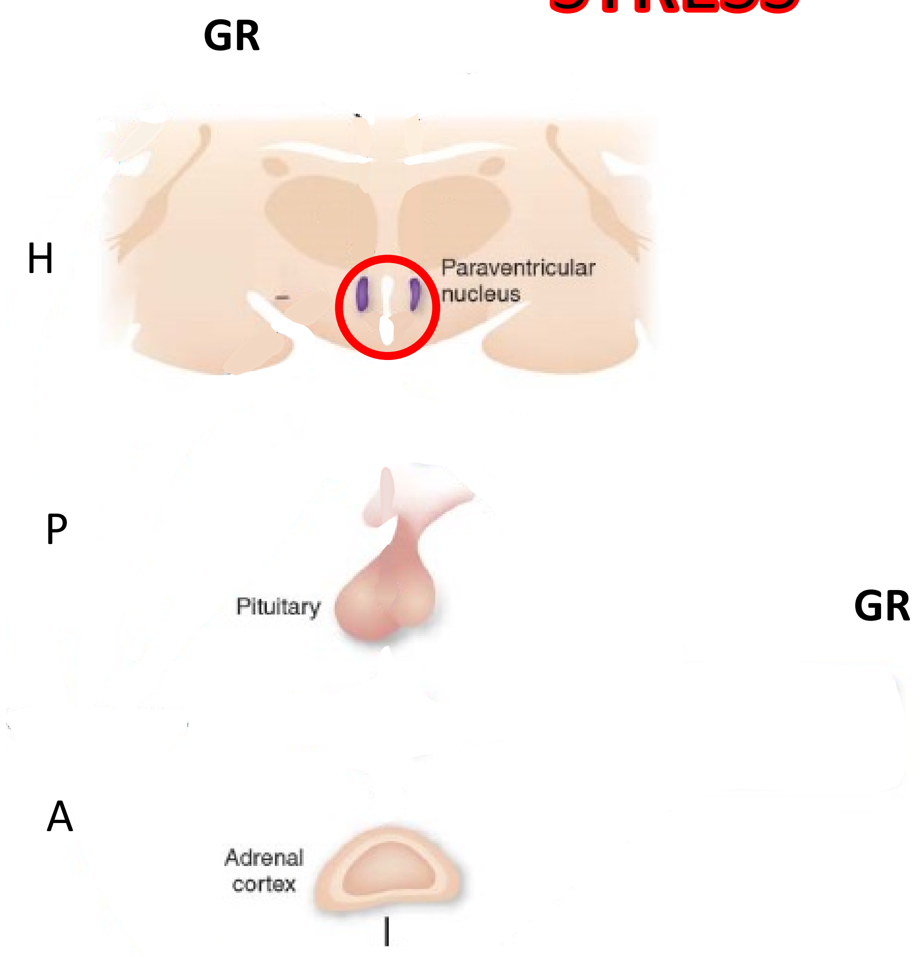
Bertie Gregory – 2020VISION

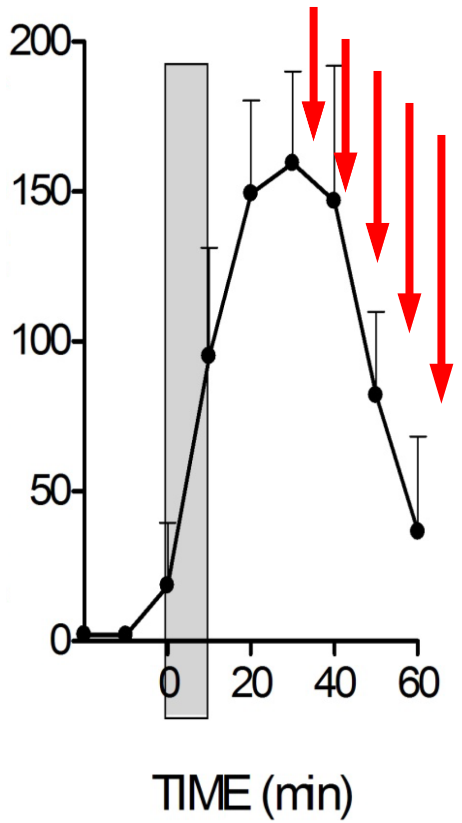
Caters News Agency

HPA axis: part of the brain’s stress response system



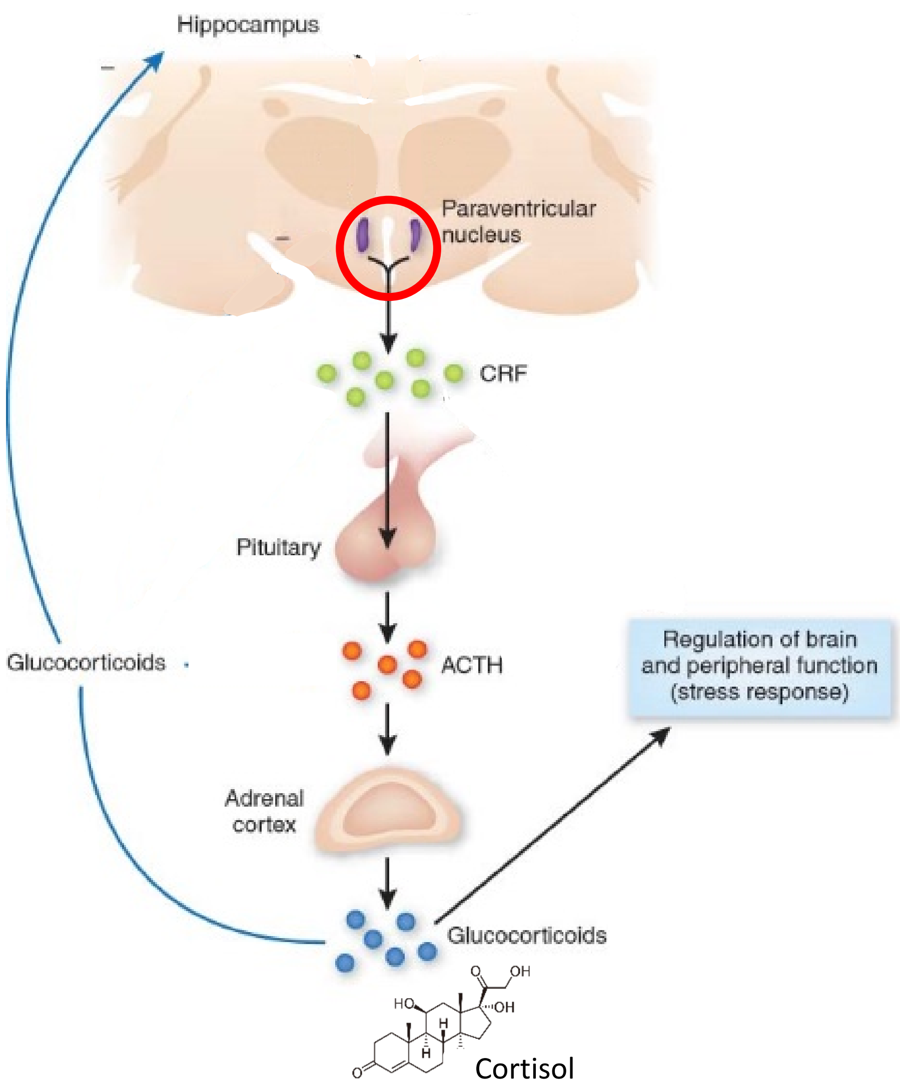
STRESS





Dysregulation of the HPA axis is linked to:

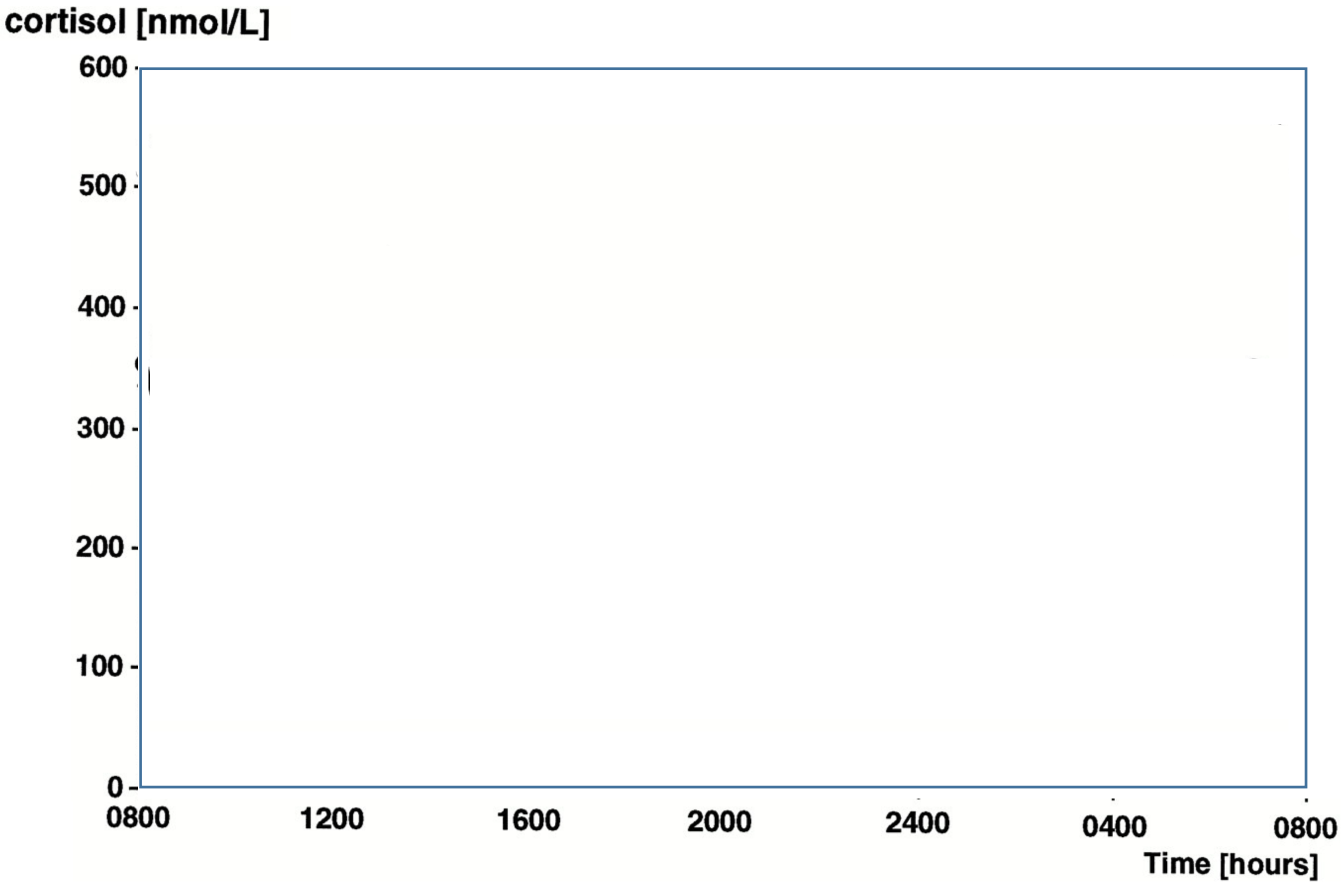
- Anxiety
- Depression
- Attention/Cognitive Impairment
- Digestive Problems
- Heart Disease
- Insomnia



HPA Axis Dysregulation in Depression

In depressed patients:

- Elevated diurnal cortisol and ACTH
- Decreased negative feedback
- Enhanced HPA axis drive



Deuschle et al (1996) J. Clin. Endo. Metab. 1997, 82, 234-238

Poverty: A multidimensional stressor

- Food/nutrition
- Housing problems (crowding, etc)
- Warmth
- Environmental safety, stability
- Family turmoil, separation
- Violence

Table 2 Frequency of Multiple-Stressor Exposure as a Function of Poverty

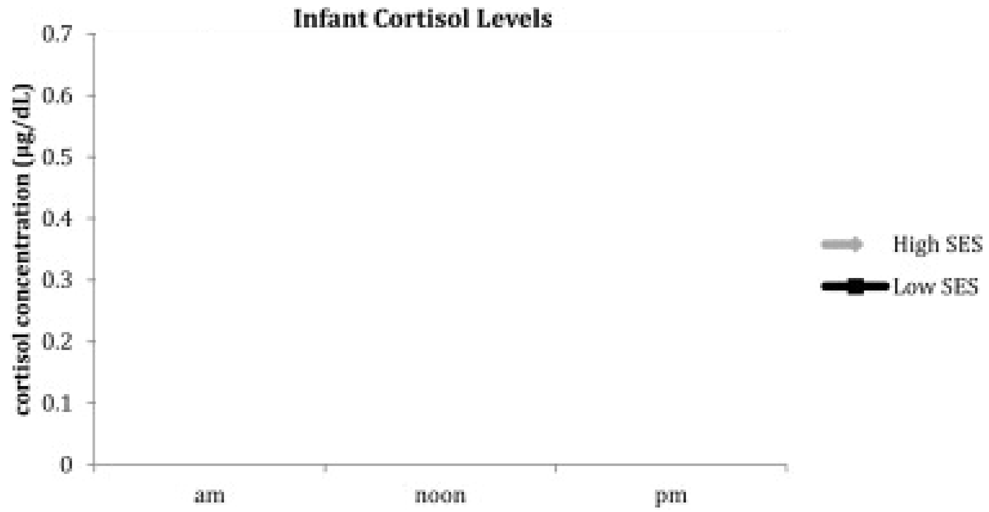
Number of Multiple Stressors	Poverty Frequency *n* (%)	Middle-Income Frequency *n* %
0	5 (3)	15 (13)
1	30 (18)	58 (49)
2	44 (25)	28 (24)
3	32 (19)	6 (5)
4	31 (19)	10 (7)
5	20 (12)	2 (2)
6	6 (4)	0 (0)

Evans & English, 2002

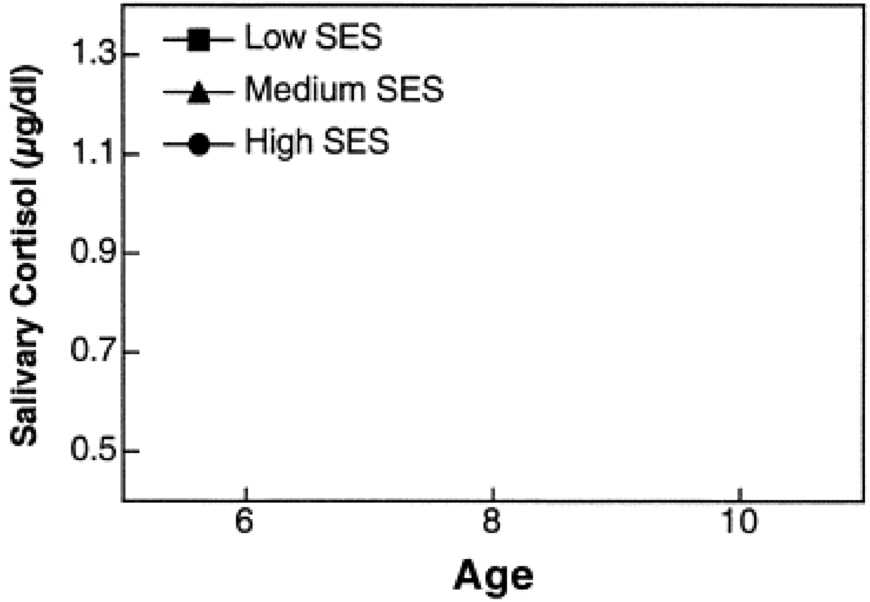
Poverty and the HPA Axis

- Low SES infants:
  - higher cortisol throughout the day
- Low, medium SES children:
  - Higher awakening cortisol

Effects on brain structure?



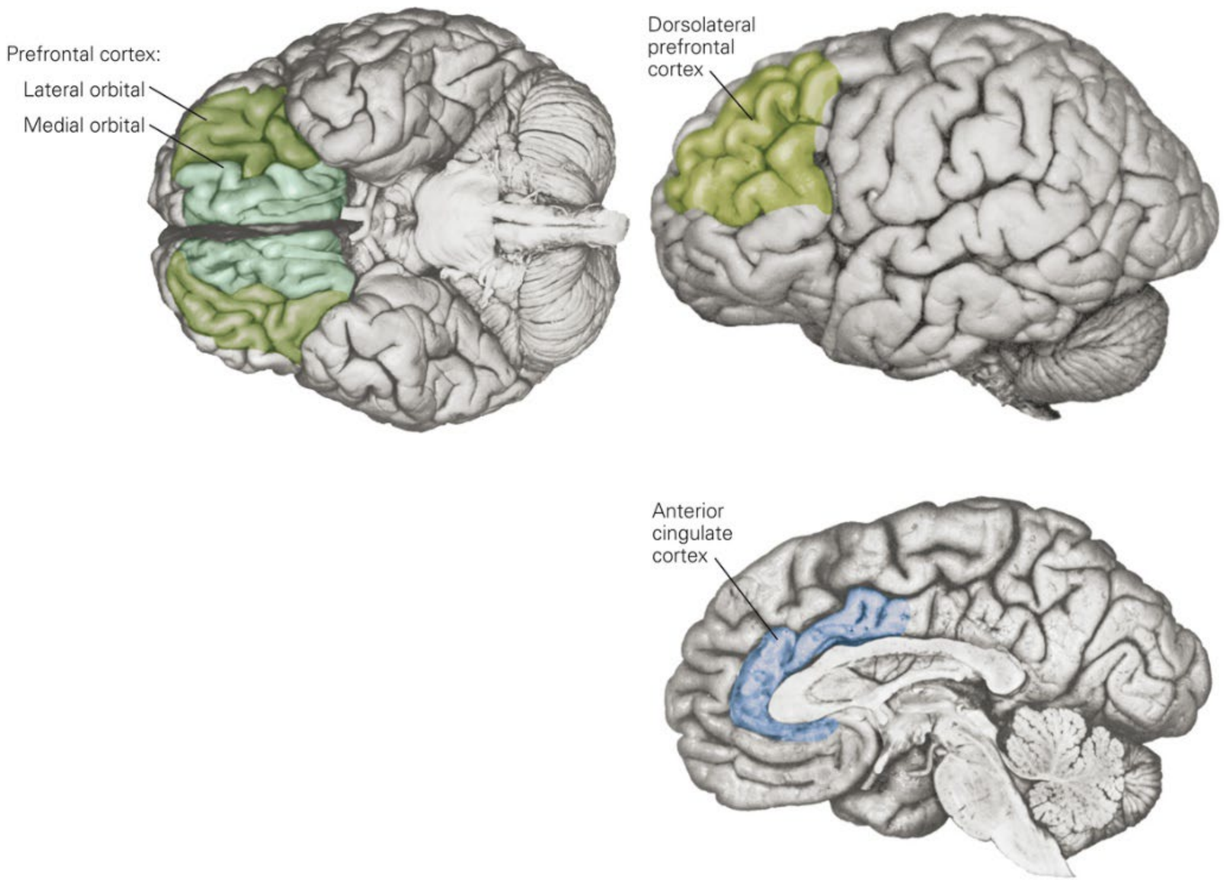
Clearfield et al (2014) *Infant Beh. Dev. 37(3), 298-304*



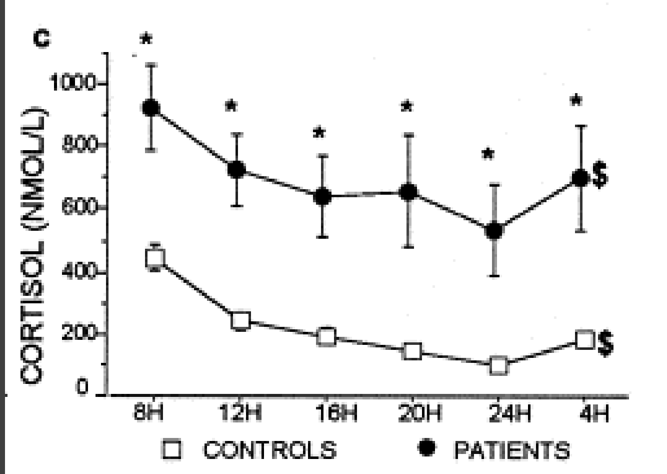
Lupien et al (2000) *Biol. Psychiatry 48(10), 976-980*

Prefrontal cortex: Executive function & Emotional control

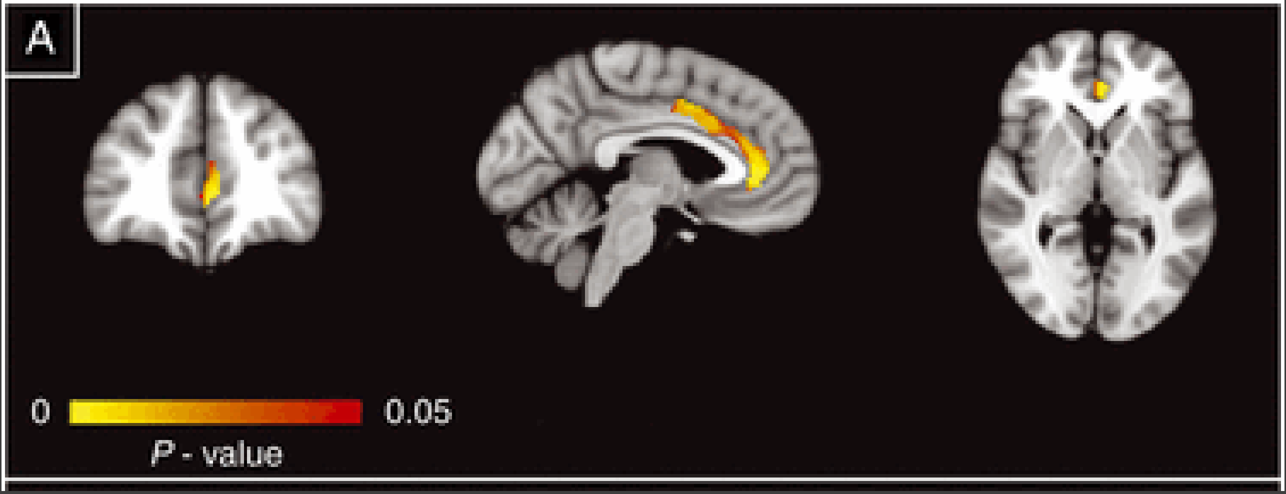
- Decision-making
- Impulse control
- Attention
- Emotional Regulation
- Stress coping



Cushing's syndrome: Chronically elevated cortisol



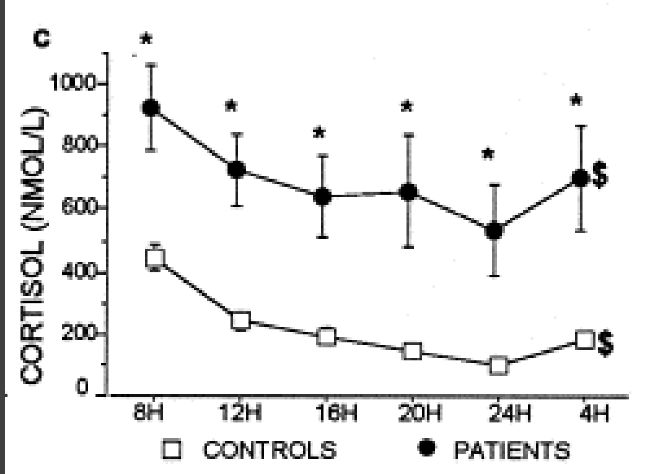
Vergely et al (2002)



Andela et al (2013) *Eur. J. Endocrinol. 169, 811- 819*

Bauduin et al (2020) *Transl. Psychiatry 10, 293-305*

Cushing's syndrome: Chronically elevated cortisol



Vergely et al (2002)

	Cushing's disease (n=25)	Matched controls (n=25)	*P* value
MADRS	6.3±5.5	1.4±1.8	**0.000**[b]
Inventory of Depression Symptomatology	46.8±13.0	36.3±5.8	**0.005**[b]
Beck Anxiety Inventory	28.4±5.7	24.0±3.1	**0.003**[b]
Fear Questionnaire	24.5±17.4	14.2±10.0	0.051[b]
Agoraphobia subscale	6.1±7.9	3.4±4.7	0.477[b]
Blood injury phobia subscale	6.2±8.3	3.2±4.1	0.118[a]
Social phobia subscale	12.2±8.0	7.6±4.9	**0.034**[b]
Irritability Scale	12.1±8.7	8.0±6.1	0.066[a]
Total score >14	9 (36%)	6 (24%)	
Apathy Scale	13.6±6.6	7.8±3.8	**0.002**[b]
Total score >14	11 (44%)	2 (8%)	
Cognitive Failures Questionnaire	38.0±16.5	27.6±9.7	**0.023**[b]

P values were tested with [a]independent-sample *t*-test and [b]Mann–Whitney *U* test. Level of significance was set at $P<0.05$ and significant values are in bold.

Andela et al (2013) *Eur. J. Endocrinol. 169, 811- 819*

Poverty effects on Brain structure

- NIH MRI Study of Normal Brain Development
- 389 children
- Income range ($5000 - $150000)
- Neuroimaging
- Effects concentrated in children from the poorest households

Table 2. Socioeconomic Status and Brain Development

Variable	Frontal Gray Matter, β (SE)
Model 1	
Below 200% of the FPL	−2.157[b] (1.24)
Model 2	
Below 150% of the FPL	−3.532[b] (1.546)
Model 3	
Below 100% of the FPL	−8.383[b] (2.597)

Poor, Near-poor

Hair et al (2015) *JAMA Pediatr. 169 (9), 822- 829*

Poverty effects on Executive function

- 1292 children
- Tasks to measure:
    - Working memory
    - Attention
    - Inhibitory control

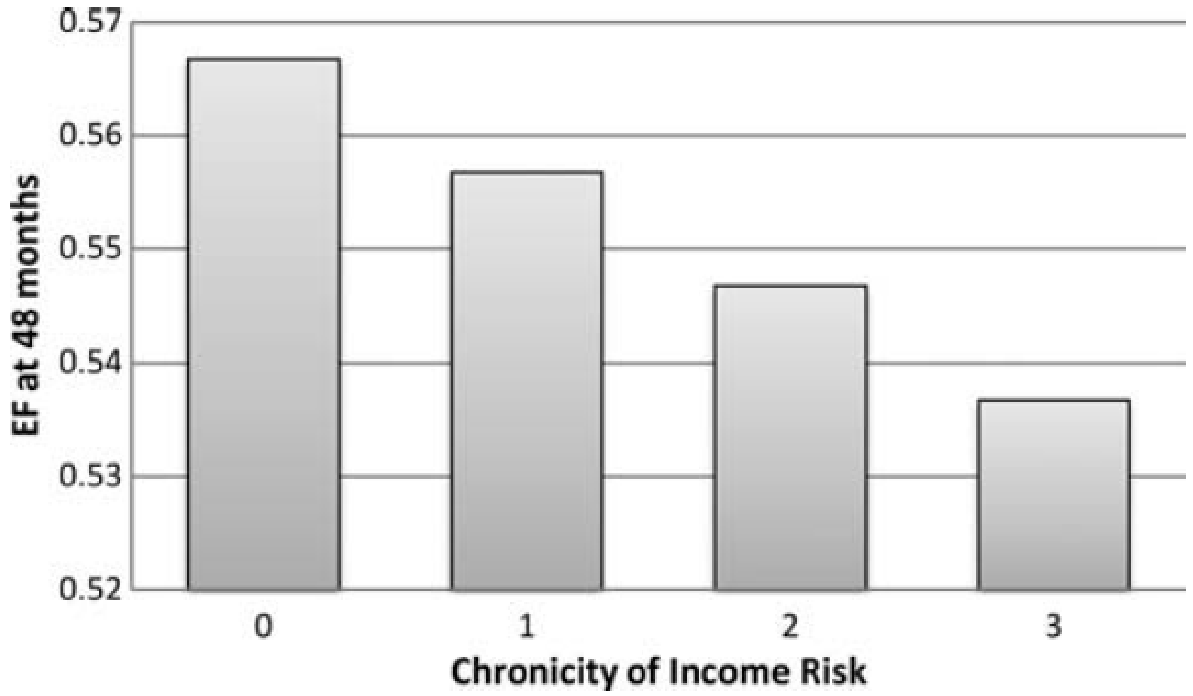
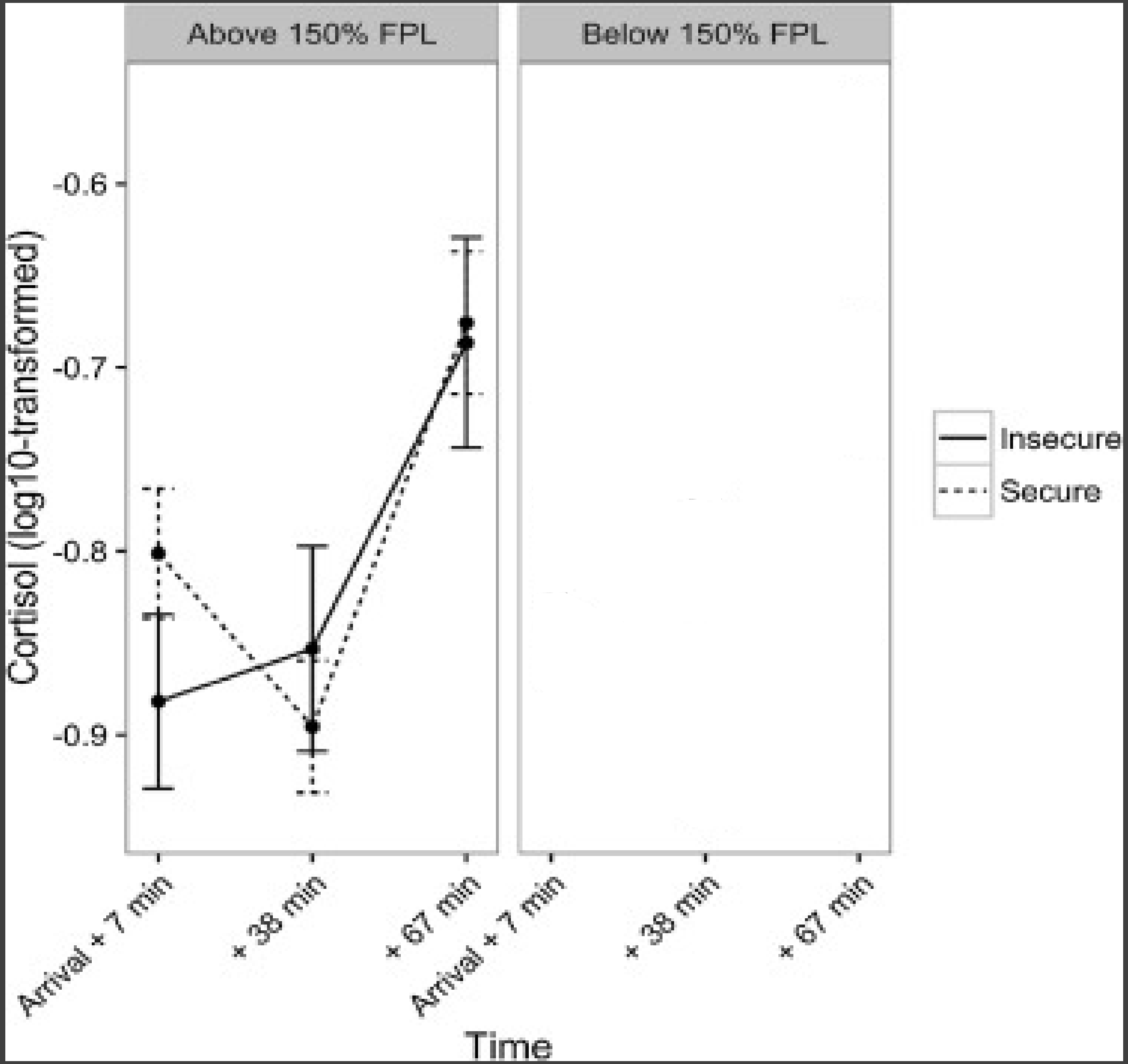


Figure 1. Executive functioning (EF) at 48 months predicted by chronicity of income risk, where chronicity (i.e., a value of 0, 1, 2, or 3) is defined as the number of 12-month time periods in which family income falls at or below the U.S. poverty threshold.

Raver et al (2012) *Dev. Psychol. 49 (2), 292-304*

Parental Attachment security buffers stress

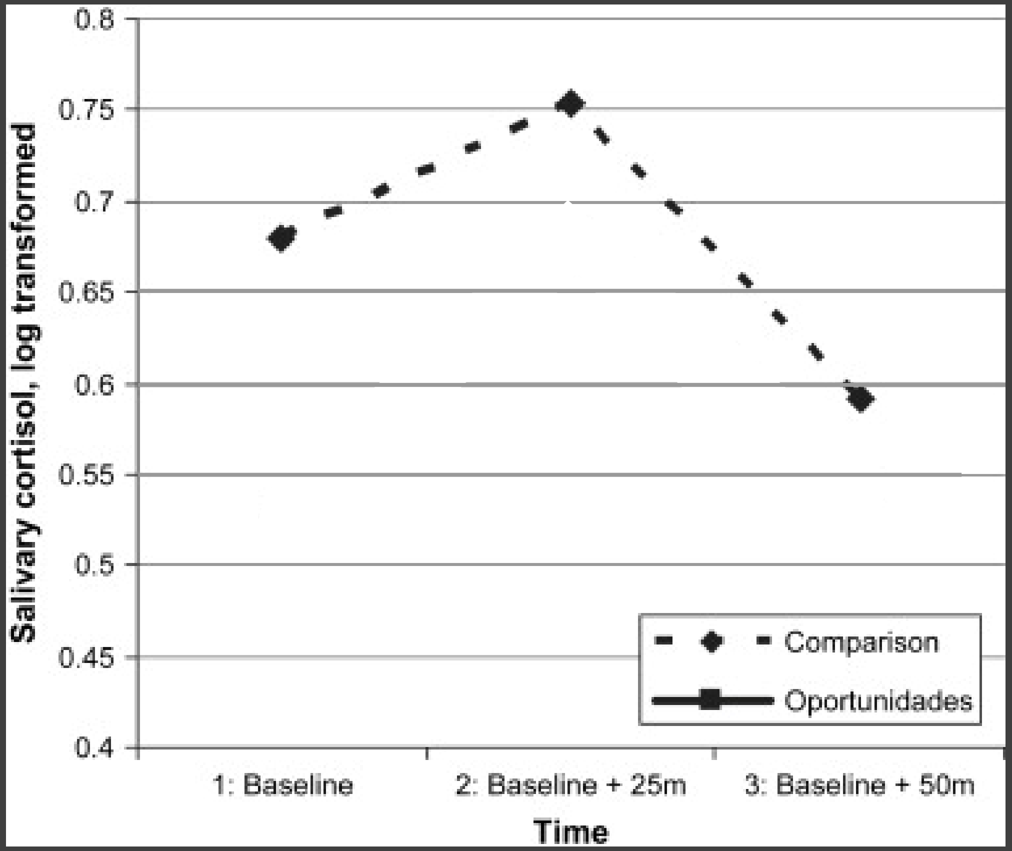
- 177 toddlers with parents
- Well-child visits with innoculations
- 52% below 150% FPL
- 50% white
- Salivary cortisol collected at 3 time points
- Attachment security scored



Johnson et al (2018) *Psychoneuroendocrinol. 95, 120-127*

Poverty-alleviation and cortisol

- 1197 children (491 intervention)
- Cash-transfer program to alleviate extreme poverty
- 20-30% of household income transferred contingent on requirements
- Child salivary cortisol and response to stressor
- Cognitive tasks



Fernald et al (2009) *Soc. Sci. Med. 68, 2180-89*

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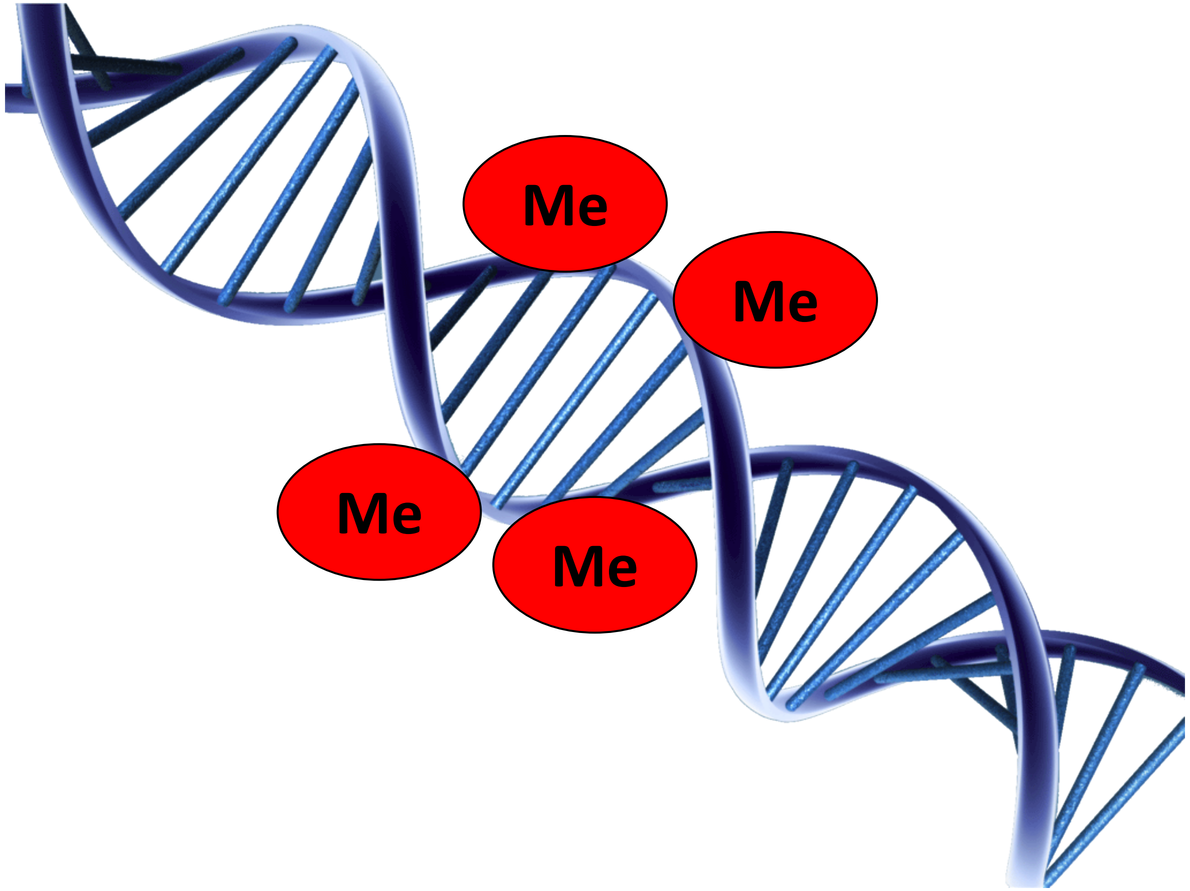
Evans & English, 2002

The Neurobiology of Stress, Trauma, and Resilience

MARQUETTE UNIVERSITY | College of Health Sciences

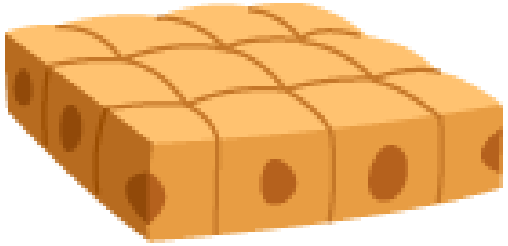
Robert A Wheeler, Ph.D.
Department of Biomedical Sciences

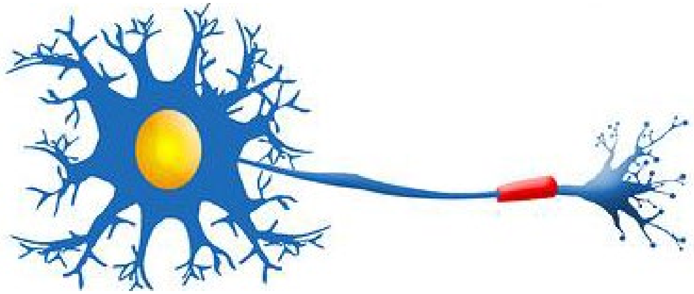
Epigenetics



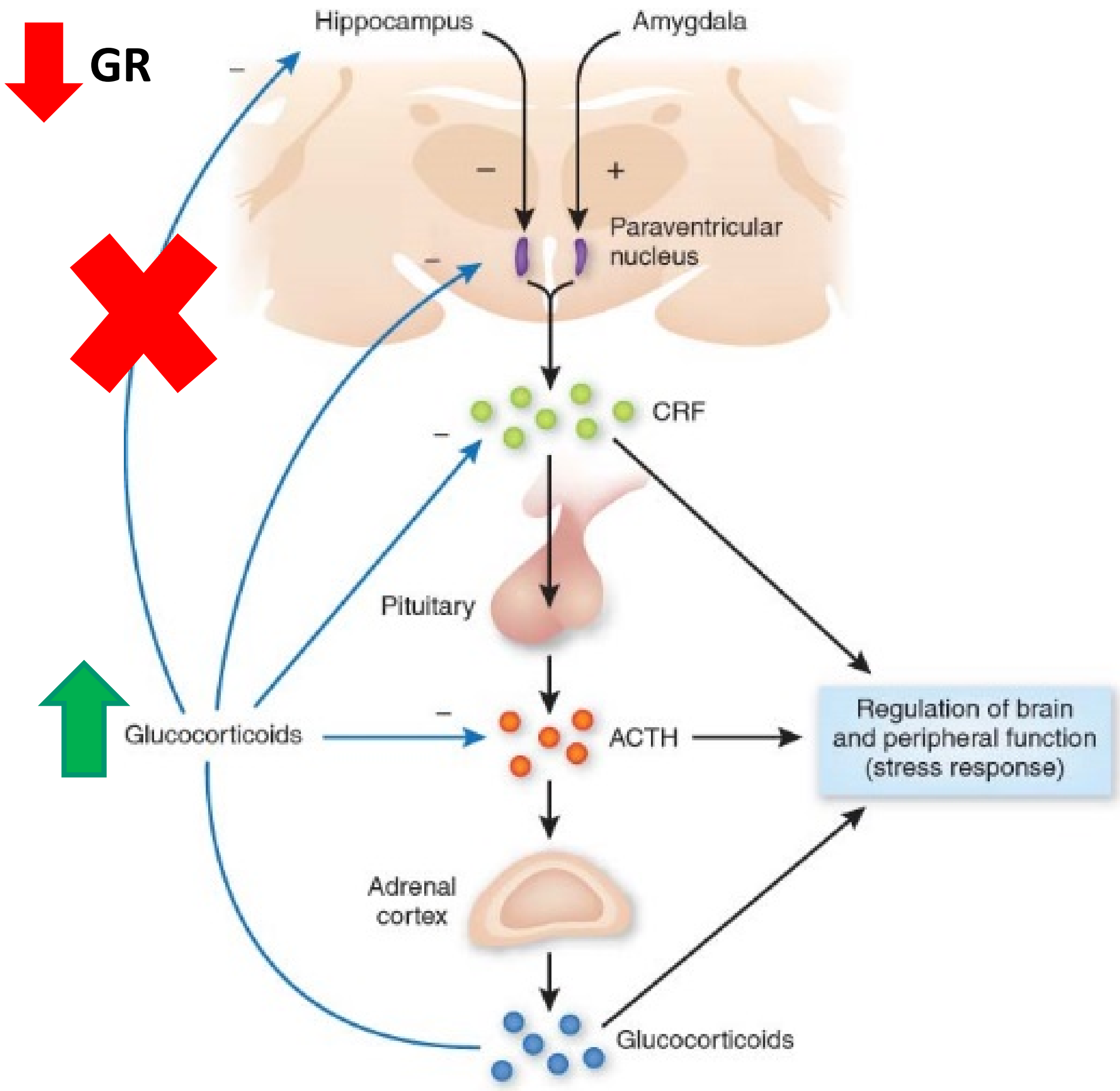
Epigenetics is the process by which changes in an organism are caused by changes in gene expression rather than changes in the genetic code.

Epigenetics

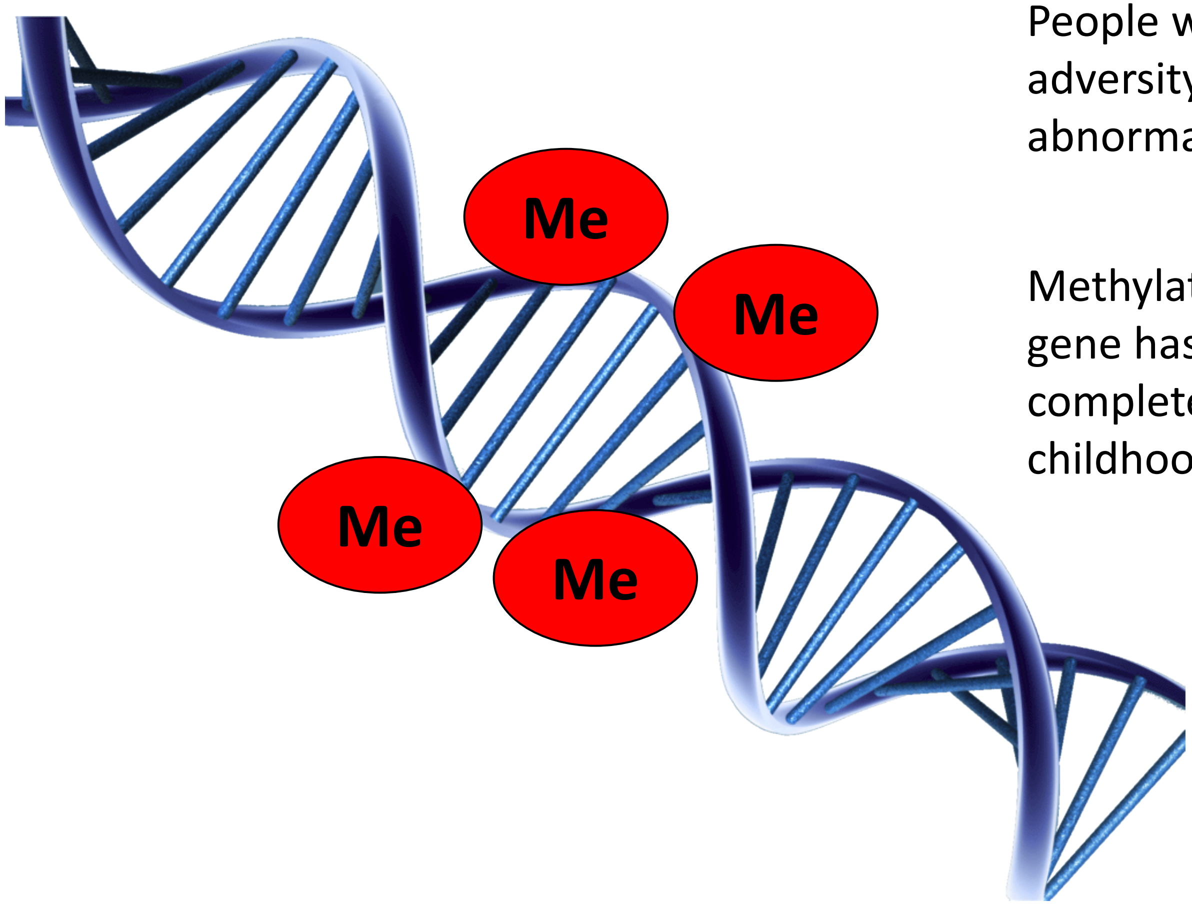




Early Life Adversity Changes the Stress Response



Epigenetic Regulation of the Glucocorticoid Receptor



People who have experienced adversity in childhood often show abnormal stress responses.

Methylation of the analogous human gene has been observed in suicide completers who have a history of childhood sexual abuse.

Early Life Adversity Changes the Developing Brain

Bucharest Early Intervention Project

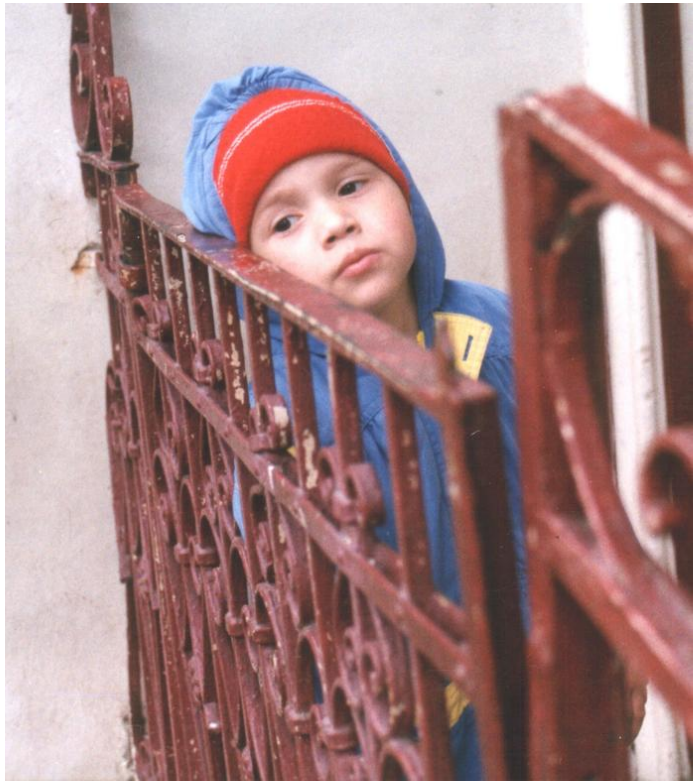
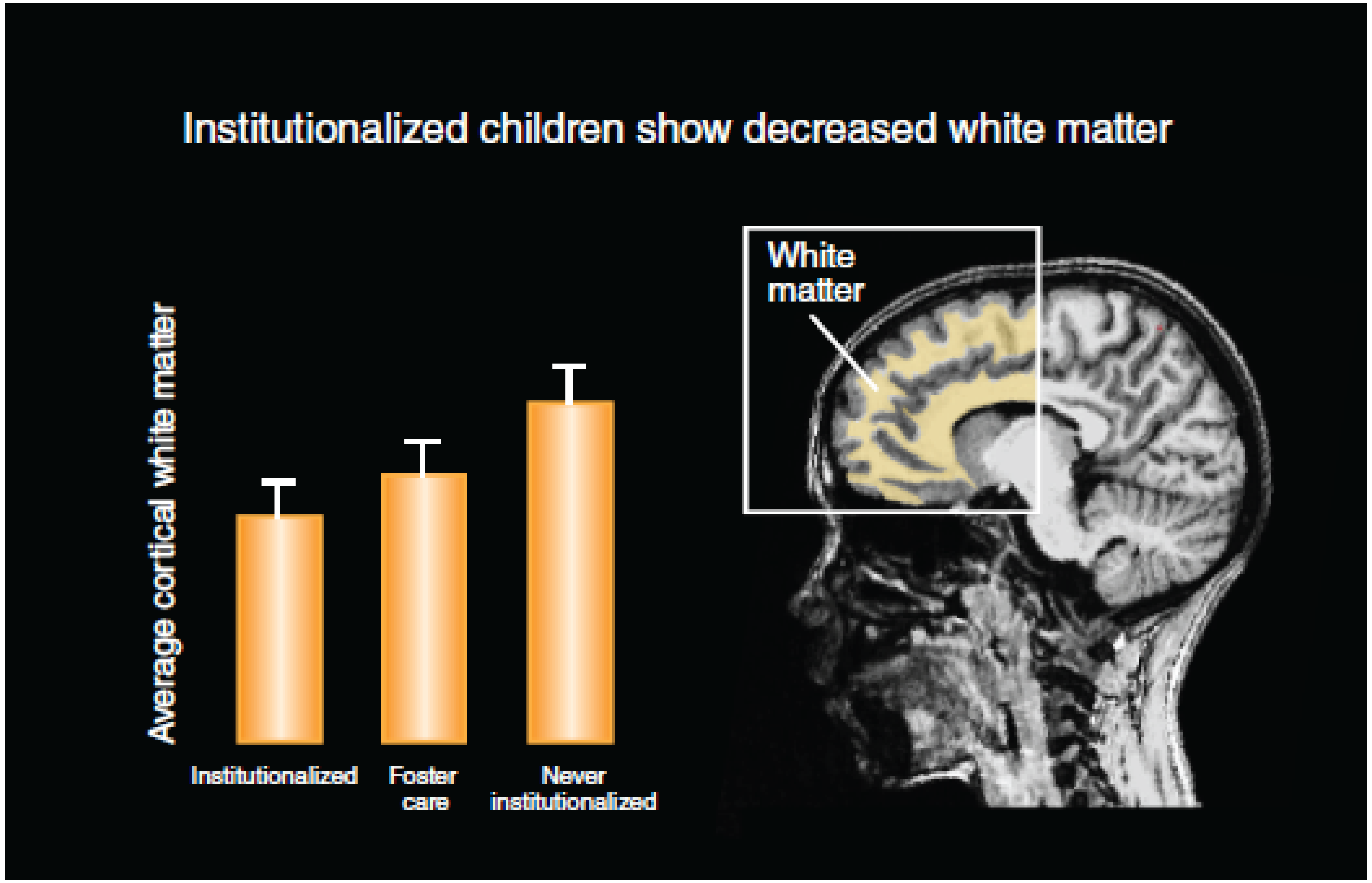


Photo by Michael Carroll

http://www.bucharestearlyinterventionproject.org/

Early Life Adversity Changes the Developing Brain



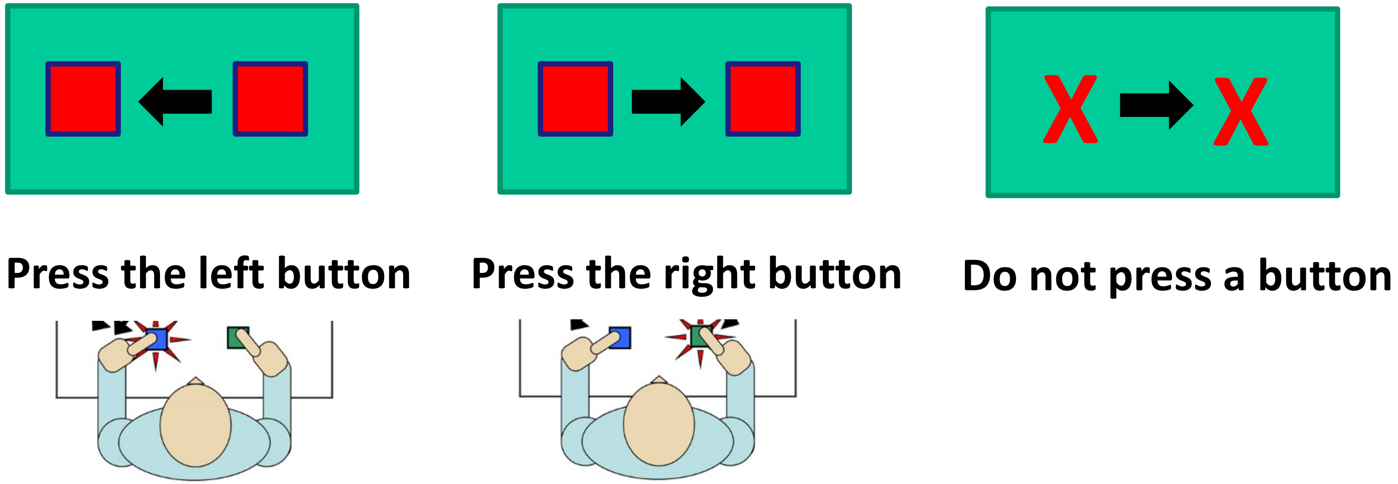
http://www.bucharestearlyinterventionproject.org/

Center on the Developing Child
HARVARD UNIVERSITY

Early Life Adversity Changes the Developing Brain

Adverse Childhood Experiences are associated with behavioral problems.

The Flanker Task

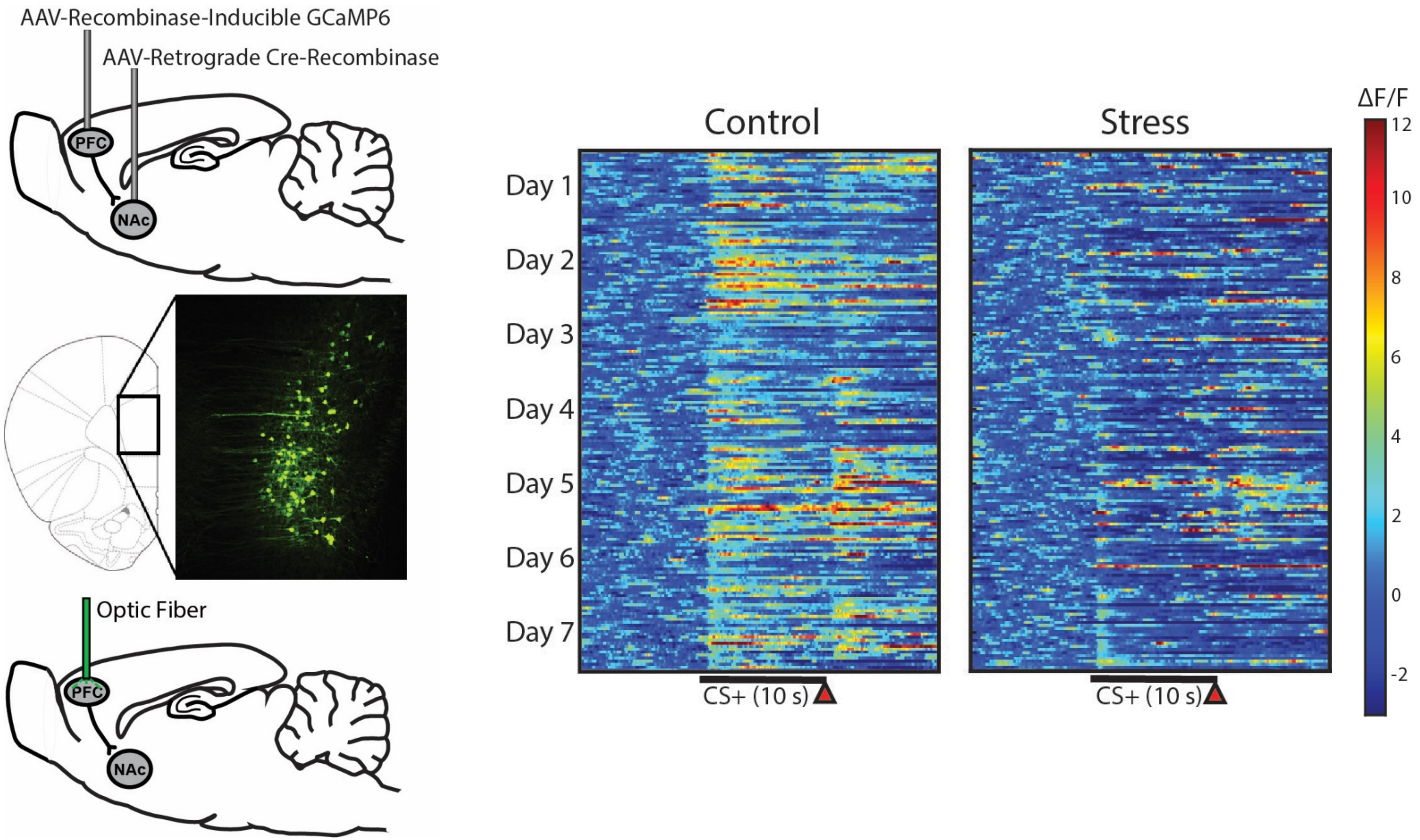


Children placed into foster care showed greater accuracy and faster response times than children who remained in the institution.

McDermott et al., 2013

Animal Models Can Show Us How this Happens

Here at Marquette, researchers are using animal models to understand how stress changes brain activity and behavior.



Spring et al., J Neurosci, 2021

Interventions Confer Resilience

These studies illustrate the biological impact of adverse childhood experiences.
They also provide hope that policy interventions can correct these physiological problems.

The Neurobiology of Stress, Trauma, and Resilience

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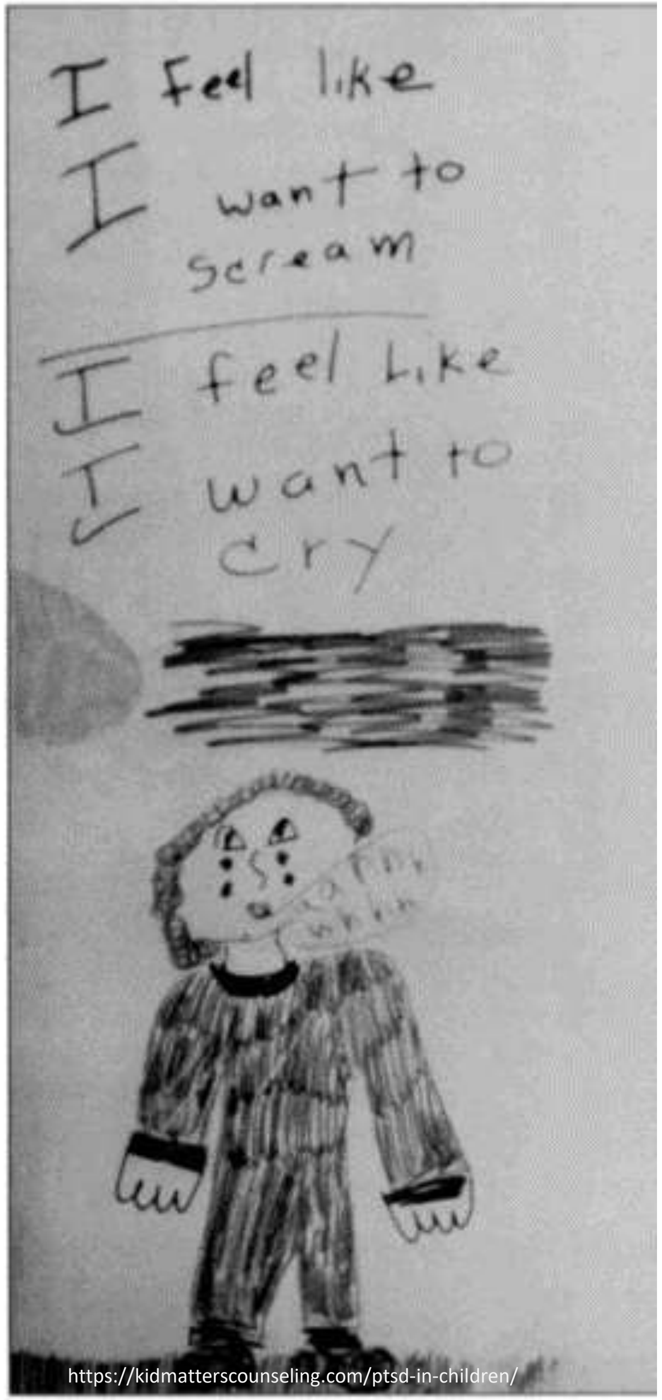
Marieke Gilmartin, Ph.D.
Department of Biomedical Sciences
May 11, 2021



https://kidmatterscounseling.com/ptsd-in-children/

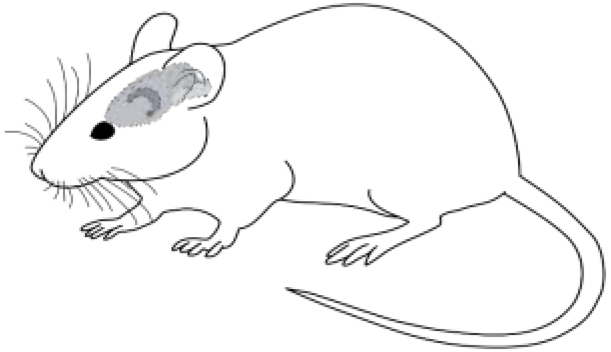
Chronic stress: a risk factor for trauma-related mental illness

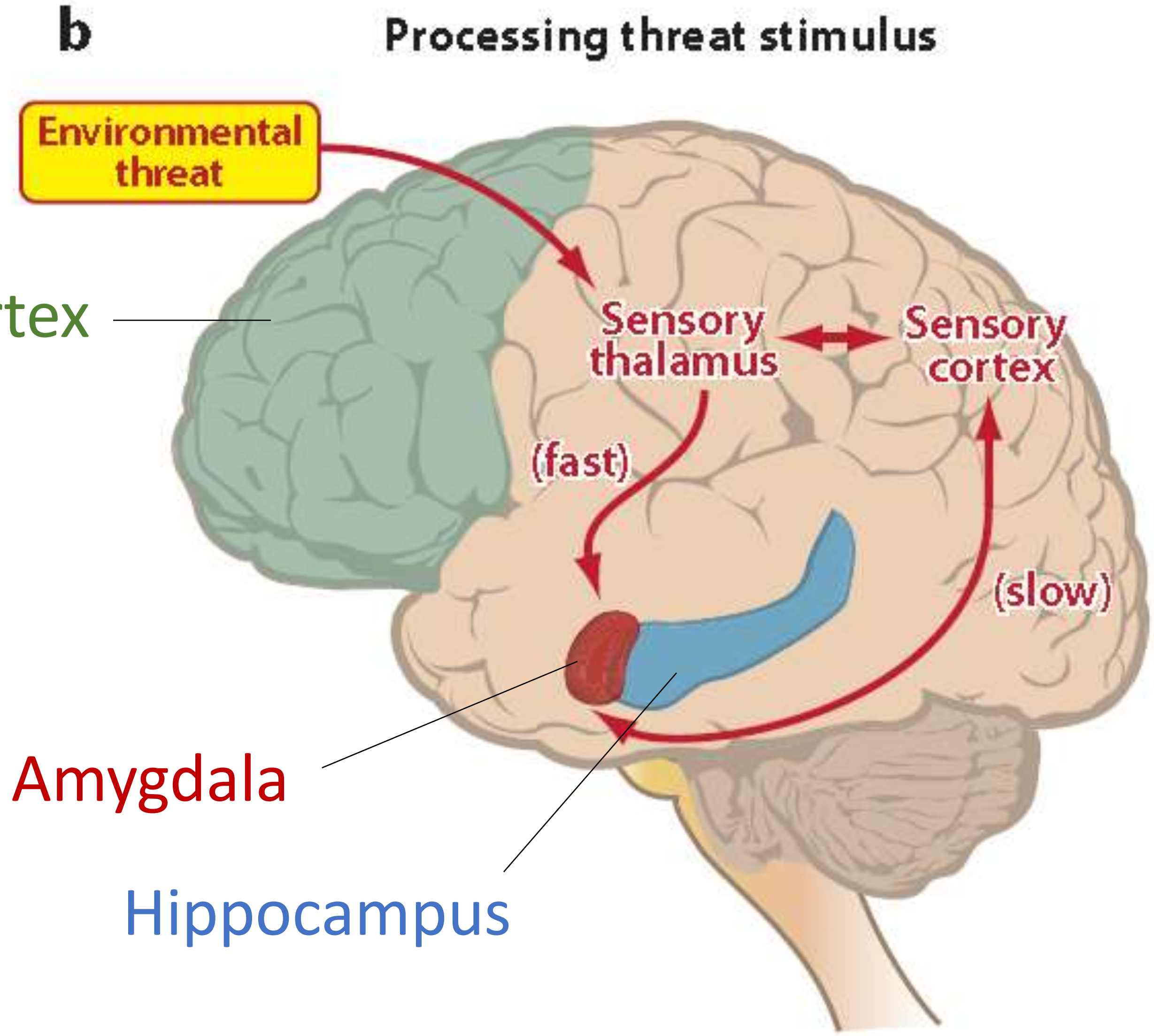
- Living through dangerous events and traumas
- Getting hurt
- Seeing another person hurt, or seeing a dead body
- Childhood trauma
- Feeling horror, helplessness, or extreme fear
- Having little or no social support after the event
- Dealing with extra stress after the event, such as loss of a loved one, pain and injury, or loss of a job or home
- Having a history of mental illness or substance abuse

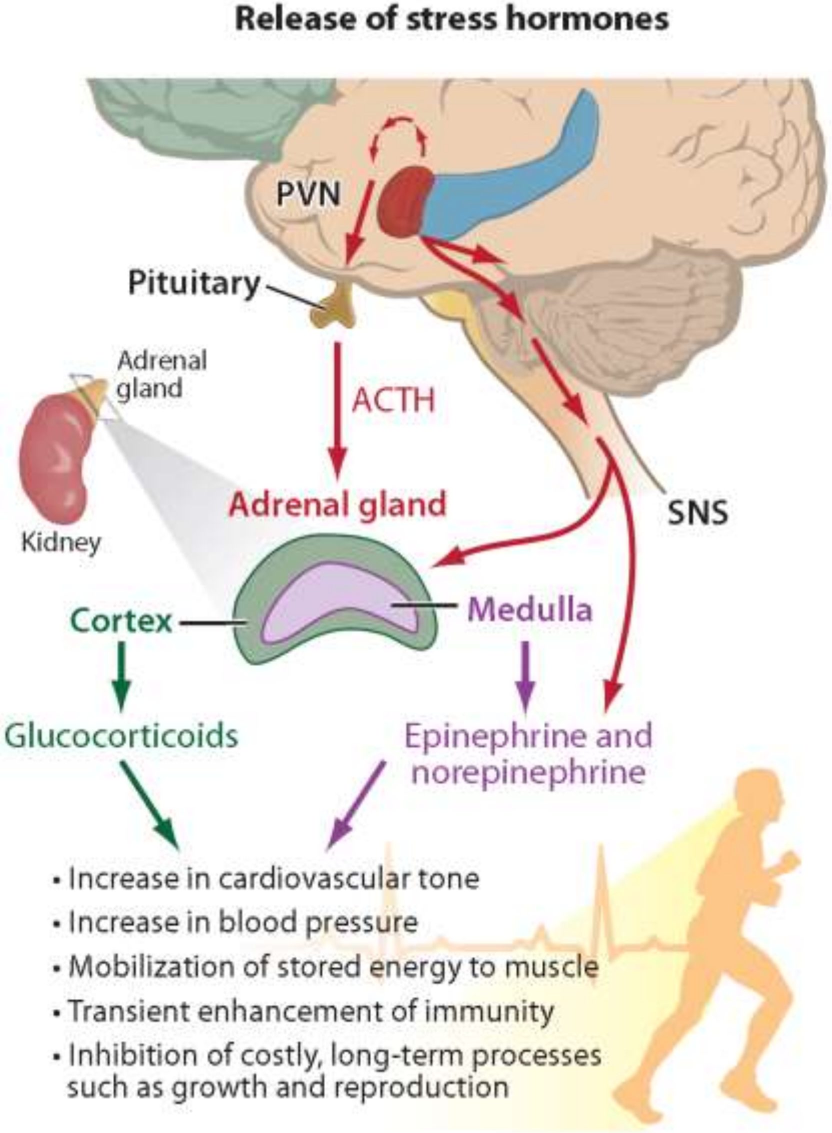
NIH National Institute of Mental Health

https://www.nimh.nih.gov/health/topics/post-traumatic-stress-disorder-ptsd/index.shtml

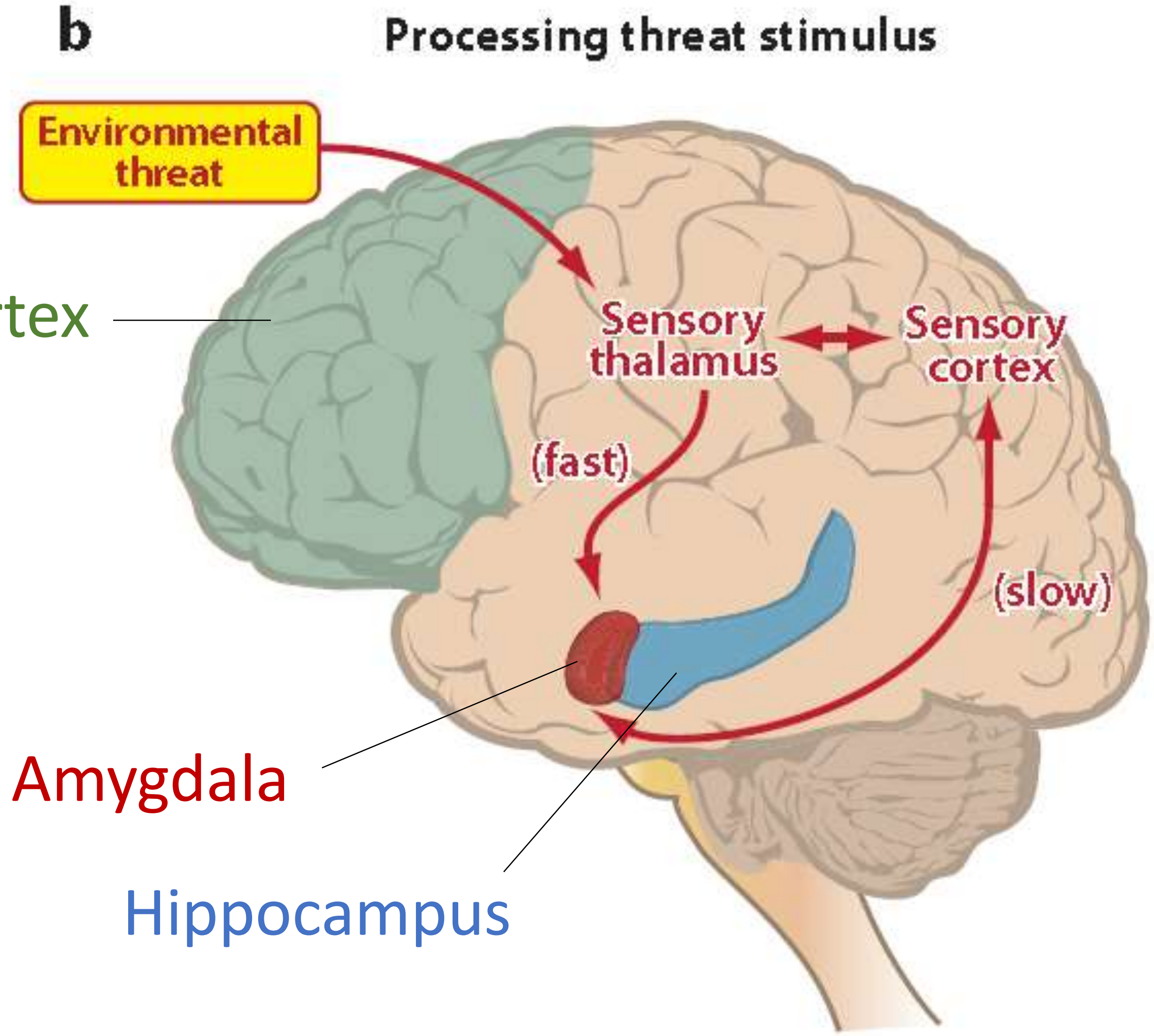
Fear circuitry

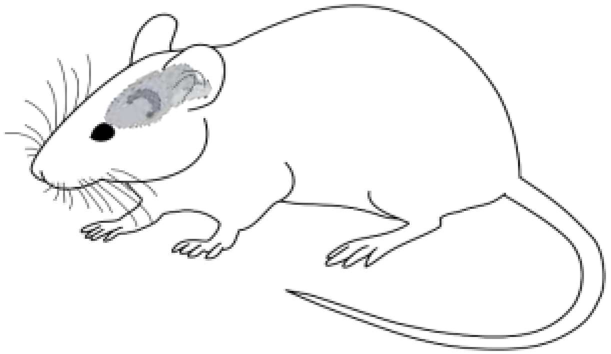




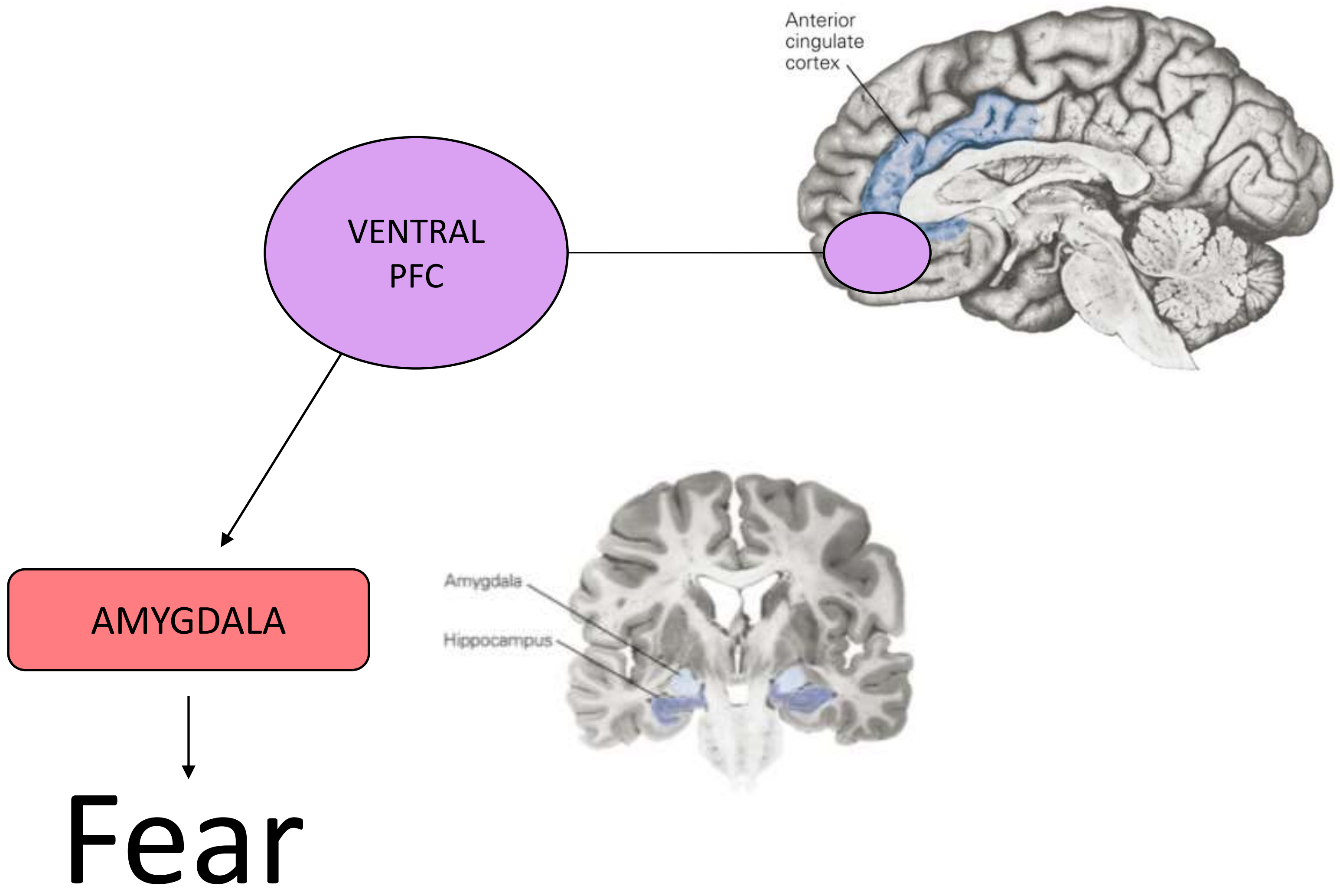

Release of stress hormones
PVN
Pituitary
Adrenal gland
ACTH
Kidney
Adrenal gland
SNS
Cortex
Medulla
Glucocorticoids
Epinephrine and norepinephrine
• Increase in cardiovascular tone
• Increase in blood pressure
• Mobilization of stored energy to muscle
• Transient enhancement of immunity
• Inhibition of costly, long-term processes such as growth and reproduction

Fear circuitry

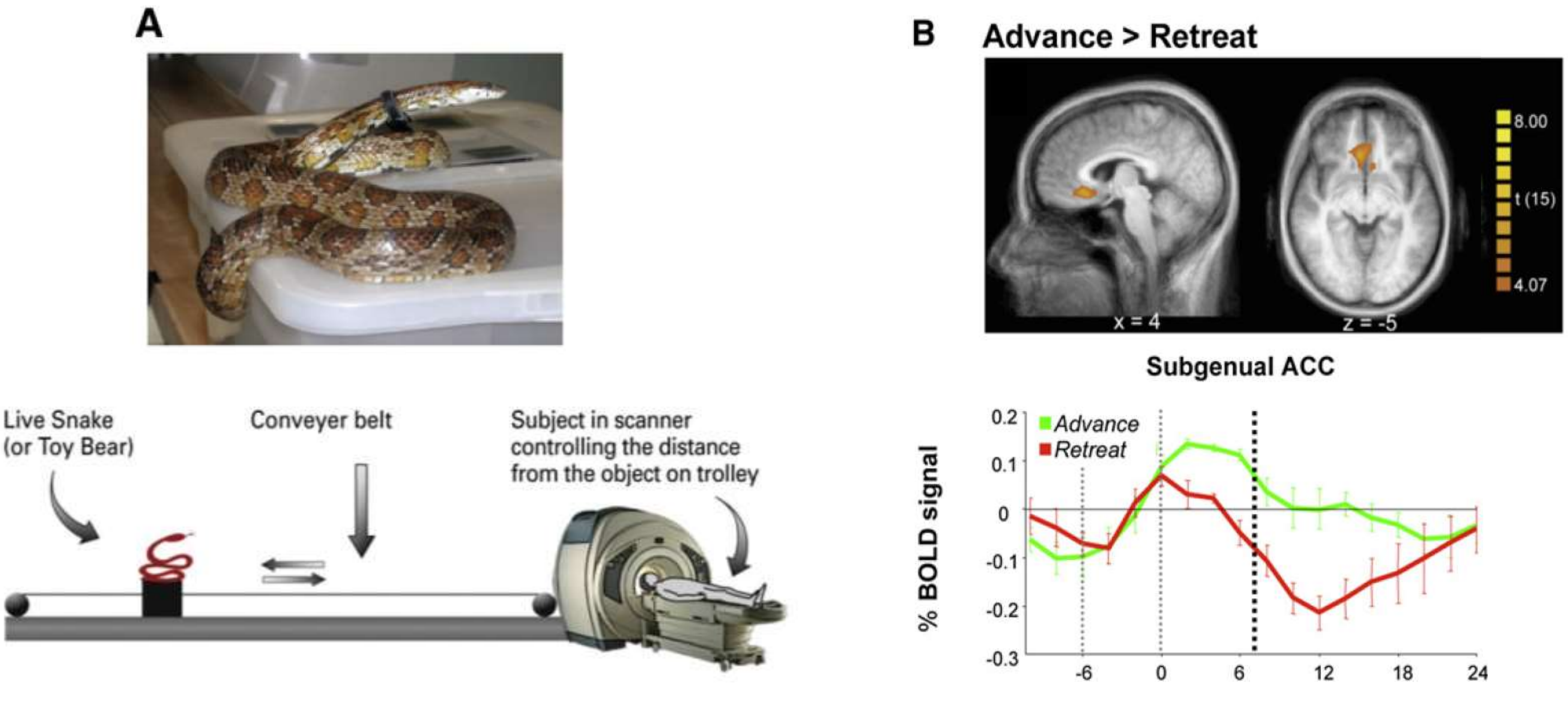




Prefrontal cortical regulation of emotion

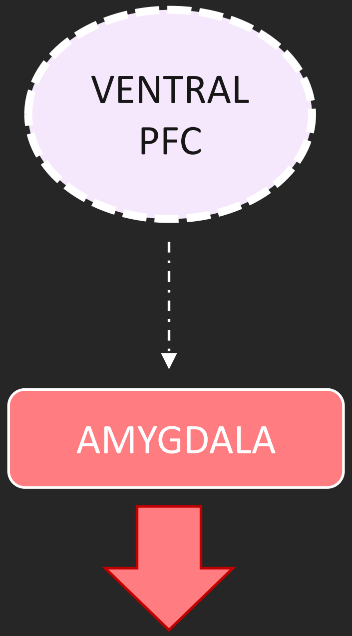


Brain mechanisms of courage



Nili et al., 2010 *Neuron*

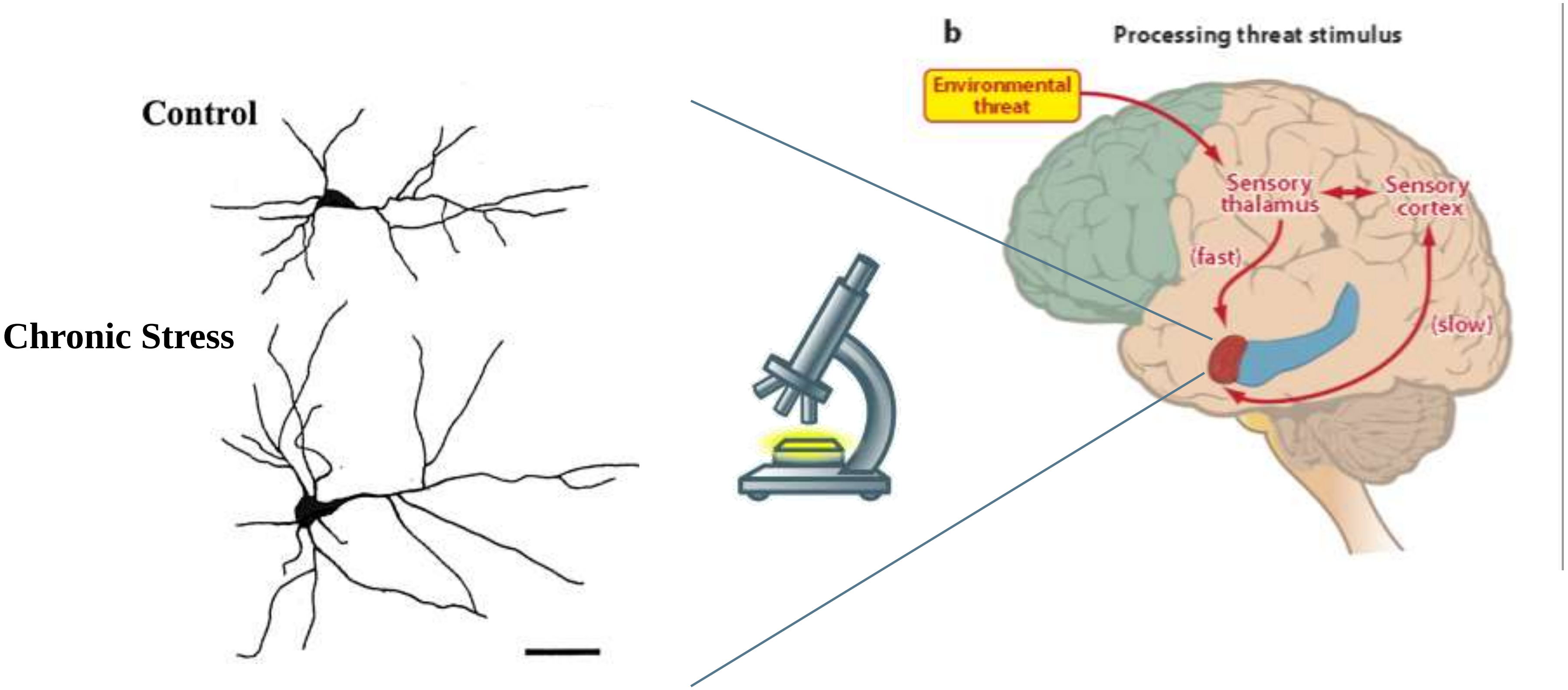
Pathological fear and anxiety



- Prolonged emotional and stress reactions when triggered
- Impaired ability to suppress or extinguish fear
- Generalization of fear to non-threatening situations
- Avoidance of anxiety-provoking situations and people

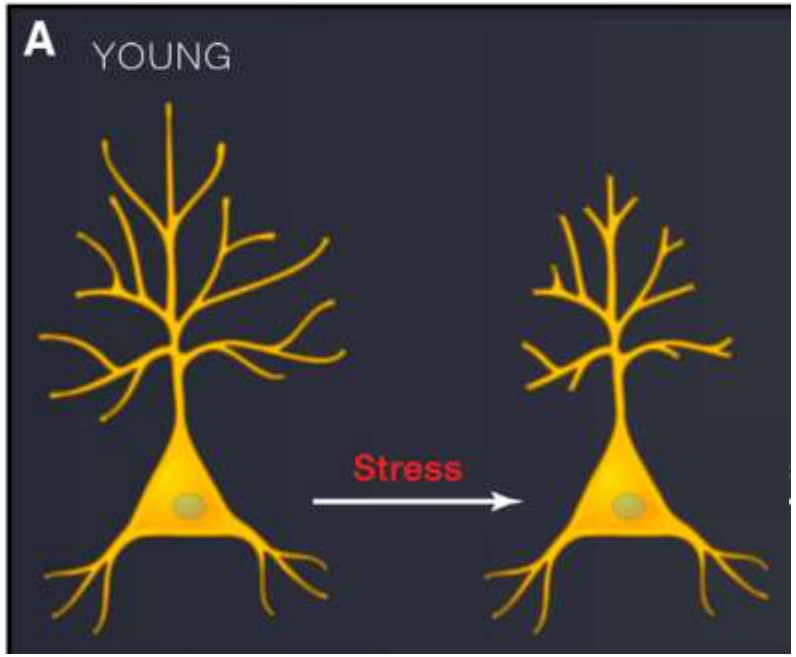
HOW DOES CHRONIC STRESS AFFECT THESE BRAIN SYSTEMS?

Amygdala neurons increase in size after prolonged stress

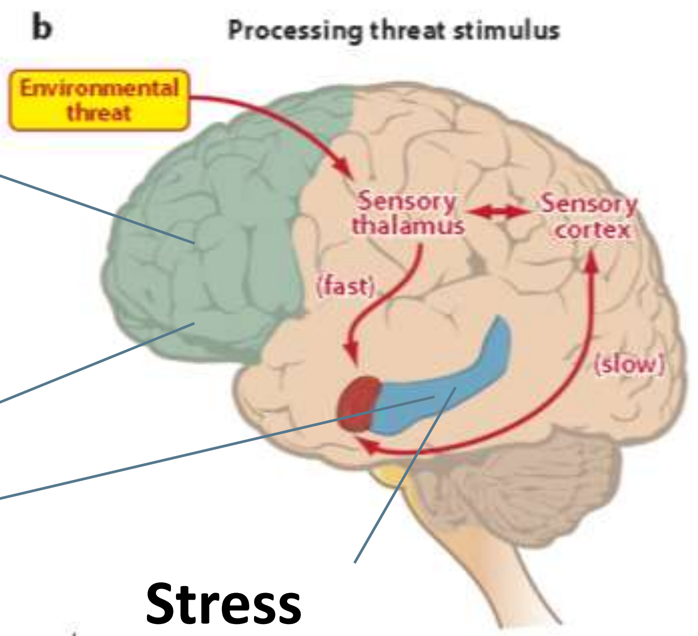


From Vyas et al., 2002

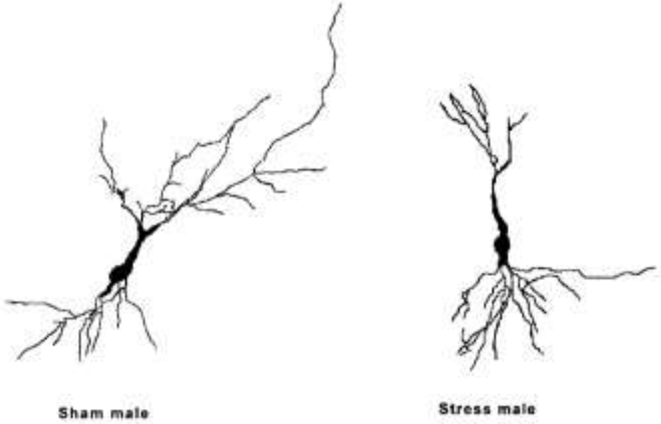
Prefrontal & hippocampal neurons shrink after prolonged stress



From McEwan & Morrison, 2013



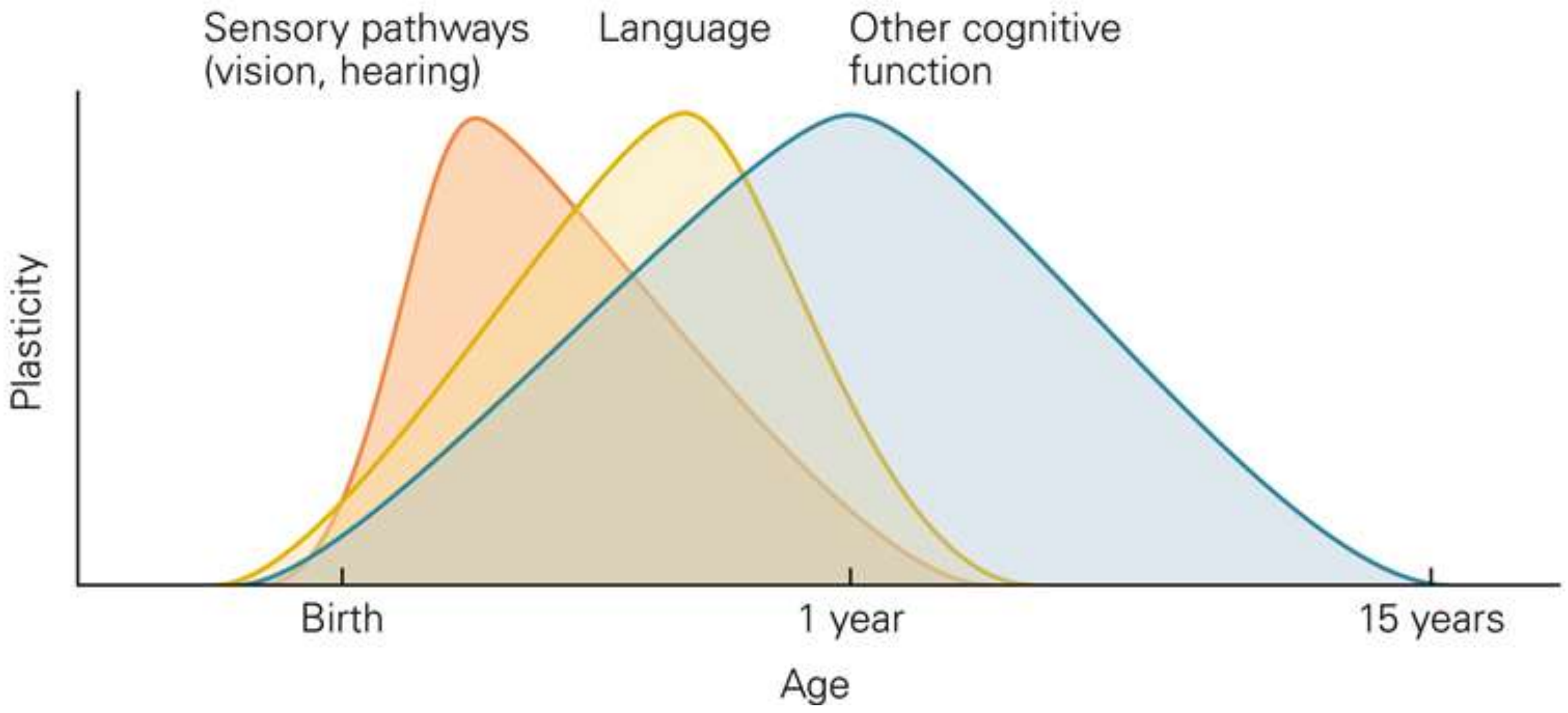
No Stress **Stress**



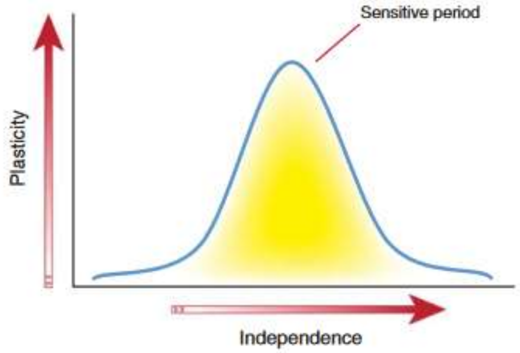
How does early life adversity affect threat-response circuits?

Childhood: a sensitive window of risk & resilience

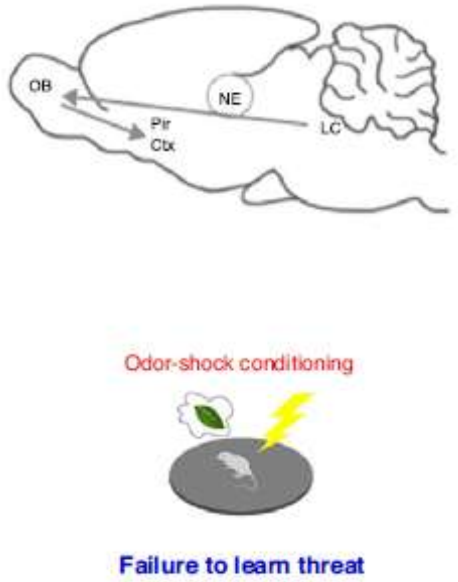
Sensitive periods for sensory and cognitive skills in humans



KT Hensch, 2005

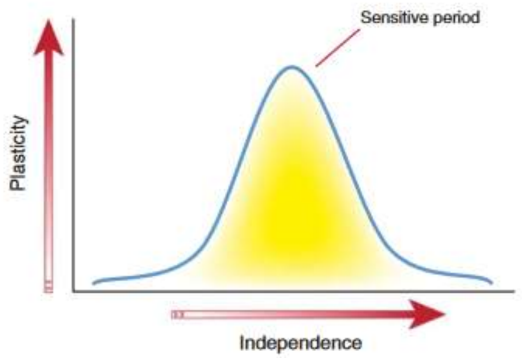


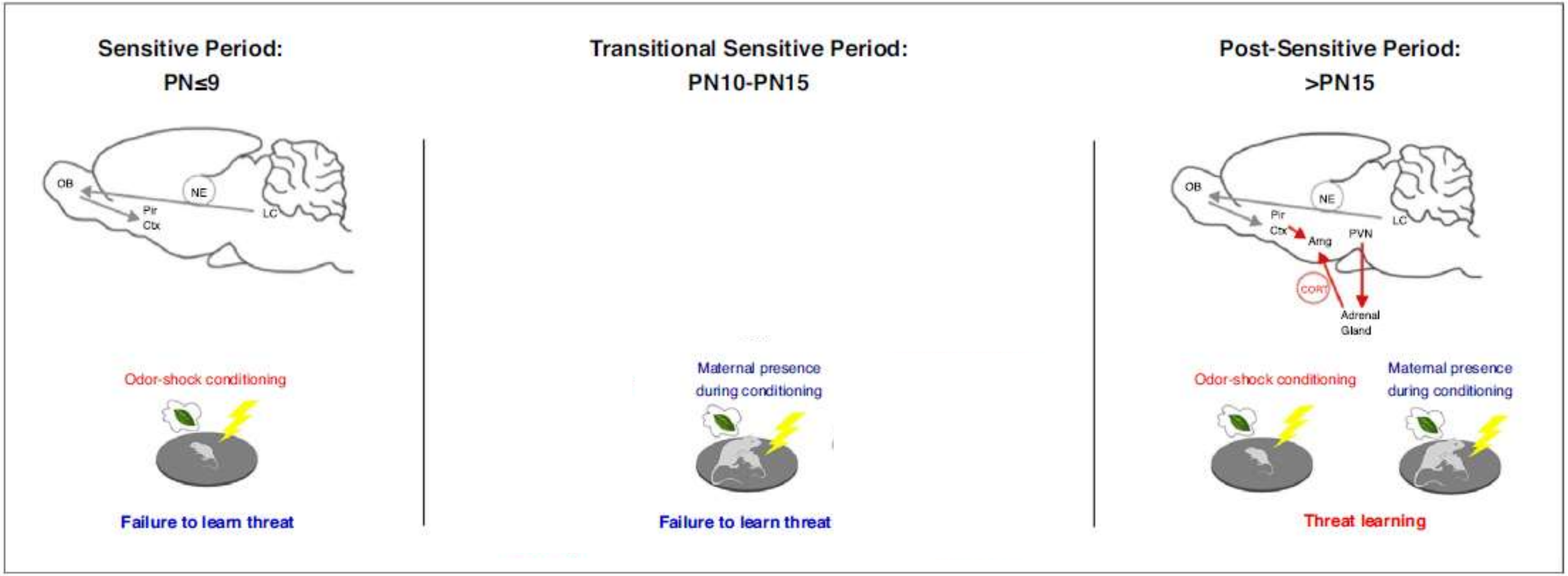
Sensitive Period:
PN≤9



Post-Sensitive Period:
>PN15

From Sullivan & Opendak, 2018

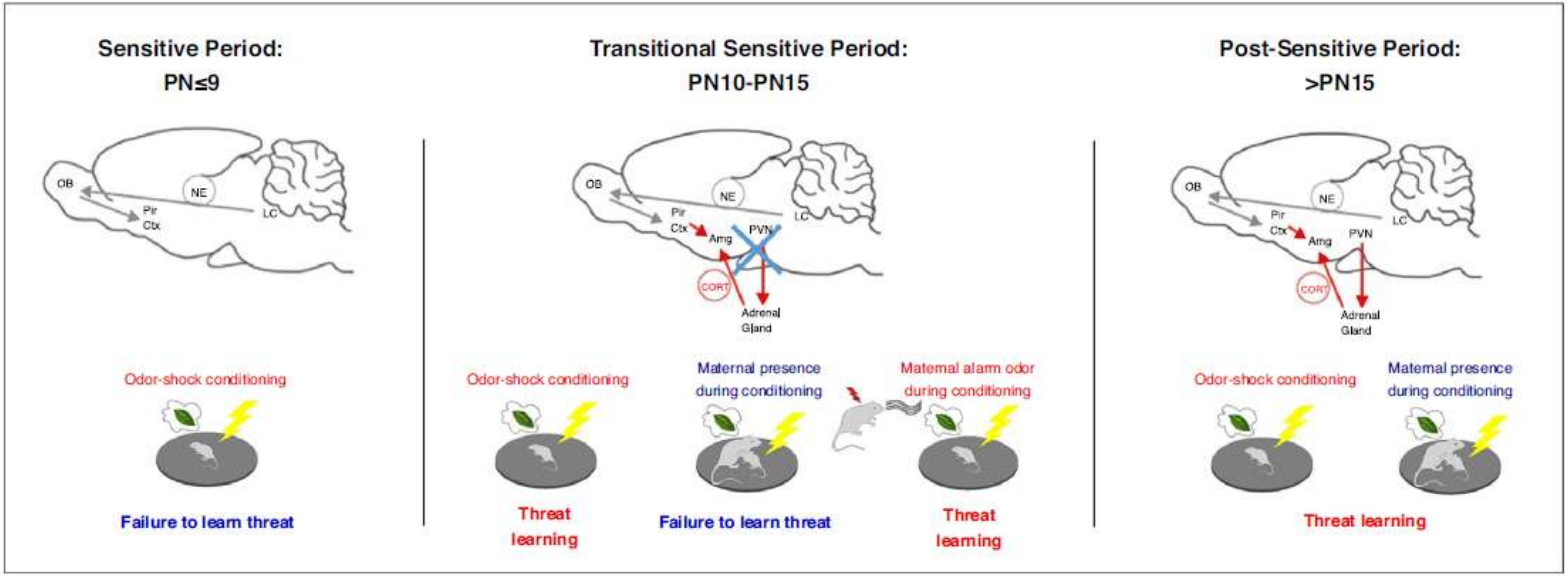




From Sullivan & Opendak, 2018

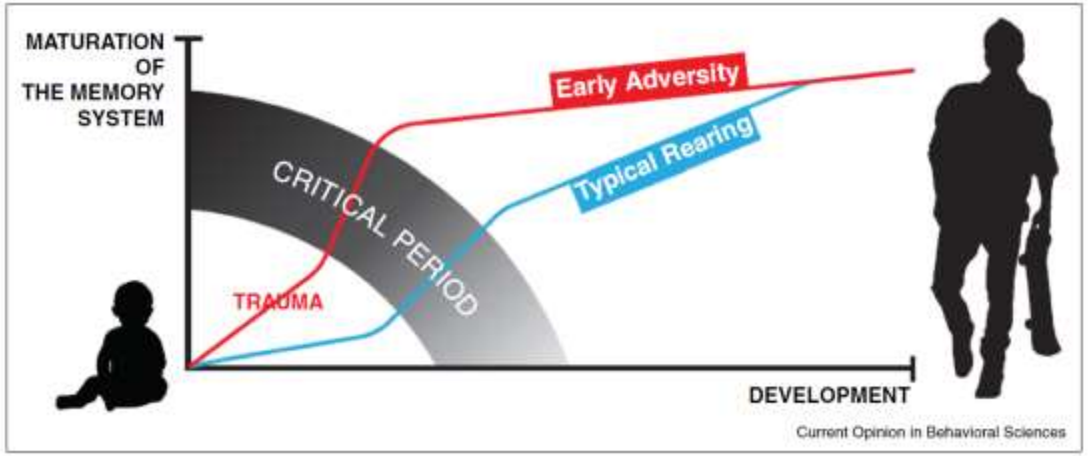
Early life adversity affects the parental buffer

Separation stress or a stressed caregiver produces adult-like activation of the fear system

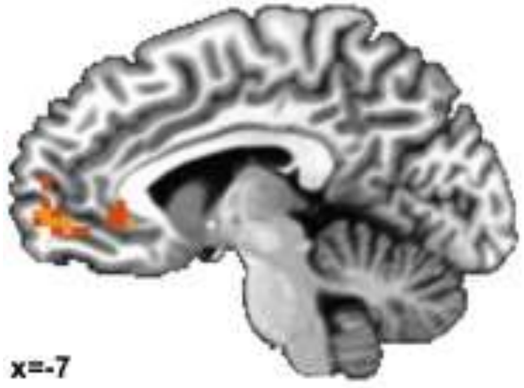


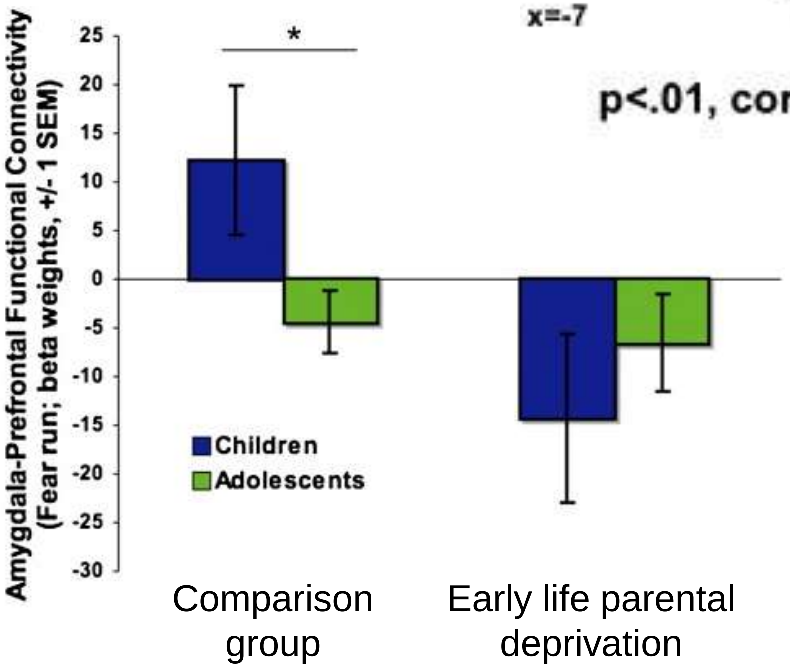
From Sullivan & Opendak, 2018

Early life stress accelerates the maturation of fear systems



Amygdala-prefrontal connectivity **matures earlier** in children following early life stress *(previously institutionalized)*





Accelerated maturation at the expense of full functional capacity

Gee et al., 2013 *PNAS*

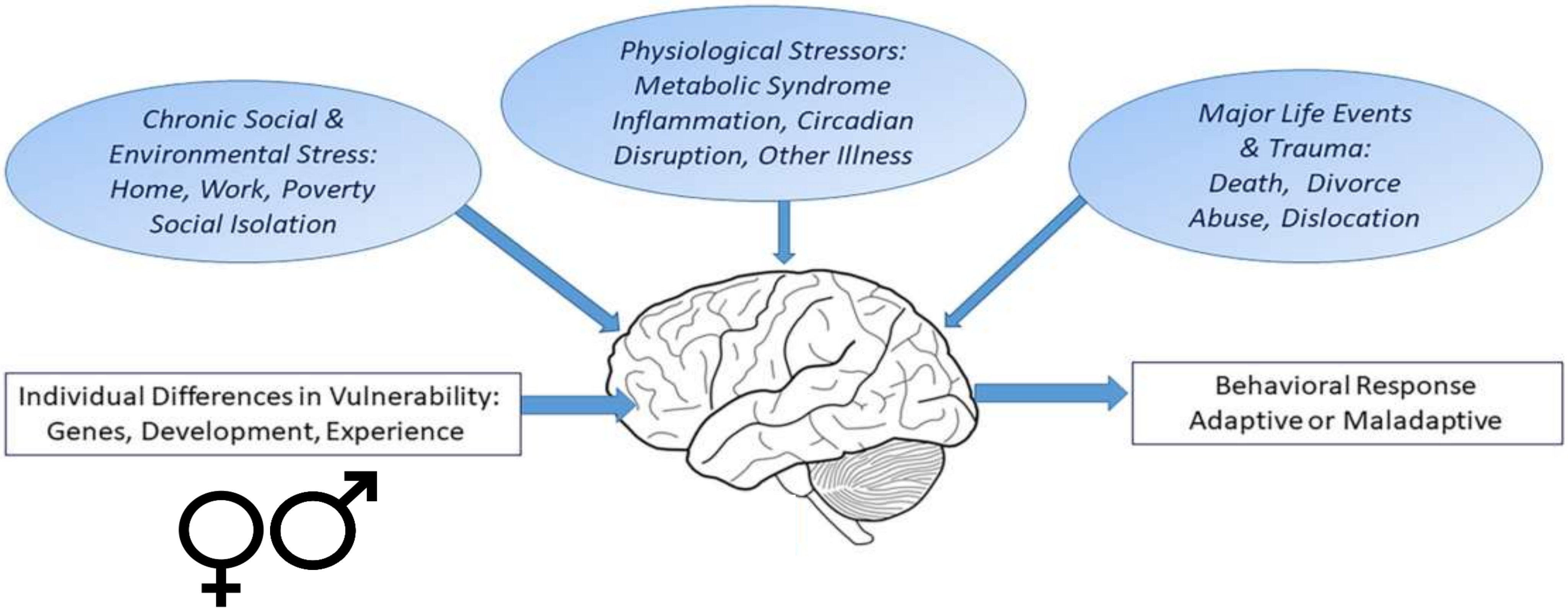
Resilience factors

Social support
(family, friends, a support group)

Learning to feel good about one's own actions in the face of danger

Having a positive coping strategy

Being able to act and respond effectively despite feeling fear

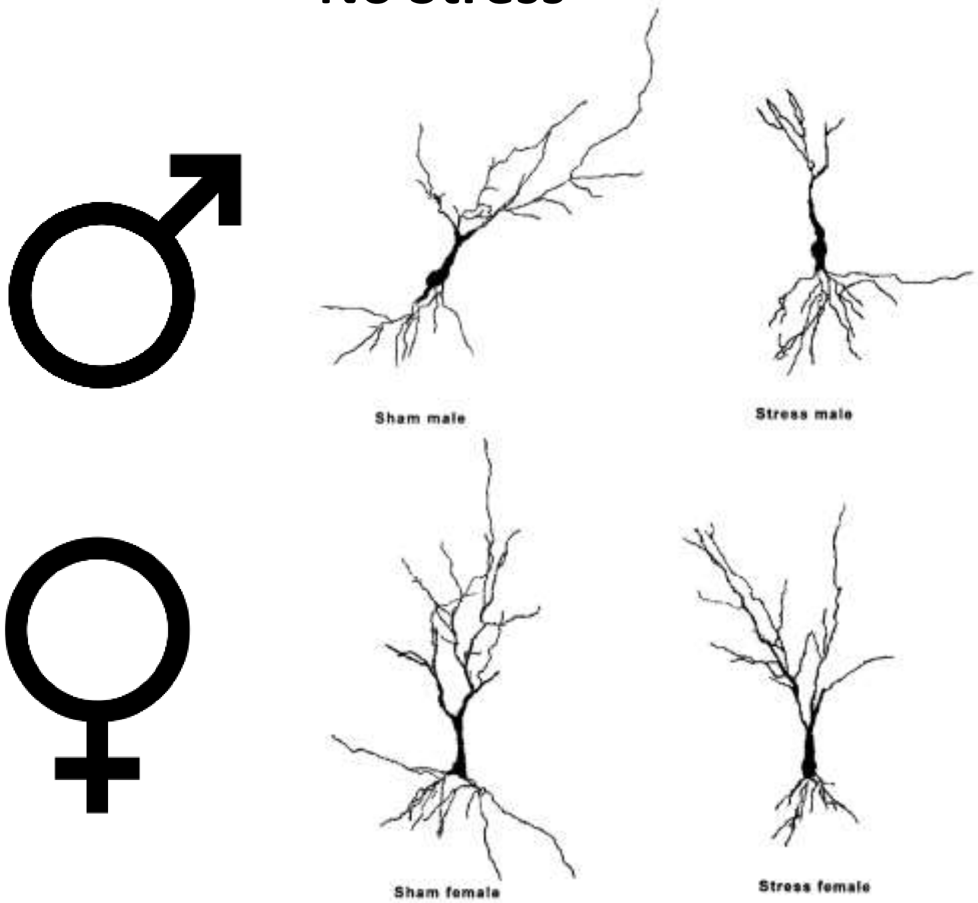


Complexity is an opportunity to identify resilience

McEwen & Akil, 2020 *J Neuro*

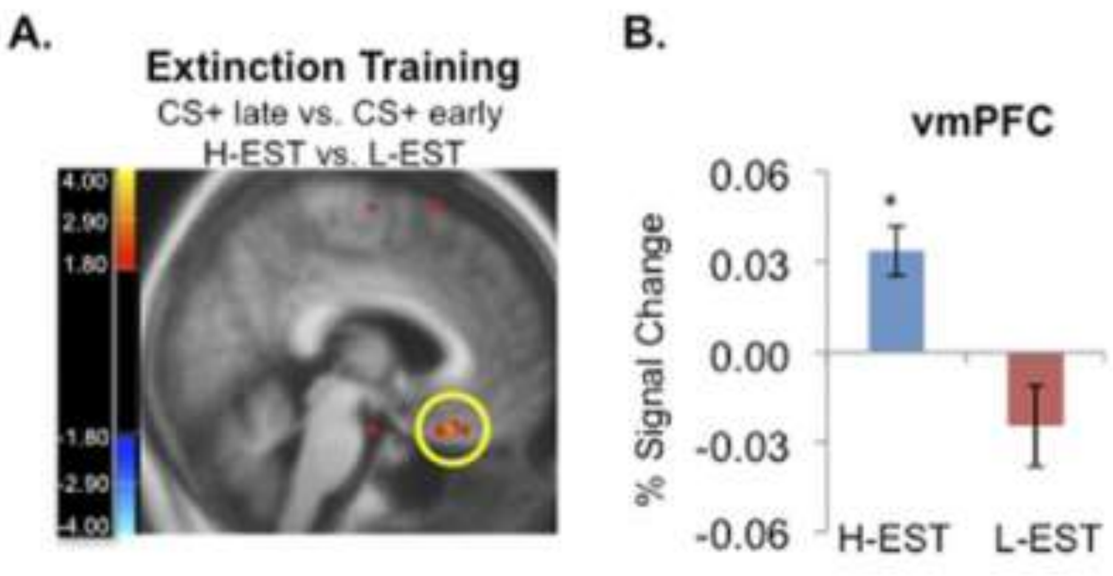
Complexity is an opportunity for resilience

No Stress **Stress**



Galea et al., 1997

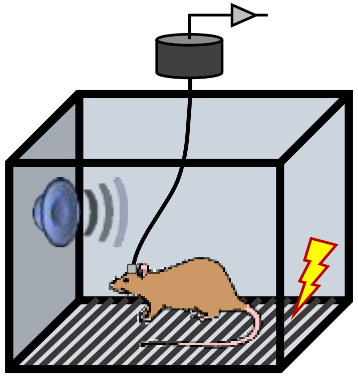
Circulating sex hormones (e.g., Estrogen, Testosterone)

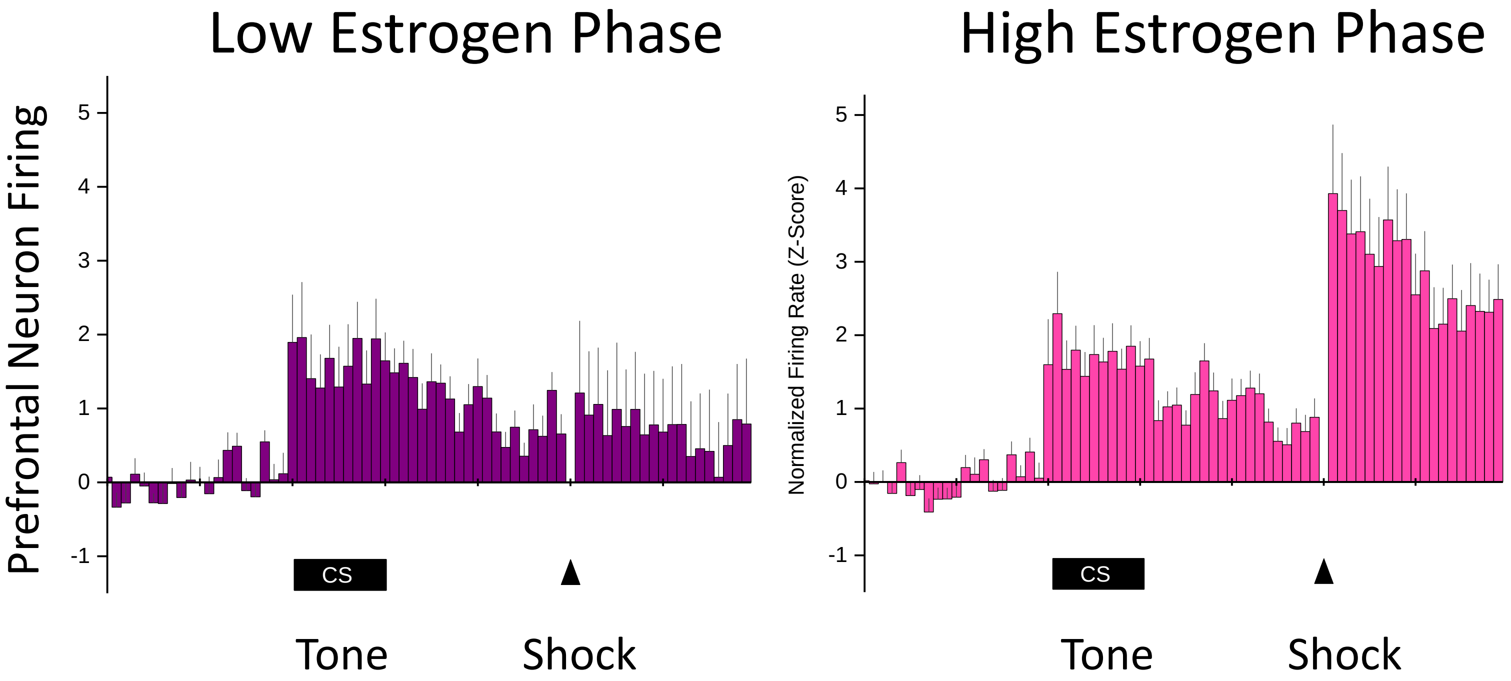


Zeidan et al., 2011

Sex hormones affect prefrontal response to shock

Matt Herbst, Matt LaViola





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