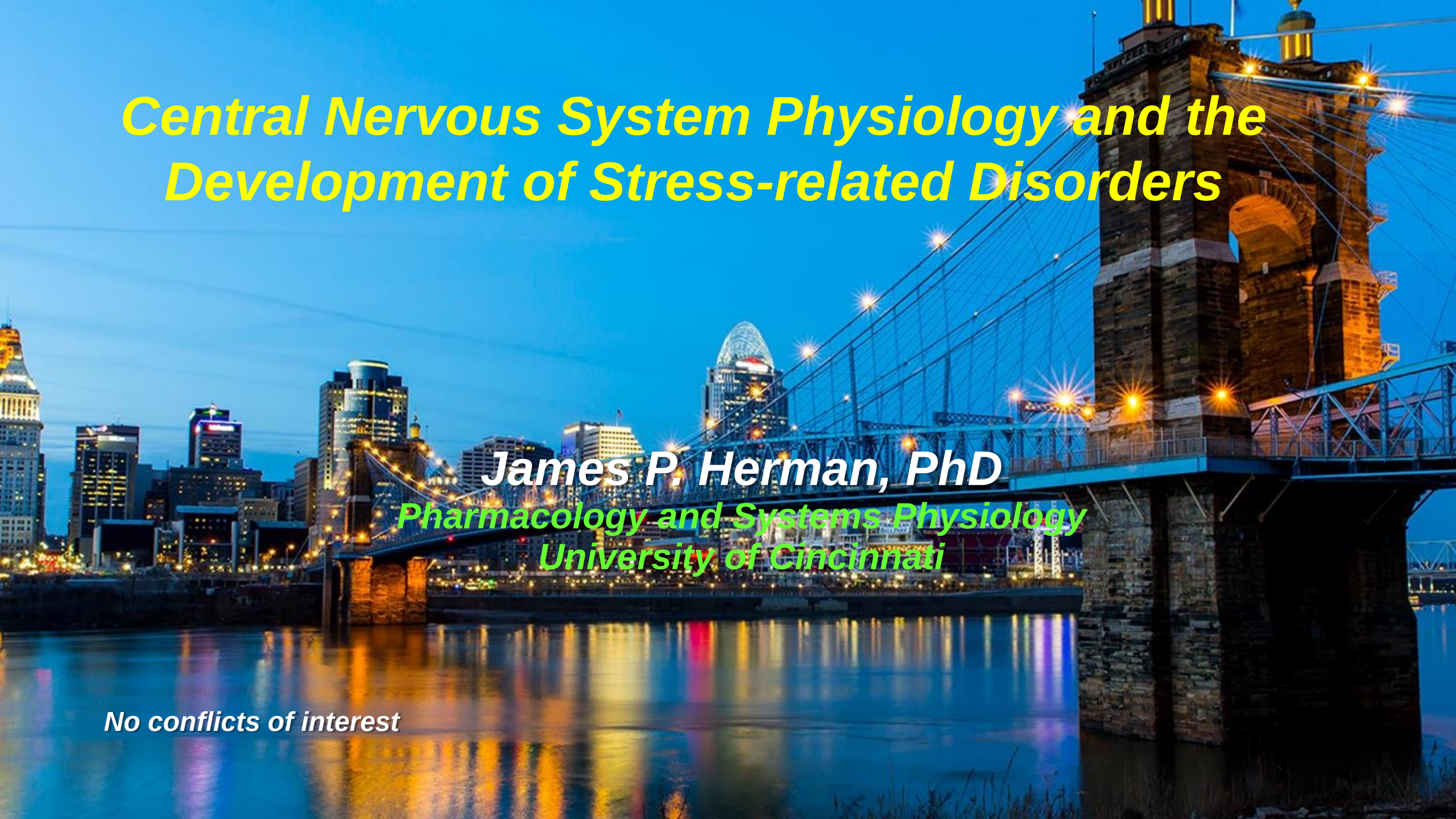


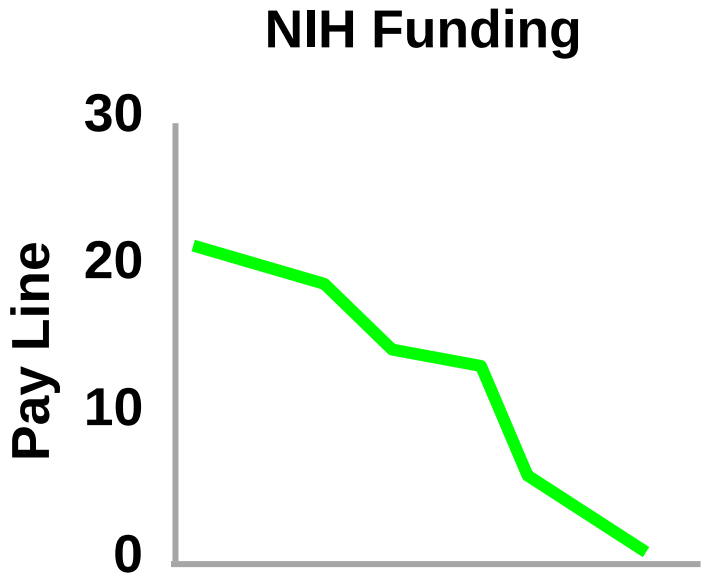
Central Nervous System Physiology and the Development of Stress-related Disorders

James P. Herman, PhD

Pharmacology and Systems Physiology

University of Cincinnati

No conflicts of interest



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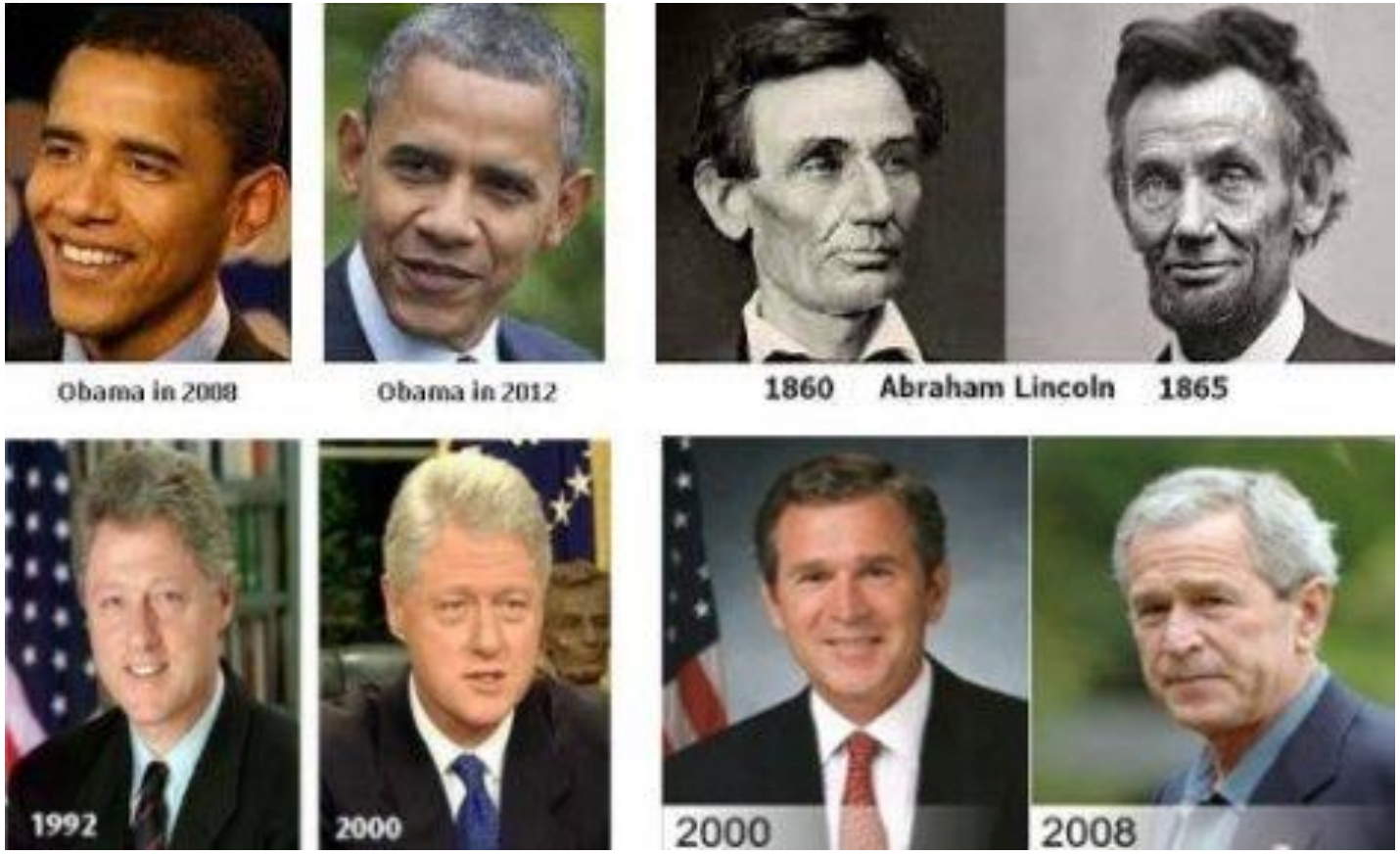
Stress and Aging



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Stress: A Whole Body Problem

- ***Integrated physiological (and behavioral) response*** **designed to optimize survival and well-being in the face of adversity (internal or external)**
- ***Widespread molecular signal conveying contextual information***
- ***Amplify ongoing cellular processes (beneficial or deleterious)***

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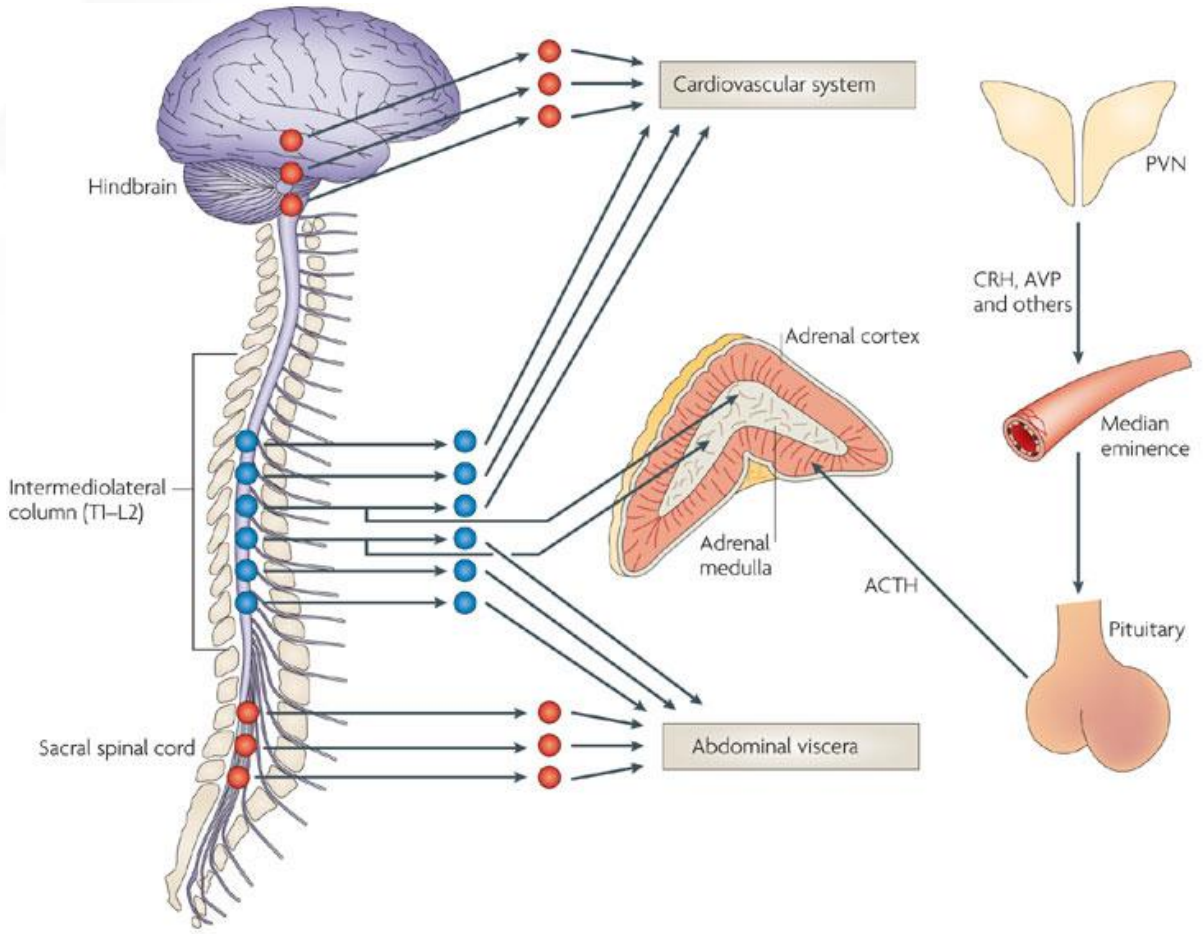

Ulrich-Lai and Herman, 2009
Nature Reviews | Neuroscience

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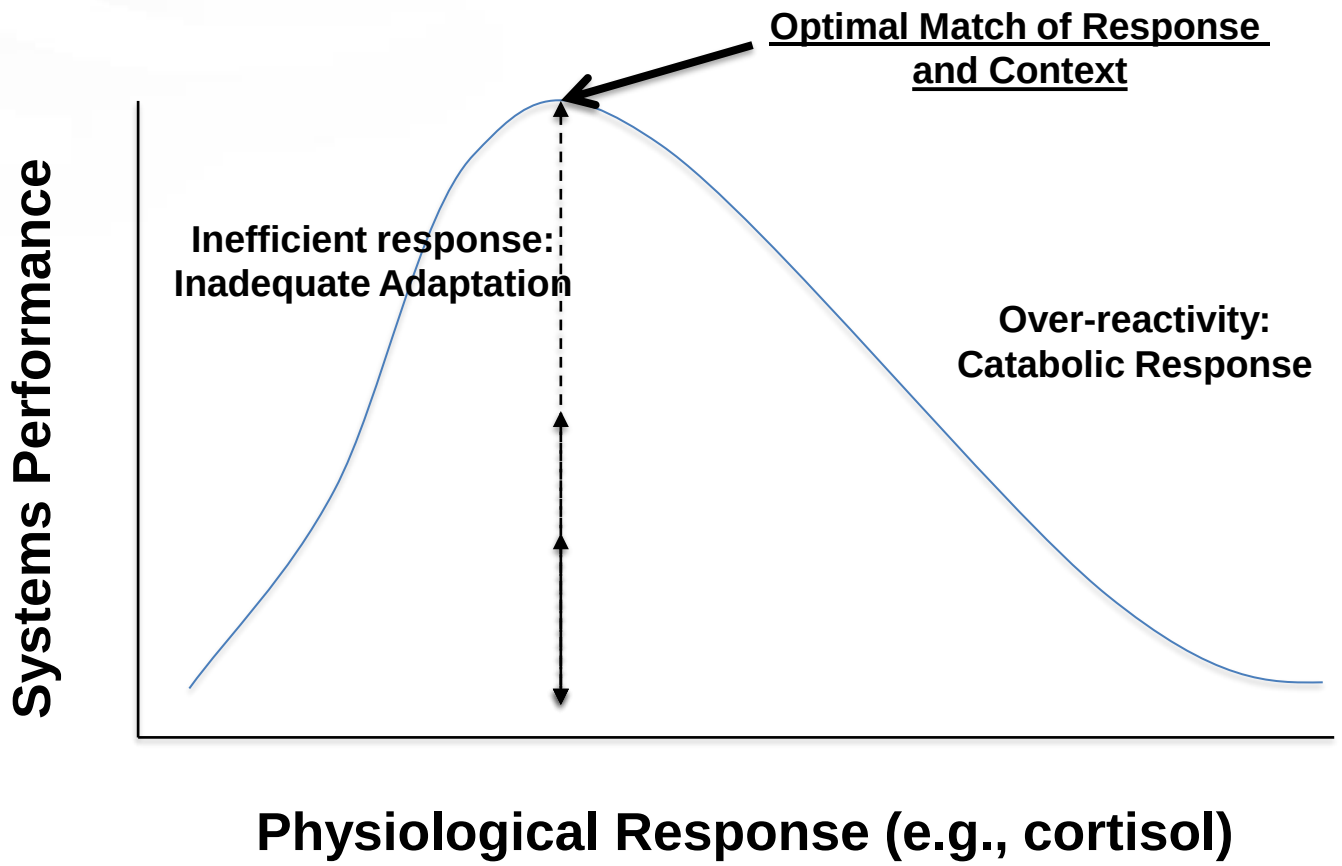
Stress Dynamics and the Inverted U: Balancing Cost, Context, and Coping



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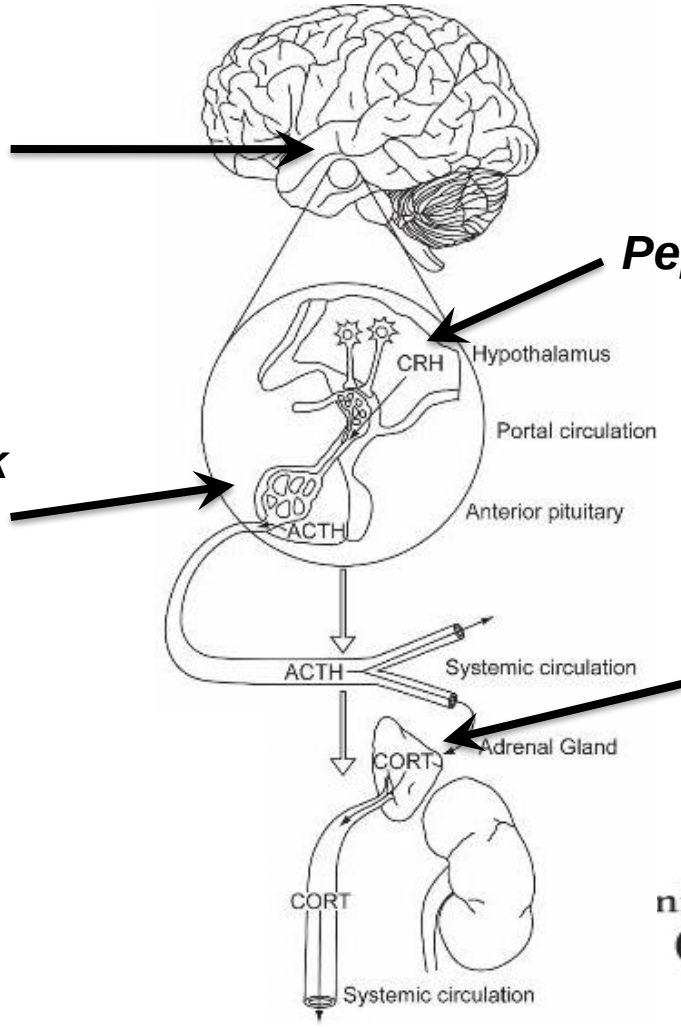
Communicating Physiological Context: Stress Responses (Hypothalamo-Pituitary-Adrenocortical Axis)

Central Feedback Control

Pituitary Feedback Control



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Glucocorticoid Signaling Mechanisms: Genomic and non-Genomic, MR and GR

Frontiers in Neuroendocrinology 49 (2018) 124–145

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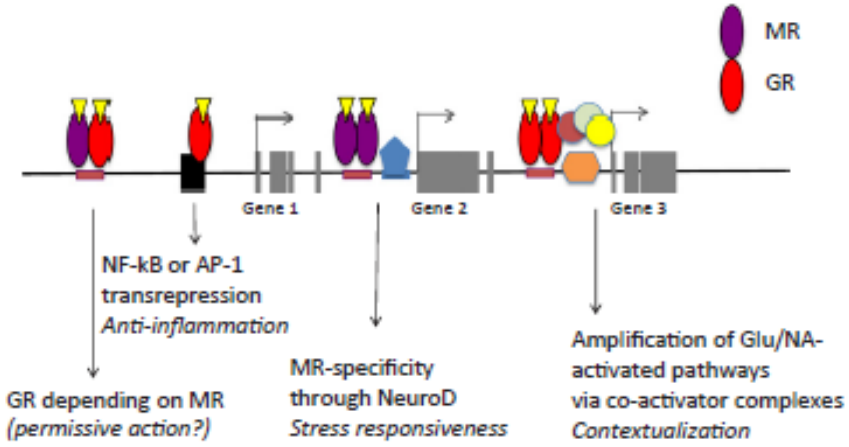
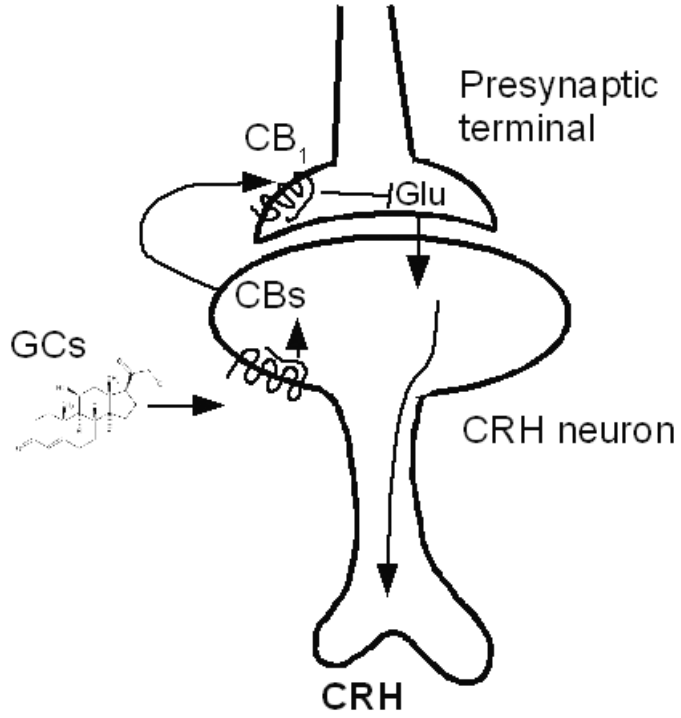
journal homepage: www.elsevier.com/locate/yfrne

Review article

Importance of the brain corticosteroid receptor balance in metaplasticity, cognitive performance and neuro-inflammation

E.R. de Kloet[a,*], O.C. Meijer[a], A.F. de Nicola[b], R.H. de Rijk[c], M. Joëls[d,e]





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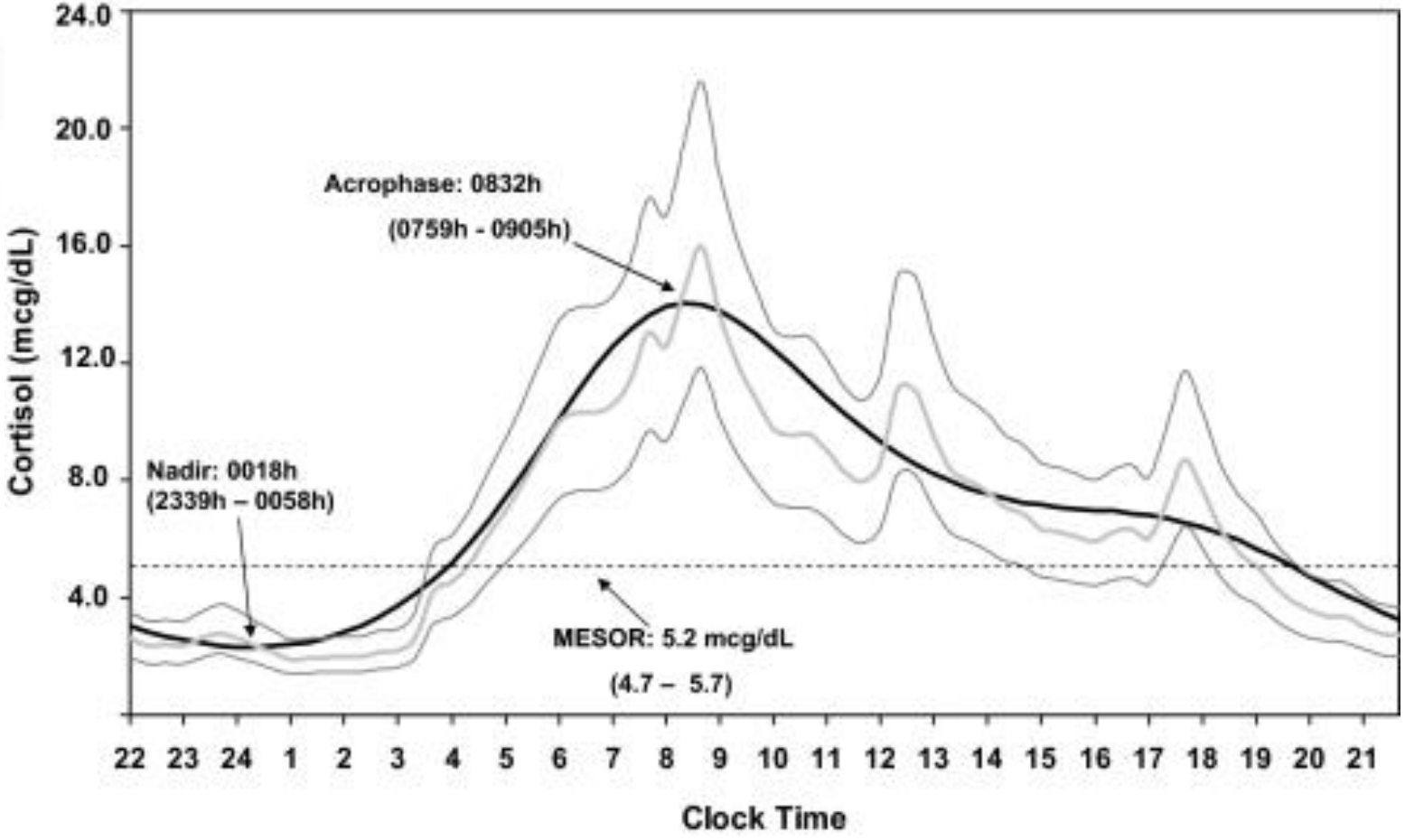
Circadian Variation in Corticosteroid Levels: Feeding a Hungry Organism



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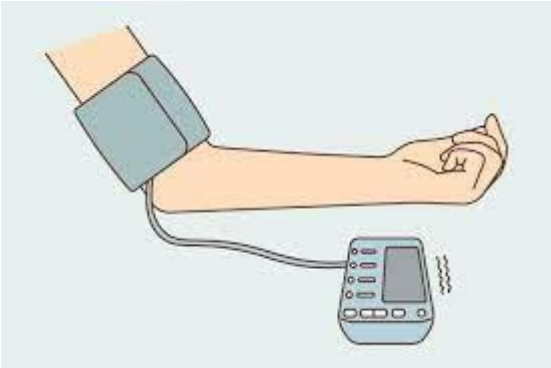
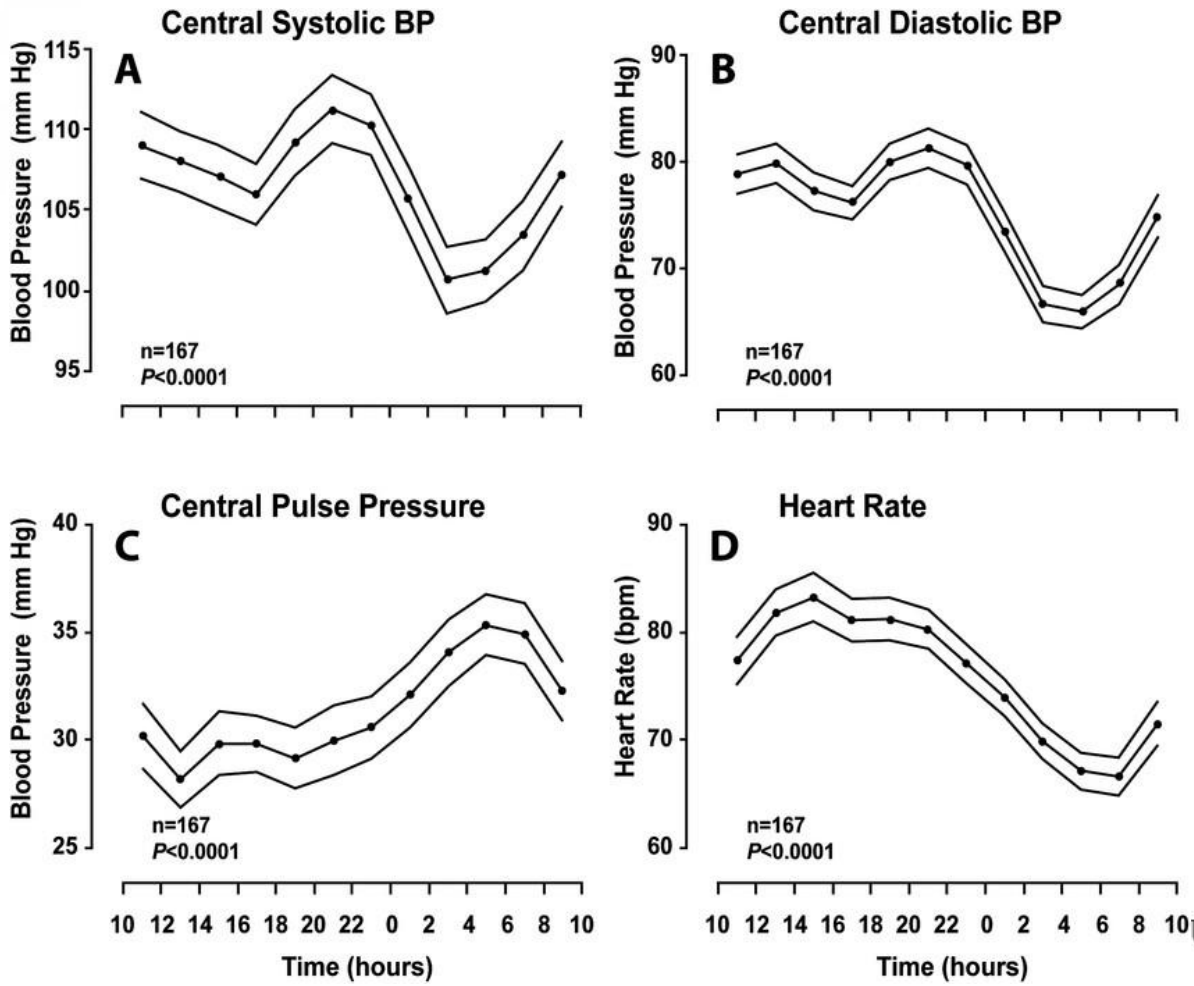
DeBono et al, JCEM (2009)

Diurnal Heart Rate and Blood Pressure Rhythms





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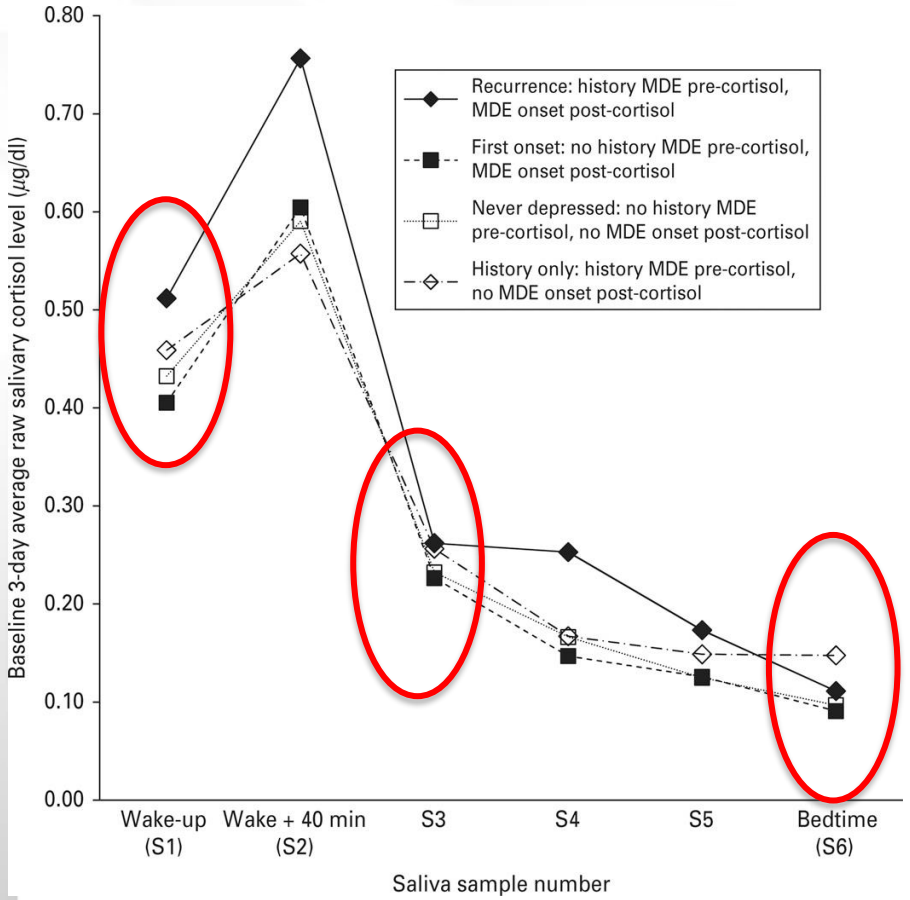
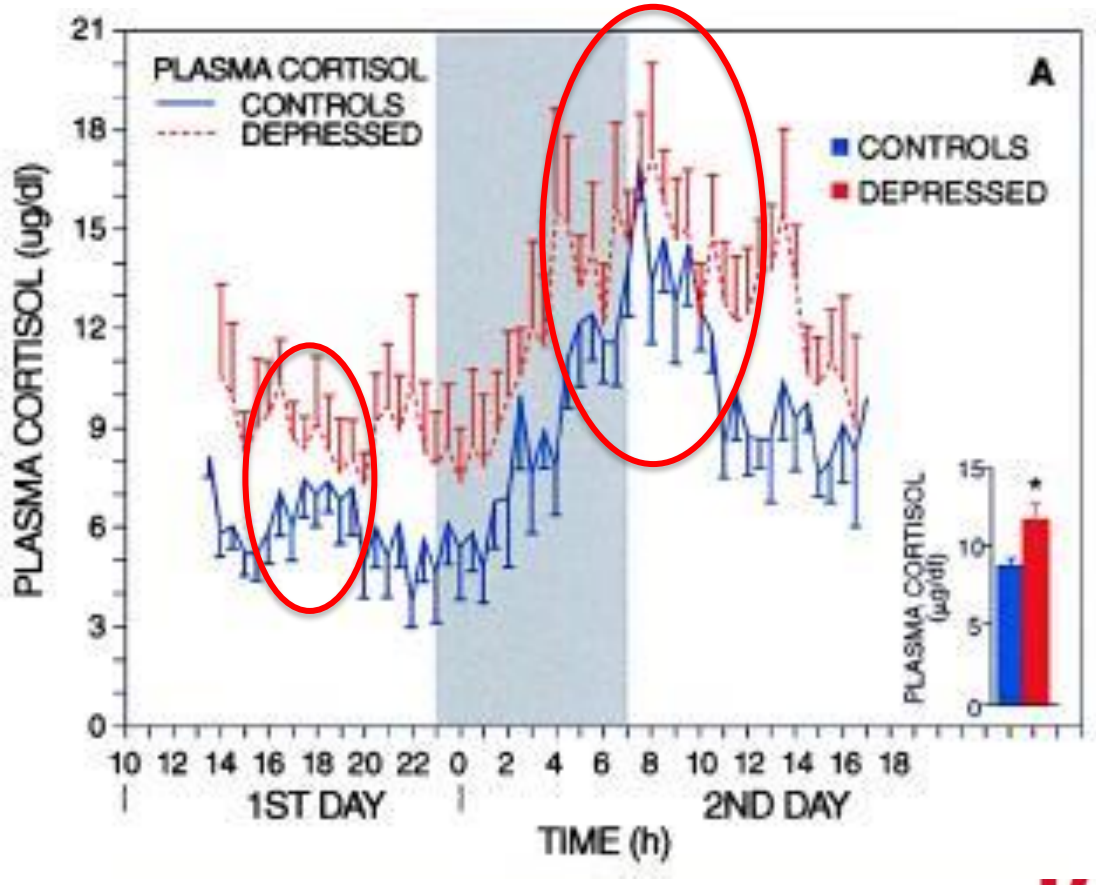
Boggia et al, Am J Hypertension (2015)

Importance of Time-course Analysis in Human



Vrshek-Schallorn et al, Psychol Med (2013)



Wong et al, PNAS (2000)

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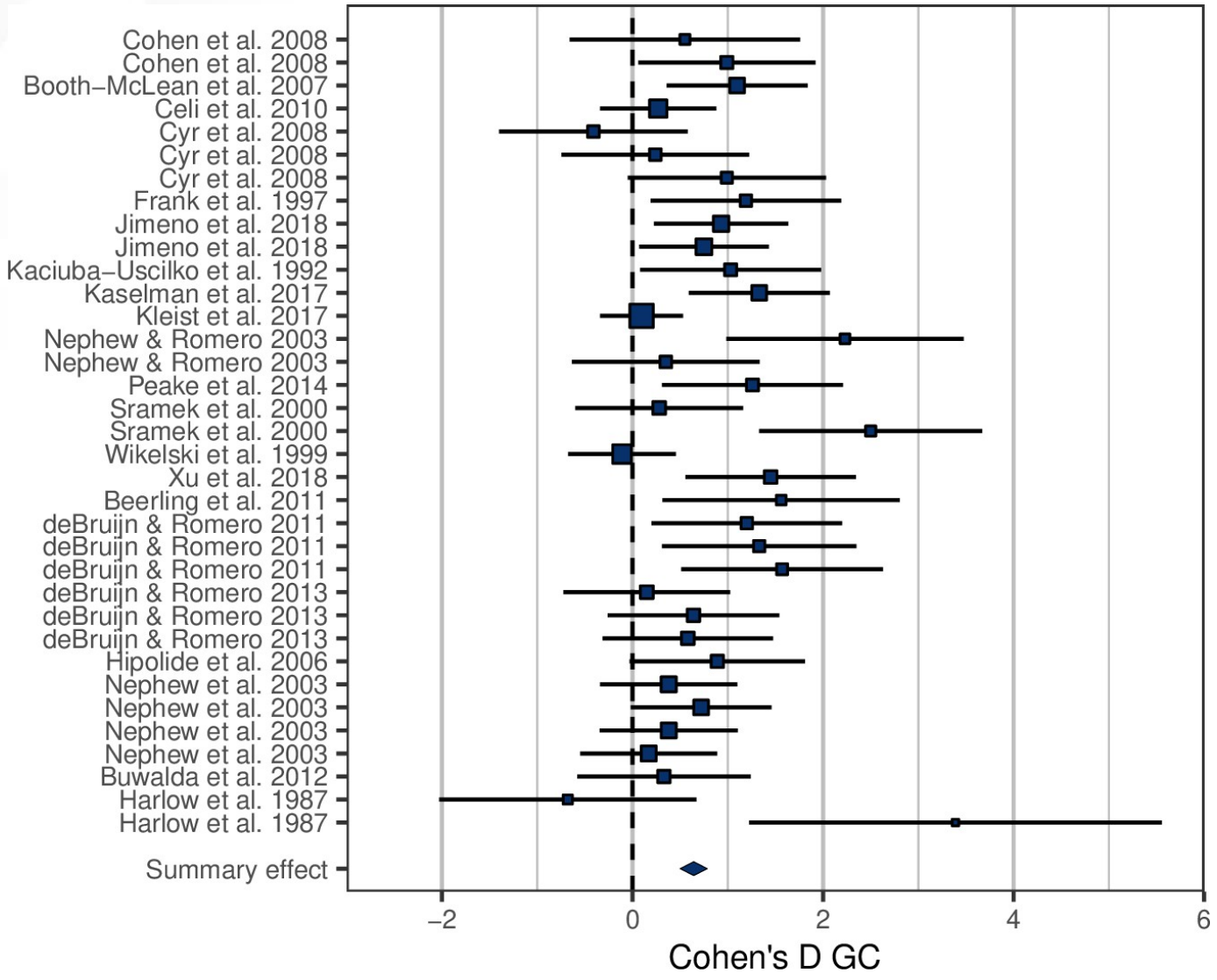
Glucocorticoids and Metabolic Rate



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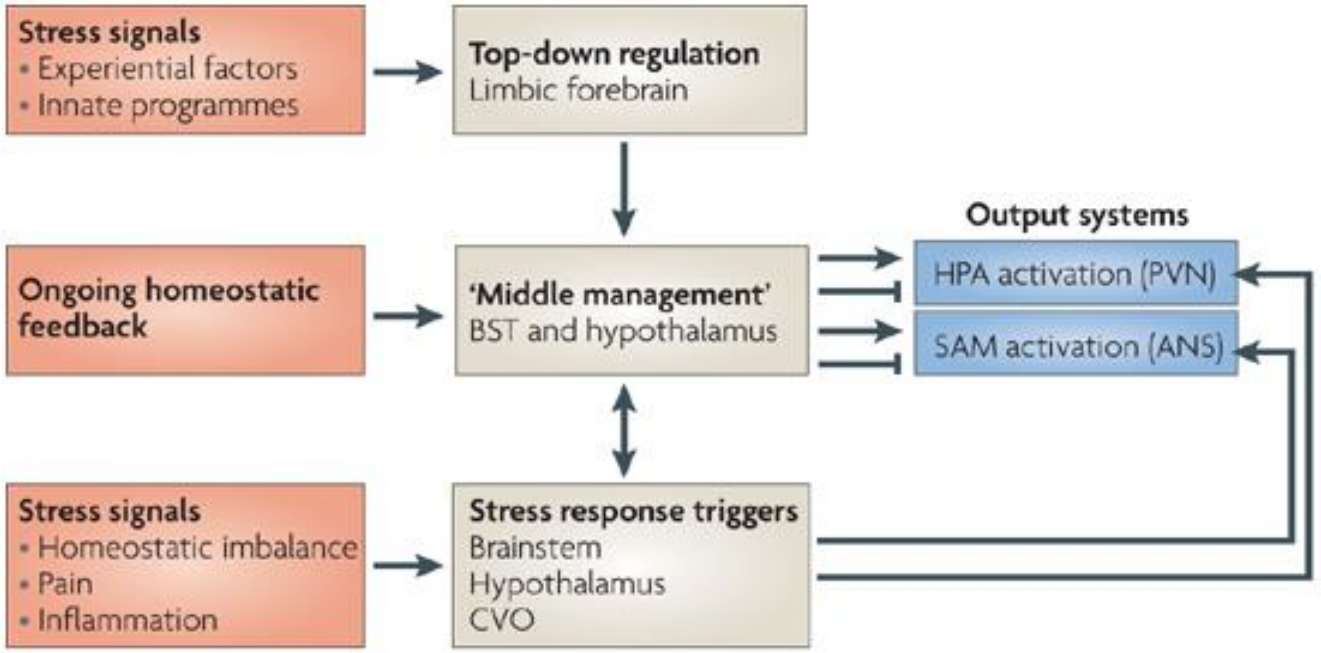
Jimeno and Verhulst, eLife (2023)

Brain Stress Processing: Top-down and Bottom-up Signaling



Nature Reviews | Neuroscience
Ulrich-Lai and Herman, 2009

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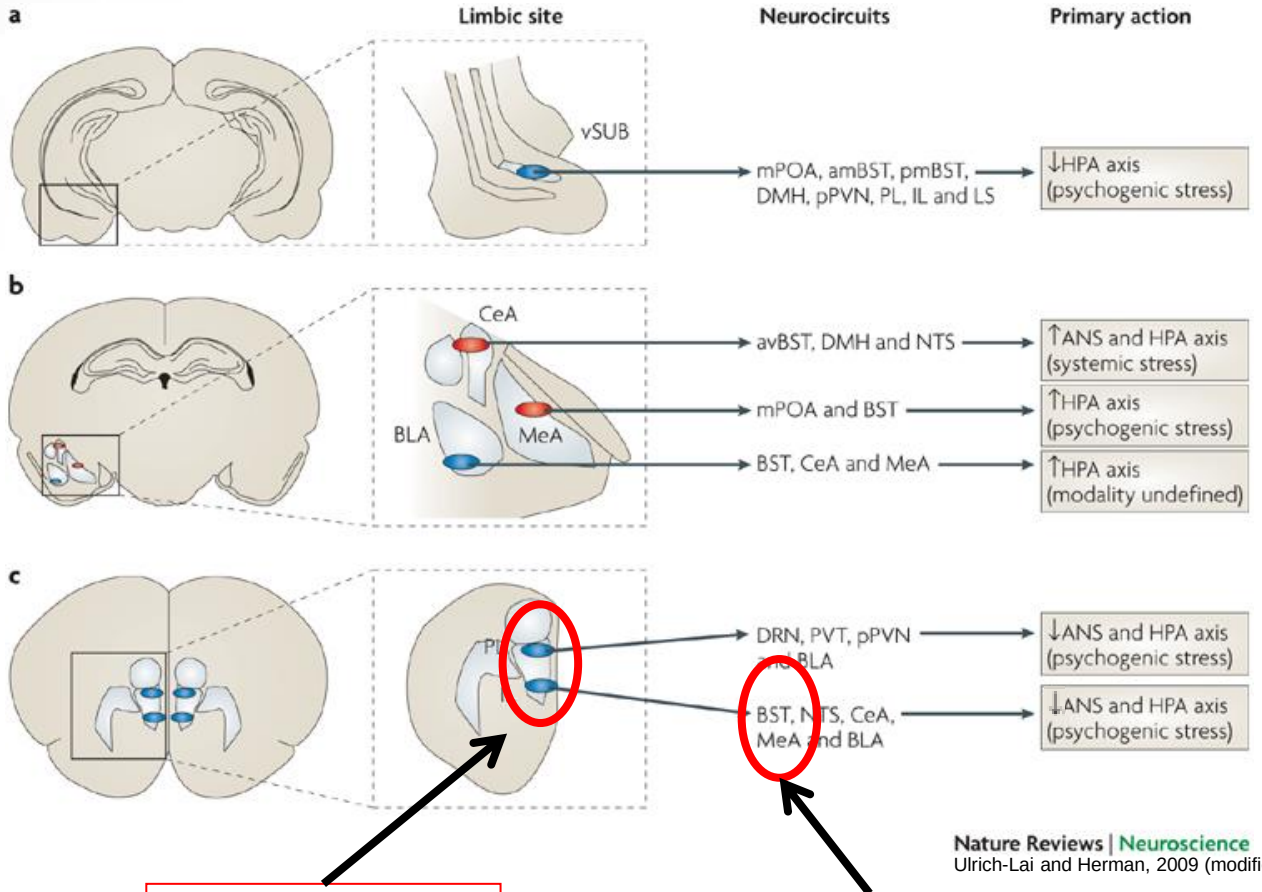
Stress responses are controlled by multisynaptic pathways in the CNS



Nature Reviews | Neuroscience
Ulrich-Lai and Herman, 2009 (modified)

Top-Down: Medial PFC

Subcortical Relays: BST

Ulrich-Lai and Herman, Nat Rev Neurosci (2009)

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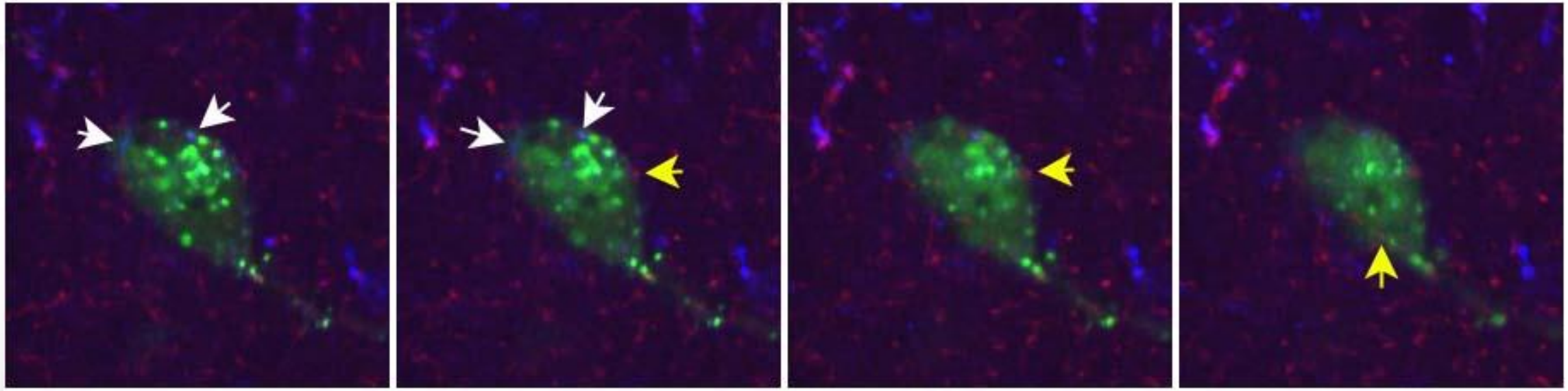
Neural mechanisms of 'Stress Control': Limbic Convergence in the BST



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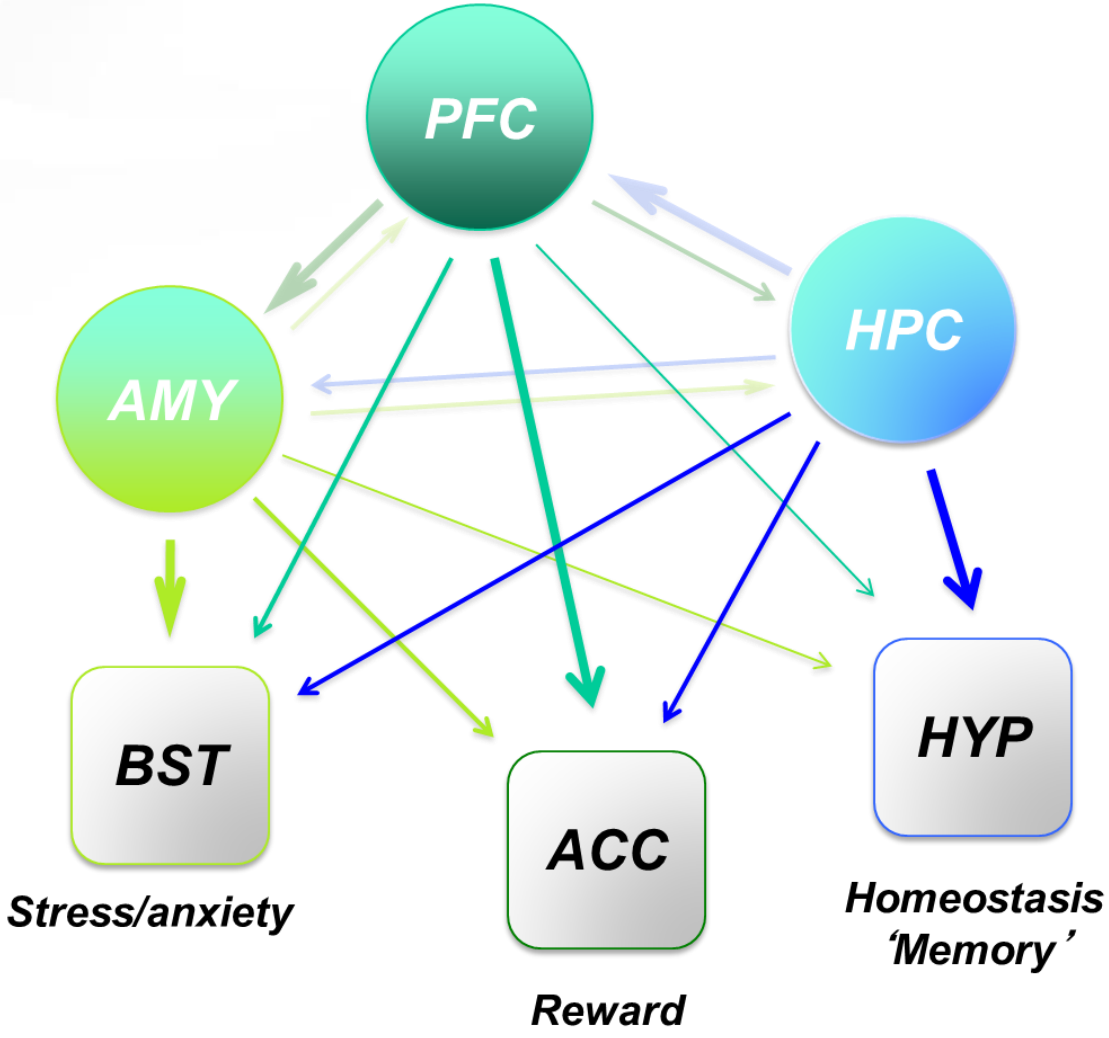
Limbic Interactions with Effector Pathways



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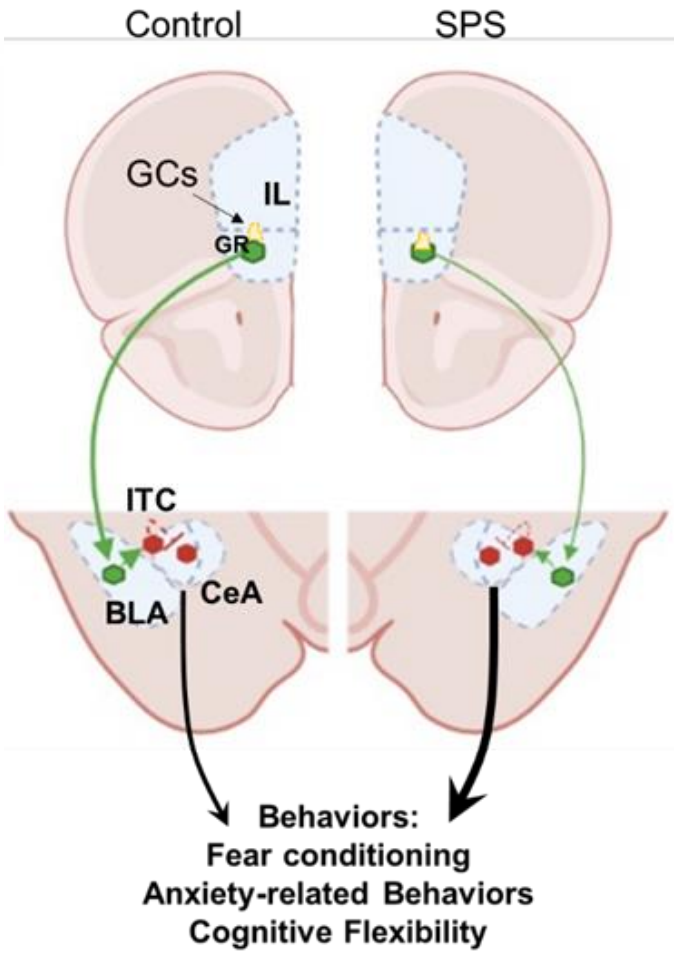
Limbic Imbalance Associated with Pathology: PTSD



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Males and females have a different glucocorticoid biology

- *The sexes differ in terms of biological priorities*
- *There are sex differences in peripheral metabolism*
- *Arguably, stress is a bigger problem for females*
  - *affects ability to reproduce and nurture*
  - *lower body mass and fat mass*
- *Definition of resilience will likely differ for females and males*

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Sex and Stress (Glucocorticoid?)-Linked Diseases

Women are disproportionally likely to be diagnosed with:

- ***Major depression***
- ***PTSD***
- ***generalized anxiety disorder***
- ***chronic fatigue***

Disease symptoms differ amongst the sexes

- ***Depressed men tend to report more physical symptoms than women***
- ***Women with PTSD tend not to exhibit changes in cortisol or acoustic startle, men manifest more physical symptoms***

Sex Differences: Pronounced and Biologically Important

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How are Stress Hormones Interpreted in the Male and Female Brain? Forebrain

Forebrain GR Deletion (Glutamate neurons)

Endpoint	Male	Female
Basal AM Cort	↑	no
Stress Response	↑	nope
FST immobility	↑	not even close
Stress Sensitization	nothing	↑

Forebrain GR Deletion (GABA neurons)

Endpoint	Male	Female
Basal AM Cort	no	no
Stress Response	no	↑
FST immobility	no	no
Center Time Open Field	no	no
Passive Avoidance	no	↓

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How are Stress Hormones Interpreted in the Male and Female Brain? Hypothalamus

Sim-1 GR Deletion (PVN/SON neurons)

Endpoint	Male	Female
Basal AM Cort	no	↑
Stressor Response (CORT)	↑	zip
Stressor Response (ACTH)	↑	↓

Solomon et al, Endo (2015)
Nahar er al, Endo (2015)

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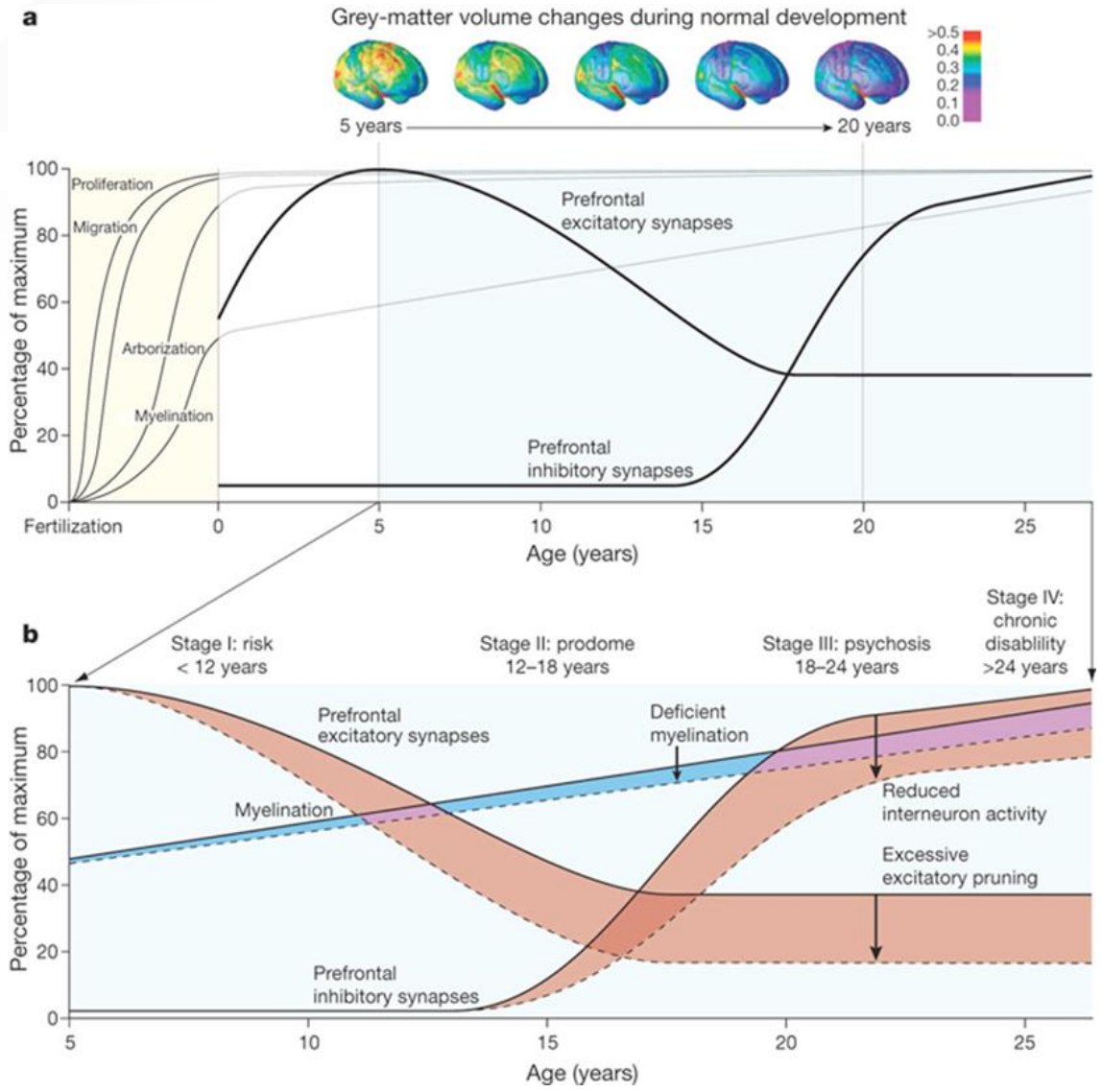
Adolescent Sculpting of Prefrontal Cortex Connectivity



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Assignment
Grades
Student loan
Friends
Self esteem
Exam
Bullying


RELATIONSHIPS
PARENTS
COLLEGE
KEEPING UP
FITTING IN
EXPECTATIONS
SCHOOL
OVER-SCHEDULING
TEEN STRESS 101


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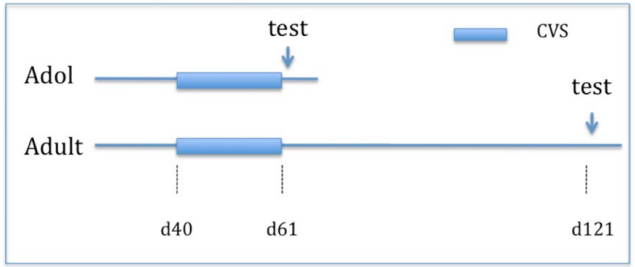
Immediate and Lasting physiological Responses to Adolescent CVS



Impact of Adolescent Chronic Stress (Relative to Adult)

Index	Male	Female
Body weight	↓	n.d.
Adrenal weight	↑	n.d.
Thymus weight	↓	n.d.
Body Fat	↓	n.d.
AM Corticosterone	↑	n.d.

Impact of Adolescent Chronic Stress (As Adults)

Index	Male	Female
Body weight	n.d.	↓, n.d.
Adrenal weight	n.d.	n.d.
Thymus weight	n.d.	n.d.
Body Fat	n.d.	n.d.
AM Corticosterone	n.d.	n.d.

Jankord et al, Endocrinology (2011), Wulsin et al, PNE (2016)

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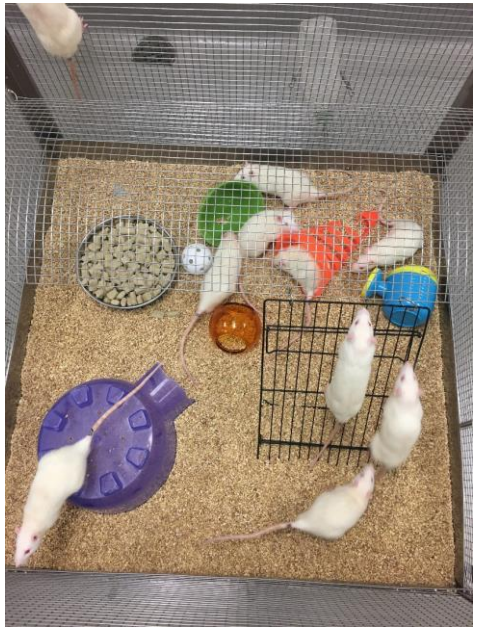
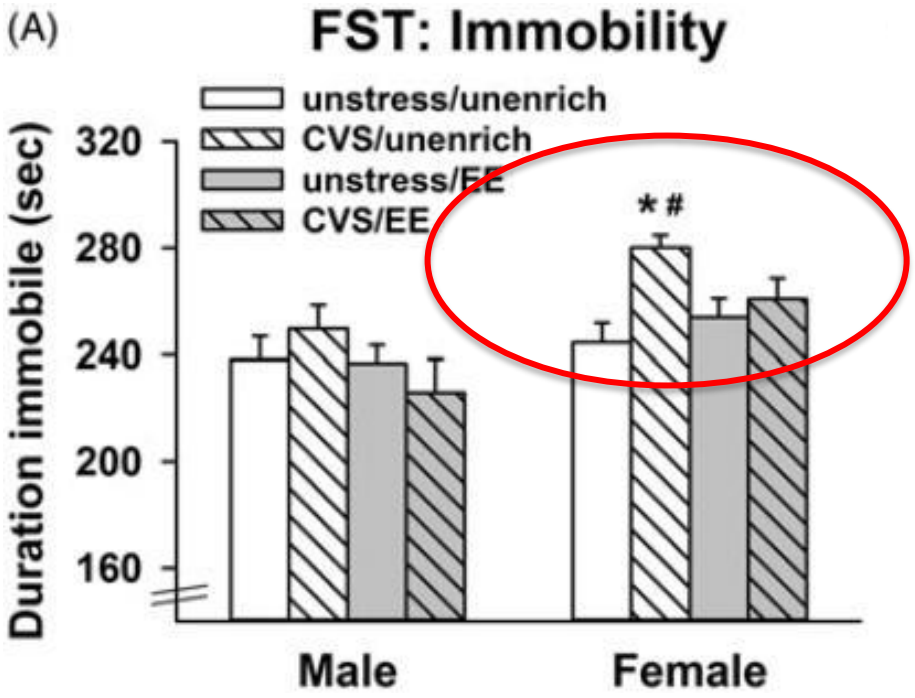
Environmental Enrichment Confers Resilience to Lasting Effects of CVS in Females but not Males





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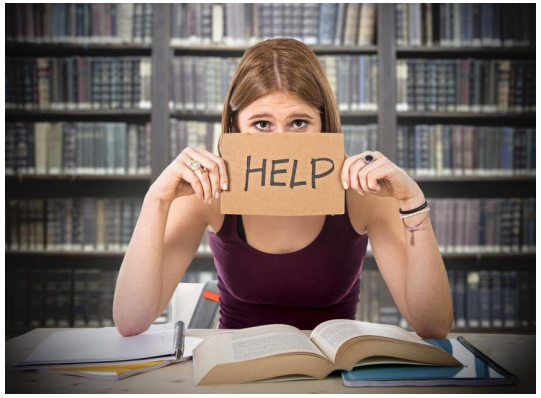
Smith et al, Stress (2018)



- ***Exaggerated chronic stress response***

- ***Adult-like chronic stress response***

- ***Resistant to stress triggers in adulthood***
- ***Reduced sensitivity to second 'hit' of stress in adulthood***

- ***Sensitivity to stress triggers in adulthood***
- ***Sensitivity to second 'hit' of stress in adulthood***

- ***Males and females use a distinct neurocircuitry to control emotional responses following stress***

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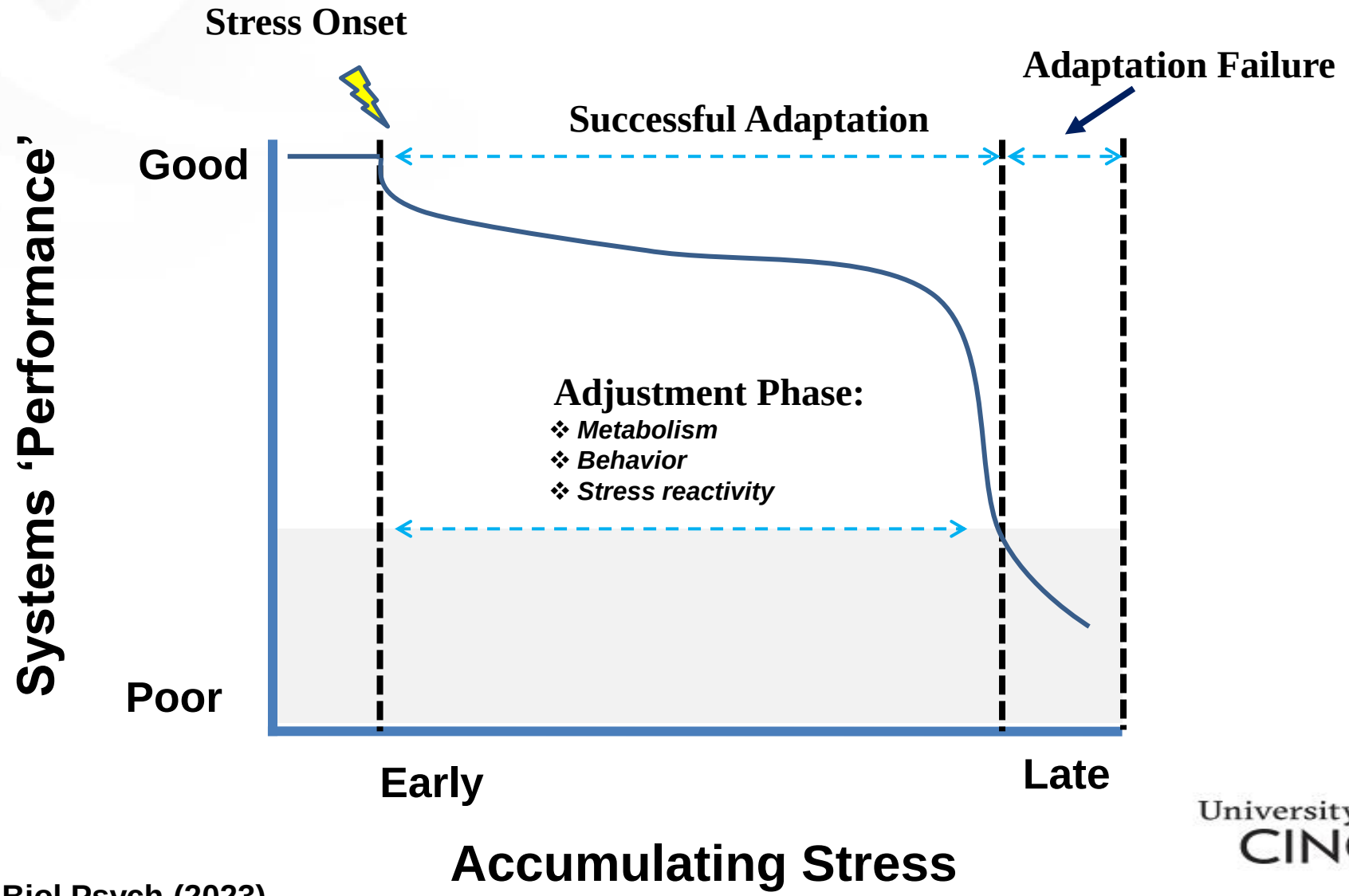
Stress responses contribute to adaptation as well as pathology



Radley and Herman, Biol Psych (2023)

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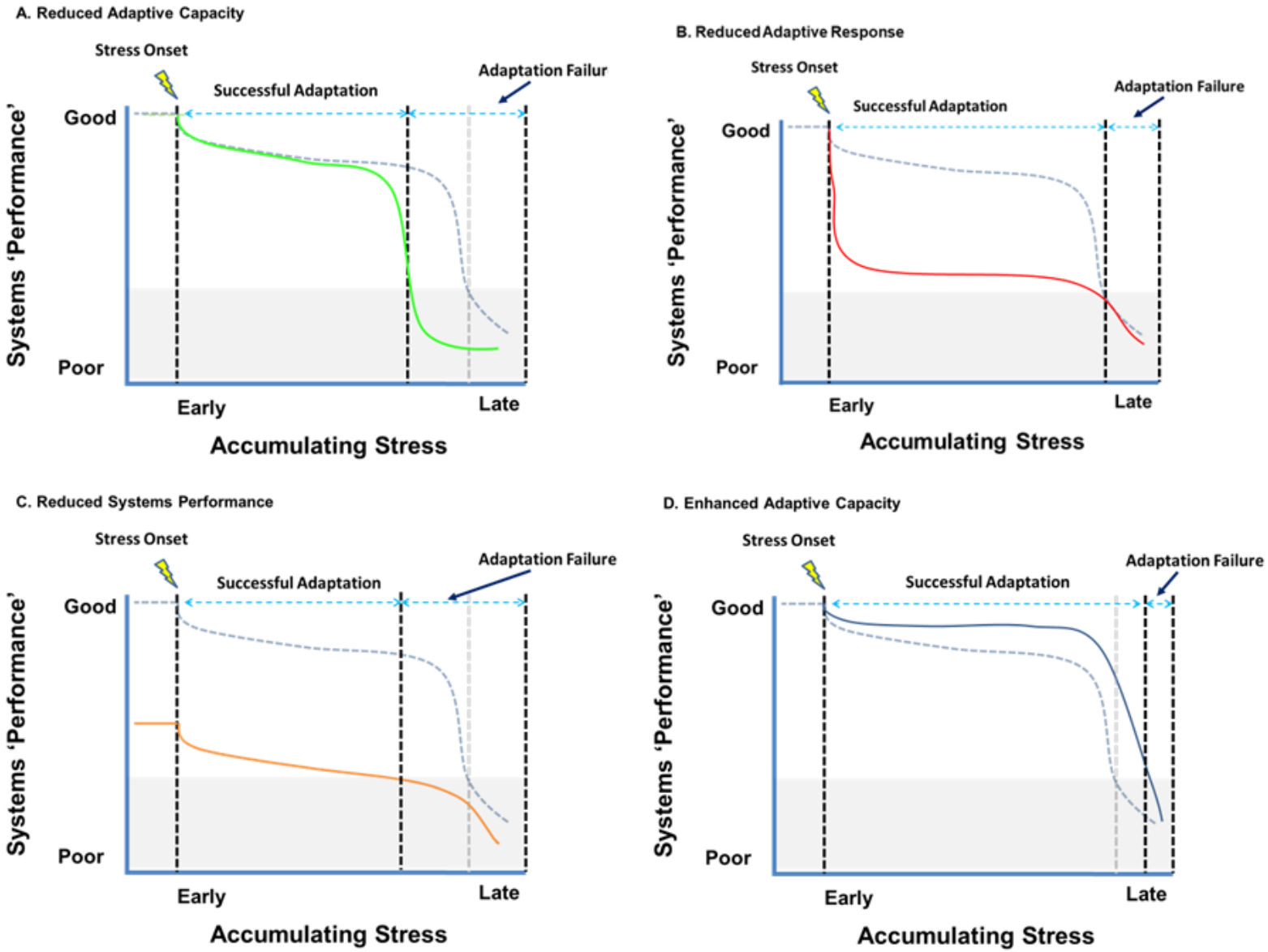
Aberrent stress responses contribute to pathology as well as resilience



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Stress and Age-related Disease: Pathology

- ***Alzheimer's Disease: chronic stress/glucocorticoids contribute to disease pathology, GR receptor antagonists improve memory and mood-related symptoms***
- ***Parkinson's Disease: stress can accelerate loss of dopamine neurons, strong depression comorbidity***
- ***Cardiovascular Disease: MI, hypertension, vascular pathology***
- ***Neurodegeneration: stress, glucocorticoids accelerate phosphorylated Tau expression, decrease neurogenesis***
-

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Stress and Affective Disease: Stress Hormone Pathology

- ***PTSD: enhanced glucocorticoid receptor signaling linked to pathology***
- ***Depression: pathology linked to impaired negative feedback regulation of the HPA axis***
- ***Addictive Disorders: stress, glucocorticoids are implicated in relapse***
- ***Chronic fatigue, fibromyalgia: connection to reduced cortisol secretion***
-

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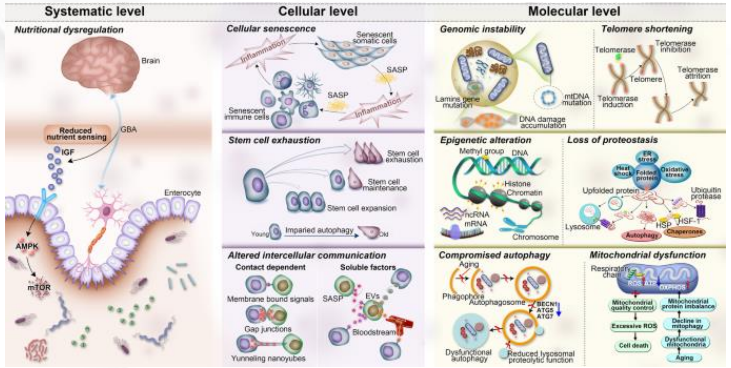
Age-related Disease: Mechanisms of Stress Pathology



Guo et al, Signal Trans Targeted Ther, (2022)

- ***Mitochondrial dysfunction (oxidative stress)***
- ***Calcium dyshomeostasis***
- ***Inflammation (enhanced cytokine production)***
- ***Telomere shortening***
- ***Enhanced cellular senescence***

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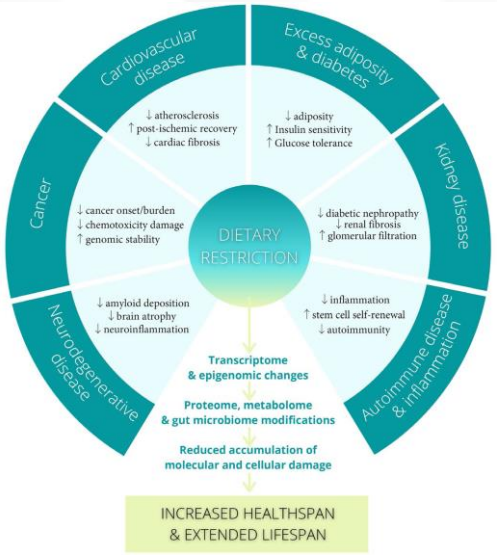
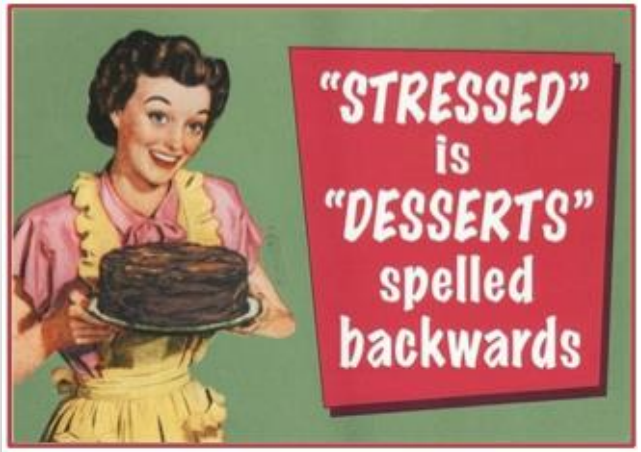
Stress and Aging: Resilience



- ***Lifespan:***
  - ***Maintenance of glucocorticoid homeostasis***
  - ***Dietary restriction: Anti-inflammatory (associated with elevated glucocorticoids?)***



- ***Well-being(?):***
  - ***Activation of reward pathways***
  - ***Environmental enrichment***

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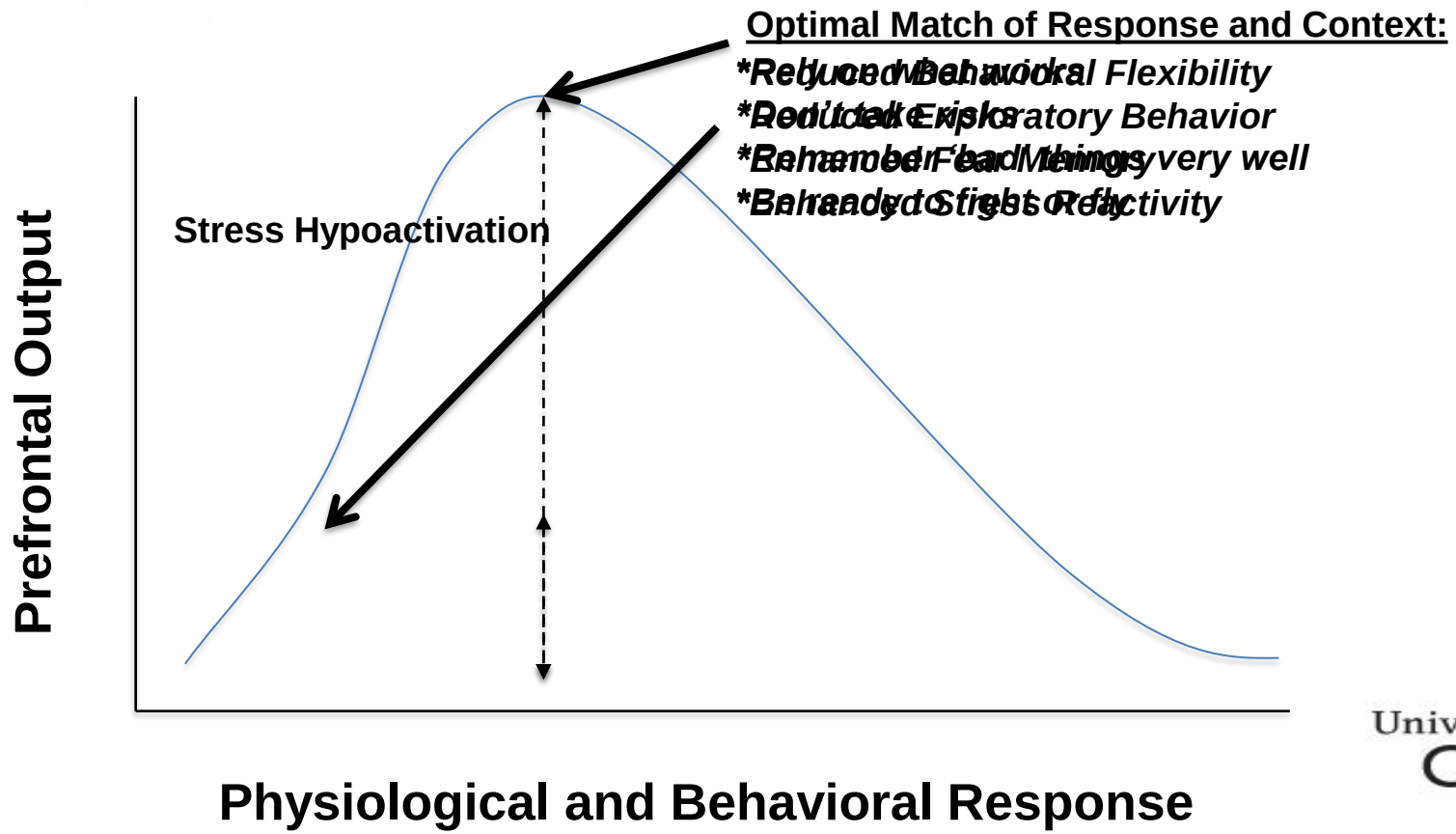
Rethinking Stress Biology: Balancing Adaptation and Pathology



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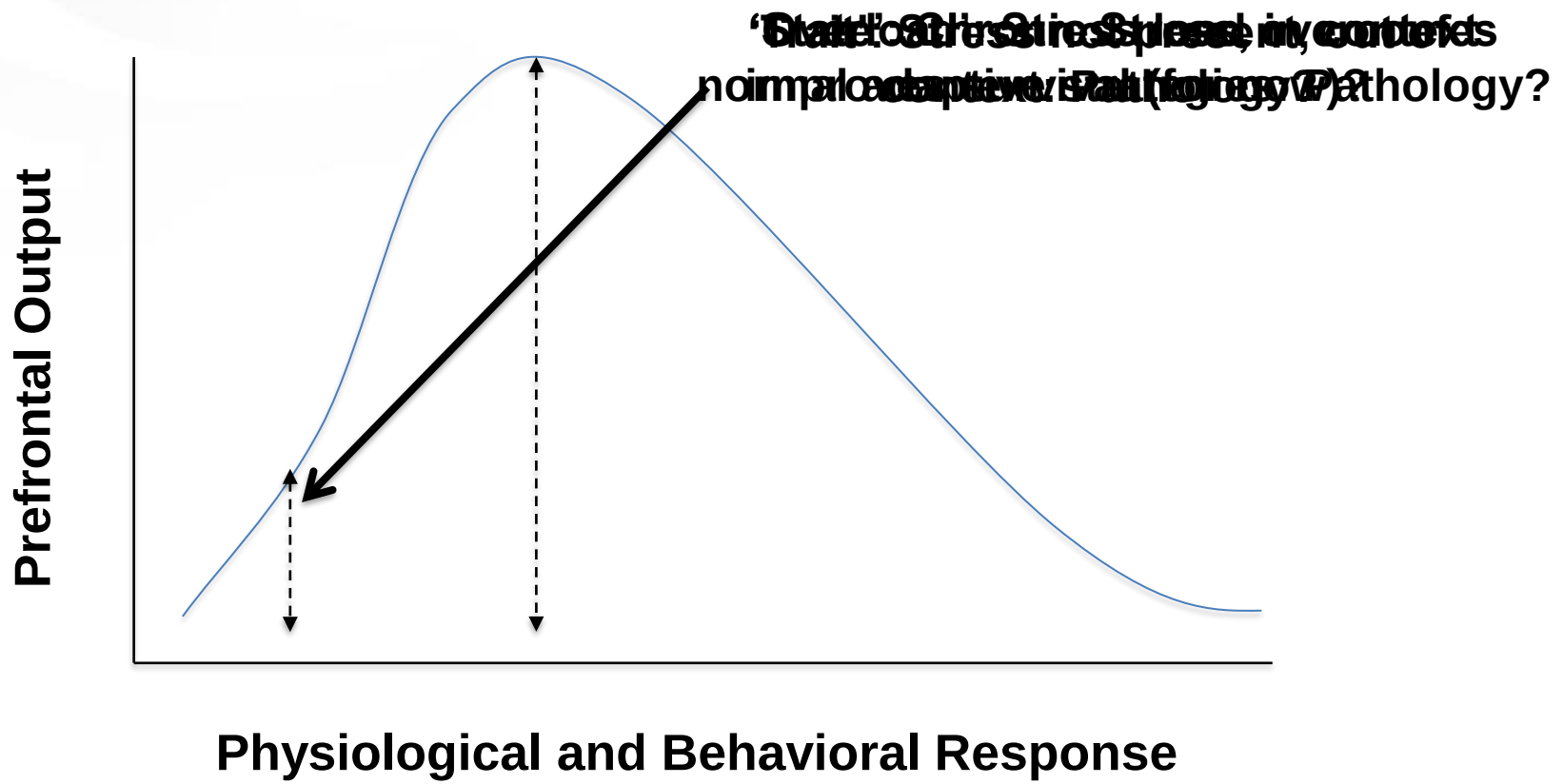
Context and Pathology



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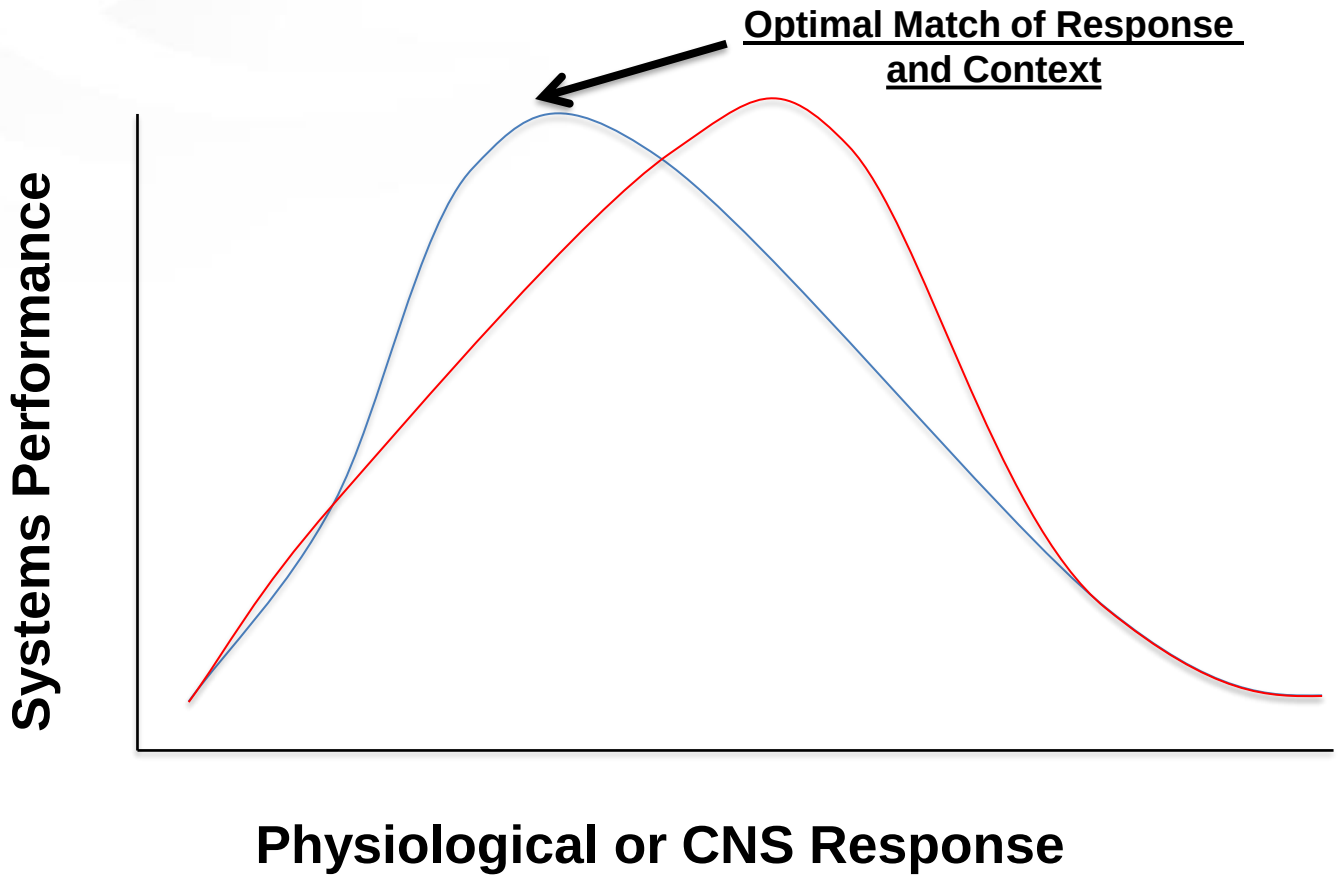
'Bending' the Inverted U?



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Nawshaba Nawreen
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Steve Danzer, CCHMC

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