Central Role of the Brain in Stress and Adaptation:

Allostasis and Allostatic Load

Bruce S. McEwen, Ph.D.

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Laboratory of Neuroendocrinology

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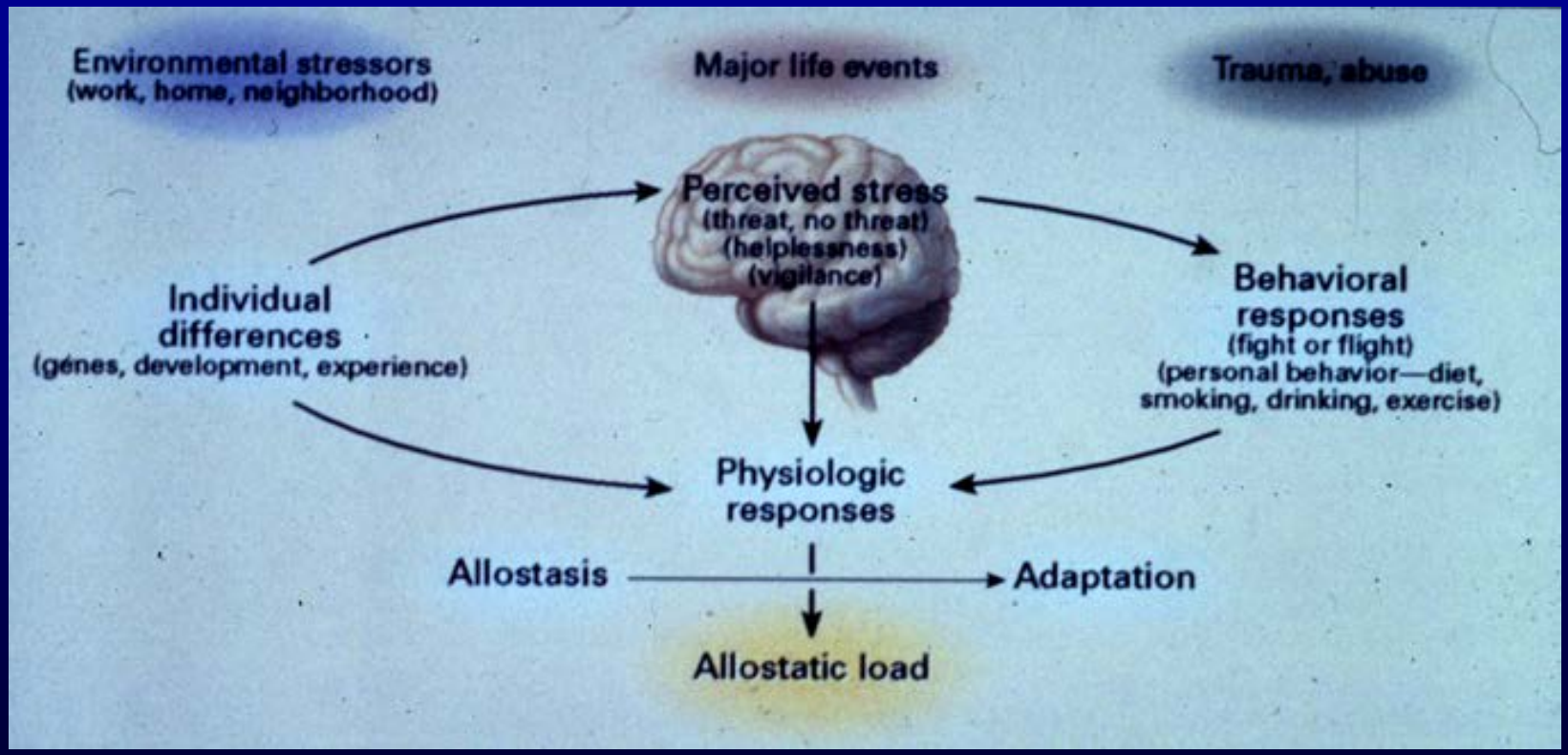
Social environment and health
Central Role of the Brain

Non-linearity abounds!!!

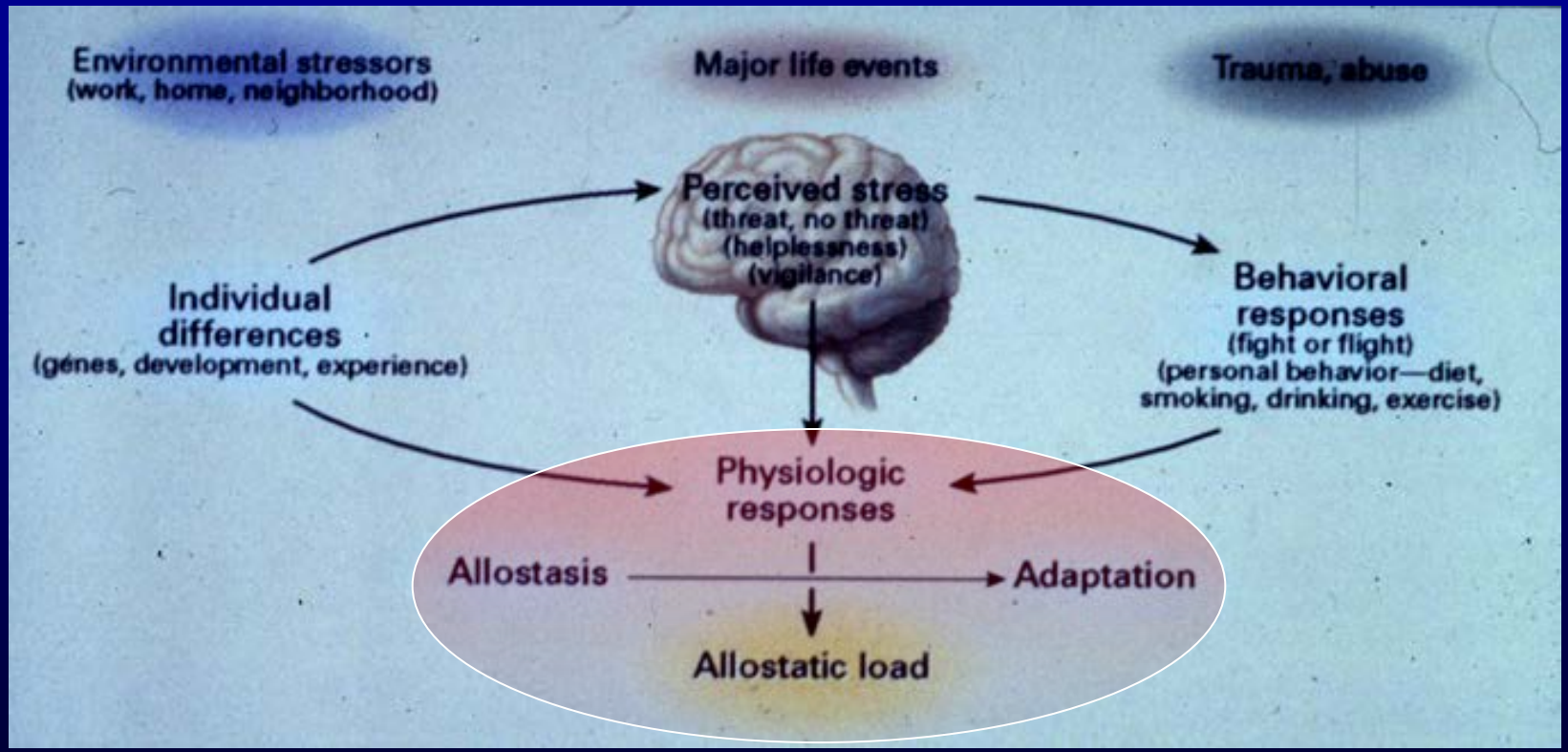


Protective and Damaging Effects of Stress Mediators

McEwen B. New England J. Med. 1998

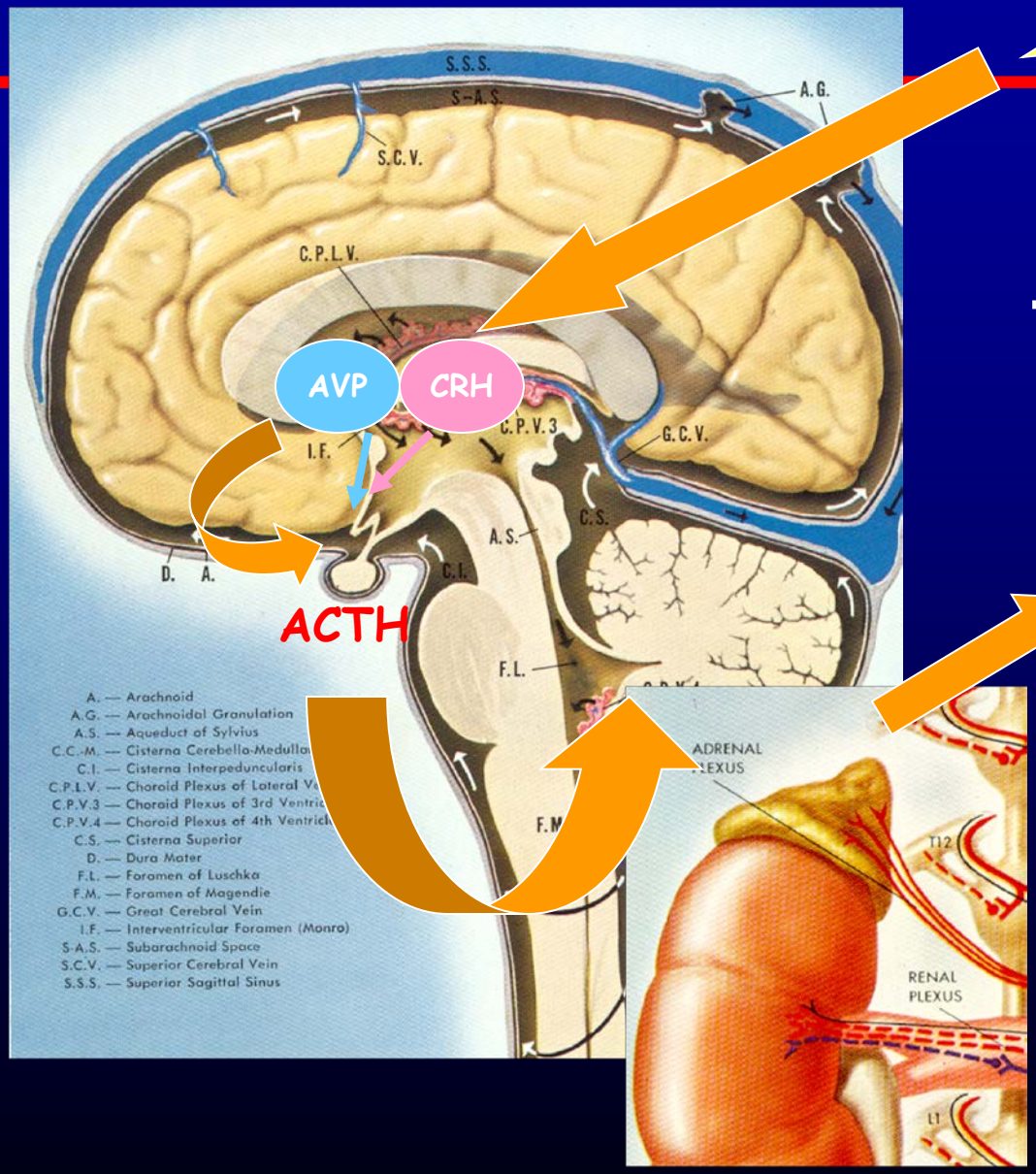
Social environment and health

Part 1: Allostasis and allostatic load



Stress, allostasis and allostatic load

STRESS



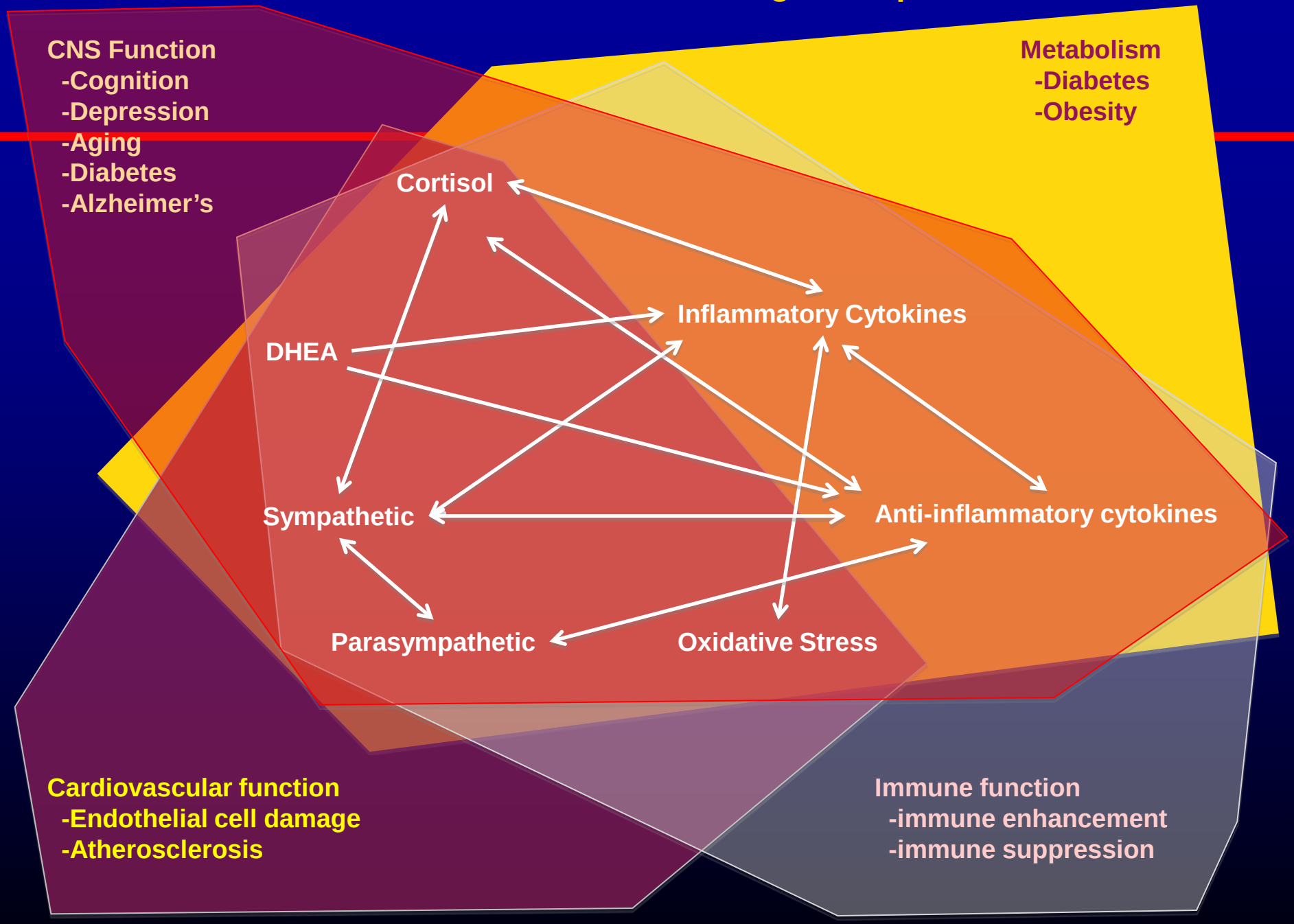
Many targets for cortisol

Cortisol

Acute - enhances immune, Memory, energy replenishment, Cardiovascular function

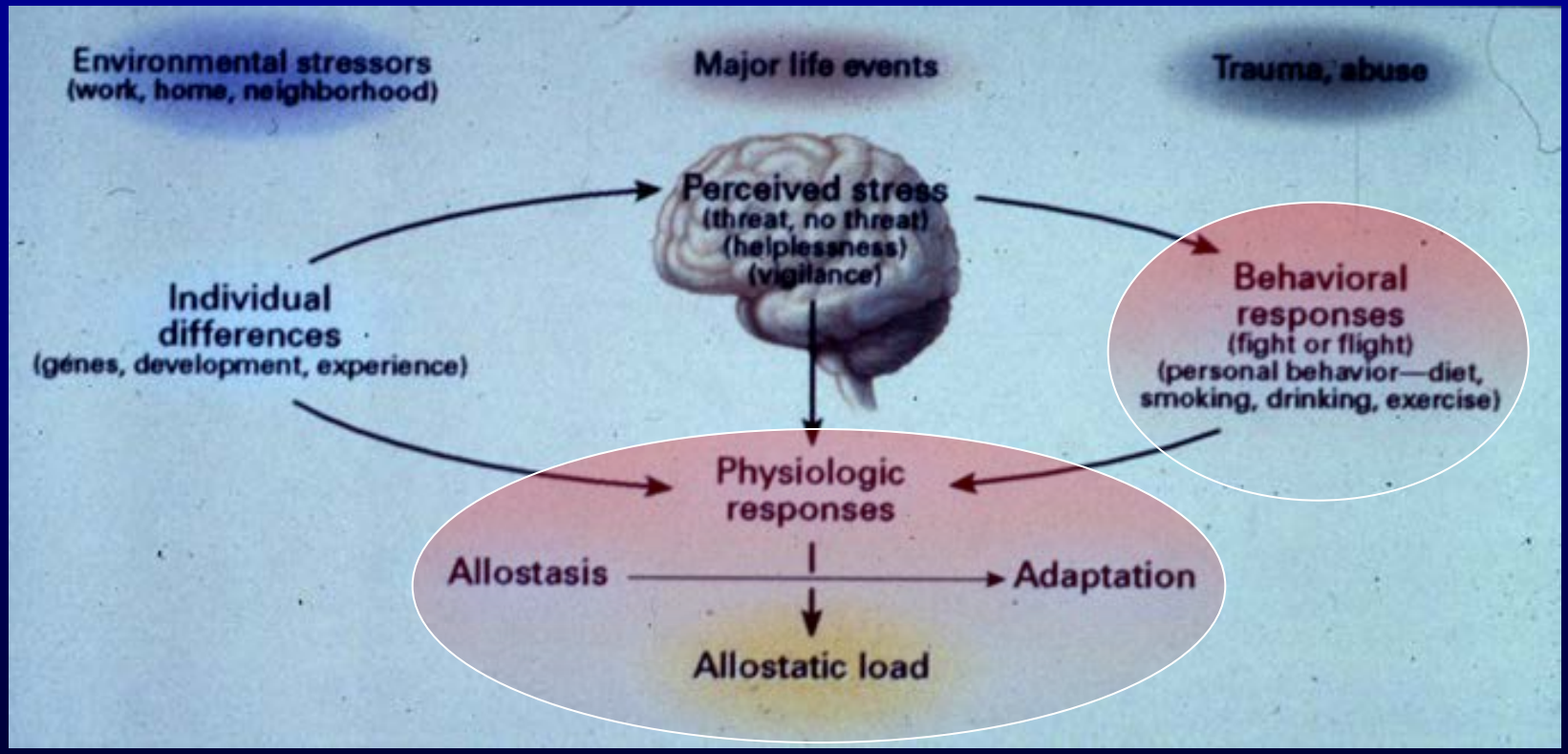
Chronic - suppresses immune, Memory, promotes bone Mineral loss, muscle wasting; Metabolic syndrome

Mediators of allostasis leading to adaptation



Social environment and health

Health-related behaviors



What we often mean by “stress” is being “stressed out”!

Feeling overwhelmed, out of control, exhausted, anxious, frustrated, angry

What happens to us?

Sleep deprivation

Eating too much of wrong things, alcohol excess, smoking

Neglecting regular, moderate exercise

Stress and your lifestyle can interact to increase allostatic load. For example, seeking solace in high-fat foods can accelerate atherosclerosis and increase secretion of cortisol, which not only adds to the accumulation of body fat but boosts your risk of heart disease, stroke, and diabetes.

All of these contribute to allostatic load
Psychosocial stress is a major factor

Allostatic Load Ancillary Study Year 2000 Exam (n=769)

- **Cardiovascular**
  - — SBP & DBP
  - — Heart Rate Variability
    - Low Freq. Power
    - High Freq. Power
    - Heart rate
- **Metabolism**
  - — HDL Cholesterol
  - — LDL Cholesterol
  - — Triglycerides
  - — Fasting Insulin
  - — Fasting Glucose
- **Waist circumference**
- **Inflammation**
  - — Fibrinogen
  - — CRP
  - — IL-6
- **SNS**
  - — Ur. Epinephrine
  - — Ur. Norepinephrine
- **HPA**
  - — Urinary Cortisol
  - — Salivary Cortisol
    - Am rise
    - Pm decline

Allostatic load score: extreme quartile of each measure; for above max score is 18

Dr. Teresa Seeman UCLA

Findings with allostatic load battery

Predictive of mortality over 7 years

Higher education - lower allostatic load score.

African Americans have higher AL scores and a flatter gradient across education.

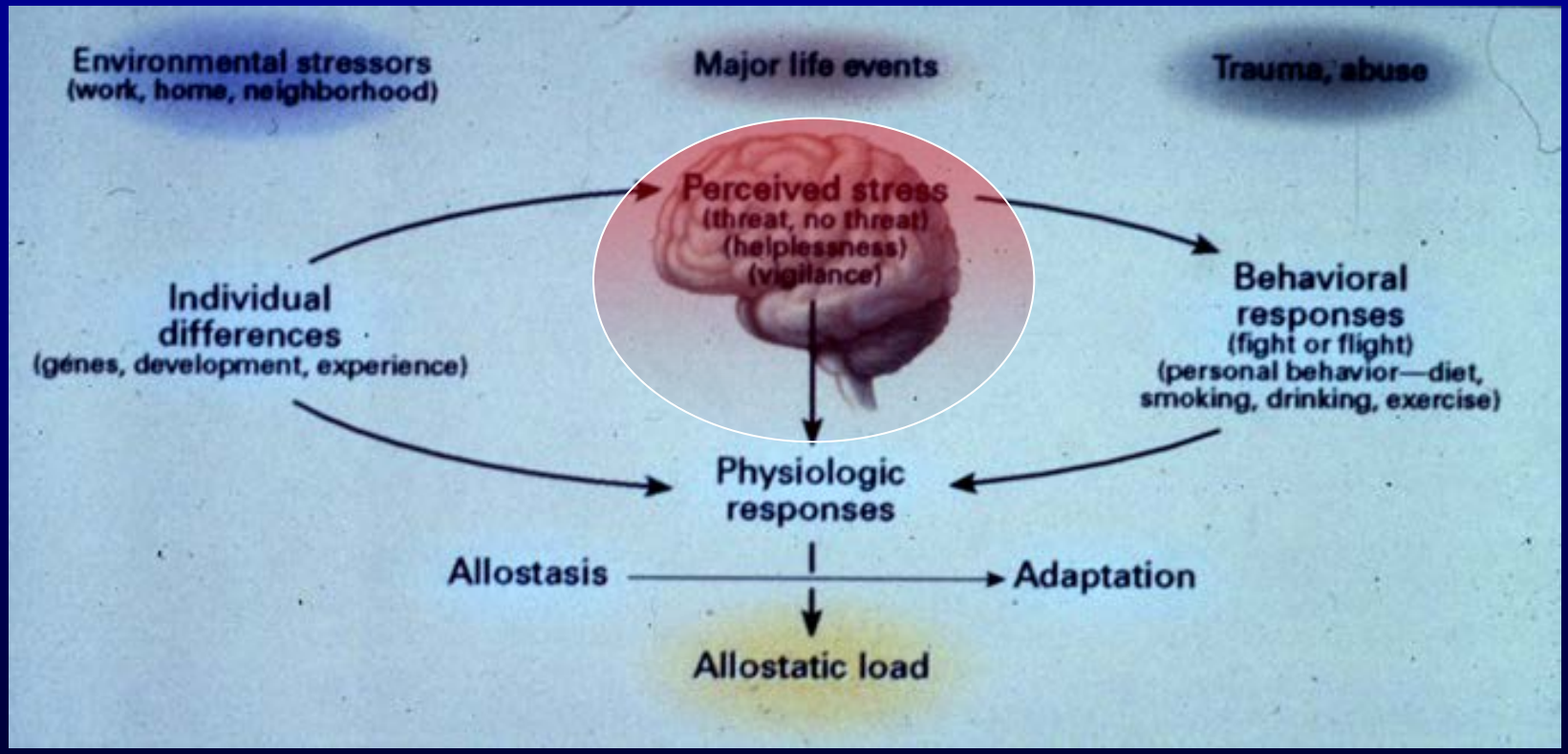
Neighborhood poverty - higher AL scores

Social conflict - higher AL score.

Social support - lower AL score.

Social environment and health

Part 2: Central Role of the Brain



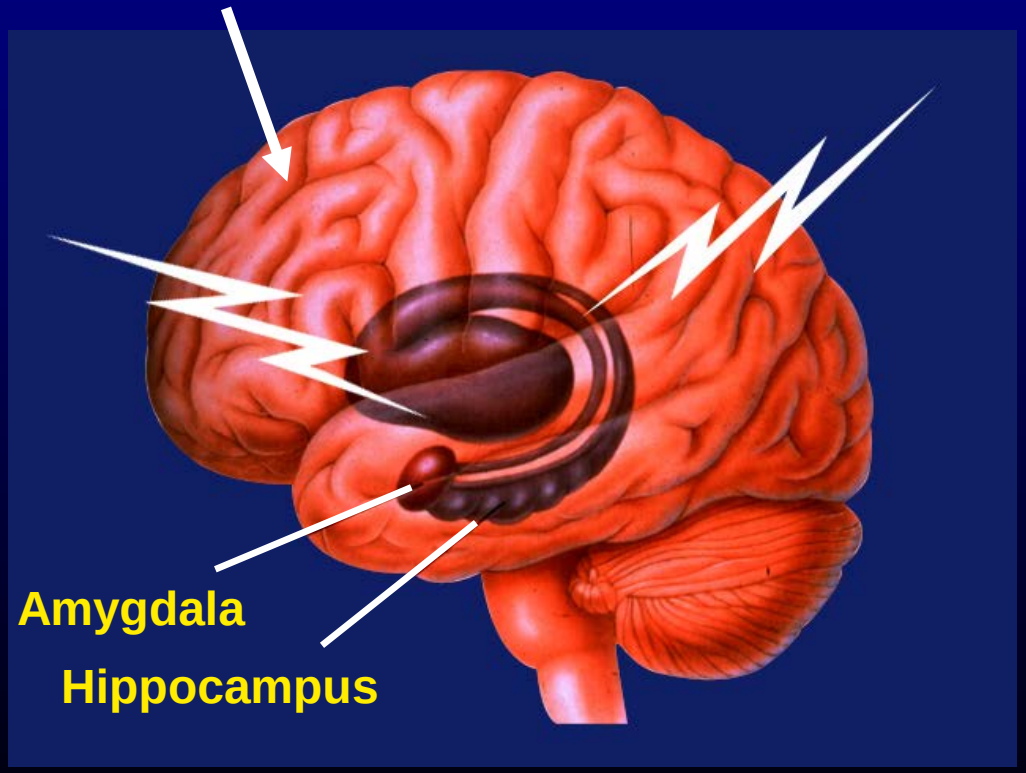
The Human Brain Under Stress

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

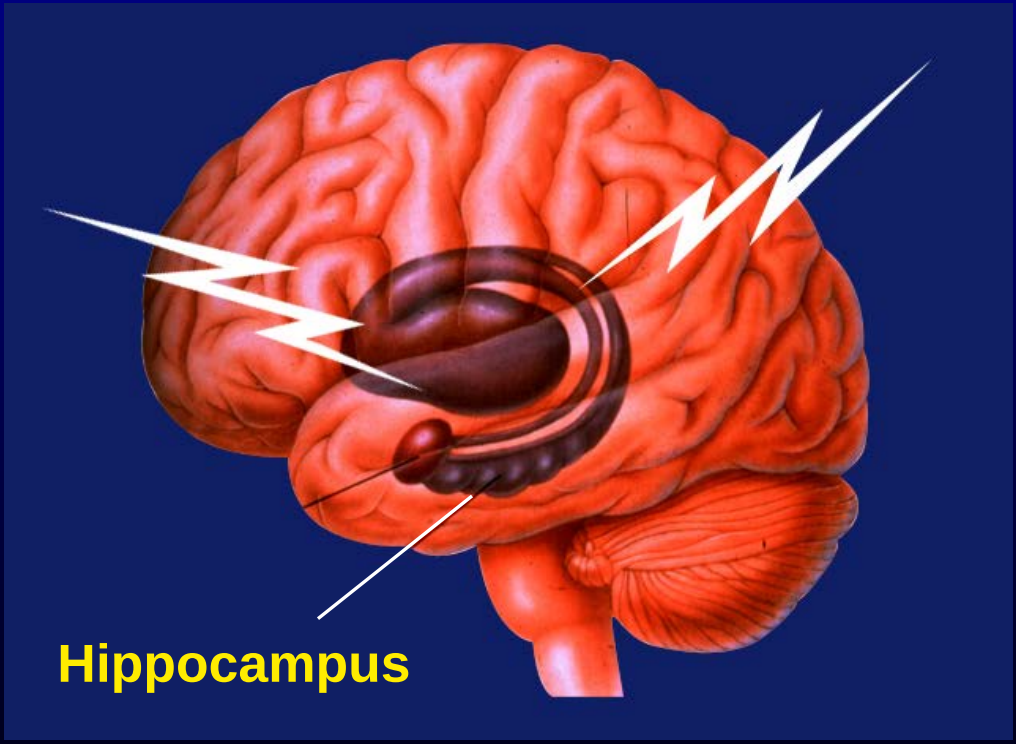
Turns on stress hormones and increases heart rate

The Brain Under Stress

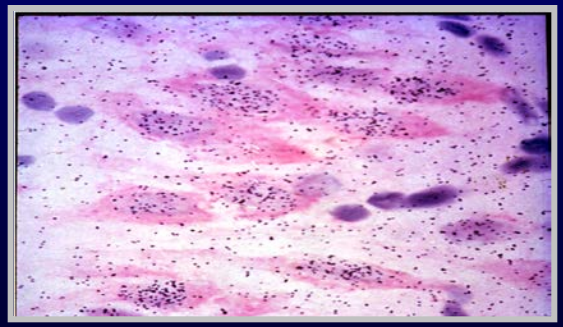
Receptors for Stress Hormone Cortisol in Hippocampus

Memory of daily events, spatial memory

Mood regulation – target of depression



Adrenal steroid receptors in hippocampus



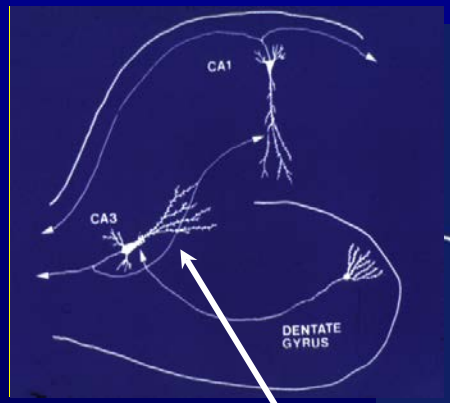
Receptors in cell nuclei regulate gene expression

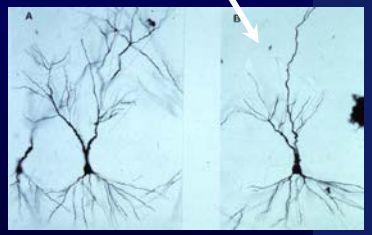
Brain Under Stress

Hippocampus

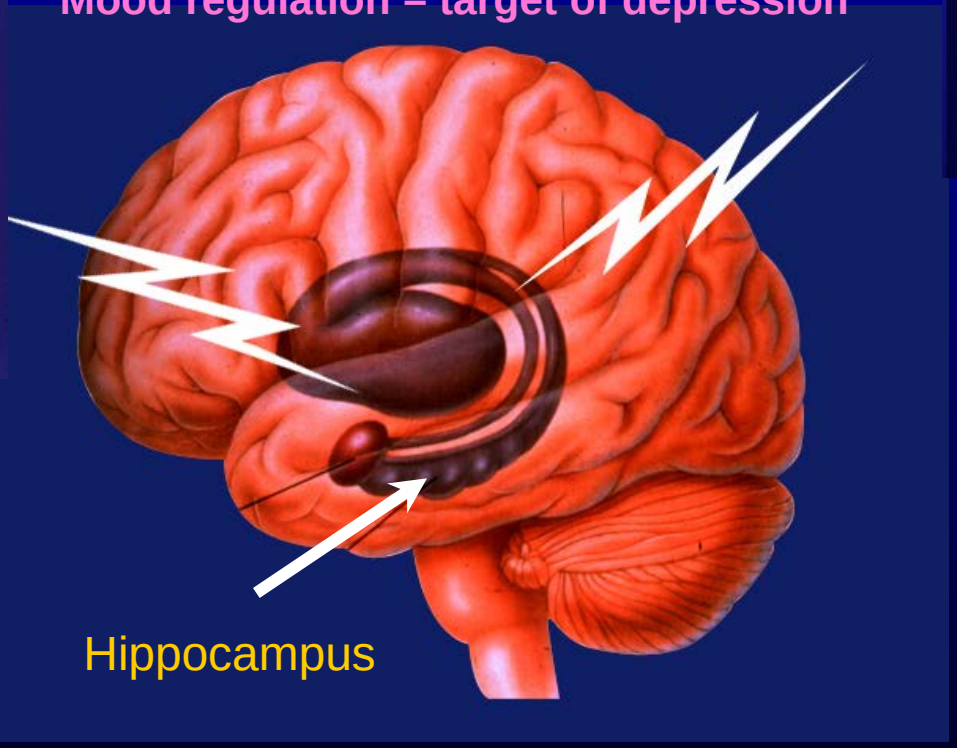
Contextual, episodic, spatial memory

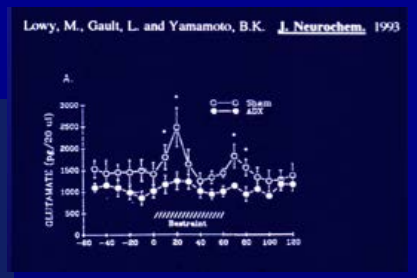
Mood regulation – target of depression





Stress-induced remodeling





Glutamate plays a key role

Prevented by….
Blocking glucocorticoid synthesis

Blocking NMDA receptors
Lithium
Dilantin

Antidepressants

Benzodiazepine

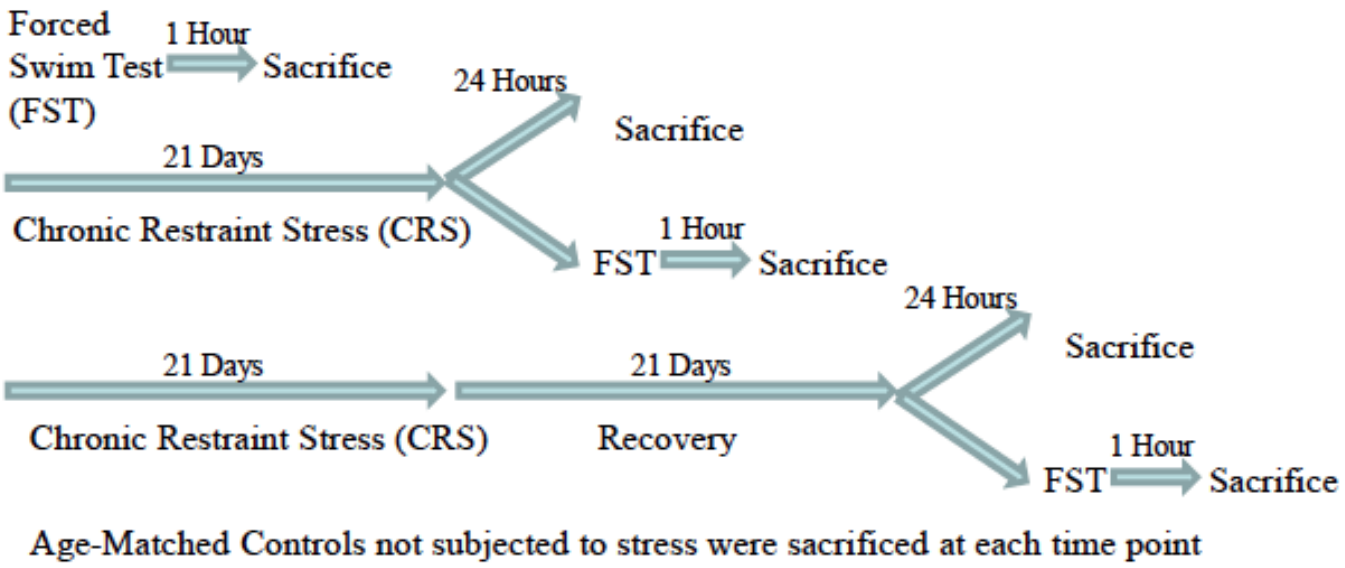
Deficiency of BDNF

Chronic Restraint Stress alters the Gene Expression Profile of the Hippocampus to a Novel, Heterotypic Stressor

899.06

Gray JD, Rubin TG, Hunter RG, and McEwen BS
Department of Neuroendocrinology, The Rockefeller University, New York, NY

Stress Paradigms



Ongoing studies in mice by Drs. Jason Gray and Carla Nasca

Chronic restraint alters the gene expression response to a novel stressor

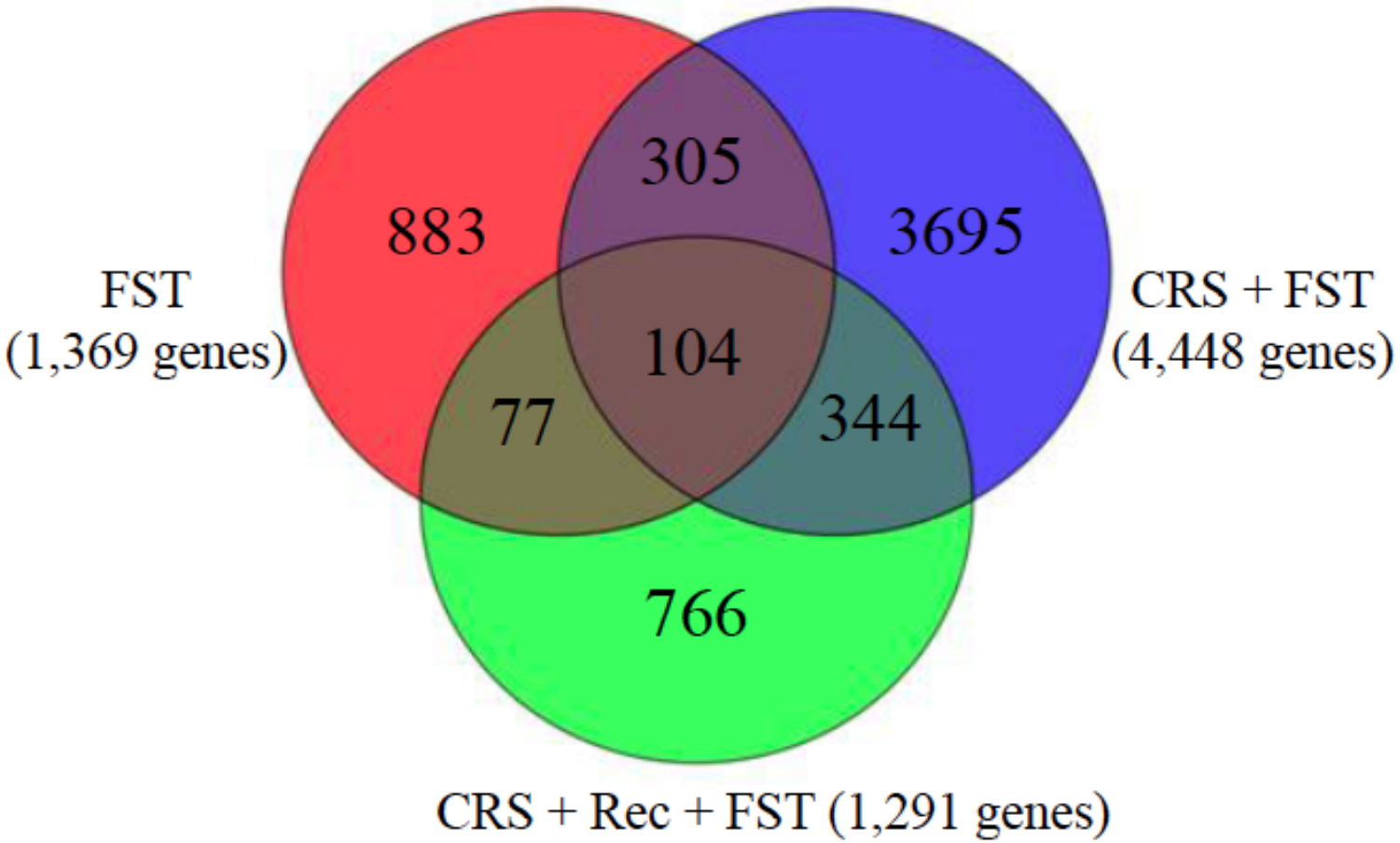


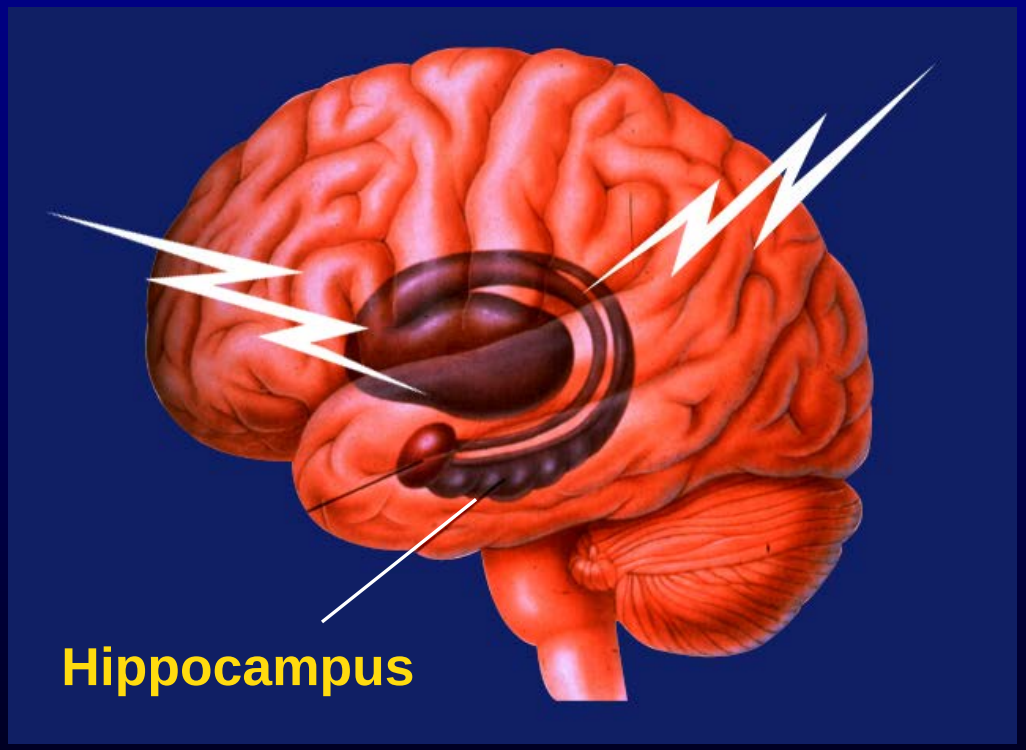
Figure 3. Venn Diagram of Differentially Expressed Genes from Three Different Stress Paradigms. Using pairwise uncorrected t-tests, FST, CRS + FST, and CRS + Rec + FST were compared to age-matched unstressed controls (n=4/group).

The Brain Under Stress:

Translation

Contextual, episodic, spatial memory

Mood regulation – target of depression



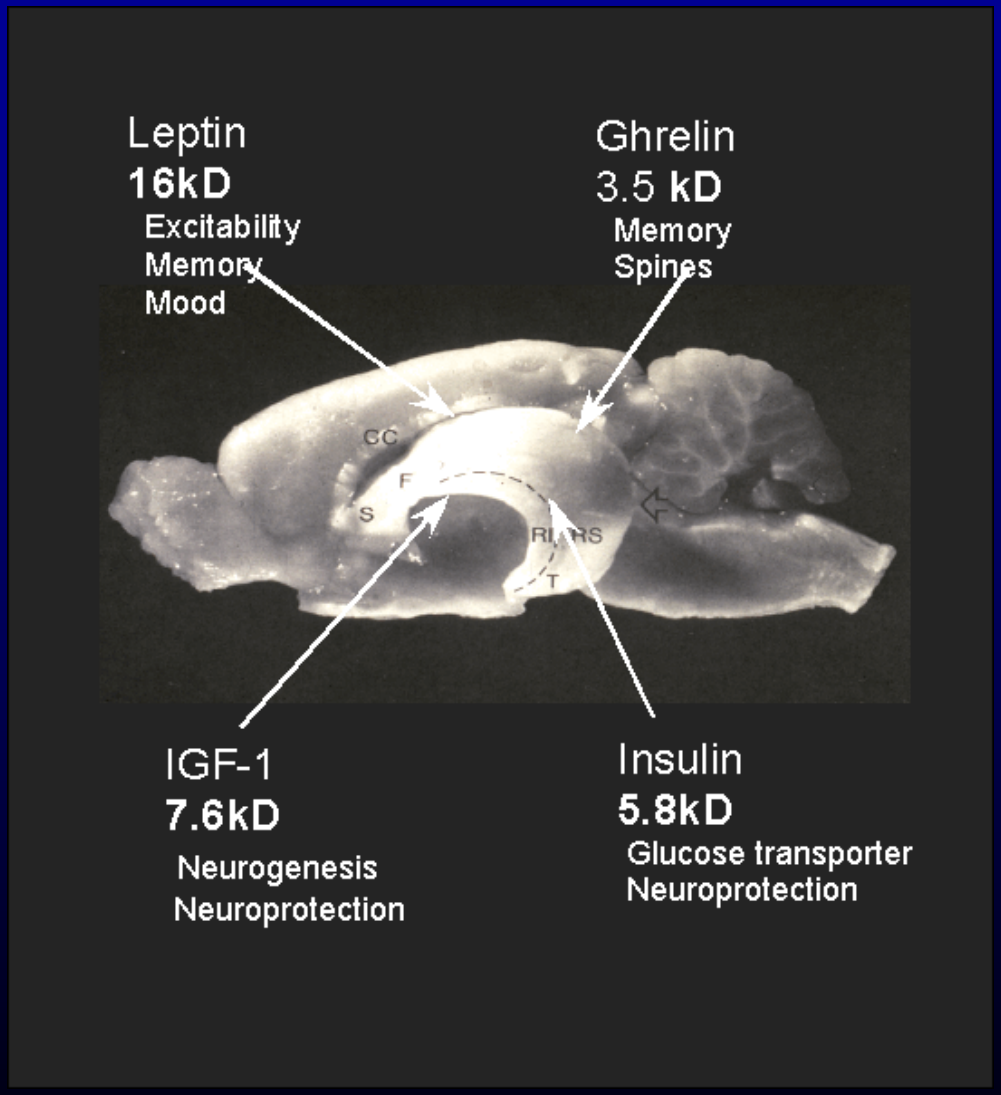
Hippocampus *ATROPHIES* in:

- **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**

Protein/peptide hormones enter and affect the brain



A Shrinking Hippocampus?

DIABETES, MILD COGNITIVE IMPAIRMENT (MCI) and GLUCOSE INTOLERANCE

Diabetologia
DOI 10.1007/s00125-007-0602-7

ARTICLE

Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes

S. M. Gold · I. Dziobek · V. Sweat · A. Tirsi · K. Rogers · H. Bruehl · W. Tsui · S. Richardson · E. Javier · A. Convit

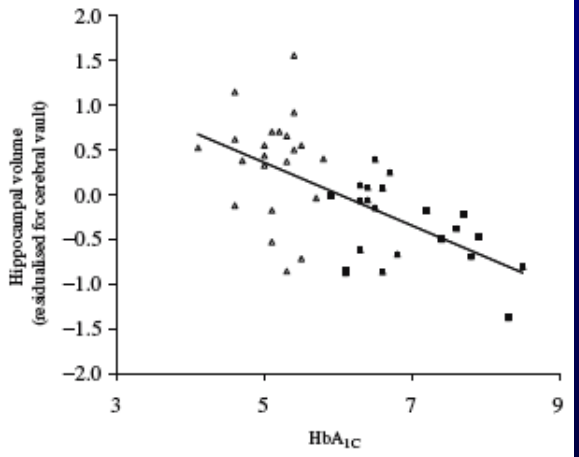


Fig. 1 Bivariate correlations of HbA_{1c} with hippocampal volume (residualised for cerebral vault size). The line shows the line of best fit for the entire study population. *Open triangles*, control subjects; *filled squares*, type 2 diabetic subjects. Descriptive characteristics of individuals with type 2 diabetes and control subjects are given in Table 1

Diabetes (type 2) - increased risk for Alzheimer's

Metabolic syndrome in adolescence: impact on brain

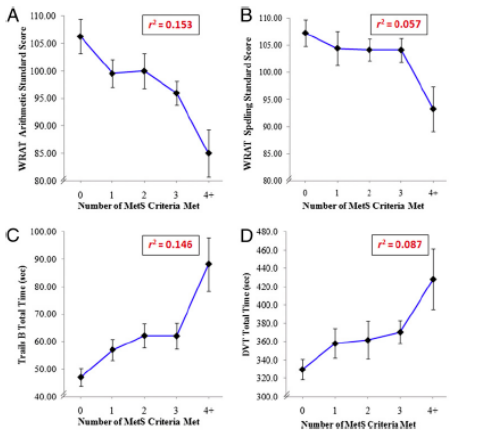


FIGURE 2
Lower cognitive performance with increasing number of MetS components present. A, WRAT arithmetic standard score. B, WRAT spelling standard score. C, Trails B total time. D, DVT total time for individuals who met 0 criterion ($n = 21$), 1 criterion ($n = 18$), 2 criteria ($n = 23$), 3 criteria ($n = 36$), or 4+ criteria ($n = 13$). Data presented are mean ± SEM.

Adolescents with MetS had

-Significantly smaller ICV-adjusted hippocampal volumes

-Larger ICV-adjusted overall CSF volume

--White matter abnormalities

We found the hippocampal volume reductions and increased CSF volumes remained significant and that the cognitive group differences were more dramatic, with 10 of the 17 (up from 7/ 17) cognitive measures now showing at least a statistical trend, all with larger effect sizes

Obesity and Metabolic Syndrome and Functional and Structural Brain Impairments in Adolescence

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KEY WORDS
metabolic syndrome, adolescence, obesity, diffusion tensor imaging, brain abnormalities, cognitive performance, hippocampal volumes, fractional anisotropy

ABBREVIATIONS
BP—blood pressure
CRP—C-reactive protein
CSF—cerebrospinal fluid
DLPFR—dorsolateral prefrontal region
DVT—Digit Vigilance Test
FA—fractional anisotropy
HDL—high-density lipoprotein
ICV—intracranial vault
IR—insulin resistance
MetS—metabolic syndrome
MPRAGE—magnetization-prepared rapid acquisition gradient echo
QUICKI—quantitative insulin sensitivity check index
T2DM—type 2 diabetes mellitus
VANCOVA—voxelwise analysis of covariance
WM—white matter
WRAML—Wide Range Assessment of Memory and Learning
WRAT—Wide Range Achievement Test

Each author made substantial contributions to this article. Dr Convit designed, performed, and supervised the study; Drs Yau and Convit, W. H. Tsui, M. G. Castro, and A. Tagani acquired and analyzed the data; Drs Yau and Convit wrote the article; all authors have seen and approved the final version of the manuscript.

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

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WHAT'S KNOWN ON THIS SUBJECT: Despite the dramatic rise in prevalence of metabolic syndrome (MetS) among children and adolescents, and that MetS is associated with cognitive and brain impairments among adults, no data on the impact of MetS on the brain exist in children.

WHAT THIS STUDY ADDS: It provides the first data on the impact of MetS on brain in adolescence. We show reductions in cognitive function and brain structural integrity in nondiabetic adolescents with MetS, thus suggesting that even pre-clinical metabolic illness may give rise to brain complications.

abstract

FREE NIH

BACKGROUND: The prevalence of metabolic syndrome (MetS) parallels the rise in childhood obesity. MetS is associated with neurocognitive impairments in adults, but this is thought to be a long-term effect of poor metabolism. It would be important to ascertain whether these brain complications are also present among adolescents with MetS, a group without clinically manifest vascular disease and relatively short duration of poor metabolism.

METHODS: Forty-nine adolescents with and 62 without MetS, matched on age, socioeconomic status, school grade, gender, and ethnicity, received endocrine, MRI, and neuropsychological evaluations.

RESULTS: Adolescents with MetS showed significantly lower arithmetic, spelling, attention, and mental flexibility and a trend for lower overall intelligence. They also had, in a MetS-dose–related fashion, smaller hippocampal volumes, increased brain cerebrospinal fluid, and reductions of microstructural integrity in major white matter tracts.

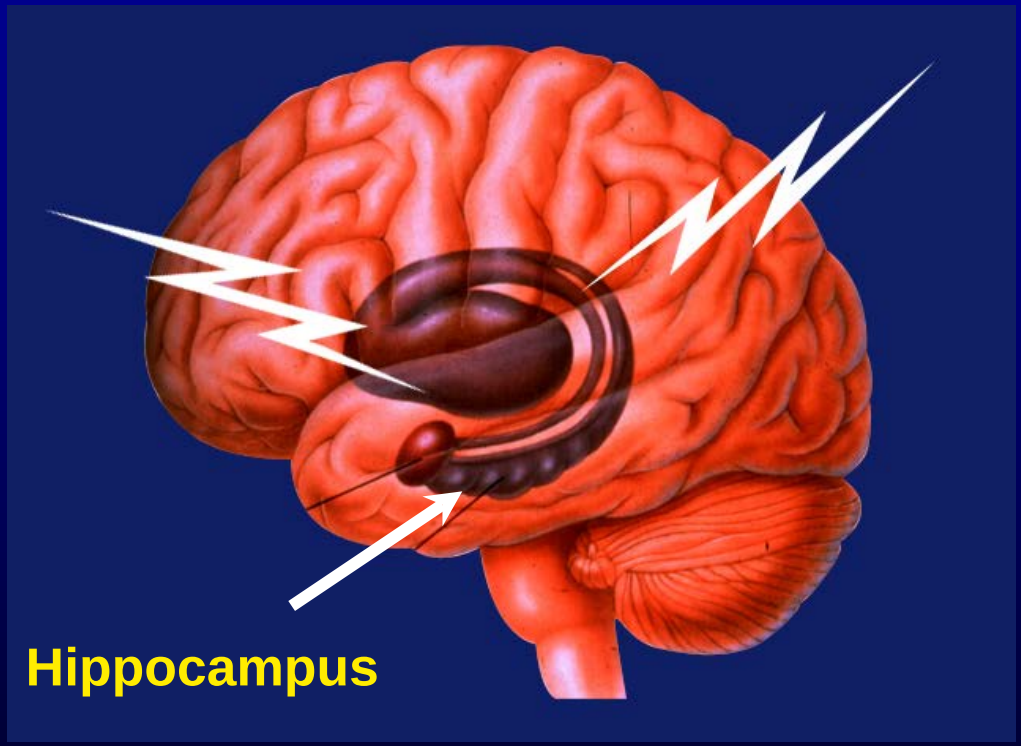
CONCLUSIONS: We document lower cognitive performance and reductions in brain structural integrity among adolescents with MetS, thus suggesting that even relatively short-term impairments in metabolism, in the absence of clinically manifest vascular disease, may give rise to brain complications. In view of these alarming results, it is plausible that obesity-associated metabolic disease, short of type 2 diabetes mellitus, may be mechanistically linked to lower the academic and professional potential of adolescents. Although obesity may not be enough to stir clinicians or even parents into action, these results in adolescents strongly argue for an early and comprehensive intervention. We propose that brain function be introduced among the parameters that need to be evaluated when considering early treatment of childhood obesity. *Pediatrics* 2012;130:1–9

The Brain Under Stress:

Translation

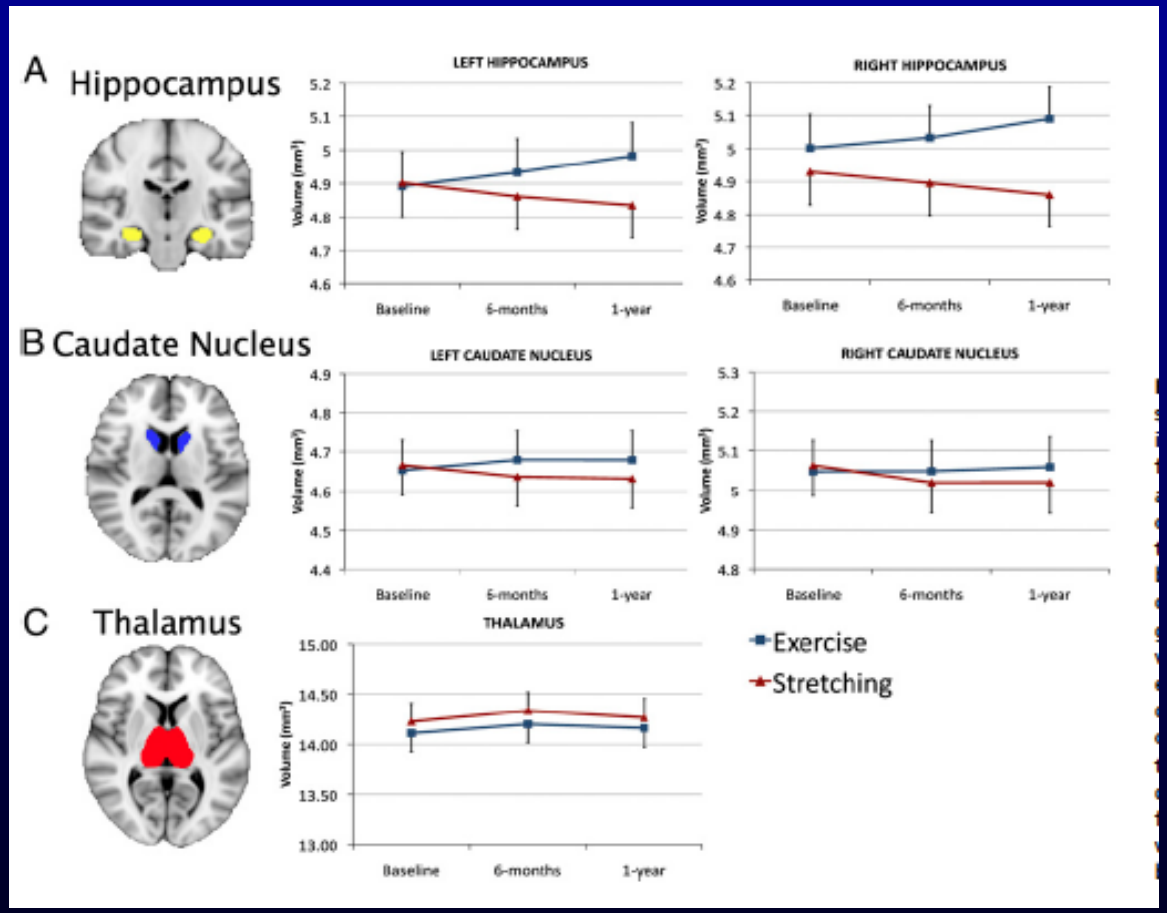
Hippocampus *INCREASES* in size with:

- Regular exercise
- Intense learning
- Anti-depressant treatment

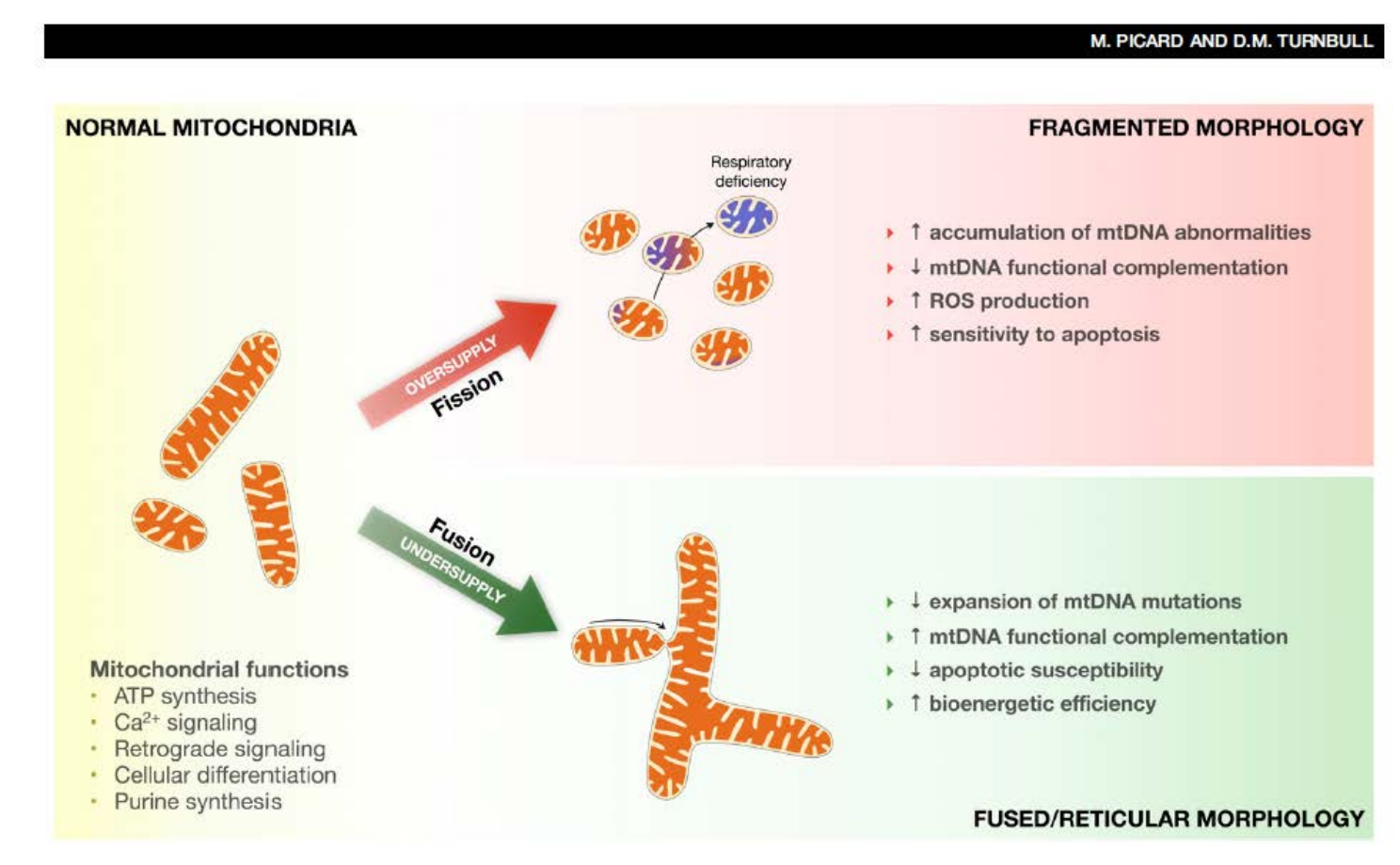


Exercise training increases size of hippocampus and improves memory

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]



Mitochondria in muscle: fragmentation with inactivity



Summary: Stress – Good and Bad

Role in Synaptic Function, Adaptive Plasticity and Damage

Synaptic functions: suppression

- Synaptic transmission.
- Long-term potentiation.
- Learning - less-important things

Synaptic functions: enhancement

- Synaptic transmission.
- Long-term potentiation.
- Learning - re: self-preservatio

Adaptive plasticity ***:

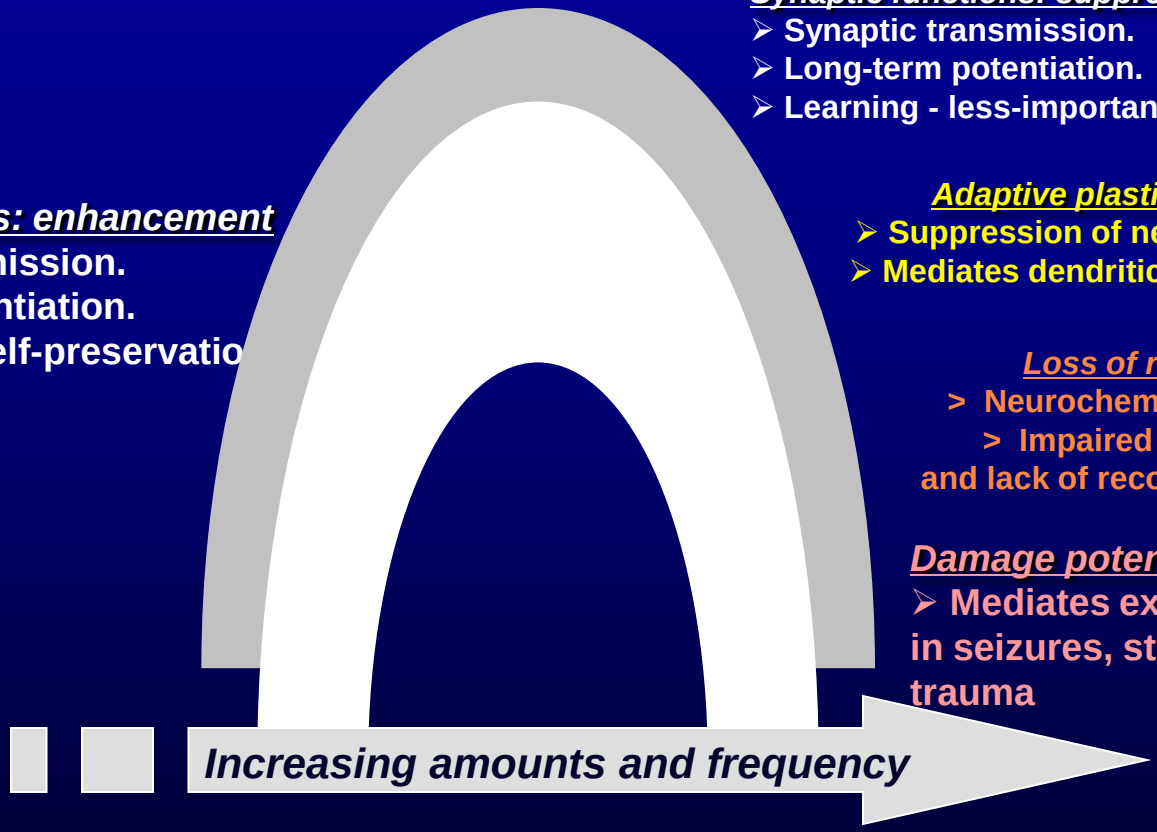
- Suppression of neurogenesis.
- Mediates dendritic remodeling.

Loss of resilience

> Neurochemical distortion
> Impaired remodeling
and lack of recovery from stress

Damage potentiation:

- Mediates excitotoxicity in seizures, stroke, & head trauma



Adrenal steroids and excitatory amino acids modulate both limbs of inverted U

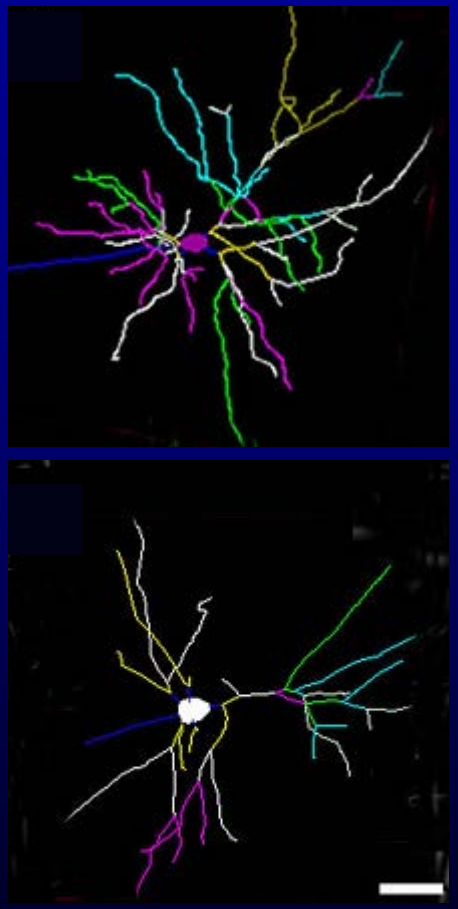
*****Chronic stress: how much protection vs. destabiization?**

Stress causes neurons to shrink or grow

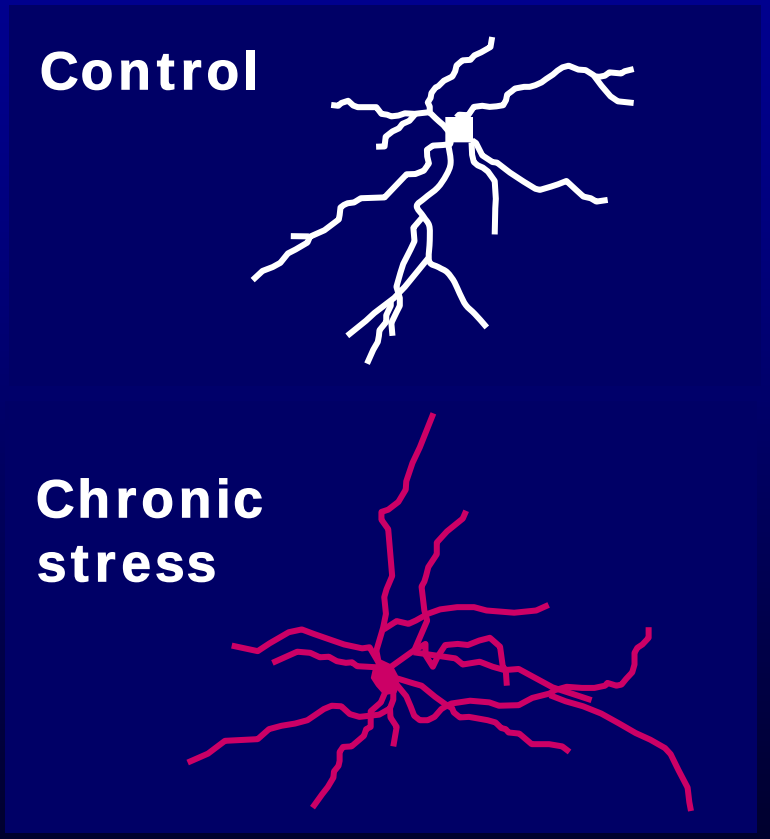
….but not necessarily to die

Control

Chronic stress



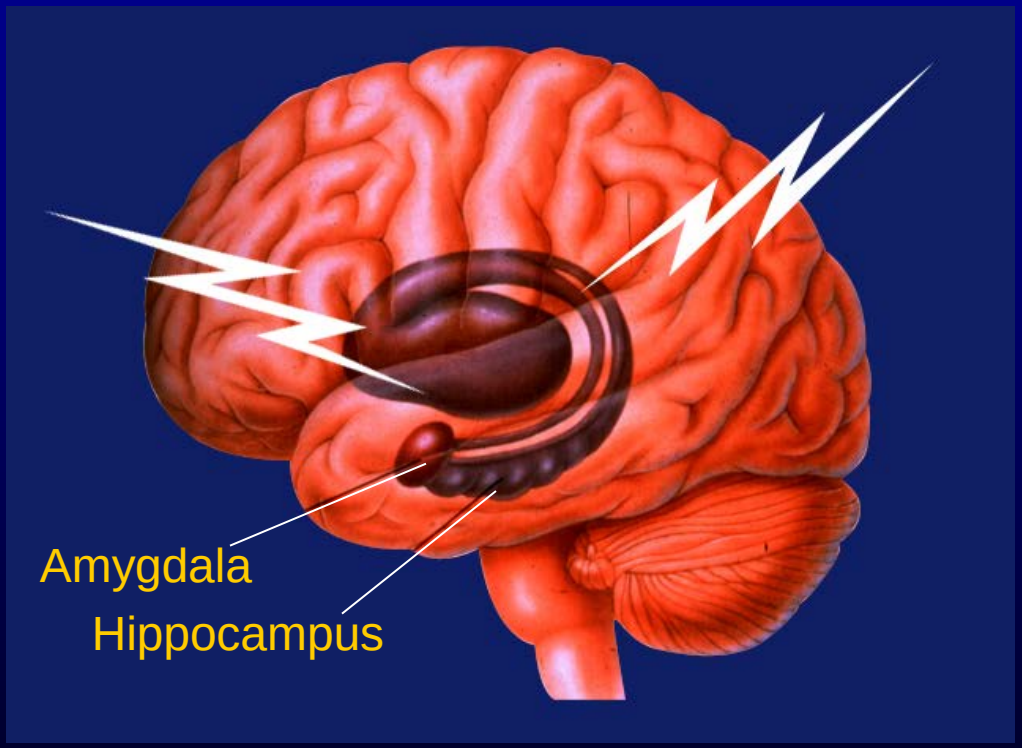
Prefrontal Cortex
And Hippocampus

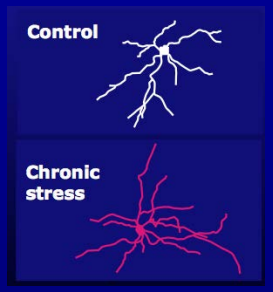


Amygdala
OFC

Brain Under Stress:

Role in cognitive function, emotion, neuroendocrine and autonomic regulation





Chronic stress –dendritic expansion

Acute stress – spine formation

Increased anxiety

S. Chattarji lab

Amygdala

Emotion, fear, anxiety,

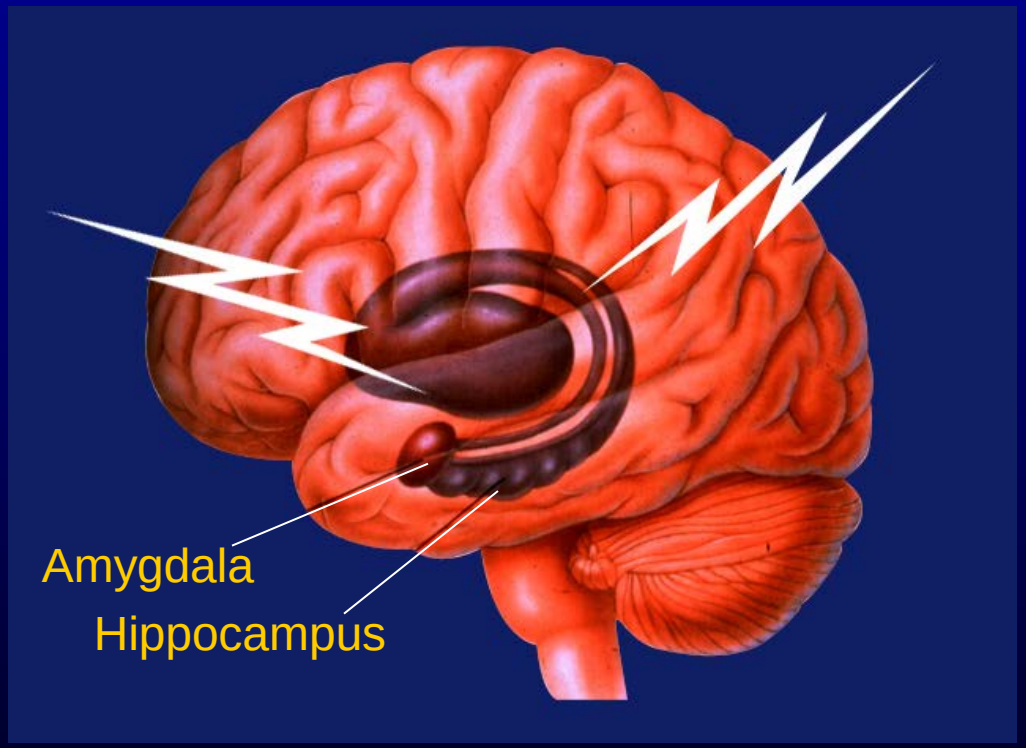
Aggression

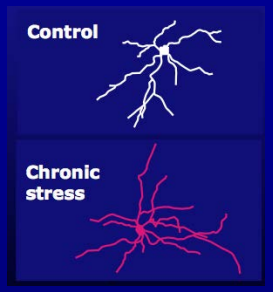
Turns on HPA and autonomic response

Overactivity in anxiety disorders and depression

Brain Under Stress:

Role in cognitive function, emotion, neuroendocrine and autonomic regulation





Chronic stress –dendritic expansion

Acute stress – spine formation

Increased anxiety

S. Chattarji lab

Independent of Glucocorticoids, which Block stress effect

Amygdala

Emotion, fear, anxiety,

Aggression

Turns on HPA and autonomic response

Overactivity in anxiety disorders and depression

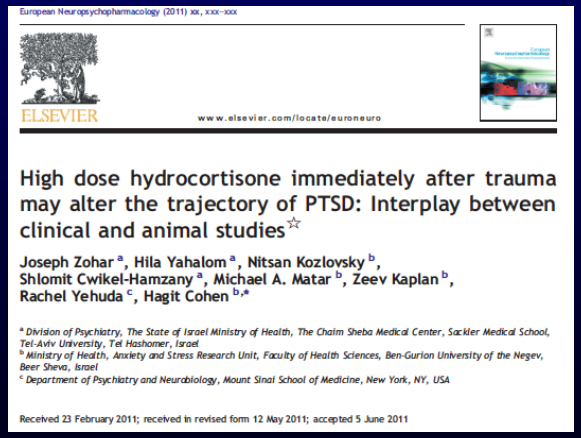
Possible relevance to PTSD

Low CORT at time of trauma – increased PTSD

-Epidemiology (Yehuda, McFarlane, Shalev)

-Supplemental CORT reduces symptoms (Schelling)

-Animal models (Hagit Cohen and colleagues)



European Neuropsychopharmacology (2011) xx, xxx–xxx

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High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: Interplay between clinical and animal studies☆

Joseph Zohar [a], Hila Yahalom [a], Nitsan Kozlovsky [b], Shlomit Cwikel-Hamzany [a], Michael A. Matar [b], Zeev Kaplan [b], Rachel Yehuda [c], Hagit Cohen [b,*]

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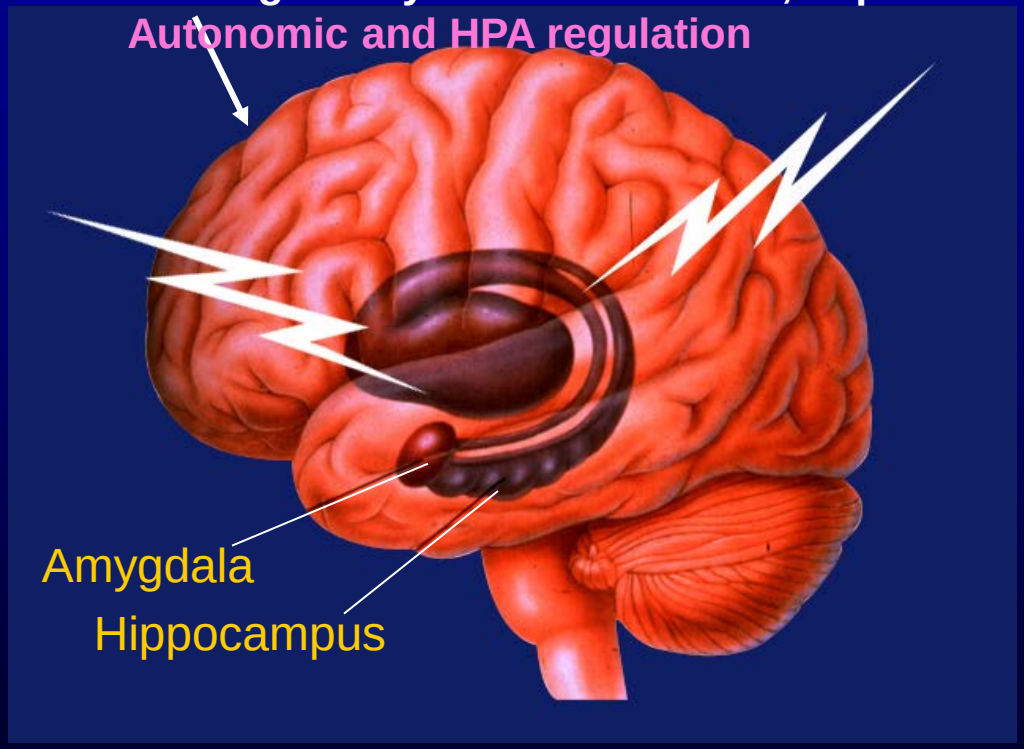
Brain Under Stress:

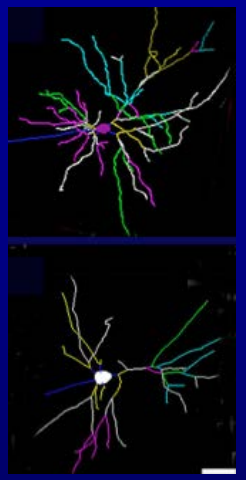
Role in cognitive function, emotion, neuroendocrine and autonomic regulation

Prefrontal cortex

Decision making, working memory,
Self regulatory behaviors: mood, impulses
Autonomic and HPA regulation



mPFC



Control

Chronic stress
Circadian disruption

Reversible in young adults.

Sensitive to circadian disruption

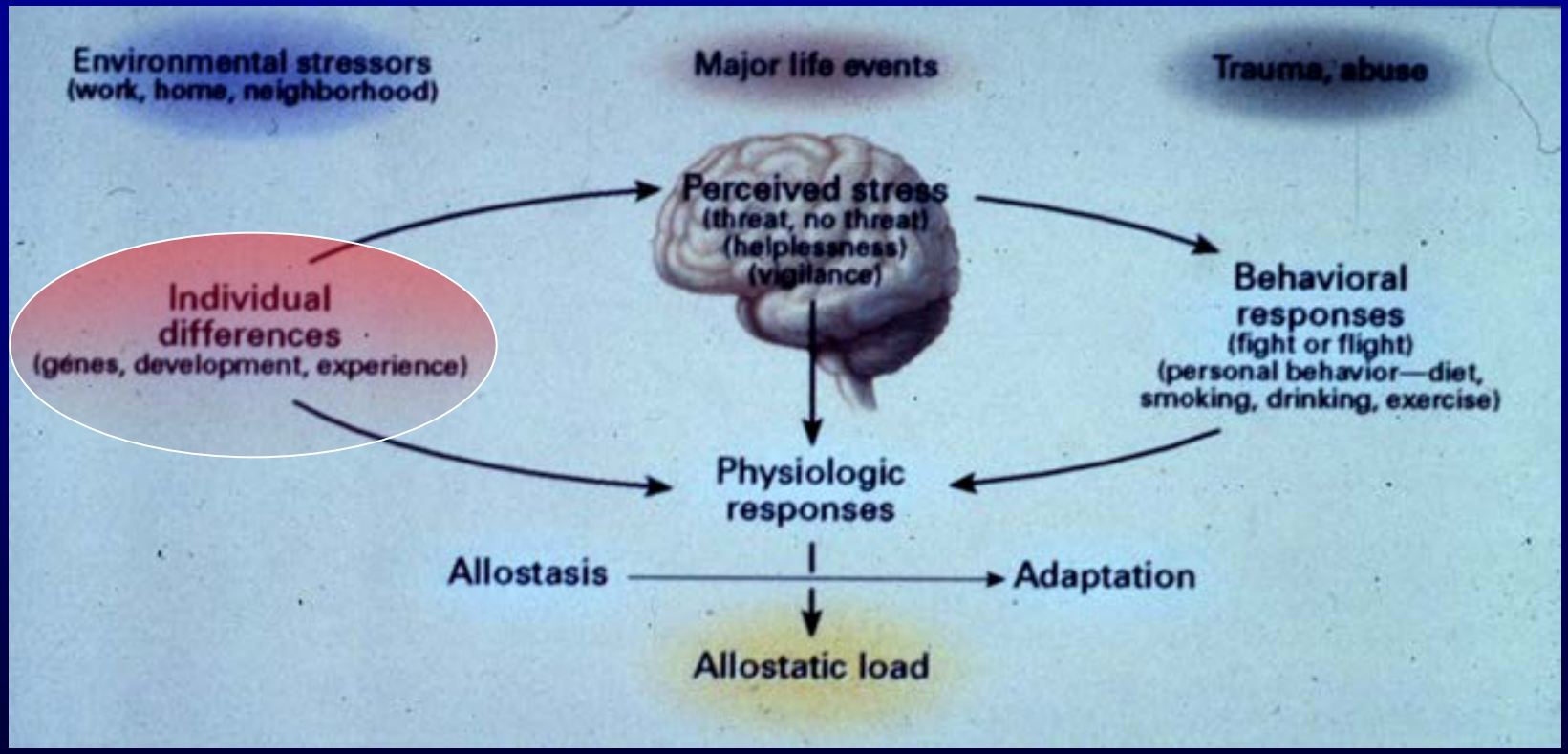
Loss of resilience with aging

Females respond differently

Collaboration with John Morrison, Patrick Hof

Social environment and health

Part 3: Biological Embedding and G x E



Reactive alleles

Epigenetic modifications – transgenerational

Types of Stress

Positive Stress

- Exhilaration from a challenge that has a satisfying outcome
- Sense of mastery and control
- Good self esteem

Tolerable Stress

- Adverse life events but good social and emotional support

Toxic Stress

- Exacerbated by chaos, abuse, neglect
- Poor social and emotional support
- *Unhealthy brain architecture*

Adverse Childhood Experience – Health Consequences

carried out in Kaiser-Permanente Health System in California

Table 1. Health and social problems and the ACE score

Problems from the baseline data	Outcomes associated with the ACE score
Prevalent diseases	Ischemic heart disease, cancer, chronic lung disease, skeletal fractures, sexually transmitted diseases, liver disease
Risk factors for common diseases/poor health	Smoking, alcohol abuse, promiscuity, obesity, illicit drug use, injection drug use, multiple somatic symptoms, poor self-rated health, high perceived risk of AIDS
Mental health	Depressive disorders, anxiety, hallucinations, panic reactions, sleep disturbances, memory disturbances, poor anger control
Sexual and reproductive health	Early age at first intercourse, sexual dissatisfaction, teen pregnancy, unintended pregnancy, teen paternity, fetal death
General health and social problems	High perceived stress, impaired job performance, relationship problems, marriage to an alcoholic, risk of perpetrating or being a victim of domestic violence, premature mortality in family members

Heart disease, smoking, obesity

Drug abuse, high risk for AIDS

Depression, anxiety, anger control

Anti-social behavior

Anda et al / Am J Prev Med 2010;39(1):93–98

Nature-Nurture Interactions

Monoamine oxidase genes influence whether childhood abuse will be transmitted from abuser to child

Caspi, A.; McClay, J.; Moffitt, T. E.; Mill, J.; Martin, J.; Craig, I. W.; Taylor, A., and Poulton, R.
Role of genotype in the cycle of violence in maltreated children.
Science. 2002; 297:851-854.

Serotonin transporter genes influence vulnerability to life-stress in causing depression

Caspi, A.; Sugden, K.; Moffitt, T. E.; Taylor, A.; Craig, I. W.; Harrington, H.; McClay, J.; Mill, J.; Martin, J.; Braithwaite, A., and Poulton, R.
Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene.
Science. 2003; 301:386-389.

Study in New Zealand

Epigenetics
Biological Embedding

"above the genome"

Refers to the gene-environment interactions that bring about the phenotype of an individual.

- Modifications of histones - unfolding/folding of chromatin to expose or hide genes

- Binding of transcription regulators to DNA response elements on genes

- Methylation of cytosine bases in DNA without changing genetic code

- MicroRNA's – regulate mRNA survival and translation

Effects can extend to next generation

Examples: obesity; parental behavior

http://www.pbs.org/wgbh/nova/sciencenow/3411/02.html

Orchids and Dandelions

Genes that appear to be "bad" may confer positive outcomes in a nurturing environment

MOST OF US HAVE GENES that make us as hardy as dandelions: able to take root and survive almost anywhere. A few of us, however, are more like the orchid: fragile and fickle, but capable of blooming spectacularly if given greenhouse care. So holds a provocative new theory of genetics, which asserts that the very genes that give us the most trouble as a species, causing behaviors that are self-destructive and antisocial, also underlie humankind's phenomenal adaptability and evolutionary success. With a bad environment and poor parenting, orchid children can end up depressed, drug-addicted, or in jail—but with the right environment and good parenting, they can grow up to be society's most creative, successful, and happy people.

Orchid Children

By David Dobbs

In 2004, Marian Bakermans-Kranenburg, a professor of child and family studies at Leiden University, started carrying a video camera into homes of families whose 1-to-3-year-olds indulged heavily in the oppositional, aggressive, uncooperative, and aggravating behavior that psychologists call "externalizing": whining, screaming, whacking, throwing tantrums and objects, and willfully refusing reasonable requests. Staple behaviors in toddlers, perhaps. But research has shown that toddlers with especially high rates of these behaviors are likely to become stressed, confused children who fail academically and socially in school, and become antisocial and unusually aggressive adults.

At the outset of their study, Bakermans-Kranenburg and her colleagues had screened 2,408 children via parental questionnaire, and they were now focusing on the 25 percent rated highest by their parents in externalizing behaviors. Lab observations had confirmed these parental ratings.

Bakermans-Kranenburg meant to change the kids' behavior. In an intervention her lab had developed, she or another researcher visited each of 120 families six times over eight months, filmed the mother and child in everyday activities, including some requiring obedience or cooperation, and then edited the film into teachable moments to show to the mothers. A similar group of high-externalizing children received no intervention.

To the researchers' delight, the intervention worked. The moms, watching the videos, learned to spot cues they'd missed before, or to respond differently to cues they'd seen but had reacted to poorly. Quite a few mothers, for instance, had agreed only reluctantly to read picture books to their fidgety, difficult kids, saying they wouldn't sit still for it. But according to Bakermans-Kranenburg, when those mothers viewed the playback they were "surprised to see how much pleasure it was for the child - and for them." Most mothers began reading to their children regularly, producing what Bakermans-Kranenburg describes as "a peaceful time that they had dismissed as impossible."

And the bad behaviors dropped. A year after the intervention ended, the toddlers who'd received it had reduced their externalizing scores by more than 16 percent, while a non-intervention control group improved only about 10 percent (as expected, due to modest gains in self-control with age). And the mothers' responses to their children became more positive and constructive.

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Biological sensitivity to context: I. An evolutionary–developmental theory of the origins and functions of stress reactivity

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Question: Are "orchids" not only more vulnerable to adversity but also more adaptable?

Some examples of ACE and low SES effects on the brain

1. Lack of verbal stimulation ("serve and return") leading to poor vocabulary as well as impaired emotional control.

2. Chaos in home – impaired self regulation; risk for hypertension and obesity

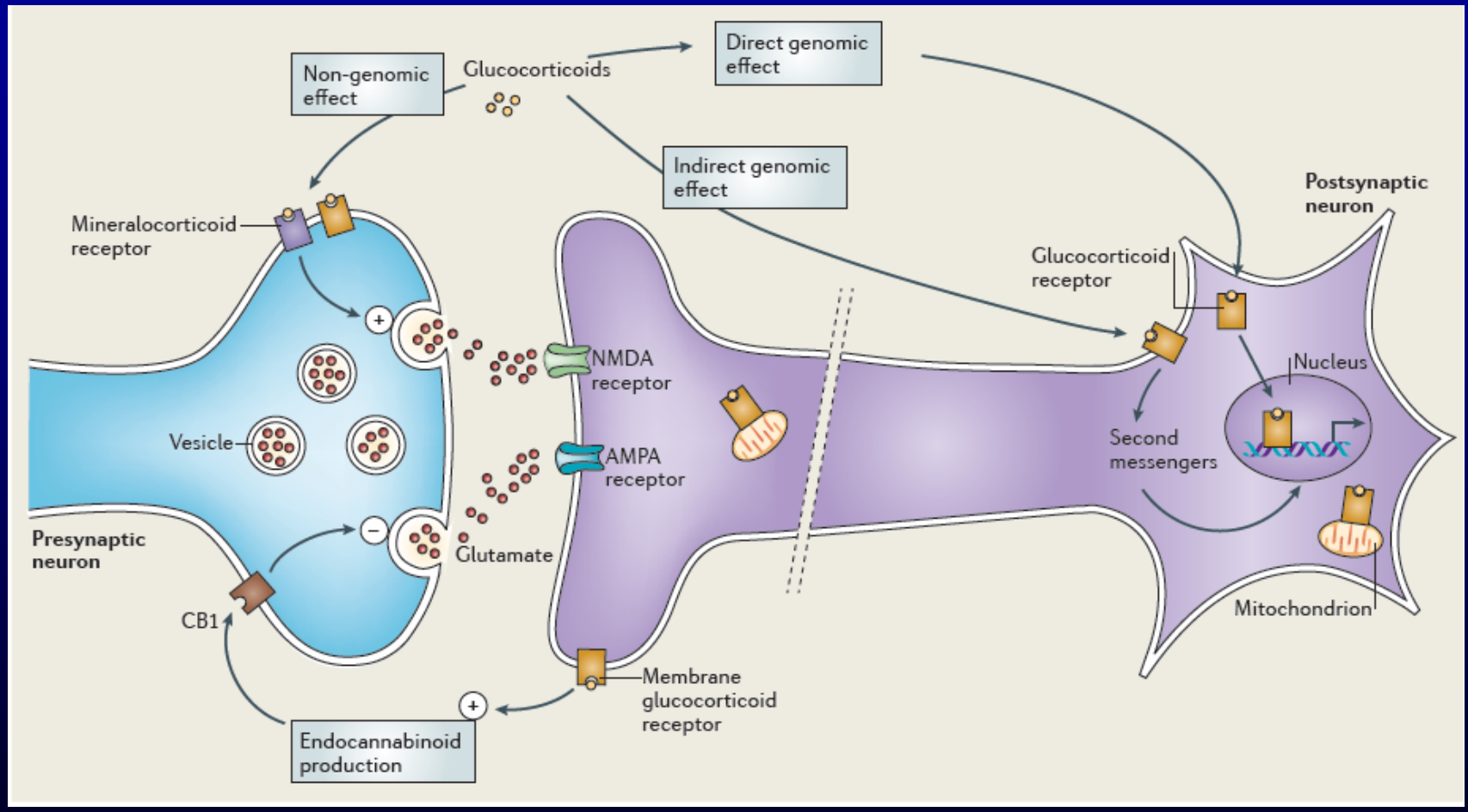
3. Low SES environment – impaired cognitive functions involving prefrontal cortex and hippocampus.

4. Children of depressed mothers have larger amygdala.

5. Low self esteem and locus of control – smaller hippocampus and impaired regulation of cortisol; increased risk for PTSD.

Diverse mechanisms of glucocorticoid action:

Non-genomic and genomic effects of glucocorticoids



Non-nuclear glucocorticoid receptors: association with PSD

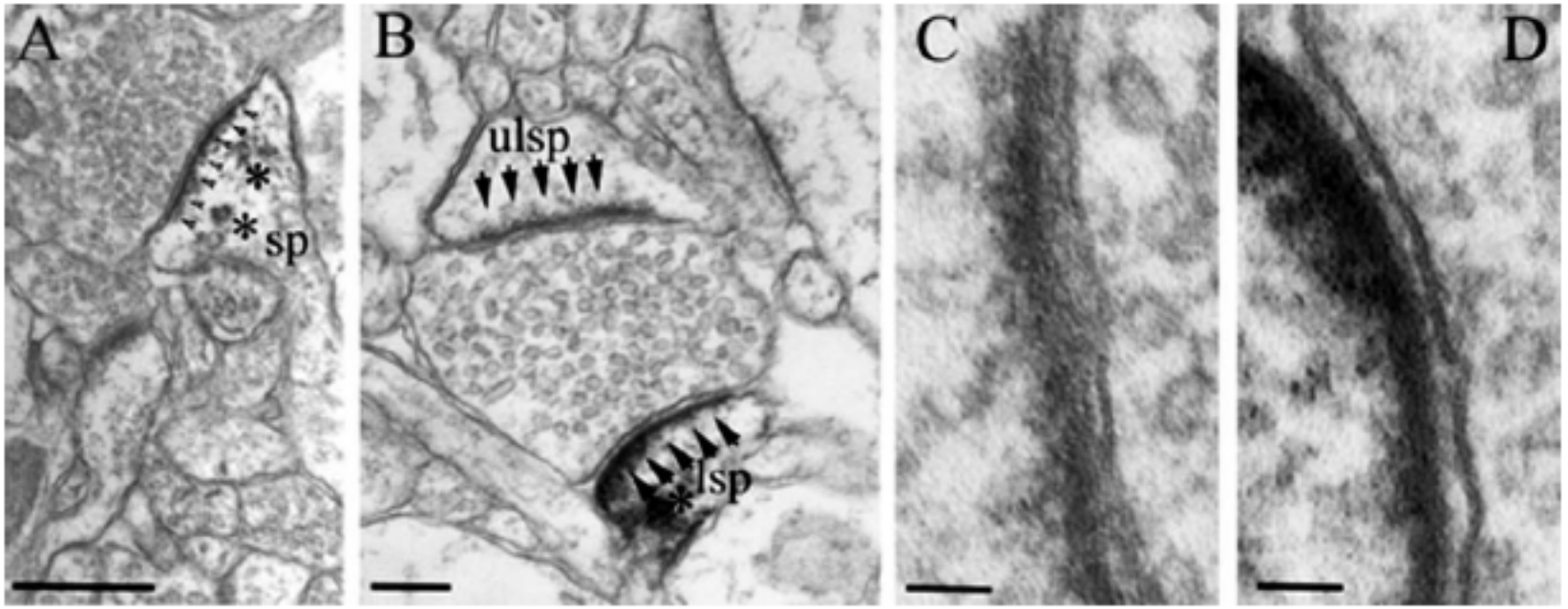


Fig. 3. GR immunolabeling of the PSD. (A) GR-ir labeling of the PSD (arrowheads) of an asymmetrical synapse located on the head of a LA spine (sp). GR-ir spine organelles are also present in the spine head (asterisk). (B) A presynaptic terminal simultaneously forms two asymmetric synapses onto spines (arrows): One spine is GR-ir labeled (lsp) at the PSD while the other spine PSD (upper spine) is unlabeled (ulsp). A labeled spine organelle (asterisks) is also present in the lsp. (C, D) Enlargement for comparison of GR-ir labeled and unlabeled PSD's shown in B. (C) Unlabeled PSD shown in B. (D) GR-ir PSD shown in B. Scale bar=(A) 500 nm (B) 200 nm (C, D) 50 nm.

Luke Johnson, Claudia Farb, Joseph Ledoux, John Morrison, Bruce McEwen

Glucocorticoid actions mediate or biphasically modulate actions of chronic stress – 3 examples

- Cocaine amphetamine related transcript (CART) mRNA and protein in dentate gyrus.
  Function: RESISTANCE TO STRESSOR

CORT mediates stress-induced increase in CART

- KA1 receptor mRNA in dentate gyrus.
  Function: PROMOTES GLUTAMATE RELEASE AND ACTIONS

CORT biphasically modulates stress-induced increase in KA1

- Glutamate transporter (Glt 1) mRNA and protein in CA1-3
  Function: REUPTAKE OF GLUTAMATE AFTER RELEASE

CORT biphasically modulates stress-induced increase in Glt1

What these stories have begun to teach us

Glucocorticoid actions involve multiple mechanisms from the epigenome to rapid signaling and participate in many aspects of adaptive plasticity.

Structural plasticity is NOT necessarily DAMAGE and is reversible up to a point…….. but that changes with age.

Stress effects involve more than glucocorticoids including molecules such as excitatory amino acids, CRF, BDNF, tPA, lipocalin-2 and endocannabinoids.

What does this say about therapies?

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Given the interacting nature of mediators and importance of behavior for plasticity, what strategies are best for stress-related disorders?

What to do? Top-down therapies

Interventions - evidence that they change brain structure and function

Regular physical activity

Increased hippocampal volume and PFC blood flow
and improved executive function and memory

Cognitive-behavioral therapy

Reducing anxiety decreases amygdala volume

Social support and integration

Experience Corps for elderly volunteers
Improved executive function, PFC blood flow and overall health

Pharmaceutical agents as adjuncts to top down interventions
and facilitators of change

What are the limits of brain plasticity?

The Antidepressant Fluoxetine Restores Plasticity in the Adult Visual Cortex
José Fernando Maya Vetencourt, *et al.*
Science **320**, 385 (2008);

Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial

François Chollet, Jean Tardy, Jean-François Albucher, Claire Thalamas, Emilie Berard, Catherine Lamy, Yannick Bejot, Sandrine Deltour, Assia Jaillard, Philippe Niclot, Benoit Guillon, Thierry Moulin, Philippe Marque, Jérémie Pariente, Catherine Arnaud, Isabelle Loubinoux

Facilitators of plasticity

Targeted behavior interventions

Corticosterone in drinking water mimics food restriction and fluoxetine treatment

ARTICLE

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Food restriction enhances visual cortex plasticity in adulthood

Maria Spolidoro[1], Laura Baroncelli[1], Elena Putignano[2], José Fernando Maya-Vetencourt[2], Alessandro Viegi[2] & Lamberto Maffei[1]

Neural circuits display a heightened sensitivity to external stimuli during well-established windows in early postnatal life. After the end of these critical periods, brain plasticity dramatically wanes. The visual system is one of the paradigmatic models for studying experience-dependent plasticity. Here we show that food restriction can be used as a strategy to restore plasticity in the adult visual cortex of rats. A short period of food restriction in adulthood is able both to reinstate ocular dominance plasticity and promote recovery from amblyopia. These effects are accompanied by a reduction of intracortical inhibition without modulation of brain-derived neurotrophic factor expression or extracellular matrix structure. Our results suggest that food restriction could be investigated as a potential way of modulating plasticity.

Diverse mechanisms of glucocorticoid action:

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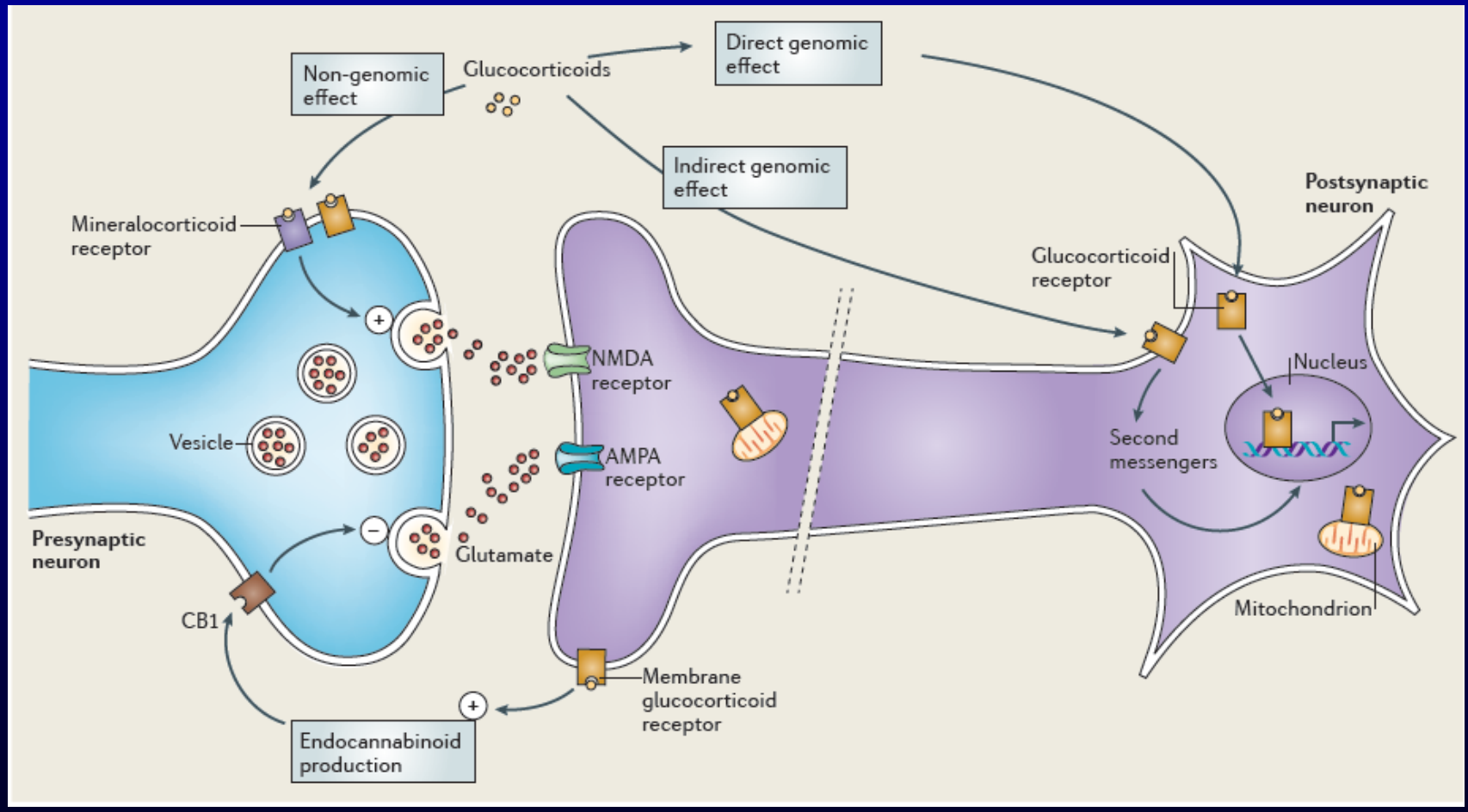

Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo

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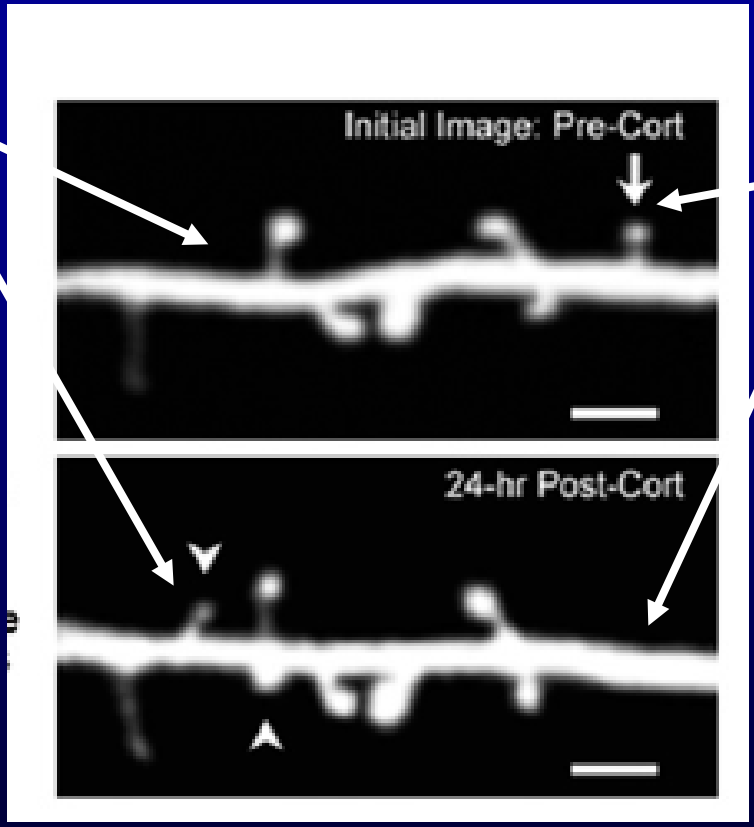
Edited by Bruce S. McEwen, The Rockefeller University, New York, NY, and approved August 12, 2011 (received for review July 1, 2011)

Spine formed over 24h



Spine lost over 24h

- Time course - hours
- Dexamethasone - reduces spine turnover;
- CORT restores
- MR - spine formation and elimination
- GR - spine formation

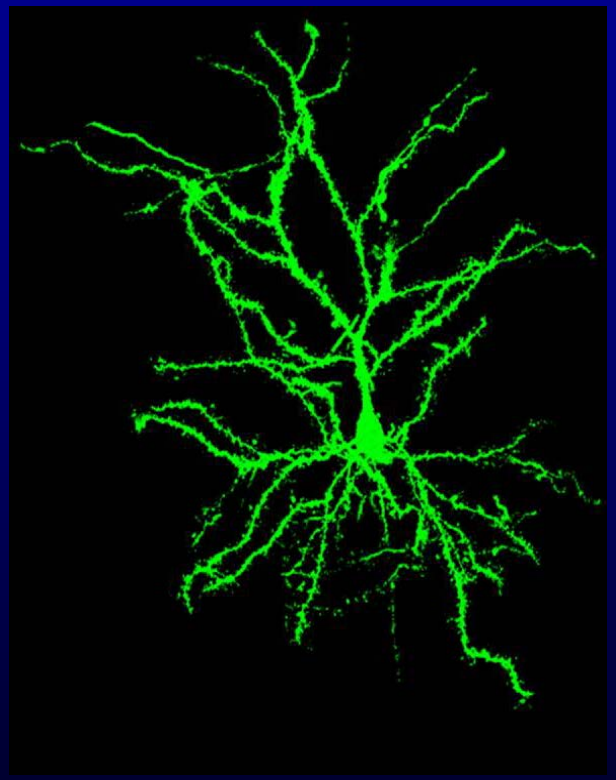
Higher CORT promotes elimination over formation

In adults as well as in young

All accessible cortical regions

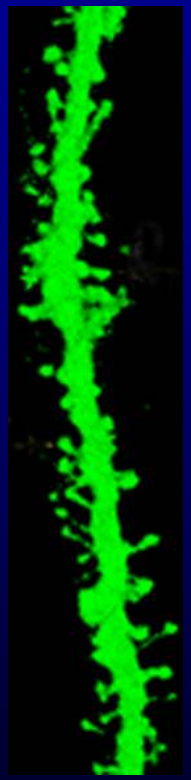
Looking to the Future

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



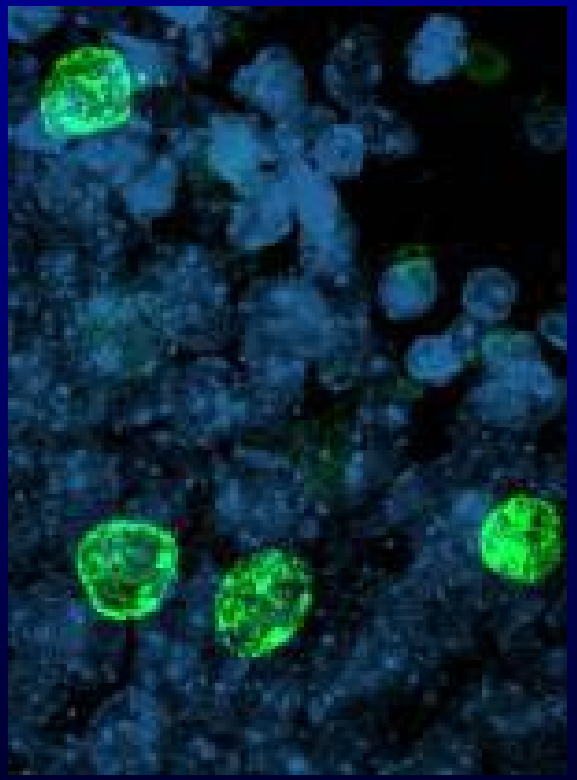
Dendrites

Shrink and expand



Synapses

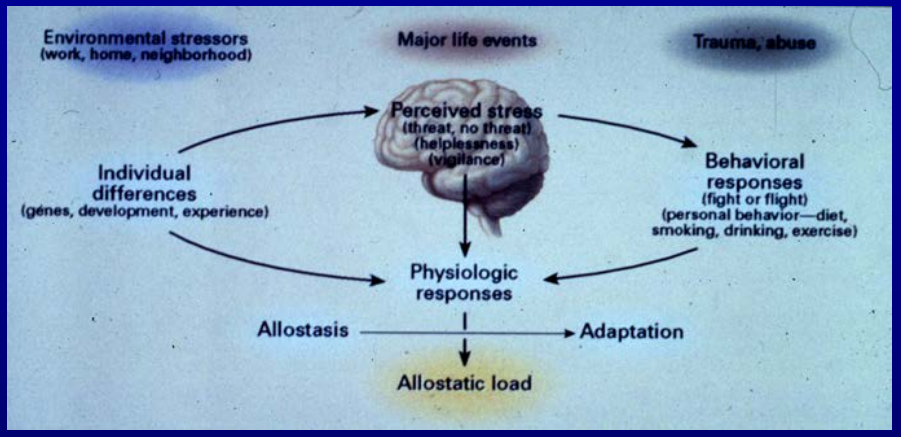
Disappear and are replaced



Neurogenesis

Continues in some brain areas

Conclusion: Social environment, brain, body and health
Non-linearity and biphasic actions



Biphasic effects and non-linearity –interactions of multiple mediators

Protection and damage by mediators of adaptation: cumulative change (allostatic load/overload)

Brain is a target and changes in brain architecture alter physiology and behavior

Powerful effects of social as well as physical environment

Biological embedding – early life; epigenetics; orchids and dandelions

Importance of "top down" interventions

Potential of brain plasticity

Breaking down silos of knowledge and practice!

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